Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial

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Summary

Background **Pneumonia is estimated to cause 2 million deaths every year in children. *Streptococcus pneumoniae* is the most important cause of severe pneumonia. We aimed to assess the efficacy of a nine-valent pneumococcal conjugate vaccine in children.**

Methods **We undertook a randomised, placebo-controlled, double-blind trial in eastern Gambia. Children age 6–51 weeks were randomly allocated three doses of either pneumococcal conjugate vaccine (n=8718) or placebo (8719), with intervals of at least 25 days between doses. Our primary outcome was first episode of radiological pneumonia. Secondary endpoints were clinical or severe clinical pneumonia, invasive pneumococcal disease, and all-cause admissions. Analyses were per protocol and intention to treat.**

Findings **529 children assigned vaccine and 568 allocated placebo were not included in the per-protocol analysis. Results of per-protocol and intention-to-treat analyses were similar. By per-protocol analysis, 333 of 8189 children given vaccine had an episode of radiological pneumonia compared with 513 of 8151 who received placebo. Pneumococcal vaccine efficacy was 37% (95% CI 27–45) against first episode of radiological pneumonia. First episodes of clinical pneumonia were reduced overall by 7% (95% CI 1–12). Efficacy of the conjugate vaccine was 77% (51–90) against invasive pneumococcal disease caused by vaccine serotypes, 50% (21–69) against disease caused by all serotypes, and 15% (7–21) against all-cause admissions. We also found an efficacy of 16% (3–28) against mortality. 110 serious adverse events arose in children given the pneumococcal vaccine compared with 131 in those who received placebo.**

Interpretation **In this rural African setting, pneumococcal conjugate vaccine has high efficacy against radiological pneumonia and invasive pneumococcal disease, and can substantially reduce admissions and improve child survival. Pneumococcal conjugate vaccines should be made available to African infants.**

Introduction

Pneumonia causes an estimated 19% of the 10 million childhood deaths worldwide.[1] Up to half of all cases of severe childhood pneumonia are caused by pneumococcus in developing countries.[2] In The Gambia[3] and other African countries,[4,5] invasive pneumococcal disease rates are up to tenfold higher than in industrialised countries, and the disease is a major cause of admissions and deaths.[5] The high burden of pneumococcal disease in The Gambia prompted studies to assess pneumococcal vaccines. Conjugate vaccines were shown to be safe, immunogenic, and induce immunological memory in Gambian infants.[6–8] In view of these findings, we aimed to assess the efficacy of a nine-valent pneumococcal conjugate vaccine against radiological pneumonia in rural areas of The Gambia.

Methods

Study setting

We undertook a randomised, double-blind, placebo-controlled trial in the Upper River Division and Central River Division of The Gambia, covering an area of 5000 km^2. The estimated population of this area was 380 000 in 2000.[9]

The prevalence of HIV-1 infection among antenatal clinic attendees in this region has remained stable at about 1% since 1993.[10] In background studies from 1989–93, the mortality rate in infants was 80 per 1000 child-years, and in children age 1–4 years it was 19 per 1000 child-years, major causes of death being pneumonia, malaria, diarrhoea, malnutrition, and sepsis.[11]

Mother-child-health clinics in the study area are provided at 15 fixed facilities, including Bansang hospital in Central River Division and Basse health centre in Upper River Division, and at about 110 outreach sites. These clinics are run one or two times a week at large facilities and one or two times a month at small facilities and outreach sites. More than 75% of all vaccinations are delivered at outreach sites. Details of trial preparation and lessons learned in implementation will be reported separately.

Participants

Infants who presented to a government vaccination post were screened for eligibility. Exclusion criteria were: non-residence in Upper and Central River Divisions; intent to move out within 4 months; previous receipt of diphtheria-pertussis-tetanus/*Haemophilus influenzae* type b (DPT/Hib) or DPT vaccine, or uncertainty about receipt; age younger than 40 days or older than 364 days; inclusion in a previous vaccine trial; or serious chronic illness. Trial staff read out the information sheet in one of the four main local languages and enrolled eligible children if their mother or guardian gave written informed consent.

The study and all protocol revisions were approved by the ethics committees of the Gambia Government/MRC and the London School of Hygiene and Tropical Medicine, and by the WHO Secretariat Committee for Research Involving Human Subjects.

Procedures

An independent statistician randomly assigned vial codes 0–9 to vaccine or placebo in a 1/1 ratio and study numbers to codes 0–9, using a blocked design with block size of ten, with the Proc Plan procedure in SAS (version 6.08, SAS Institute, Cary, NC, USA). Independent contractors labelled vaccine and placebo vials, prepared study stickers detailing the unique study identity number with window stickers showing the vial code and dose number (1, 2 or 3), and sealed these in opaque envelopes. Only the data safety monitoring board and the safety monitor in The Gambia had access to the code before data were locked.

After a child was enrolled, staff opened the next envelope, attached the study sticker to the health card, and at every vaccination peeled off the window sticker to put it on the case report form. After the third dose of vaccine or placebo no record was present of the randomisation assignment on the health card. The nine-valent pneumococcal conjugate vaccine (Wyeth Vaccines, Collegeville, PA, USA) contains 2 μg of type 1, 4, 5, 9V, 14, 19F, and 23F polysaccharides, 4 μg of type 6B polysaccharide, and 2 μg of type 18C oligosaccharide linked to the diphtheria toxoid protein CRM197. Pneumococcal vaccine and placebo lyophilised powders were identical in appearance. Powder in a vial of the appropriate code was reconstituted with liquid DPT/Hib (Tetramune; Wyeth Vaccines) and administered by intramuscular injection into the child's right thigh, an approach supported by immunogenicity data.[6] Consistent with Gambian policy, any mild or moderate illness was not a contraindication to vaccination, and children received concurrent hepatitis B and oral polio vaccines.

Study members provided 24-h cover to document outpatient consultations and admissions at Basse health centre or Bansang hospital. From 2002 onwards, we also visited the nine closest health facilities and their main outreach sites regularly and referred children with suspect pneumonia or invasive pneumococcal disease to Basse or Bansang for investigation. We trained nurses from all health facilities on the WHO Integrated Management of Childhood Illness (IMCI) guidelines[12] and monitored study nurses' accuracy in counting respiratory rates and classifying pneumonia throughout 2002–04. Standard operating procedures required a chest radiograph for patients with a raised respiratory rate for age (≥50 breaths per min for children <1 year old and ≥40 per min for children ≥1 year old) or lower chest-wall indrawing. Before February, 2002, fever was an additional requirement for outpatients. Of children screened by study personnel who met these criteria, radiographs were obtained from 51% (n=287) of inpatients and 3% (23) of outpatients in 2000–01 and from more than 95% of outpatients (6490) and inpatients (1926) thereafter.

We took blood for bacterial culture and malaria microscopy from outpatients with a raised respiratory rate and an axillary temperature of 38°C or more and from inpatients with signs of pneumonia, impaired consciousness, fitting, meningism, localised musculo-skeletal swelling, or a temperature of 38°C or more. If a doctor suspected meningitis, cerebrospinal fluid was also cultured. Lung aspirates were done at Basse on inpatients with right-sided peripheral consolidation on their radiograph. In August, 2003, we changed standard operating procedures for outpatient investigation so that blood cultures were not taken from children with parasitaemia (based on data for August, 2000, to July, 2003, we estimated that this change would reduce the number of blood cultures by a third while missing three or fewer potential pneumococcal isolates), and no cultures were taken for 6 weeks when the town and field station flooded. Overall, 80% of children with raised respiratory rate and a temperature of 38°C or more had a blood culture.

At Basse and Bansang facilities, and at Basse outreach sites, all outpatient consultations within 1 week of every dose of vaccine or placebo, and all admissions and their outcomes, were recorded on standard case report forms. Deaths were monitored at hospitals and by home visits every 3 months to every child. For medically observed deaths or admissions within 1 week of vaccination (serious adverse events), the attending doctor assessed any relation to vaccination. In a nested safety study, 425 children were visited at home 2 and 7 days after every vaccination.

We obtained isolates of *Streptococcus pneumoniae* from blood with an automated blood-culture system (Bactec 9050, Becton Dickinson, Temse, Belgium), from lung aspirate by inoculation of culture media at the patient's bedside, and from cerebrospinal fluid using standard microbiological procedures.[13] Identification was by cultural morphological analysis, susceptibility to ethylhydrocupreine hydrochloride and bile solubility,

with further testing of isolates of doubtful ethylhydrocupreine hydrochloride susceptibility by PCR, using the primers for pneumolysin gene.[14] Serotyping was undertaken at MRC Fajara Laboratories, Banjul, The Gambia, with capsular and factor-typing sera (Statens Serum Institut, Copenhagen, Denmark), using a latex agglutination assay. External quality control in Europe confirmed all serotyping results. One untyped isolate is included in rates of all invasive pneumococcal disease but not serotype-specific disease.

Immunogenicity was investigated in a subsample of children 4 weeks after the third dose of vaccine or placebo with a standardised ELISA.[15] Results will be reported separately.

The primary endpoint was originally all-cause child mortality,[9] but because of practical constraints on the sample size, we changed it to radiologically confirmed pneumonia in February, 2002. We defined radiological pneumonia as the presence of a dense or fluffy opacity that occupied a portion or whole of a lobe or of the entire lung, presence of fluid in the lateral pleural space between the lung and chest wall, or both.[16,17] One paediatrician (GE) and a paediatric radiologist (AA) read films independently. For films with discordant conclusions, consensus readings of two WHO radiologists were taken as final.

Secondary endpoints were clinical or severe clinical pneumonia, invasive pneumococcal disease, and all-cause admissions. We also specified a-priori investigation of efficacy against all-cause mortality and admissions with potentially invasive pneumococcal disease-related diagnoses of pneumonia, meningitis, or septicaemia. We defined clinical pneumonia as history of cough or breathing difficulty of less than 14 days' duration, with a raised respiratory rate for age or lower chest-wall indrawing. If a doctor diagnosed indrawing, we classified the pneumonia as severe. We defined invasive pneumococcal disease as illness with isolation of *S pneumoniae* from a normally sterile site. We classified this disease by serotype: vaccine serotypes are those in the vaccine; vaccine-related serotypes are others in the serogroups in the vaccine; and non-vaccine serotypes are all others.

Statistical analysis

Our study was designed to have 80% power to detect a vaccine efficacy against pneumonia of 20% (pooled estimates of findings from California and South Africa showed an efficacy of 22% [95% CI 11–31] against radiological pneumonia[18]) at the 5% significance level, assuming rates of radiological pneumonia in controls at least half those in baseline studies in clinics near to Basse.[3] This calculation meant that 13 200 children needed to complete per-protocol follow-up of 2 years.

We did per-protocol and intention-to-treat analyses. The intention-to-treat analysis included all children according to the group to which they were randomised.

***Panel:* Calculation for vaccine efficacy (VE)**

$$VE = 1 - \frac{\text{incidence in children allocated pneumococcal vaccine}}{\text{incidence in children allocated placebo}}$$

The per-protocol analysis included only children who received three doses of the correct study product, with the first dose given when the child was age 40–364 days, and at least 25 days' interval between doses. Follow-up time was calculated from randomisation for the intention-to-treat analysis and from 14 days after the third dose for the per-protocol analysis to the earliest of: first episode of the relevant endpoint, withdrawal, death, age 30 months, or the end of follow-up on April 30, 2004.

The panel shows how we calculated vaccine efficacy. Exact methods were used for calculating 95% CIs, with the assumption of Poisson event rates. In the analysis of multiple episodes of radiologically confirmed pneumonia, we took clustering into account using a Poisson random intercepts model, assuming a gamma distribution for the random effects.

We developed an analytical plan, approved by the international steering committee and US Food and Drug Administration (FDA), and data were audited before locking and unmasking. We decided a-priori to stratify vaccine efficacy by age at event, admission status, and season of vaccination (all three doses in the rainy season of July–November, all three in the dry season of

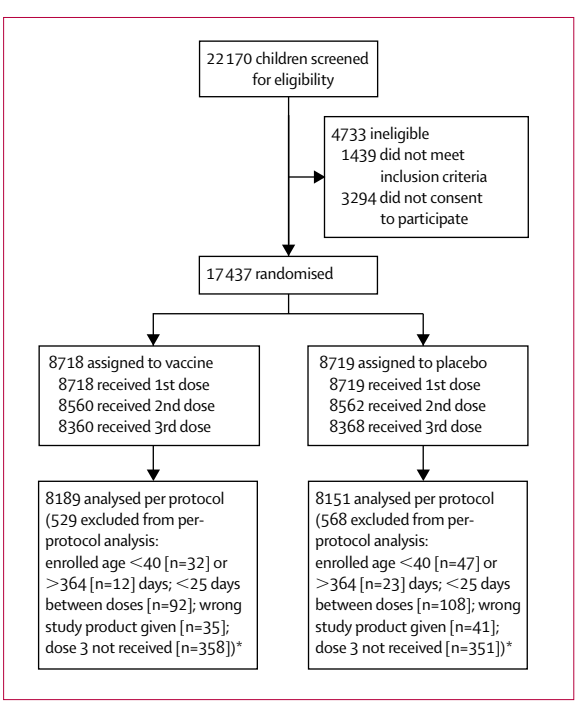

***Figure:* Trial profile for per-protocol analysis**
Deaths (n=917) and withdrawals (115) are not shown as losses to follow-up because these children contributed person-time to the estimation of rates of every endpoint. *Can be more than one reason per child.

	Vaccine (n=8189)	Placebo (n=8151)
Sex		
Boy	4100 (50%)	4074 (50%)
Girl	4089 (50%)	4077 (50%)
Age (days)		
Dose 1	75 (59–108)	75 (59–109)
Dose 2	122 (97–166)	122 (98–167)
Dose 3	169 (136–225)	170 (136–226)
Place of recruitment		
Basse base	897 (11%)	918 (11%)
Basse outreach	1477 (18%)	1458 (18%)
Bansang base	244 (3%)	199 (2%)
Bansang outreach	431 (5%)	439 (5%)
Other base	1086 (13%)	1093 (13%)
Other outreach	4054 (49%)	4044 (50%)

Data are number of children (%) or median (IQR).

Table 1: **Characteristics of children in the per-protocol analysis**

December–June, or some doses in each season). We also stratified by season of illness: July–Nov (malaria peak); Dec–Feb (respiratory syncytial virus peak); and March–June (bacteraemia peak). We assessed effect modification with the likelihood ratio test.

Role of the funding source

The National Institute of Allergy and Infectious Diseases was involved in the design of the trial and analytical plan, organised trial monitoring by an independent contractor and the data safety monitoring board, and was the sponsor of the study that was done under an Investigational New Drug Application with the FDA. WHO organised an international steering committee that, in addition to the data safety monitoring board, closely reviewed the conduct and results of the trial. The other funding agencies and Wyeth Vaccines had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

	Vaccine (n=8189)		Placebo (n=8151)		Vaccine efficacy (%) (95% CI)
	Number	Rate per 1000 child-years (95% CI)	Number	Rate per 1000 child-years (95% CI)	
Overall	333	26·0 (23·3–28·9)	513	40·9 (37·5–44·6)	37 (27 to 45)
Age (months)					
3–11	124	34·4 (28·8–41·0)	188	53·0 (45·9–61·1)	35 (19 to 48)
12–23	181	25·8 (22·3–29·9)	285	41·7 (37·1–46·8)	38 (25 to 49)
24–29	28	12·7 (8·8–18·4)	40	18·7 (13·7–25·4)	32 (−10 to 58)
Sex					
Boy	182	28·4 (24·5–32·8)	266	42·6 (37·7–48·0)	33 (19 to 45)
Girl	151	23·5 (20·1–27·6)	247	39·3 (34·7–44·6)	40 (27 to 45)
Season of receipt of all three doses					
July–Nov	67	36·4 (28·7–46·2)	72	39·7 (31·5–50·0)	8 (−30 to 35)
Dec–June	116	28·1 (23·4–33·7)	176	43·0 (37·1–49·8)	35 (1 to 49)
Mixed	150	21·9 (18·7–25·7)	265	40·0 (35·5–45·2)	45 (33 to 56)
Season of illness					
July–Nov	171	32·9 (28·3–38·3)	239	47·0 (41·4–53·3)	30 (14 to 43)
Dec–Feb	42	12·3 (9·1–16·7)	70	21·1 (16·7–26·7)	42 (13 to 61)
March–June	120	28·4 (23·8–34·0)	204	49·4 (43·1–56·7)	43 (28 to 55)
Admission status					
Outpatient	180	14·0 (12·1–16·2)	253	20·2 (17·8–22·8)	30 (15 to 43)
Inpatient	153	11·9 (10·2–14·0)	260	20·7 (18·4–23·4)	42 (30 to 53)

Table 2: **Vaccine efficacy against first episode of radiological pneumonia (per-protocol analysis)**

Results

We recruited children from August, 2000, to February, 2003. Vaccination ended in April, 2003, and clinical follow-up ended in April, 2004. 22 170 children were screened for eligibility, of whom 17 437 (79%) participated in the study (figure). Table 1 shows characteristics of children in the per-protocol analysis. Median age at receipt of the first dose of vaccine or placebo was 11 weeks (IQR 8–16) and for the third dose it was 24 weeks (19–32). Median length of follow-up was 103 weeks (84–116) by intention to treat and 87 weeks (69–98) in the per-protocol analysis. The following results refer to efficacy against the first detected occurrence of every endpoint.

Of 978 first episodes of radiological pneumonia detected, 92% (n=896) arose after the change in endpoint in February, 2002. Table 2 shows vaccine efficacy in the per-protocol analysis. By intention to treat, 388 first episodes arose in vaccinated children (24 per 1000 child-years) and 590 in unvaccinated children (37 per 1000 child-years); vaccine efficacy was 35% (95% CI 26–43). The absolute rate reduction was 15 cases per 1000 child-years (95% CI 10–19) in the per-protocol analysis and 13 cases per 1000 child-years (9–17) by intention to treat. Efficacy did not vary substantially according to admission status, age, sex, or season of illness, either in the per-protocol analysis (table 2) or by intention to treat (data not shown). Vaccine efficacy was reduced, although not significantly (p=0·1), in children who received all three doses in the malaria season (July–Nov). Malaria microscopy was done for 74% (n=626) of first episodes in the per-protocol analysis. Presence or absence of parasitaemia had no effect on efficacy (data not shown). Vaccine efficacy against all episodes of radiological pneumonia was 37% (95% CI 27–45) in the per-protocol analysis and 36% (27–43) by intention-to treat.

First episodes of clinical pneumonia were reduced overall by 7% (95% CI 1–12) in the per-protocol analysis and by 6% (1–11) by intention to treat. Protection by the vaccine was only evident against clinical and severe clinical pneumonia in children whose radiograph showed the primary radiological endpoint (table 3).

115 children had an episode of invasive pneumococcal disease, of whom 96 (83%) were admitted—34 given vaccine and 62 receiving placebo. Only one child, who received pneumococcal vaccine, had more than one episode; serotype 33F pneumococcus was obtained in the first episode and serotype 22F in the second, 182 days later. Clinical details of pneumococcal and other bacteraemic illnesses will be reported separately. Efficacy

against invasive pneumococcal disease attributable to serotypes present in the vaccine was 77% (95% CI 51–90) in the per-protocol analysis and 71% (46–86) by intention to treat, and efficacy against all serotypes of invasive pneumococcal disease was 50% (21–69) and 45% (19–62), respectively. Efficacy did not vary by age or sex (table 4). Significant protection by the vaccine was shown against the three commonest serotypes: 14, 5, and 23F (data not shown). Absolute rate reductions were about 2 episodes per 1000 child-years for serotypes in the pneumococcal vaccine and all serotypes in both per-protocol and intention-to-treat analyses. In children given pneumococcal conjugate vaccine, a relative reduction was recorded in invasive pneumococcal disease associated with vaccine-related serotypes, and an increase was noted in this disease associated with non-vaccine serotypes, although neither difference was significant (table 4). No isolate was resistant to penicillin.

Admissions were reduced by 15% (95% CI 7–21) in the per-protocol analysis and by 13% (6–19) by intention-to-treat; absolute rate reductions were 15 admissions per 1000 child-years (7–23) and 13 admissions per 1000 child-years (6–20), respectively. There was some evidence that vaccine efficacy was greater in boys than girls (p=0·04; table 5). Admissions with potentially invasive pneumococcal disease-related diagnoses were reduced by 19% (95% CI 11–27) in the per-protocol analysis and by 17% (9–25) by intention to treat; respective absolute rate reductions were 12·5 episodes per 1000 (6·5–18·5) and 11 episodes per 1000 (5–16).

Vaccination reduced overall all-cause mortality by 16% (95% CI 3–28) in the per-protocol analysis (table 5) and by 14% (2–24) by intention to treat. The absolute rate reduction was 4·8 deaths per 1000 child-years (0·8–8·9) and 4·1 deaths per 1000 child-years (0·4–7·7), respectively.

110 serious adverse events arose within 7 days of receipt of any dose of pneumococcal vaccine (101 admissions [three children died] and nine deaths at home) compared with 131 within 7 days of receipt of any dose of placebo (119 admissions [three children died] and 12 deaths at home). Only one serious adverse event, in a child given pneumococcal vaccine, was judged definitely related to vaccination (admission for cellulitis at the injection site). Persistent abnormality was reported after two serious adverse events, both in children given placebo.

Of 5545 children vaccinated at sites monitoring adverse events, more outpatient visits were made within 1 week after dose 1 in pneumococcal vaccine recipients than in those given placebo (table 6). No differences were seen in consultation rates after subsequent doses.

In the nested safety study of 425 infants, more mothers of children given pneumococcal vaccine (26%) than of those given placebo (19%) reported that their child was hot or feverish on day 7 (p=0·1), but no differences were found in recorded temperatures on day 2 or 7. Fewer than 4% of children had a recorded temperature of 38°C or more on day 2 or 7 after vaccination, and none had a recorded temperature of more than 40°C. Rates or degree of swelling, tenderness, or redness at the injection site after any dose did not differ between groups.

	Vaccine (n=8189)		Placebo (n=8151)		Vaccine efficacy (%) (95% CI)
	Number	Rate per 1000 child-years (95% CI)	Number	Rate per 1000 child-years (95% CI)	
Clinical pneumonia					
Overall	2172	231·5 (222·0–241·5)	2284	248·5 (238·6–258·9)	7 (1 to 12)
Findings on radiograph					
Endpoint	207	22·1 (19·3–25·3)	323	35·1 (31·5–39·2)	37 (25 to 48)
No endpoint	1740	185·5 (177·0–194·4)	1715	186·6 (178·0–195·7)	0·5 (–6·5 to 6·9)
No radiograph	225	24·0 (21·0–27·3)	246	26·8 (23·6–30·3)	10 (–8 to 26)
Severe clinical pneumonia					
Overall	172	13·4 (11·5–15·6)	192	15·2 (13·2–17·5)	12 (–9 to 29)
Findings on radiograph					
Endpoint	42	3·3 (2·4–4·4)	64	5·1 (4·0–6·5)	35 (3 to 57)
No endpoint	122	9·5 (8·0–11·4)	123	9·7 (8·2–11·6)	2 (–27 to 25)
No radiograph	8	0·6 (0·3–1·2)	5	0·4 (0·2–1·0)	–58 (–510 to 55)

Table 3: **Vaccine efficacy against first episode of clinical or severe clinical pneumonia (per-protocol analysis)**

Discussion

We have shown that pneumococcal conjugate vaccine has high efficacy against radiological pneumonia and substantially reduces admissions and improves child survival. Similar to findings from the USA[19,20] and South Africa,[21] we found that conjugate pneumococcal vaccine is efficacious against invasive pneumococcal disease. We

	Vaccine (n=8189)		Placebo (n=8151)		Vaccine efficacy (%) (95% CI)
	Number	Rate per 1000 child-years (95% CI)	Number	Rate per 1000 child-years (95% CI)	
Vaccine serotypes					
All clinical conditions	9	0·6 (0·3–1·1)	38	2·5 (1·8–3·4)	77 (51 to 90)
Radiological pneumonia	8	0·6 (0·3–1·2)	26	2·0 (1·4–3·0)	70 (31 to 88)
Lung aspirate positive	3	0·2 (0·07–0·7)	11	0·8 (0·5–1·5)	73 (–2 to 95)
Meningitis or sepsis	1	0·08 (0·01–0·5)	12	0·9 (0·5–1·6)	92 (44 to 100)
Age (months)					
3–11	1	0·3 (0·04–1·9)	14	3·9 (2·3–6·6)	93 (54 to 100)
12–23	5	0·7 (0·3–1·7)	20	2·8 (1·8–4·4)	75 (32 to 93)
24–29	3	1·3 (0·4–4·1)	4	1·8 (0·7–4·8)	26 (–339 to 89)
Sex					
Boy	6	0·8 (0·3–1·7)	22	2·9 (1·9–4·3)	73 (31 to 91)
Girl	3	0·4 (0·1–1·2)	16	2·1 (1·3–3·4)	82 (36 to 97)
Admission status					
Outpatient	2	0·1 (0·03–0·5)	6	0·4 (0·2–0·9)	67 (–84 to 97)
Inpatient	7	0·4 (0·2–0·9)	32	2·1 (1·5–2·9)	78 (50 to 92)
All serotypes					
All clinical conditions	30	1·9 (1·3–2·8)	59	3·8 (3·0–5·0)	50 (21 to 69)
Radiological pneumonia	19	1·5 (0·9–2·3)	45	3·5 (2·6–4·7)	58 (27 to 77)
Lung aspirate positive	6	0·5 (0·2–1·0)	20	1·5 (1·0–2·4)	68 (18 to 89)
Meningitis or sepsis	11	0·8 (0·5–1·5)	14	1·1 (0·6–1·8)	22 (–84 to 68)
Vaccine-related serotypes					
All clinical conditions	6	0·4 (0·2–0·9)	11	0·7 (0·4–1·3)	46 (–59 to 84)
Non-vaccine serotypes					
All clinical conditions	15	1·0 (0·6–1·6)	9	0·6 (0·3–1·1)	–65 (–327 to 32)

Table 4: **Vaccine efficacy against first episode of invasive pneumococcal disease (per-protocol analysis)**

	Vaccine (n=8189)		Placebo (n=8151)		Vaccine efficacy (%) (95% CI)
	Number	Rate per 1000 child-years (95% CI)	Number	Rate per 1000 child-years (95% CI)	
Admissions					
Overall	1065	89·4 (84·2–95·0)	1216	104·7 (99·0–110·8)	15 (7 to 21)
Age (months)					
3–11	388	111·6 (101·0–123·3)	469	137·6 (125·7–150·6)	19 (7 to 29)
12–23	576	89·0 (82·0–96·6)	612	97·0 (90·0–104·9)	8 (0 to 18)
24–29	101	51·5 (42·4–62·6)	135	71·3 (60·2–84·4)	28 (7 to 44)
Sex					
Boy	554	93·3 (85·8–101·4)	679	118·6 (110·0–127·9)	21 (12 to 30)
Girl	511	85·6 (78·5–93·3)	537	91·2 (83·8–99·2)	8 (–10 to 17)
Season of receipt of all three doses					
Jul–Nov	284	99·6 (88·7–111·9)	329	120·5 (108·2–134·3)	17 (3 to 30)
Dec–June	211	75·2 (65·7–86·1)	241	86·1 (75·9–97·7)	13 (–5·5 to 28)
Mixed	570	91·1 (84·0–98·9)	646	106·1 (98·3–114·7)	14 (4 to 23)
Mortality					
Overall	330	25·2 (22·6–28·1)	389	30·1 (27·2–33·2)	16 (3 to 28)
Age (months)					
3–11	92	25·3 (20·6–31·0)	100	27·8 (22·8–33·8)	9 (–20 to 31)
12–23	189	26·3 (22·8–30·3)	224	31·5 (27·6–35·9)	17 (0 to 31)
24–29	49	21·6 (16·3–28·6)	65	28·9 (22·7–36·9)	25 (–10 to 48)
Sex					
Boy	161	24·5 (21·0–28·6)	182	28·1 (24·3–32·5)	13 (–10 to 29)
Girl	169	25·8 (22·2–30·0)	207	31·9 (27·9–36·6)	19 (1 to 33)
Season of receipt of all three doses					
Jul–Nov	76	23·9 (19·1–29·9)	90	29·1 (23·7–35·8)	18 (–13 to 40)
Dec–June	62	20·3 (15·8–26·0)	91	29·5 (24·0–36·2)	31 (4 to 51)
Mixed	192	28·0 (24·3–32·3)	208	30·7 (26·8–35·2)	9 (–12 to 25)

Table 5: **Vaccine efficacy against first admission and all-cause mortality (per-protocol analysis)**

have confirmed and defined more precisely vaccine efficacy against pneumonia with consolidation, and shown that the preventable burden of pneumococcal-related pneumonia is at least seven times greater than that of invasive pneumococcal disease (absolute rate reduction 15 *vs* 2 episodes per 1000 child-years, respectively). The finding of a 16% reduction in mortality in young children lends support to the hypotheses that pneumonia contributes to many more deaths than are directly attributed to pneumonia in studies using verbal autopsies,[1] and that community-acquired bacteraemia is a greater cause of childhood mortality than previously recognised.[5]

	Dose 1		Dose 2		Dose 3	
	Vaccine	Placebo	Vaccine	Placebo	Vaccine	Placebo
Outpatient consultations						
Nurse's clinical diagnosis						
Clinical malaria	32	23	52	51	60	52
Pneumonia	16	6	5	14	10	8
Upper respiratory infection	9	9	12	12	11	11
Acute diarrhoea	14	6	13	6	8	14
Other	34	27	25	24	19	27
Total consultations	105	71	107	107	108	112
Admissions						
Paediatrician's clinical diagnosis						
Clinical malaria	5	6	3	5	5	12
Clinical pneumonia	21	20	16	20	21	22
Acute diarrhoea	4	1	2	4	5	4
Sepsis	1	2	0	0	2	2
Other	6	6	5	10	5	5
Total admissions	37	35	26	39	38	45

Table 6: **Number of consultations, with primary diagnoses, in the week after every dose of vaccine or placebo (intention-to-treat analysis)**

The pneumococcal conjugate vaccine had efficacy against pneumonia diagnosed radiologically but not against pneumonia diagnosed solely on IMCI criteria. Much of the observed difference might be attributable to misclassification of clinical pneumonia[22] because vaccine efficacy would be biased downwards by low specificity of diagnosis.[23] In South Africa, in addition to 25% efficacy shown against radiological pneumonia,[21] high efficacy was reported against pneumonia associated with viral infections.[24] Future virological studies are planned in our trial.

The preventable burden of clinical and radiological pneumonia was about 15 episodes per 1000 child-years. This figure is likely to be an underestimate because many radiographs were not acquired in children seen in the first year, surveillance was passive, and the study population was widely dispersed. Only 14% of all children were recruited at the facilities where study staff were permanently onsite, the rest living in areas served by intermittent mother-child-health clinics, thus many cases would not have been detected. We plan further analyses of geographic variations in case ascertainment and their potential effect on burden estimates. We noted no decrease in efficacy of the pneumococcal conjugate vaccine with age, by contrast with findings from California.[25] The preventable burden was greatest in young children because rates of pneumonia fall strikingly after age 2 years.[3]

We recorded some evidence that receiving all three doses of pneumococcal conjugate vaccine in the rainy season (July–Nov) might reduce efficacy against radiological pneumonia. Malaria and other febrile illnesses diminish antibody responses to Hib conjugate vaccine,[26] and their effect on response to vaccination with pneumococcal conjugate vaccine needs further study. Little variation of vaccine efficacy with season of illness was noted, which we investigated as a proxy for intercurrent infections.

Efficacy against invasive pneumococcal disease and disease caused by serotypes in the vaccine accorded with findings of previous studies.[19–21] Of the 13 cases of invasive pneumococcal disease caused by serotypes in the pneumococcal vaccine in children randomised to receive conjugate vaccine, none was homozygous for sickle-cell haemoglobinopathy, and only one child—with clinical signs of Down's syndrome—was malnourished. Although we did not test for HIV infection, as of December, 2004, all 13 children were still alive with a median age of 40 months (IQR 34–50); thus immune suppression was unlikely.

In children given pneumococcal conjugate vaccine, we noted a non-significant increase in invasive pneumococcal disease from non-vaccine serotypes that was of a similar size to the reduction in disease from vaccine-related serotypes. Our study focused on direct effects of

vaccination, having randomised children individually,[27] and thus could not fully assess the potential for either replacement infection[28] or indirect protection of contacts.[29] Further assessment of the indirect effects of vaccination in developing country settings is indicated.

Overall, the safety profile of pneumococcal conjugate vaccine was very good. Outpatient visits, but not admissions, were increased in children given the conjugate vaccine in the week after the first dose, especially for those with a nurses' clinical diagnosis of pneumonia, and we cannot exclude a viral cause for these cases.[21] We saw no increase in asthma in children given the pneumococcal conjugate vaccine, by contrast to observations in South Africa.[21]

Our results provide evidence that pneumococcal conjugate vaccine is a valuable intervention to reduce pneumonia, bacteraemia, admissions, and mortality in African children. In the placebo group, 65% of invasive disease episodes were of serotypes contained in the nine-valent trial vaccine, and 48% were of serotypes in the licensed seven-valent vaccine (Prevenar; Wyeth Vaccines). Vaccines containing more serotypes could have even greater effect. Identification of means to make pneumococcal conjugate vaccines available as soon as possible to children who need them most is important.

Contributors

F T Cutts joined the trial as director and principal investigator in June, 2001, coordinated and supervised all subsequent phases of study implementation, revised the protocol, standard operating procedures, and case report forms, designed and implemented a quality assurance programme, wrote the analytical plan, and assisted in data analysis. She wrote the final report with input from S M A Zaman, G Enwere, S Jaffar, O S Levine, N F Pierce, B M Greenwood, and R A Adegbola, and comments from all other investigators, international steering committee members, and the chair of the data safety monitoring board. S M A Zaman supervised fieldwork from November, 2001, onwards, and participated in clinical and adverse events surveillance and in data management and analysis. G Enwere was clinical coordinator for most of the trial, participated in revision of the protocol, interpreted all radiographs, and had primary responsibility for clinical training and quality control. S Jaffar participated in study design and led the statistical analysis. O S Levine participated in study design and implementation and in writing the analytical plan. J B Okoko, C Oluwalana, and A Vaughan were responsible for clinical and safety surveillance, clinical training, and quality control. S K Obaro participated in study design, was initial project leader and set up and coordinated clinic-based field work until March, 2001. A Leach participated in study design, organised mapping of the study area, and set up and coordinated village-based field-work for the first 8 months of the trial. K P McAdam was co-principal investigator at the start of the trial and supported implementation for most of the study. E Biney ran the field laboratory and supervised microbiological and haematological procedures. M Saaka did serological assays. U Onwuchekwa was data manager. F Yallop was project manager, enabled the trial to be implemented, and liaised with Government health officials. N F Pierce chaired the international steering committee and participated in all phases of the trial. B M Greenwood had the idea for the study, wrote the original protocol, obtained the grant, and was co-principal investigator for the first year and scientific adviser for the duration of the trial. R A Adegbola participated in study design, coordinated and supervised all laboratory aspects of the trial, and was acting principal investigator from March to May, 2001. A Akano (consultant radiologist) interpreted all radiographs. B Hunter designed the new data management system in 2001 with input from U Onwuchekwa, F T Cutts, and S M A Zaman. A Njie was Expanded Programme on Immunization programme manager during the vaccination phase of the trial. M Touray was project administrator and supported trial implementation. A B Darbo and P Suso coordinated fieldwork and its quality control and served as community liaison officers.

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Conflict of interest statement

SKO has received honoraria from Wyeth Vaccines for consultancies in the past 3 years. Since her involvement in the trial, AL has become an employee of GlaxoSmithKline Biologicals, who are developing a pneumococcal vaccine, and owns shares in GlaxoSmithKline. The other authors declare that they have no conflict of interest.

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