Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial

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Summary

Background *Streptococcus pneumoniae* is the main cause of invasive bacterial disease in children aged younger than 2 years. Navajo and White Mountain Apache children have some of the highest rates of invasive pneumococcal disease documented in the world. We aimed to assess the safety and efficacy of a seven-valent polysaccharide protein conjugate pneumococcal vaccine (PnCRM7) against such disease.

Methods In a group-randomised study, we gave this vaccine to children younger than 2 years from the Navajo and White Mountain Apache Indian reservations; meningococcal type C conjugate vaccine (MnCC) served as the control vaccine. Vaccine schedules were determined by age at enrolment. We recorded episodes of invasive pneumococcal disease and serotyped isolates. Analyses were by intention to treat and per protocol.

Findings 8292 children enrolled in the trial. In the per protocol analysis of the primary efficacy group (children enrolled by 7 months of age) there were eight cases of vaccine serotype disease in the controls and two in the PnCRM7 group; in the intention-to-treat analysis we noted 11 cases of vaccine serotype disease in the MnCC control group and two in the PnCRM7 group. After group randomisation had been controlled for, the per protocol primary efficacy of PnCRM7 was 76·8% (95% CI −9·4% to 95·1%) and the intention-to-treat total primary efficacy was 82·6% (21·4% to 96·1%).

Interpretation PnCRM7 vaccine prevents vaccine serotype invasive pneumococcal disease even in a high risk population. Other regions with similar disease burden should consider including this vaccine in the routine childhood vaccine schedule.

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Introduction

Streptococcus pneumoniae (pneumococcus) is a major cause of morbidity and mortality in people of all ages, but especially in those at the extremes of age, and in those who live in developing countries. Before the introduction of pneumococcal conjugate vaccine, the rate of invasive pneumococcal disease in children younger than 2 years was 166·9 per 100 000 child-years in the USA.[1] The burden of invasive pneumococcal disease in young children in developing countries is substantially higher than that in developed countries. For example, the incidence of invasive pneumococcal disease in children younger than 12 months was reported to be 224 and 349 per 100 000 in The Gambia and South Africa, respectively.[2,3] Rates of non-bacteraemic pneumococcal pneumonia in young children are estimated to be two to ten times those of invasive disease. There are an estimated 1·9 million deaths worldwide from acute respiratory illness in children younger than 5 years each year, many of these deaths are caused by *S pneumoniae*.[4]

People of the Navajo and White Mountain Apache tribes in southwestern USA, and Alaska Native populations are at high risk of invasive pneumococcal disease.[5–8] Between 1983 and 1990, the rate of invasive pneumococcal disease in White Mountain Apache children younger than 2 years was 1820 per 100 000, and for Navajo children the rate was 537 per 100 000 between 1989 and 1996—frequencies that do not compare favourably with those in of the general US population. Reasons for the increased risk of disease are unknown.

For young children, pneumococcal polysaccharide vaccines provide little protection against pneumococcal disease because those younger than 2 years of age respond poorly to T-cell independent antigens such as pure polysaccharide antigens. However, infants and young children are very capable of mounting a brisk immune response to T-cell dependent antigens. As a result, serotype-specific pneumococcal polysaccharide-protein conjugate vaccines, which result in a T-cell dependent immune response have been developed. One such vaccine, a seven-valent pneumococcal vaccine conjugate to CRM_{197}(PnCRM7), has proved efficacious against invasive pneumococcal disease in children younger than 2 years of age in a Northern California population[9] and against pneumococcal otitis media in young children in Finland.[10]

We aimed to determine the efficacy of this pneumococcal conjugate vaccine against invasive pneumococcal disease in American Indian children at high risk of invasive pneumococcal disease. Unlike the Northern California Kaiser Permanente (NCKP) study, we used a group-randomised design to assess the potential effect of the vaccine in a community, measuring indirect effects of the vaccine through reduction in carriage and secondary attack rates. Analyses of indirect effects of the vaccine will be reported separately.

Methods

Population sites

On the Navajo and White Mountain Apache Indian reservations, health care is provided through the Indian Health Service (IHS) agency of the federal Department of Health and Human Services. Each reservation is divided into geographic administrative areas called service units that vary in size and scope of healthcare facilities.

The Navajo Nation is one of the largest Indian tribes in the USA with about 200 000 members and the largest reservation in the country, which covers more than 25 000 square miles in Arizona, New Mexico, and Utah. Six of the Navajo service units operate hospitals, and two smaller service units operate full-time clinics. Additionally, there are seven full-time health centres and 12 part-time health stations in the reservation.

The White Mountain Apache tribe consists of about 14 000 enrolled members, and the reservation, roughly 1·6 million acres in size, is located in central Arizona. The Whiteriver service unit serves the whole reservation through a 45-bed inpatient hospital and two full-time outpatient clinics.

Participants

Between April 30, 1997, and May 31, 2000, we recruited children from the Navajo and White Mountain Apache tribes, who resided on or adjacent to the Navajo or White Mountain Apache Indian reservations. Children aged between 6 weeks and 24 months were eligible to enrol. Parents of children were approached either in the paediatric clinic or by American Indian field workers. We excluded children who had: hypersensitivity to any components of the vaccine; contraindications specified on the manufactures' package inserts for any routine non-study vaccines that the child would receive; any medical condition (eg, one that required frequent or long-term referrals to health-care facilities off the reservation) which, in the opinion of the investigator, might interfere with the assessment of the study objectives; or a moderate or severe illness with or without fever until resolved.

The study was approved by the Institutional Review Boards of the Johns Hopkins School of Medicine, the Navajo Nation, the Phoenix Area Indian Health Service, and the National Indian Health Service. Tribal approval was given by the Navajo Nation and the White Mountain Apache Tribe. Parents or guardians of all enrolled children signed a written informed consent document after reading the document and having the study explained to them in English or in their native language.

Procedures

This was a group-randomised trial with 38 randomisation units: 36 units for Navajo, two for Apache. Randomisation units were clusters of existing, well defined communities,

	Vaccines received			
Age				
Birth	Hepatitis B			
6 weeks	Comvax*	DtaP	Injected or oral poliomyelitis vaccine	
4 months	Hib-OMP	DtaP	Injected or oral poliomyelitis vaccine	
6 months		DtaP		
12–15 months	Comvax	DtaP	Oral poliomyelitis vaccine	MMR Varicella
4–6 years		DtaP	Oral poliomyelitis vaccine	MMR

DtaP=Diphtheria-tetanus-acellular pertussis. MMR=measles, mumps, and rubella vaccine. *Haemophilus influenzae type b-OMP vaccine and hepatitis B vaccine. OMP=outer membrane protein.

Table 1: **Schedule of routine vaccinations for participants**

	Age at first dose	Primary series		Booster dose	
		Doses	Dose interval	Age	Dose interval
Primary efficacy	6 weeks– <7 months	3 by 12 months	≥30 days	>12 months –<24 months	>60 days after primary series
7–11 month catch-up	7 months– <12 months	2 by 12 months	≥30 days	>12 months– <24 months	>60 days after primary series
12–23 catch-up	12 months– <24 months	2 by 24 months	≥60 days	NA	NA

NA=not applicable.

Table 2: **Criteria for inclusion in subgroup analyses**

and within the units every child who consented to participate in the study was given the same vaccine. Combinations of communities were allocated to randomisation units taking into account social interactions, day-care centres, preschools, schools, towns, major roads, and geographic barriers such that children and adults in any randomisation unit would be expected to have little interaction with those of other randomisation units. A blocking scheme with three blocks of four units and 13 blocks of two units was used to ensure that randomisation units covered roughly the same geographical area and included about the same number of children. Therefore, roughly equal numbers of control vaccinations and study vaccinations would be given from a specific health-care facility, to protect against bias due to variability in blood culture practices across facilities. Further details of the randomisation procedures have been published elsewhere.[11]

Vaccine was provided in single-use vials, which were labelled with one of six letter codes; three letters encoded the intervention vaccine and three the control vaccine. Children in any specific randomisation group, although they all received only one type of vaccine, were assigned various letter codes to further mask the structure of the randomisation groups and the vaccine allocation. Vaccine codes and randomisation units were concealed from study staff and participants.

The intervention vaccine was a seven-valent (4, 6B, 9V, 14, 18C, 19F, 23F) pneumococcal polysaccharide protein conjugate vaccine, PnCRM7 (Wyeth Vaccines, Pearl River, NY, USA). Each 0·5 mL dose of PnCRM7 vaccine contained 2 μg each of serotypes 4, 9V, 14, 19F, and 23F polysaccharides; 2 μg of serotype 18C oligosaccharide; 4 μg of serotype 6B polysaccharide, all independently conjugated to the protein carrier CRM_{197} protein; and 0·5 mg of aluminum phosphate as an adjuvant.

The control vaccine was *Neisseria meningitidis* group-C protein conjugate vaccine, MnCC (Wyeth Vaccines), which is an unlicensed investigational vaccine in the USA. Every 0·5 mL dose of MnCC vaccine contained 10 μg of group-C oligosaccharides coupled to CRM_{197} by reductive amination, and 0·5 mg of aluminum phosphate as an adjuvant.

Infants in the primary efficacy group were those who were enrolled between age 6 weeks and 7 months, received three doses of vaccine 2 months apart (minimum of 4 weeks apart), and a booster dose at 12–15 months of age (at least 2 months after the third dose). Infants enrolled between 7 and 11 months of age (7–11 catch-up group) received two doses of vaccine 2 months apart (minimum of 4 weeks) and a booster dose at age 12–15 months (at least 2 months after the second dose). Infants enrolled between 12 and 23 months of age (12–23 catch-up group) received two doses of vaccine at least 2 months apart. Children enrolled in the study received routine childhood vaccines along with the study vaccine (table 1).

All enrolled children were followed up for serious adverse events, which were defined as: admission, death, or life-threatening event that occurred for any reason in the first 24 months of life, or a seizure, allergic event, or severe local reaction within 72 h of a study vaccine dose. All serious adverse events were assessed by a study physician to assign causality in relation to the study vaccine.

An independent data safety and monitoring board reviewed adverse events and advised investigators on the progress of the study. The end of the study was determined by advice from the data safety and monitoring board on the basis of their unblinded assessment of the cases accrued, at the time PnCRM7 became licensed and recommended for use in the USA. We also included a subset of children in an assessment of immunogenicity, the results of which will be published separately.

The IHS physicians at each site were encouraged to obtain a blood culture for all infants younger than 2 years (irrespective of enrolment in the efficacy trial) in whom sepsis, meningitis, or a pneumococcal invasive disease episode was suspected, or who were without focal findings on examination, and had a temperature higher than 39·4°C, in line with published guidelines.[12,13] Furthermore, if a focal infection such as meningitis, septic arthritis, or empyema was suspected, physicians were encouraged to obtain cultures of the appropriate, normally sterile body fluid such as cerebrospinal fluid, joint fluid, and pleural fluid.

We used laboratory-based active surveillance to detect invasive pneumococcal and meningococcal disease in the study population. We contacted reservations' health facilities to ascertain cases of invasive pneumococcal disease. We reviewed all admissions at IHS hospitals, contract facilities, and referral hospitals for study participants. Subisolates of all positive pneumococcal and meningococcal cultures from normally sterile body fluids were obtained; pneumococcal isolates were serotyped with the Quellung reaction. A random subsample of pneumococcal serotyped isolates and all isolates that were non-typeable were confirmed at the Streptococcal Reference Laboratory at the Centers for Disease Control and Prevention in Atlanta, GA, USA. The CDC also serogrouped the meningococcal isolates.

Statistical analysis

We planned to continue the study until 48 cases of invasive pneumococcal disease had been reported. In a trial that randomised individuals to treatment, 40 cases would be needed to give 80% power for the lower limit of a 95% CI for vaccine efficacy to be above 20% efficacy, if the true vaccine efficacy were 70%. We used a design effect of 1·2, based on historical Navajo data, to yield a final sample size of 48 cases. We estimated that it would take 28 months to record this number of cases, on the basis of past incidence, current estimated birth cohort size, estimated participation rate, 20% loss to follow-up, and an assumption that 80% of cases would be caused by serotypes included in the vaccine. We planned an interim analysis after 18 cases had been reported.

Per protocol and intention-to-treat analyses were done for all of the three enrolment groups and for the three groups together. Because we used a group-randomised design, the meaning of vaccine efficacy is somewhat different than that in an individually-randomised trial. All efficacy estimates reported here are based on standard calculations for those enrolled in the trial, and are the result of what has been termed the total effect of the vaccine, which has been previously defined.[14] This effect is a combination of the direct effect (that conferred to

individuals because they themselves received the vaccine) plus any indirect effect (that conferred to individuals because they live in a community where a large number of other individuals have received the vaccine, thus reducing exposure to the organism).[14] The direct effect is what is usually estimated in individually-randomised trials.

All enrolled children who were Native American, residents of the Navajo Nation or the White Mountain Apache Reservation were included in intention-to-treat analyses.
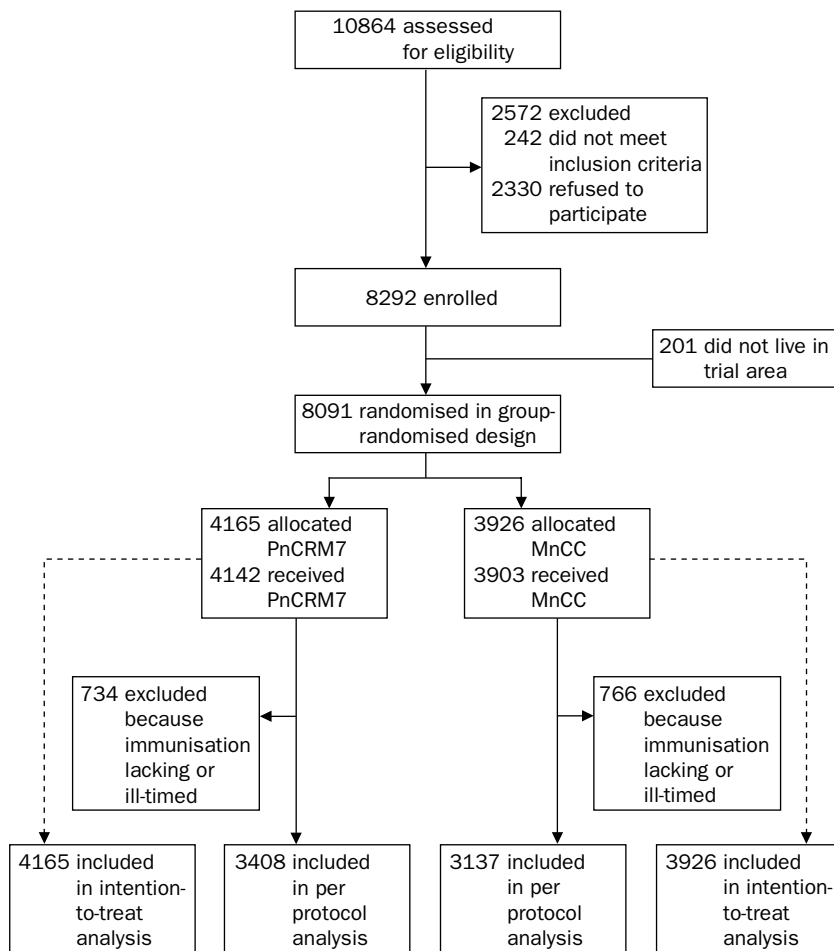
To be included in the per-protocol subgroup analysis at a given age, the participant must fulfil all age-appropriate criteria (table 2). Participants were excluded from the per protocol analysis at the age of first violation of these criteria. Participants were excluded from the per protocol analysis if they had not received their booster dose by age 16 months. Total follow-up time of participants was censored at death or May 31, 2000, whichever occurred first.

Invasive disease episodes were included in the per protocol or intention-to-treat analyses if they occurred on or before May 31, 2000 (including episodes of disease after age 24 months). Invasive pneumococcal disease episodes were categorised as vaccine type (ie, 4, 6B, 9V, 14, 18C, 19F, or 23F), and non-vaccine type if the serotype was anything other than these, including non-typeable isolates. Numerator outcomes for the primary efficacy group qualified for the per protocol analysis if they occurred during a window of time starting 14 days after the primary series and ending at 16 months of age if the booster had not been given. All outcomes that took place at any time after the booster dose also qualified for the per protocol analysis. Outcomes for the 7–11 catch-up group qualified for the per protocol analysis if they occurred at least 14 days after completion of three doses of study vaccine and for the 12–23 catch-up group if they arose at least 14 days after the second dose. Outcomes that occurred at any time after the first dose of vaccine were included in intention-to-treat analyses.

Efficacy estimates and their 95% CI were obtained by fitting Poisson regression models with an over-dispersion parameter. This parameter accounts for within-randomisation unit correlation.[14] The time from first immunisation (intention-to-treat analysis) or per protcol-qualifying immunisation (per protocol analysis) to date of culture or censoring was used as the exposure time. Efficacy was calculated as (1–risk ratio [RR])×100, where RR is the rate of infection in children who had the PnCRM7 vaccine divided by that for the children who had MnCC. We used SAS version 8.0. Serious adverse events in the two study vaccine groups were compared with Fisher's exact test for several time periods (3 days, 7 days, 30 days, and the entire follow-up period after a dose), vaccine doses (primary doses and booster dose) and enrolment groups (primary efficacy, 7–11 catch-up, and 12–23 catch-up). The unit of analysis was participants so that the same event arising more than once in an individual participant was only counted once for the time period of interest. We tabulated all diagnoses for a specific event. No correction was made for multiple comparisons or for group randomisation in the adverse event analysis. We set the level of significance as p<0·05.

Role of the funding source

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                    │   10864 assessed    │
                    │   for eligibility   │
                    └─────────────────────┘
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                               │─────────→│  2572 excluded       │
                               │          │   242 did not meet   │
                               │          │     inclusion criteria│
                               │          │  2330 refused to     │
                               │          │     participate      │
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                    │   8292 enrolled     │
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                               │          │   trial area         │
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                    │ 8091 randomised in  │
                    │ group-randomised    │
                    │ design              │
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Trial profile

	4165 allocated PnCRM7 4142 received PnCRM7	3926 allocated MnCC 3903 received MnCC	
	734 excluded because immunisation lacking or ill-timed	766 excluded because immunisation lacking or ill-timed	
4165 included in intention-to-treat analysis	3408 included in per protocol analysis	3137 included in per protocol analysis	3926 included in intention-to-treat analysis

Results

We assessed 10 864 infants for eligibilty—about 80% of children within the target age range (figure). After exclusion of children who were ineligible and those whose parents declined to participate, we enrolled 8292 (76·3%) infants in the study between April 30, 1997, and Dec 31, 1999. Therefore, about 60% of the age-eligible population participated in the trial. Of the 8292 enrolled infants, 8091 (97·5%) resided in one of the 38 units of randomisation. The remaining 201 infants resided in communities immediately surrounding the reservations that were not randomised; these children were allocated study vaccine on the basis of the randomised community that was geographically closest to them, but they were not included

	PnCRM7	MnCC
Primary efficacy group	2974	2818
Protocol completed	2472	2283
Primary series not complete	240	276
Primary series not properly timed	244	242
Incorrect vaccine received	18	17
7–11 month catch-up group	315	295
Protocol completed	142	126
Primary series incomplete or improperly timed	116	122
Booster not received or improperly timed	55	45
Incorrect vaccine received	2	2
12–23 month catch-up group	876	813
Protocol completed	794	728
Booster not received or improperly timed	79	81
Incorrect vaccine received	3	4

Table 3: **Vaccine allocation by study group and main reasons for exclusion from per protocol analysis**

in analyses because their vaccine was not randomly allocated. None of these children had pneumococcal invasive disease.

Table 3 shows vaccine allocation by study group. 46 (0·6%) children received at least one dose of incorrect study vaccine and these children are excluded from per protocol analyses, but are included in the intention-to-treat analysis.

The trial was stopped early following advice from the data safety monitoring board. Their recommendation was based on an unblinded assessment that at the time of PnCRM7 licensing and recommendations for its routine use in the USA, data from the accrued cases showed a significant public health benefit for the study population.

Primary efficacy group

Table 4 shows characteristics of participants in the primary efficacy group. Efficacy estimates, case splits, and denominators for various per protocol and intention-to-treat analyses are in table 5. Between April 30, 1997, and May 31, 2000, ten cases of per protocol vaccine serotype invasive pneumococcal disease arose in children in the primary efficacy group—eight in the MnCC control group and two (serotypes 9V and 14) in participants who received PnCRM7. Of these ten cases, six were in separate randomisation units, and four occurred in one MnCC unit. In an intention-to-treat analysis, 11 vaccine-type cases were noted in the MnCC controls and two in the PnCRM7 group. After community randomisation was controlled for, the per protocol total primary efficacy of PnCRM7 was 76·8% (95% CI –9·4% to 95·1%) and the intention-to-treat total primary efficacy was 82·6% (21·4% to 96·1%). The serotype distribution of the invasive primary efficacy cases is shown in table 6.

Two children developed invasive pneumococcal disease after PnCRM7 vaccination. The first child received three doses of PnCRM7 vaccine at age 2, 6, and 8 months. At age 11·8 months, 122 days after the third vaccine dose, the child developed fever associated with tachypnoea and an oxygen requirement. The child also had a white blood-cell count of 33 200, a right middle-lobe infiltrate on chest radiograph, and type 9V pneumococcus isolated from blood culture. The second child received three doses of PnCRM7 at age 2, 4, and 8 months. At 9·6 months of age, 53 days after the third vaccine dose, the child had acute onset of fever associated with seizure. The child had a white blood-cell count of 7700 and a normal chest radiograph. Type 14 pneumococcus was isolated from blood culture. This second child was also enrolled in a nested immunogenicity study of PnCRM7. Results of the child's serological response to study vaccine will be included in a separate report of vaccine immunogenicity in this population. Neither of the two children with breakthrough vaccine serotype invasive disease had any evidence of immunodeficiency in their history, from their physical examination, or suggested during clinical course, or subsequent follow-up to age 2 years.

	PnCRM7 (n=2974)	MnCC (n=2818)
Girls	1466 (49·3%)	1433 (51·2%)
Mean age at first immunisation (days)	81 (45·8)	83 (46·6)
Ever breastfed	2516 (84·6%)	2378 (84·4%)
Mean birthweight (g)	3353 (531)	3328 (521)
Mean number children <6 years in house	1·97 (0·95)	1·95 (0·94)

Data are number (%) or mean (SD).

Table 4: **Characteristics of participants in the primary efficacy group**

Catch-up groups

One vaccine-type case of invasive pneumococcal disease (type 14 bacteraemia) was noted in the 610 children from randomised communities enrolled in the 7–11 month catch-up immunisation group. This case was in a child who had been given MnCC vaccine. Likewise, one vaccine-type invasive pneumococcal disease episode occurred in the 1689 children from randomised communities enrolled at age 12–23 months. This was a type 14 bacteraemia, which was also in a child who had received MnCC.

Clinical syndromes

Of the 16 vaccine-type cases in participants from randomised communities, 15 had *S pneumoniae* isolated from a blood culture and one child had *S pneumoniae* isolated from the cerebrospinal fluid. The clinical syndromes documented at the time of discharge for these invasive pneumococcal disease episodes were: otitis media (six), bacteraemia without a source (five); pneumonia (four); and meningitis (one).

Non-vaccine-type invasive disease

There were 18 episodes of invasive, non-vaccine serotype disease (11 from the PnCRM7 group and seven in children who had MnCC); 13 of these children were enrolled before age 7 months (seven had PnCRM7, six had MnCC). Of the remaining five children, four had PnCRM7 and one had MnCC. None of the per protocol or intention-to-treat case splits reached statistical significance. The serotypes represented were: 12F (eight cases), 7F (two cases), 5 (two cases) and one each of 3, 6A, 18B, 19A, 23B, and 38. Of the 18 episodes of non-vaccine type invasive disease that occurred, clinical diagnoses at discharge were: otitis media (two); bacteraemia without a source (11); pneumonia (three); and meningitis (two).

	PnCRM7 cases (person-years)	MnCC cases (person-years)	PnCRM7 efficacy (95% CI)
Per protocol			
Enrolled			
<7 months, VT	2 (2879)	8 (2674)	76·8% (−9·4 to 95·1)
≥7 months, VT	0 (1735)	2 (1559)	100·0% (−378 to 100)
≥7 months, all types	2 (1735)	2 (1559)	10·2% (−794 to 91·0)
<24 months, VT	2 (4614)	10 (4233)	81·7% (16·3 to 96·0)
<24 months, all types	7 (4614)	14 (4233)	54·1% (−13·6 to 81·5)
Intention to treat			
Enrolled			
<7 months, VT	2 (4951)	11 (4742)	82·6 (21·4 to 96·1)
<7 months, all types	9 (4951)	18 (4742)	52·1 (−6·6 to 78·5)
<24 months, VT	2 (7532)	14 (7151)	86·4 (40·3 to 96·9)
<24 months, all types	13 (7532)	23 (7151)	46·3 (−16·5 to 75·3)

VT=vaccine type.

Table 5: **Frequency of invasive disease and PnCRM7 vaccine efficacy by analysis group and vaccine type**

	PnCRM7/MnCC case counts	
	Per protocol	Intention to treat
Vaccine type	2/8	2/11
4	0/0	0/0
6B	0/4	0/5
9V	1/1	1/1
14	1/1	1/3
18C	0/0	0/0
19F	0/1	0/1
23F	0/1	0/1
Non–VT*	3/4	7/7
Non-VT or cross reactive	1/1	2/1
Non-tyepable	0/1	0/1
Non-VT or non-cross reactive	2/2	5/5
All serotypes	5/12	9/18

VT=vaccine type. *Including non-typeable.

Table 6: **Serotype distribution of invasive disease in primary efficacy group as of May 31, 2001**

Safety

During the study, 981 (22·8%) PnCRM7 and 886 (22·2%) MnCC recipients were admitted at least once, with 1664 and 1494 admissions, respectively. Of these, three (0·07%) of those receiving at least one dose of PnCRM7 vaccine and one (0·03%) of those who had at least one dose of MnCC control vaccine were assessed to be possibly, probably, or definitely vaccine related (p=0·63). Of 1087 discharge diagnoses category comparisons made between the two vaccine groups over various time windows for each of the three age groups, the distribution of episodes between the two vaccine groups was statistically significant for only 15. Of these discharge diagnosis categories, two had p values less than 0·01: skin and appendages (there were eleven different diagnoses in this category), in the primary efficacy group with 19 who received PnCRM7 and 5 who had MnCC; and otitis media in the 12–23 catch-up group, with 12 from the PnCRM7 recipients and two who received MnCC.

By May 31, 2000, 22 study participants had died, 15 who had received PnCRM7 and seven who had had MnCC (p=0·14). Of the deaths, 11 resulted from injuries (eg, drowning, house fires, motor vehicle accidents, suffocation), five from sudden infant death syndrome (two in the MnCC group and three in PnCRM7), and one each of viral myocarditis (MnCC), Respiratory Syncytial Virus pneumonia (MnCC), type 5 pneumococcal sepsis (PnCRM7), histiocytosis (PnCRM7), brain cancer (PnCRM7), and apnoea or seizure of unknown cause (PnCRM7). None of these events was judged to be associated with vaccine.

15 children had adverse events within 72 h of a dose of vaccine that were cliniclally significant, but did not result in admission: five developed urticaria or rash (two MnCC and three PnCRM7), six had a seizure (two MnCC and four PnCRM7), four of which were also associated with fever (one MnCC and three PnCRM7), two children had inconsolable crying or hypotonic reactions (two PnCRM7), one had a transient, blanching, erythematous, vascular-like reaction of the legs and feet (MnCC), and one had a reaction at the local injection site (PnCRM7). Ten of these events were classified as possibly related to the study vaccine (four MnCC and six PnCRM7) and five were categorised as remote or unrelated (one MnCC and three PnCRM7). Of the 15 children, eight received no further study vaccine (two because the adverse event arose after the fourth dose) and seven children received additional study vaccine doses without event.

Discussion

From this group-randomised study, we have shown that PnCRM7 vaccine has high total efficacy against invasive pneumococcal disease in an American Indian population with a high burden of such disease. The reported primary efficacy of 76·8% (95% CI –9·4 to 95·1%) against vaccine serotype disease does not differ from that of 97·4% (79·6–98·5) reported in the NCKP study, the only other published study of efficacy against invasive pneumococcal disease of any conjugate pneumococcal vaccine product. Because about half of all invasive pneumococcal disease in children younger than 2 years on the Navajo Nation is caused by serotypes not included in the PnCRM7 vaccine, the efficacy against all serotype pneumococcal disease was 54·1%.[6] This rate is in striking contrast to the 89·1% reduction in all cases of invasive pneumococcal disease in the NCKP study.

Rates of invasive pneumococcal disease and the proportion that are included in the seven-valent conjugate pneumococcal vaccine used in children on the Navajo Nation are very similar to those in many developing countries around the world. The performance of conjugate pneumococcal vaccines is likely to vary in accordance with many epidemiological and population characteristics, including age at acquisition of *S pneumoniae* in the nasopharynx, density and frequency of pneumococcal nasopharyngeal colonisation, rate of invasive pneumococcal disease, rate of non-invasive pneumococcal disease, pneumococcal serotype distribution, crowding, exposure to other children, exposure to particulate matter from smoke, coincident respiratory viral infections, and nutritional status. Some, but certainly not all of these epidemiological, pathogen, and host characteristics of the Navajo and White Mountain Apache populations are similar to those in other populations of children worldwide. Therefore, the efficacy results from this study could be an important benchmark for expected vaccine efficacy in some developing world settings with high burden of disease, broad serotype distribution, and where HIV infection is not prevalent.

If increases in non-vaccine serotype invasive disease are going to occur as a result of community antibody pressure from administration of conjugate pneumococcal vaccine products, they are most likely to occur in settings where circulation of non-vaccine serotypes is prevalent and where invasive disease from these serotypes occurs. Both of these conditions are present in the American Indian study areas. Therefore, emphasis that no significant increases in non-vaccine type invasive disease rates were noted in this study is important. However, in an intention-to-treat analysis, more cases of such disease were noted in the PnCRM7 group than were in the MnCC control group (12 and 8, respectively). Thus, surveillance for serotype-specific invasive disease in this population will be essential to provide continuing information about the effect of community-wide use of conjugate pneumococcal vaccine.

In the Finnish Otitis Media trial of PnCRM7 and another investigational conjugate pneumococcal vaccine (PnOMPC [Merck, Bluebell, PA, USA]), replacement otitis media with non-vaccine serotypes was noted in children who received either product.[10,15] Up to now, there has been no such significant events for invasive pneumococcal disease in the NCKP population or in this American Indian population.

Our study design allowed for enrolment of all children younger than 2 years to estimate the efficacy of catch-up vaccination schedules and to assess indirect vaccine effects when a large proportion of young children in a community are immunised with a conjugate pneumococcal vaccine product. Although the number of children included in the analysis was only 1299, there were no cases of vaccine serotype invasive disease in children who were vaccinated with PnCRM7 at age 7 months or older. Furthermore, there were no cases of vaccine serotype pneumococcal disease in partly immunised PnCRM7 randomised children at any age.

We did note two cases of disease after three doses of PnCRM7 vaccine. One of these children had a classic pneumococcal-associated lobar pneumonia. The other child had an occult bacteraemia syndrome that resolved without antibiotics. Neither of these children has any evidence of an immune deficiency and both have continued to thrive.

The safety data derived from this study accored with those observed in a US multicentre immunogenicity trial that included 106 children immunised with PnCRM7 and the NCKP in which there were 18 927 children immunised with PnCRM7.[9,16] There was no pattern of increased adverse events in children who had PnCRM7 vaccine compared with those who received MnCC, nor with specific types of adverse events in the PnCRM7 group. Results of one analysis showed an increase in the number of admissions for which otitis media was one of the clinical diagnoses in children 12–23 months old who received PnCRM7. Because we did many serious adverse events comparisons and we noted no other increase in otitis media diagnoses in any other subgroup, it is unlikely that this finding is clinically significant.

Our study had several limitations. Children in this trial, and those in the NCKP study all received either PnCRM7 or MnCC control vaccine, both of which were investigational at the time of the study. Furthermore, children were receiving licensed routine vaccines concomitant with the study vaccine. Therefore, we are only able to assess the rates of adverse events among PnCRM7 vaccinees relative to those among MnCC control vaccinees, but we cannot ascribe causality to events.

Our study was designed to serve as a pivotal trial for vaccine licensing. Group-randomised trials of vaccines can be used to determine vaccine efficacy as well as indirect effects of vaccines and should be given strong consideration as a trial design for future vaccine studies where issues of indirect protection are important. That this protection can be measured is the major scientific advantage of a group-randomised trial design.

Limitations of this trial design include increased difficulty maintaining the masking in the trial, reduction of effective sample size, and mixing of the intervention and control populations. The rate of invasive pneumococcal disease in the control study participants (ie, those aged <24 months) during the course of the vaccine trial was 322 per 100 000 person-years (and about 355 per 100 000 person-years in those not enrolled but living in MnCC randomisation areas). This rate was less than that recorded in the decade before the trial began. Reasons for this finding are probably related to true rate reductions, although improved living conditions as well as a reduced propensity to obtain blood cultures from febrile children in an era of routine conjugate *Haemophilus influenzae* type b vaccine use. Furthermore, there has been a shift away from vaccine serotypes: in our study, only 11 of 18 (61%) invasive pneumococcal cases in the MnCC control group were vaccine serotypes. The combination of these lower rates, a reduced proportion of disease caused by vaccine serotypes and the early stopping of the trial partly because the vaccine had been licensed, resulted in small numbers of cases and, hence, fairly low precision of our efficacy estimates.

The PnCRM7 vaccine was highly efficacious against vaccine serotype invasive pneumococcal disease in this

high-risk population. We have shown the robust nature of the PnCRM7 vaccine to prevent disease not only in a general US population setting but also in a setting where pneumococcal colonisation frequency is 50% at 2 months of age, and the invasive disease incidence has been among the highest documented worldwide.

Conjugate pneumococcal vaccine provides significant public health benefit in this high risk population and should be considered as part of the routine childhood vaccination schedule in other countries or regions with high pneumococcal disease burden.

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