ORIGINAL ARTICLE

A Trial of a 7-Valent Pneumococcal Conjugate Vaccine in HIV-Infected Adults

Neil French, Ph.D., F.R.C.P., Stephen B. Gordon, M.D., F.R.C.P., Thandie Mwalukomo, M.B., B.S., Sarah A. White, Ph.D., Gershom Mwafulirwa, Dip.Med.Sci., Herbert Longwe, M.Phil., Martin Mwaiponya, M.B., B.S., Eduard E. Zijlstra, M.D., Ph.D., Malcolm E. Molyneux, M.D., F.R.C.P., and Charles F. Gilks, D.Phil., F.R.C.P.

ABSTRACT

BACKGROUND

Streptococcus pneumoniae is a leading and serious coinfection in adults with human immunodeficiency virus (HIV) infection, particularly in Africa. Prevention of this disease by vaccination with the current 23-valent polysaccharide vaccine is suboptimal. Protein conjugate vaccines offer a further option for protection, but data on their clinical efficacy in adults are needed.

METHODS

In this double-blind, randomized, placebo-controlled clinical efficacy trial, we studied the efficacy of a 7-valent conjugate pneumococcal vaccine in predominantly HIV-infected Malawian adolescents and adults who had recovered from documented invasive pneumococcal disease. Two doses of vaccine were given 4 weeks apart. The primary end point was a further episode of pneumococcal infection caused by vaccine serotypes or serotype 6A.

RESULTS

From February 2003 through October 2007, we followed 496 patients (of whom 44% were male and 88% were HIV-seropositive) for 798 person-years of observation. There were 67 episodes of pneumococcal disease in 52 patients, all in the HIV-infected subgroup. In 24 patients, there were 19 episodes that were caused by vaccine serotypes and 5 episodes that were caused by the 6A serotype. Of these episodes, 5 occurred in the vaccine group and 19 in the placebo group, for a vaccine efficacy of 74% (95% confidence interval [CI], 30 to 90). There were 73 deaths from any cause in the vaccine group and 63 in the placebo group (hazard ratio in the vaccine group, 1.18; 95% CI, 0.84 to 1.66). The number of serious adverse events within 14 days after vaccination was significantly lower in the vaccine group than in the placebo group (3 vs. 17, P=0.002), and the number of minor adverse events was significantly higher in the vaccine group (41 vs. 13, P=0.003).

CONCLUSIONS

The 7-valent pneumococcal conjugate vaccine protected HIV-infected adults from recurrent pneumococcal infection caused by vaccine serotypes or serotype 6A. (Current Controlled Trials number, ISRCTN54494731.)

From the Malawi–Liverpool–Wellcome Trust Clinical Research Programme (N.F., S.B.G., S.A.W., G.M., H.L., M.E.M.) and the Department of Medicine, College of Medicine (T.M., M.M., E.E.Z.) — both in Blantyre; and the London School of Hygiene and Tropical Medicine/Karonga Prevention Study, Karonga (N.F.) — all in Malawi; and the Liverpool School of Tropical Medicine, Liverpool (S.B.G., M.E.M.), and Imperial College, London (C.F.G.) — both in the United Kingdom. Address reprint requests to Dr. French at the Karonga Prevention Study, P.O. Box 46, Chilumba, Malawi, or at neil.french@lshtm.ac.uk.

N Engl J Med 2010;362:812-22.

Streptococcus pneumoniae is a leading cause of death and complications in adults with human immunodeficiency virus (HIV) infection, particularly in sub-Saharan Africa.[1,2] The risk of invasive pneumococcal disease is 30 to 100 times as high in patients with HIV infection as in age-matched controls without such infection.[3,4] Recurrent invasive pneumococcal disease is common, with up to 25% of patients having an additional episode, predominantly reinfection, in the subsequent 12 months.[1,5] Even among patients who have access to timely and effective care, the case fatality rate with invasive pneumococcal disease is at least 8%[6] and rises to 50% in African populations with meningitis.[7] The frequency and serious nature of this disease make prevention by vaccination desirable.

The 23-valent pneumococcal polysaccharide vaccine has suboptimal activity in HIV-infected adults and is not recommended for use in Africa.[5,8] In regions where the 23-valent vaccine is used, administration of the vaccine is recommended early in the course of HIV disease.[9] Pneumococcal conjugate vaccines offer an alternative approach to preventing pneumococcal disease. The 7- and 9-valent conjugate vaccines have been shown to be highly efficacious.[10-13] Such vaccines are effective at preventing invasive pneumococcal disease in HIV-infected children,[11] although with a lower efficacy and duration of effect than in children without HIV infection.[14]

There are no definitive data on the clinical efficacy of pneumococcal conjugate vaccines in adult populations. In studies involving HIV-infected adults, the vaccine was immunogenic, with similar quantitative antibody responses to those seen with the pneumococcal polysaccharide vaccine.[15,16] Data showing improved qualitative responses, evidence of boosting with a two-dose regimen,[16] and mucosal responses[17] suggest that the conjugate vaccine is processed in a manner that differs immunologically from that of the polysaccharide vaccine in HIV-infected adults. With no validated serologic correlate of protection for adults, a clinical trial was required to provide information on the efficacy of this vaccine and its potential role in the management of HIV infection.

We report the results of a randomized, placebo-controlled trial of a 7-valent pneumococcal conjugate vaccine to prevent recurrent invasive pneumococcal disease (secondary prophylaxis) in a cohort of predominantly HIV-infected Malawian adults, defined as persons 15 years of age or older for the purposes of this study. We first considered a primary-prophylaxis trial, but since the available 7-valent vaccine has low serotype coverage,[18] such a study would have required a large sample and a costly, complex, multisite design. We chose to conduct a secondary-prophylaxis study, since it could be performed with a smaller sample and more rapid accumulation of end points. Furthermore, a demonstration of efficacy in a population of persons who had HIV infection and a documented history of pneumococcal disease and who were at substantial risk for subsequent pneumococcal infection would make a plausible clinical case for the use of the conjugate vaccine as primary prophylaxis.

METHODS

PATIENTS

From February 2003 through May 2007, we recruited patients at the Queen Elizabeth Central Hospital in Blantyre, Malawi, which is the main public hospital serving a population of approximately 1 million people. Follow-up continued until October 2007. We identified potential study participants on the adult medical wards through a review of culture analyses of blood and cerebrospinal fluid from which *S. pneumoniae* had been isolated. Patients who had survived a pneumococcal infection were invited to return to the study clinic for screening 1 week after discharge. All patients were 15 years of age or older, resided within the Blantyre district, and were willing to undergo an HIV test. All patients provided written informed consent.

To avoid possible stigmatization of the study as an HIV trial, we offered enrollment to all patients in whom a pneumococcal infection had been diagnosed, regardless of their HIV status. We recognized that the subgroup without HIV infection would be small (estimated at 10% of enrollees[19]) and that the number of recurrent episodes of invasive pneumococcal disease was unlikely to be large enough for a meaningful subgroup analysis. Thus, as prespecified in the protocol and analysis plan, the patients of primary interest were those with HIV infection.

STUDY DESIGN

The enrollment of patients and the performance of laboratory investigations followed standard procedures (for details, see the Methods section in

the Supplementary Appendix, available with the full text of this article at NEJM.org). Two doses of vaccine were given 4 weeks apart, after which patients were requested to attend regular appointments every 3 months. Patients who moved out of the study area, could not be traced because of an inaccurate address on record, or declined further follow-up were considered to have been lost to follow-up. We encouraged patients to go to the hospital medical ward for assessment by the study clinical team in the event of any illness that occurred between scheduled visits. Patients with HIV infection were encouraged to enroll in public-sector programs of HIV care, including antiretroviral therapy provided at public clinics, since such services were set up in Blantyre over the course of the trial.

Patients received two doses of either a 7-valent pneumococcal conjugate vaccine (Prevnar, Wyeth Pharmaceuticals) or matching placebo (Nova Laboratories). The randomization list was generated by a statistician who was a member of the data and safety monitoring board, and randomization was performed in permuted groups of random size up to 20. The blinding of vaccine administration is described in the Supplementary Appendix.

An episode of invasive pneumococcal disease was defined by the isolation of *S. pneumoniae* from a normally sterile site (i.e., blood, cerebrospinal fluid, or pleural fluid) in the context of a consistent clinical presentation. *S. pneumoniae* was identified by standard methods (for details, see the Supplementary Appendix).

PRIMARY AND SECONDARY END POINTS

The primary end point was an episode of pneumococcal disease caused by one of the vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). During the course of the study and before unblinding, the trial's steering group agreed to broaden the primary end point to include infection with serotype 6A on the basis of published data showing cross-protection to serotype 6A.[20,21]

MONITORING FOR ADVERSE EVENTS

Adverse events were defined and recorded according to the Harmonised Tripartite Guideline for Clinical Safety Data Management of the International Conference on Harmonisation. Grade 3 or 4 events in the 14 days after vaccination were defined as serious adverse events. Such events were recorded at the time of hospitalization, during a study visit, or by the report of a relative (in the case of out-of-hospital death).

To investigate possible harmful effects of vaccine, as seen with the use of the pneumococcal polysaccharide vaccine in Uganda,[5] an additional safety end point was included (probability of death from pneumococcal infection). All deaths were reviewed by the senior study clinician and classified in terms of the perceived association with *S. pneumoniae* into four categories: definite or probable, possible, unlikely, or unclassifiable owing to inadequate information. Since many deaths occurred outside a medical setting, as is typical in this region, several sources of information (including oral reports and individual health records retained by relatives) were synthesized to reach a final decision before unblinding.

STUDY OVERSIGHT

A placebo-controlled efficacy trial was deemed to be ethically acceptable after the failure of the pneumococcal polysaccharide vaccine in the earlier Ugandan trial.[5] The study was approved by the ethics committee at the College of Medicine in Malawi and by the institutional review board at the Liverpool School of Tropical Medicine. The funders of the study (the Wellcome Trust), the vaccine suppliers (Wyeth Pharmaceuticals), and the study sponsors (the University of Liverpool) had no part in the study design, collection or analysis of data, or the decision to submit the manuscript for publication. The trial's steering committee approved the statistical-analysis plan, which was submitted to the committee's chair, along with a cleaned data set before unblinding. All authors vouch for the completeness and accuracy of the data presented.

STATISTICAL ANALYSIS

To show a 60% reduction in the rate of episodes of invasive pneumococcal disease caused by vaccine serotypes (with a beta level of 0.2 and an alpha level of 0.05), we determined that we would need 402 person-years of observation to accumulate 42 first-event primary end points in a 1:1 assignment ratio. We also estimated that the rate of pneumococcal disease would be 250 episodes per 1000 person-years and that 60% of these episodes would be caused by vaccine serotypes. We estimated that 100 patients would be lost to follow-up and 250 would die per 1000 person-years. Insufficient end-point accumulation before the

planned end date of March 2006 led the data and safety monitoring board to recommend continuing the study until October 2007 or until the target of 42 end points had been achieved, whichever came first.

The primary analysis was performed according to the intention-to-treat principle. A per-protocol analysis was performed for the primary end point, for which the second dose of vaccine must have been received between 4 and 8 weeks after the first dose, with the at-risk period starting 2 weeks after the second vaccination. Hazard ratios for the first event in the vaccine group, as compared with the placebo group, were estimated by means of a Cox proportional-hazards regression model. Vaccine efficacy was calculated as 1 minus the hazard ratio, times 100.

Adjusted hazard ratios were estimated by incorporating terms representing clinical stage (3 or 4, according to World Health Organization criteria), baseline CD4+ T-cell count (<200, 200 to 500, or >500 cells per cubic millimeter), viral load (<100,000 or ≥100,000 copies per milliliter), sex, and age (15 to 24, 25 to 34, or 35 to 75 years) as the most important modifiers of disease risk.[1,5,22] When the proportional-hazards assumption was violated, the Cox model was stratified according to the year of recruitment and the baseline CD4+ count, and data were analyzed separately for the first 12 months.

Data from individual records were censored on October 31, 2007, or the date of death or loss to follow-up, whichever came first. We used negative binomial regression models to estimate incidence-rate ratios for multiple-event analyses. All tests of significance were two-sided, and a P value of <0.05 was considered to indicate statistical significance. One interim analysis was planned and performed after 2 years for the data and safety monitoring board (alpha level of 0.10). Three additional analyses were requested and performed on the basis of an alpha level of 0.10; the Haybittle–Peto approach to significance levels was used.[23] There was no adjustment of the overall significance level.

We report baseline findings for the whole cohort and efficacy results for HIV-infected patients only, unless otherwise indicated. We performed one post hoc analysis of vaccine efficacy in the subgroup with a CD4+ count of less than 200 cells per cubic millimeter in order to confirm efficacy in this high-risk subgroup. We report the interaction between the category of CD4+ count and the study group.

RESULTS

PATIENTS

During study enrollment, we identified 977 adults who had survived a confirmed episode of invasive pneumococcal disease (Fig. 1). Of this group, 496 (50.8%) were enrolled, of whom 439 (88.5%) had HIV infection, 465 (93.8%) received two doses of vaccine, and 445 (89.7%) received vaccine within the window of 28 to 56 days, as specified in the protocol (Table 1). The reasons for not receiving two doses of vaccine were death (19 patients), withdrawal of consent (5 patients), and loss to follow-up (7 patients). The study groups were well balanced, except that the proportion of patients who reported receiving previous tuberculosis therapy was larger in the placebo group.

At study termination, 273 patients were included in the follow-up analysis; of these patients, 239 had HIV infection, with similar numbers in the two study groups and an accumulated 798 person-years of observation (682 of which were in patients with HIV infection). The median follow-up time was 1.2 years (range, 2 days to 4.7 years). A total of 81 patients (16.3%) were lost to follow-up, for a rate of 102 per 1000 person-years of observation (Fig. 1). More patients in the placebo group than in the vaccine group were lost to follow-up.

END POINTS

All episodes of invasive pneumococcal disease and pneumonia occurred in patients with HIV infection. A total of 67 episodes of invasive pneumococcal disease occurred in 52 patients (98 per 1000 person-years), including 10 episodes of meningitis, 32 episodes of bacteremic pneumonia, 24 episodes of bacteremic illness with unconfirmed focus, and 1 episode of empyema. Among these episodes, 24 (35.8%) were caused by vaccine serotypes or the 6A serotype (Table 2).

Of the episodes that were caused by vaccine serotypes or the 6A serotype (the primary end point), 5 occurred in vaccine recipients and 19 in placebo recipients (Table 3). The unadjusted vaccine efficacy for prevention of infection caused by vaccine serotypes and the 6A serotype was 74% (95% confidence interval [CI], 30 to 90) among patients with HIV infection (hazard ratio, 0.26;

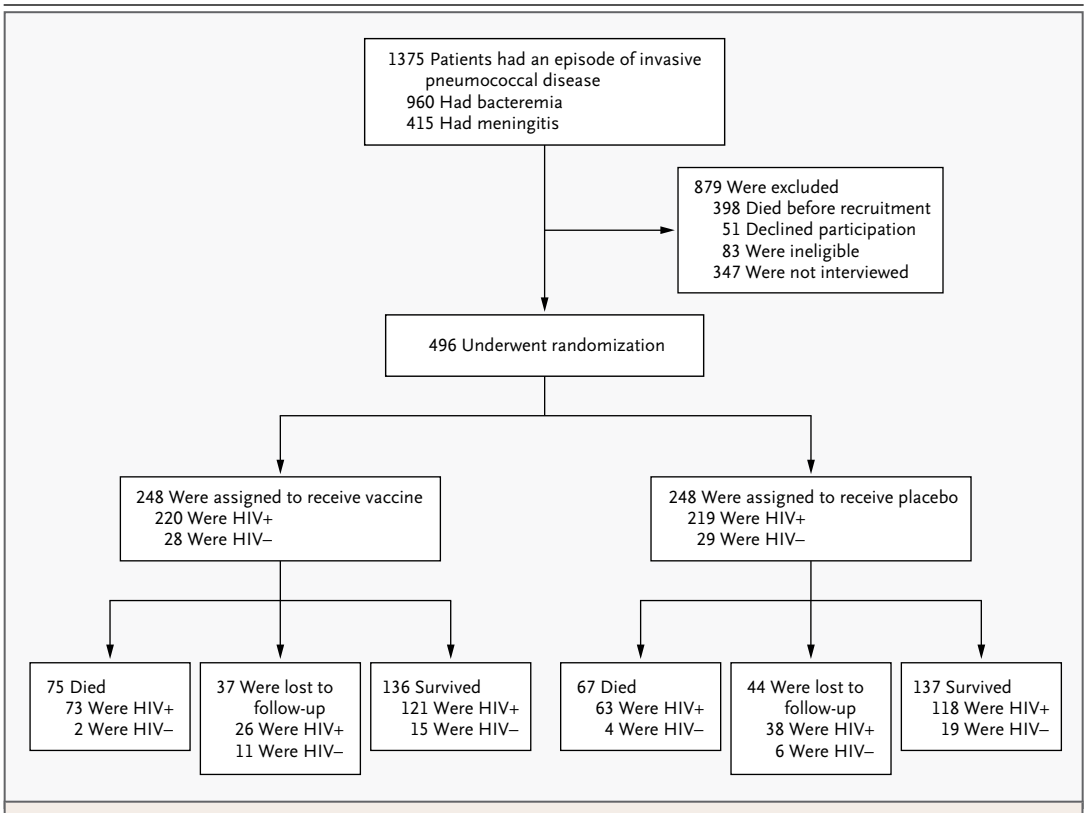

Figure 1. Enrollment and Outcomes.

Data regarding the status of human immunodeficiency virus (HIV) infection were missing for one patient in each study group. Both patients were considered to have HIV infection for the purpose of analysis.

95% CI, 0.10 to 0.70) (Table 3). Among all the patients, including those without HIV infection, the vaccine efficacy was 73% (95% CI, 23 to 89).

During the first 12 months after randomization, there were 17 episodes of illness caused by vaccine serotypes and the 6A serotype (2 in the vaccine group and 15 in the placebo group), for an estimated efficacy of 85%. In the period after the first 12 months, there were 7 episodes (3 in the vaccine group and 4 in the placebo group), for an estimated efficacy of 25%. The difference between the two periods was not significantly heterogeneous (P=0.12).

Episodes of invasive pneumococcal disease were most common in the subgroup of 220 patients who had a CD4+ T-cell count of less than 200 cells per cubic millimeter at baseline. In this subgroup, 2 episodes of illness caused by vaccine serotypes and the 6A serotype occurred in the vaccine group, and 16 episodes occurred in the placebo group (Table 3). The vaccine efficacy in this subgroup was 86% (95% CI, 41 to 97; P=0.06 for heterogeneity among three CD4+ categories). Of the 220 patients in this subgroup, 19 were receiving antiretroviral therapy at baseline (9 in the vaccine group and 10 in the placebo group).

In a multivariable analysis, the CD4+ count at baseline was identified as the strongest risk factor for invasive pneumococcal disease. Patients with a CD4+ count of less than 200 cells per cubic millimeter at baseline were 7.1 times as likely to have an invasive pneumococcal event as those with a CD4+ count of more than 500 (Table 4). A low CD4+ count was also associated with pneumonia from any cause and death.

ADVERSE EVENTS

Minor adverse events occurred in 10.9% of patients in the vaccine group and 3.6% of those in the placebo group. These events included self-limiting injection-site pain (35% of reported symptoms) and self-reported fever (28%) (Table 5 in the Supple-

Table 1. Baseline Demographic and Clinical Characteristics and Follow-up Data.*

Variable	Vaccine (N=248)	Placebo (N=248)	P Value†
At baseline			
Male sex — no. (%)	106 (42.7)	111 (44.8)	0.92
Age — yr			
Median	31	33	0.74
Range	16–72	15–75	
Previous invasive pneumococcal disease — no. (%)			
Bacteremic pneumonia	187 (75.4)	196 (79.0)	0.74
Meningitis	60 (24.2)	51 (20.6)	
Other invasive syndrome	1 (0.4)	1 (0.4)	
Days since previous episode of invasive pneumococcal disease			
Median	19	20	0.70
Range‡	7–1946	7–1715	
History of tuberculosis — no. (%)	60 (24.2)	83 (33.5)	0.02
History of pneumonia before enrollment episode — no. (%)	99 (39.9)	116 (46.8)	0.25
Presence of HIV infection — no. (%)			
Any stage	219 (88.3)	218 (87.9)	0.70
WHO clinical stage 4	42 (16.9)	45 (18.2)	
Unknown status	1 (0.4)	1 (0.4)	
CD4+ count at baseline — cells/mm^3			
Median	212	214	0.60
Range	1–1342	1–1200	
Viral load at baseline — $\log_{10}$ copies/ml§			
Median	4.9	5.0	0.16
Range	2.5–5.9	2.5–6.8	
Antiretroviral therapy§¶			
At baseline — no./total no. (%)	32/219 (14.6)	26/218 (11.9)	0.48
Duration — days			
Median	91	84	
Range	3–337	2–652	
Trimethoprim–sulfamethoxazole at baseline — no./total no. (%)	20/219 (9.1)	20/218 (9.2)	1.00
At follow-up			
Combined antiretroviral therapy and trimethoprim–sulfamethoxazole at any time during study — no./total no. (%)	89/219 (40.6)	95/218 (43.6)	0.56
Second dose of vaccine received 28 to 56 days after first dose — no. (%)	221 (89.1)	224 (90.3)	0.62
Lost to follow-up because of withdrawal from study — no. (%)	37 (14.9)	44 (17.7)	0.28

* HIV denotes human immunodeficiency virus, and WHO World Health Organization.
† Between-group comparisons are only for patients with HIV infection. Comparisons were calculated with the use of Fisher's exact test, Pearson's chi-square test, or the Wilcoxon rank-sum test.
‡ For 13 patients, the interval between the episode of invasive pneumococcal disease and enrollment was more than 12 months.
§ Data on viral load and receipt of antiretroviral therapy are provided only for patients with HIV infection.
¶ All patients received Triomune (Cipla Pharmaceuticals), consisting of stavudine, lamivudine, and nevirapine. For patients who had side effects, efavirenz was substituted for nevirapine in two patients, and zidovudine was substituted for stavudine in two patients.

Table 2. Invasive Pneumococcal Isolates That Were Identified in Patients, According to Serotype.*

Serotype	Vaccine (N=248)	Placebo (N=248)	Total (N=496)
		no. of patients	
Any serotype	29	38	67
Vaccine serotypes and serotype 6A†			
All patients	5	19	24
4	1	2	3
6A	1	4	5
6B	1	2	3
9V	2	3	5
14	0	5	5
19F	0	2	2
23F	0	1	1
Other vaccine serogroup‡			
All patients	2	1	3
9L	1	1	2
23	1§	0	1
Nonvaccine serotype			
All patients	22	18	40
0	0	4§	4
1	5	2	7
3	5	0	5
7A	1	0	1
10B	0	1	1
12F	0	5	5
12B	2	0	2
15	0	1§	1
15A	3	0	3
16¶	3	1	4
22¶	2	0	2
25¶	0	1	1
33F	0	1	1
35B	0	1	1
46	1	1	2

* The 6A serotype was confirmed with the use of polymerase-chain-reaction analysis of the *wciN* region of the capsular locus.
† No invasive pneumococcal disease caused by serotype 18C was identified.
‡ A serogroup is a group of serotypes having one or more antigens in common.
§ These isolates lost viability before completion of serotyping.
¶ These isolates did not undergo factor typing.

mentary Appendix). Serious adverse events were significantly more common in the placebo group (Table 6 in the Supplementary Appendix).

Rates of death were 199 per 1000 person-years among patients with HIV infection and 52 per 1000 person-years among those without HIV infection. Of the 136 deaths among patients with HIV infection, 111 (81.6%) occurred in patients who were not receiving antiretroviral therapy (270 per 1000 person-years), as compared with 25 (18.4%) among those who were receiving antiretroviral therapy (92 per 1000 person-years). There was a nonsignificant excess of deaths in vaccine recipients. This excess occurred 2 years or more after vaccination among patients with HIV infection who were not receiving antiretroviral therapy (Fig. 2 in the Supplementary Appendix). There was no between-group difference in the total number of deaths that were classified as definitely, probably, or possibly associated with pneumococcal disease (Table 3).

DISCUSSION

In this secondary-prophylaxis trial, a 7-valent conjugate pneumococcal vaccine prevented 74% of recurrent episodes of invasive pneumococcal disease caused by vaccine serotypes or serotype 6A in patients with HIV infection. The efficacy was highest during the first 12 months after vaccination. The vaccine also prevented pneumococcal disease in a subgroup of patients with a CD4+ T-cell count below 200 cells per cubic millimeter.

There was no overall effect on mortality, with similar proportions of patients who were alive and participating in follow-up at study termination in the two study groups. There was a nonsignificant excess in the number of reported deaths in the vaccine group, specifically in the subgroup of patients who had a CD4+ count below 500 per cubic millimeter at baseline and who never received antiretroviral therapy. These deaths were not categorized as deaths attributable to pneumococcal disease. The up-regulation of HIV by vaccines has been postulated and could theoretically be manifested as an increase in mortality among patients who are not receiving antiretroviral therapy.[24] However, more patients in the placebo group than in the vaccine group were lost to follow-up, a finding that probably skewed the comparison of rates of death. Other investigators have highlighted the problem of loss to follow-up in trials involving patients in low-income settings and have emphasized the frequency of death in these groups.[25-28]

Our study spanned a period of change in HIV care in Malawi with the initiation of a national

Table 3. Primary and Secondary End Points, Adverse Events, and Loss to Follow-up in 437 Patients with HIV Infection.*

End Point	Vaccine		Placebo		Hazard Ratio for First Event (95% CI)†		Incidence Rate Ratio for Recurrent Events (95% CI)	
					Unadjusted	Adjusted	Unadjusted	Adjusted
	no. of patients	*no. of events*	*no. of patients*	*no. of events*				
Primary end point								
Vaccine serotype or serotype 6A (intention-to-treat analysis)	5	5	19	19	0.26 (0.10–0.70)	0.31 (0.11–0.84)‡		
CD4+ count								
<200 cells/mm³	2	2	16	16				
200–500 cells/mm³	3	3	1	1				
>500 cells/mm³	0	0	1	1				
Data missing	0	0	1	1				
Vaccine serotype or serotype 6A (per-protocol analysis)	4	4	18	18	0.22 (0.08–0.66)	0.26 (0.08–0.78)		
Secondary end point								
Vaccine serogroup	7	7	19	20	0.37 (0.15–0.87)	0.41 (0.17–1.02)	0.19 (0.06–0.66)	0.30 (0.09–1.02)
Any invasive pneumococcal disease§	22	29	30	38	0.72 (0.42–1.25)	0.80 (0.45–1.44)	0.35 (0.12–1.01)	0.34 (0.11–1.02)
Any type of pneumonia	32	44	41	58	0.75 (0.47–1.19)	0.71 (0.43–1.17)	0.54 (0.26–1.14)	0.49 (0.20–1.21)
Adverse events								
Minor¶	27	41	9	13				
Serious‖	3	3	17	17				
Death								
Any cause**	73		63		1.18 (0.84–1.66)	1.24 (0.88–1.75)		
Definite, probable, or possible association with pneumococcal disease††	35		35		1.02 (0.64–1.63)	1.14 (0.71–1.85)		
Loss to follow-up	26		38					

* No episodes of pneumococcal disease or pneumonia were recorded in the 57 patients who were not infected with the human immunodeficiency virus (HIV). Data regarding the status of HIV infection were missing for one patient in each study group. Secondary end points and loss to follow-up numbers that have been stratified according to the CD4+ cell count are available in the Supplementary Appendix.

† Hazard ratios are for the vaccine group, as compared with the placebo group. Values were adjusted for age, sex, and the viral load, clinical stage, and CD4+ cell count at baseline.

‡ When the proportional-hazards assumption was violated, the Cox model was stratified according to the year of recruitment and the baseline CD4+ cell count.

§ In the vaccine group, two patients each had two recurrent events, and one patient had six recurrent events. In the placebo group, six patients had two recurrent events, and one had three recurrent events.

¶ P=0.003 by Fisher's exact test.

‖ P=0.002. The serious adverse events consisted of 2 deaths and 1 hospitalization in the vaccine group and 7 deaths and 10 hospitalizations (5 of which were for invasive pneumococcal disease, 1 of which was caused by a vaccine serotype) in the placebo group.

** Of the patients who died, 11 in the vaccine group and 14 in the placebo group were receiving antiretroviral therapy.

†† Of the 70 deaths in this category, 9 were definitely associated with pneumococcal disease, 4 were probably associated, and 57 were possibly associated; of these 70 patients, 6 in the vaccine group and 7 in the placebo group were receiving antiretroviral therapy.

Table 4. Hazard Ratios for the Primary and Secondary End Points.*

Variable	Hazard Ratio (95% CI)			
	Primary End Point†	Any Invasive Pneumococcal Disease	Any Type of Pneumonia	Death
Receipt of vaccine	0.25 (0.08–0.71)	0.74 (0.41–1.35)	0.70 (0.42–1.16)	1.38 (0.97–1.97)
Age				
15–24 yr (reference)				
25–34 yr	1.17 (0.28–4.78)	1.95 (0.65–5.89)	1.61 (0.62–4.22)	1.57 (0.81–3.06)
35–74 yr	0.65 (0.14–3.13)	1.37 (0.43–4.35)	1.00 (0.37–2.73)	1.43 (0.72–2.84)
Male sex	1.41 (0.52–3.85)	1.21 (0.65–2.25)	1.57 (0.94–2.64)	0.82 (0.55–1.19)
CD4+ count				
<200 cells/mm^3 (reference)				
200–500 cells/mm^3	NA	0.61 (0.34–1.13)	0.43 (0.24–0.78)	0.34 (0.22–0.53)
>500 cells/mm^3	NA	0.14 (0.02–1.06)	0.29 (0.07–1.23)	0.47 (0.21–1.04)
Viral load ≥100,000 copies/ml	1.30 (0.50–3.38)	1.40 (0.75–2.62)	2.68 (1.51–4.74)	1.75 (1.20–2.57)
WHO stage 4 disease	0.94 (0.32–2.76)	1.08 (0.51–2.27)	1.30 (0.73–2.32)	2.11 (1.43–3.11)
Use of antiretroviral therapy	0.49 (0.12–2.01)	0.73 (0.31–1.73)	1.09 (0.55–2.19)	0.34 (0.19–0.58)
Use of trimethoprim–sulfamethoxazole	0.60 (0.13–2.76)	0.52 (0.20–1.34)	0.81 (0.43–1.51)	0.92 (0.59–1.43)

* Hazard ratios were derived from multivariable proportional-hazards regression models and included the use of antiretroviral therapy and trimethoprim–sulfamethoxazole as time-dependent covariates for the primary end points of invasive pneumococcal disease caused by vaccine serotypes or serotype 6A, any invasive pneumococcal disease, any type of pneumonia, and death for patients with HIV infection. Data regarding the baseline CD4+ cell count were missing for 31 patients (15 in the vaccine group and 16 in the placebo group), who were excluded from the analysis. NA denotes not applicable.

† When the proportional-hazards assumption was violated, the Cox model was stratified according to the year of recruitment and the baseline CD4+ cell count.

program for antiretroviral therapy and promotion of prophylaxis with trimethoprim–sulfamethoxazole. Modification of the primary end point and prolongation of the study were in part a consequence of these changes. The study did not have the power to investigate the interaction between the use of the pneumococcal conjugate vaccine and antiretroviral therapy, and refinements in the use of such therapy with vaccine administration should be investigated further — specifically, whether a two-dose vaccine regimen (which was based on evidence from immunogenicity studies involving HIV-infected Ugandans who were not receiving antiretroviral therapy[16]) is optimal and how initial and repeat doses of vaccine should best be administered in relation to antiretroviral therapy to maximize the efficacy and duration of protection.

This was a secondary-prophylaxis trial undertaken in a population of predominantly HIV-infected adults. Since there were no primary end points or pneumonia episodes among patients without HIV infection, no conclusions can be made about vaccine efficacy in this subgroup. By extension of our results in HIV-infected adults, it seems likely that the pneumococcal conjugate vaccine would also work as primary prophylaxis. The episodes of pneumococcal disease that occurred before enrollment may have primed patients for a response to a matching serotype, but with a recognized low risk of recurrent disease caused by the same serotype,[1,5] the contribution of any potential priming to efficacy is probably small.

Pneumococci with vaccine serotype and serotype 6A antigens accounted for 50% of the episodes of invasive pneumococcal disease in the placebo group, and broader serotype coverage would be desirable. Conjugate vaccines with a higher valency will soon be available, but responses to these vaccines should be evaluated, in particular those with different carrier proteins. HIV-infected adults have sustained responses to toxoid vaccines such as those containing diphtheria antigens, but this may not be true of other carrier

proteins. The use of pneumococcal conjugate vaccine in HIV-infected adults will also have to be considered in the context of pediatric vaccination programs, including how such programs might alter the distribution of disease-causing serotypes in adults.[29,30]

We have shown that HIV-infected adults can have a clinically relevant response to a pneumococcal conjugate vaccine, leading to protection against a common and serious coinfection. The ability of a conjugate vaccine to generate protective responses in patients with a low CD4+ count is of particular note and merits further study to elucidate the immune mechanisms involved and how such mechanisms may be used to produce other vaccines for this population. The pneumococcal conjugate vaccine provides an additional therapeutic intervention for improving the care of HIV-infected adults that is both simple and safe to administer, which makes its use highly relevant in Africa.

Supported by the Wellcome Trust. Through an investigator-originated protocol agreement, Wyeth Pharmaceuticals provided the Prevnar vaccine to be administered during the study and to placebo recipients after the release of results.

Presented in part at the Sixth International Symposium on Pneumococcus and Pneumococcal Disease, Reykjavik, Iceland, June 8–12, 2008.

Dr. French reports serving as a paid member of advisory panels for GlaxoSmithKline and Novartis. No other potential conflict of interest relevant to this article was reported.

We thank the members of the trial steering group, including Keith Klugman (chair), James Whitworth (former chair), Helena Makela, John Macfarlane, Di Gibb, Ed Wilkins, and Henry Mwandumba; members of the data and safety monitoring board Tim Peto, Johnstone Kumwenda, and Andrew Nunn; members of the Queen Elizabeth Central Hospital staff, including Rose Malamba, Marie Kunkeyani, Neema Mtunthama, and Mary Matemba; Anne von Gottberg at the Respiratory and Meningeal Pathogens Research Unit, Johannesburg, South Africa; Steve Graham and Michael Boele van Hensbroek for vaccine and placebo blinding; and Helen Tolmie at the Liverpool School of Tropical Medicine and Pontiano Kaleebu at the Medical Research Council, Uganda Virus Research Institute, Entebbe, Uganda.

REFERENCES

1. Gilks CF, Ojoo SA, Ojoo JC, et al. Invasive pneumococcal disease in a cohort of predominantly HIV-1 infected female sex-workers in Nairobi, Kenya. Lancet 1996;347:718-23.
2. Klugman KP, Madhi SA, Feldman C. HIV and pneumococcal disease. Curr Opin Infect Dis 2007;20:11-5.
3. Janoff EN, Breiman RF, Daley CL, Hopewell PC. Pneumococcal disease during HIV infection: epidemiologic, clinical, and immunologic perspectives. Ann Intern Med 1992;117:314-24.
4. Heffernan RT, Barrett NL, Gallagher KM, et al. Declining incidence of invasive Streptococcus pneumoniae infections among persons with AIDS in an era of highly active antiretroviral therapy, 1995-2000. J Infect Dis 2005;191:2038-45.
5. French N, Nakiyingi J, Carpenter LM, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. Lancet 2000;355:2106-11.
6. Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. Arch Intern Med 2005;165:1533-40.
7. Scarborough M, Gordon SB, Whitty CJ, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. N Engl J Med 2007;357:2441-50.
8. 23-Valent pneumococcal polysaccharide vaccine: WHO position paper. Wkly Epidemiol Rec 2008;83:373-84.
9. Masur H, Kaplan JE, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons — 2002: recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. Ann Intern Med 2002;137:435-78.
10. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000;19:187-95.
11. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003;349:1341-8.
12. O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. Lancet 2003;362:355-61.
13. Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 2005;365:1139-46.
14. Madhi SA, Adrian P, Kuwanda L, et al. Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a booster dose of vaccine. Vaccine 2007;25:2451-7.
15. Feikin DR, Elie CM, Goetz MB, et al. Randomized trial of the quantitative and functional antibody responses to a 7-valent pneumococcal conjugate vaccine and/or 23-valent polysaccharide vaccine among HIV-infected adults. Vaccine 2001;20:545-53.
16. Miiro G, Kayhty H, Watera C, et al. Conjugate pneumococcal vaccine in HIV-infected Ugandans and the effect of past receipt of polysaccharide vaccine. J Infect Dis 2005;192:1801-5.
17. Gordon SB, Kayhty H, Molyneux ME, et al. Pneumococcal conjugate vaccine is immunogenic in lung fluid of HIV-infected and immunocompetent adults. J Allergy Clin Immunol 2007;120:208-10.
18. Gordon SB, Kanyanda S, Walsh AL, et al. Poor potential coverage for 7-valent pneumococcal conjugate vaccine, Malawi. Emerg Infect Dis 2003;9:747-9.
19. Gordon SB, Chaponda M, Walsh AL, et al. Pneumococcal disease in HIV-infected Malawian adults: acute mortality and long-term survival. AIDS 2002;16:1409-17.
20. Whitney CG, Pilishvili T, Farley MM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet 2006;368:1495-502.
21. Klugman KP, Cutts FT, Adegbola RA, et al. Meta-analysis of the efficacy of conjugate vaccines against invasive pneumococcal disease. In: Siber G, Klugman KP, Makela H, eds. Pneumococcal vaccines: the impact of conjugate vaccine. Washington, DC: ASM Press, 2008:317-26.
22. Janoff EN, Rubins JB. Invasive pneumococcal disease in the immunocompromised host. Microb Drug Resist 1997;3:215-32.
23. Piantadosi S. Clinical trials: a methodologic perspective. New York: John Wiley, 1997:248.
24. Brichacek B, Swindells S, Janoff EN, Pirrucello S, Stevenson M. Increased plasma human immunodeficiency virus type 1 burden following antigenic challenge with

pneumococcal vaccine. J Infect Dis 1996; 174:1191-9.
25. Anglaret X, Toure S, Gourvellec G, et al. Impact of vital status investigation procedures on estimates of survival in cohorts of HIV-infected patients from Sub-Saharan Africa. J Acquir Immune Defic Syndr 2004;35:320-3.
26. Braitstein P, Brinkhof MW, Dabis F, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006;367:817-24. [Erratum, Lancet 2006;367:1902.]
27. Yu JK, Chen SC, Wang KY, et al. True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. Bull World Health Organ 2007;85: 550-4.
28. Brinkhof MW, Dabis F, Myer L, et al. Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. Bull World Health Organ 2008;86:559-67.
29. Flannery B, Heffernan RT, Harrison LH, et al. Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. Ann Intern Med 2006; 144:1-9.
30. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein–polysaccharide conjugate vaccine. N Engl J Med 2003;348:1737-46.

Folgefonna National Park, Sweden James J. Cimino, M.D.