

ORIGINAL ARTICLE

A Trial of a 9-Valent Pneumococcal Conjugate Vaccine in Children with and Those without HIV Infection

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ABSTRACT

BACKGROUND

Acute respiratory tract infections caused by *Streptococcus pneumoniae* are a leading cause of morbidity and mortality in young children. We evaluated the efficacy of a 9-valent pneumococcal conjugate vaccine in a randomized, double-blind study in Soweto, South Africa.

METHODS

At 6, 10, and 14 weeks of age, 19,922 children received the 9-valent pneumococcal polysaccharide vaccine conjugated to a noncatalytic cross-reacting mutant of diphtheria toxin (CRM197), and 19,914 received placebo. All children received *Haemophilus influenzae* type b conjugate vaccine. Efficacy and safety were analyzed according to the intention-to-treat principle.

RESULTS

Among children without human immunodeficiency virus (HIV) infection, the vaccine reduced the incidence of a first episode of invasive pneumococcal disease due to serotypes included in the vaccine by 83 percent (95 percent confidence interval, 39 to 97; 17 cases among controls and 3 among vaccine recipients). Among HIV-infected children, the efficacy was 65 percent (95 percent confidence interval, 24 to 86; 26 and 9 cases, respectively). Among children without HIV infection, the vaccine reduced the incidence of first episodes of radiologically confirmed alveolar consolidation by 20 percent (95 percent confidence interval, 2 to 35; 212 cases in the control group and 169 in the vaccinated group) in the intention-to-treat analysis and by 25 percent (95 percent confidence interval, 4 to 41; 158 and 119 cases, respectively) in the per-protocol analysis (i.e., among fully vaccinated children). The incidence of invasive pneumococcal disease caused by penicillin-resistant strains was reduced by 67 percent (95 percent confidence interval, 19 to 88; 21 cases in the control group and 7 in the vaccinated group), and that caused by strains resistant to trimethoprim-sulfamethoxazole was reduced by 56 percent (95 percent confidence interval, 16 to 78; 32 and 14 cases, respectively).

CONCLUSIONS

Vaccination with a 9-valent pneumococcal conjugate vaccine reduced the incidence of radiologically confirmed pneumonia. The vaccine also reduced the incidence of vaccine-serotype and antibiotic-resistant invasive pneumococcal disease among children with and those without HIV infection.

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ACUTE RESPIRATORY TRACT INFECTIONS are a major cause of death in children under the age of five years.¹ *Streptococcus pneumoniae*, the leading bacterial pathogen,² has become increasingly resistant to antibiotics.^{3,4} Administration of a 7-valent vaccine conjugated to a noncatalytic cross-reacting mutant of diphtheria toxin (CRM197) reduced the incidence of invasive pneumococcal disease in children.⁵ The formulation lacks serotypes 1 and 5, which are important causes of invasive pneumococcal disease throughout the world.⁶ The efficacy of conjugate vaccine in the prevention of invasive pneumococcal disease among children infected with human immunodeficiency virus (HIV) is unknown. Therefore, we conducted a prospective, randomized, double-blind trial of a 9-valent pneumococcal conjugate vaccine that included serotypes 1 and 5 in Soweto, South Africa, a community where antibiotic-resistant strains of pneumococci are common and HIV infection has increased the burden of invasive pneumococcal disease and pneumonia among children.⁷

METHODS

STUDY DESIGN

Children were enrolled in a double-blind randomized trial and assigned to receive the 9-valent pneumococcal vaccine or a placebo at approximately 6, 10, and 14 weeks of age. Children who were 28 to 84 days old were eligible for inclusion if they were unvaccinated or had received only bacille Calmette-Guérin and oral poliovirus vaccine at birth. Infants were excluded if they had a progressive underlying neurologic disorder, a history of seizures or infantile spasms, or a low likelihood of receiving three doses of vaccine because they were apt to move from Soweto.

The vaccine comprised 2 µg of capsular polysaccharide (serotypes 1, 4, 5, 9V, 14, 19F, and 23F), 4 µg of serotype 6B, and 2 µg of oligosaccharide 18C. Doses of vaccine and placebo were made up in a blinded fashion, appeared identical, and were color-coded with the use of 10 colors at 21 vaccination centers in Soweto in randomized blocks of 10. No booster dose was given. For the benefit of the controls, all children received *Haemophilus influenzae* type b conjugate vaccine (HibTITER, Wyeth), which was not part of the expanded program of immunization in South Africa at the start of the trial. Concurrently administered vaccines were diphtheria, tetanus, and whole-cell pertussis (DTwP, Aventis Pasteur); hepa-

titis B (Hepaccine-B, Cheil Sugar Organization); and oral live, trivalent poliovirus types 1, 2, and 3 (Polioral, Biovac).

Children included in the per-protocol analysis received three doses, with an interval of at least 21 days between doses, and received their last dose before 270 days of age. The analysis of safety and efficacy conducted according to the intention-to-treat principle included all randomized children. Follow-up continued until 15 children without HIV infection who were included in the per-protocol analysis met the primary end point of invasive pneumococcal disease caused by a serotype included in the vaccine. HIV status was confirmed when a child was hospitalized for any reason. Twenty-four-hour surveillance was conducted at the admission ward of Chris Hani Baragwanath Hospital, a secondary and tertiary hospital that serves more than 90 percent of the children in Soweto. Data for all children born after December 1997 were compared at the time of admission with the data base of all children enrolled in the trial. Hospitalized children were examined by one of four study doctors within 24 hours after admission to determine the clinical diagnosis, but the study doctors were not involved in the children's care. Secondary end points were invasive pneumococcal disease and pneumonia in HIV-infected children and antibiotic-resistant strains in the entire study group.

The study was approved by the Committee for the Study of Human Subjects at the University of the Witwatersrand, and permission for the trial was obtained from the Medicines Control Council of South Africa. All participants were enrolled after written informed consent had been obtained from a parent or legal guardian.

MICROBIOLOGIC ANALYSIS

Pneumococci were isolated from blood samples with the use of an automated blood-culture system (BacT-Alert, Organon Teknika). Species were identified with the use of routine microbiologic methods, including sensitivity to ethylhydrocupreine (optochin) and bile solubility. Antimicrobial susceptibility was determined with the use of the Kirby-Bauer disk-diffusion test, and minimal inhibitory concentrations were confirmed by the broth-microdilution method or the E test (AB Biodisk). Susceptibility criteria were those of the National Committee for Clinical Laboratory Standards.⁸

Viral pneumonia was diagnosed on the basis of either clinical or radiologic evidence of pneumonia

plus a positive immunofluorescence assay for a respiratory virus from a nasopharyngeal aspirate.⁹ Radiographs were archived by digital scanning with the use of a film digitizer (VXR-12, Vidar Systems) and were read independently by a pediatrician and a radiologist. When the results were discordant for alveolar consolidation, the radiographs were reviewed by a pediatrician and a radiologist who were members of a World Health Organization expert panel, and their decision was considered final.¹⁰

HIV-negative status was confirmed by a negative enzyme-linked immunosorbent assay (ELISA) for HIV antibody (AxSYM system, HIV 1/2, Abbott) or by a negative HIV DNA polymerase-chain-reaction (PCR) assay (Amplicor version 1.5, Roche) in children who were younger than 18 months of age and whose ELISA was reactive for HIV antibodies. In the secondary analysis of HIV-infected children, HIV infection was confirmed by a positive PCR assay in children younger than 18 months old or by two positive ELISAs for HIV antibody (AxSYM and Murex HIV 1+2, Murex Diagnostic) in those who were 18 months of age or older. Children with a nonreactive ELISA in whom HIV infection was suspected on the basis of clinical signs of the acquired immunodeficiency syndrome (Centers for Disease Control and Prevention criteria B or C)¹¹ were also evaluated with use of the HIV DNA PCR assay.

STATISTICAL ANALYSIS

Before the trial began, the incidence of vaccine-serotype-specific invasive pneumococcal disease was estimated to be 112 cases per 100,000 children. Our study was designed to include 19,231 children in each group who were followed for two years and thus to have a power of 80 percent to detect a 70 percent reduction in the incidence with a two-sided type I error of 5 percent. Since children may be seen at other hospitals in the same city or in other cities, any estimation of the absolute incidence but not of the relative incidence may be subject to ascertainment bias. The randomized double-blind design of the study ensured that any ascertainment bias would affect the two groups equally. The investigators, who were independent of the sponsor, collected all the data and had full access to the analyses and primary data. Relative risk and vaccine efficacy, based on the occurrence of a first event in each child, were estimated and confidence limits were calculated with the use of the exact conditional binomial distribution,¹² with a follow-up ratio between treatment groups of 0.5. The results presented are for analyses

conducted according to the intention-to-treat principle and include all cases of invasive pneumococcal disease and pneumonia. Qualitatively similar results were obtained with the use of per-protocol analyses. Any qualitative differences that occurred are described. No interim analyses were planned or performed. The predefined primary end points were a first episode of invasive pneumococcal disease and an episode of radiologically confirmed pneumonia that occurred at least 14 days after the third dose in children without HIV infection who were included in the per-protocol analyses. Invasive pneumococcal disease was defined on the basis of the isolation from blood, cerebrospinal fluid, or both of a pneumococcal serotype included in the vaccine (confirmed by the Statens Serum Institut, Copenhagen, Denmark). All reported P values are two sided.

RESULTS

A total of 39,836 children were included in the intention-to-treat analysis: 19,922 were randomly assigned to receive the 9-valent conjugate pneumococcal vaccine, and 19,914 to receive placebo (Table 1). Enrollment was begun on March 2, 1998, and ended on October 30, 2000. Follow-up continued until November 15, 2001.

INVASIVE PNEUMOCOCCAL DISEASE

The incidence of first episodes of invasive pneumococcal disease is presented in Table 2. Among chil-

Table 1. Characteristics of the Participants.

Characteristic	Vaccinated Group (N=19,922)	Control Group (N=19,914)
Sex (%)		
Male	50.3	49.9
Female	49.7	50.1
Follow-up		
Average (days)	847.5	847.0
Range (days)	60–1354	63–1354
Total (person-yr)	46,258	46,213
Age (wk)*		
Dose 1	6.6±1.2	6.6±1.2
Dose 2	11.2±2.6	11.2±2.4
Dose 3	15.9±4.0	15.8±3.7
No. of doses received (no. of children)		
0 Doses	0	0
1 Dose	595	595
2 Doses	770	769
3 Doses	18,557	18,550

* Plus-minus values are means ±SD.

dren without HIV infection, there were 17 first episodes caused by serotypes included in the vaccine in the control group (3 children had bacteremia without a focus, 1 of whom had a febrile convulsion; 7 had bacteremic pneumonia; 6 had meningitis; and 1 had a mesenteric presentation of pneumococcal sepsis) and 3 in the vaccinated group (2 had bacteremic pneumonia and 1 had meningitis). The efficacy of the vaccine was 83 percent (95 percent confidence interval, 39 to 97; $P=0.003$). There were no underlying conditions predisposing these children to invasive pneumococcal disease. Three children (two vaccine recipients and one child in the control group) had been exposed to HIV but were not infected, and one child in the control group had pneumococcal meningitis and an underlying condition listed as spastic cerebral palsy.

In the per-protocol analysis, the efficacy of the vaccine was 85 percent (95 percent confidence interval, 32 to 98) for the predefined primary end point of invasive pneumococcal disease in fully immunized children without HIV infection (13 cases in the control group vs. 2 in the vaccinated group). For HIV-infected children, the efficacy against vaccine serotypes was 65 percent (95 percent confidence interval, 24 to 86; $P=0.006$). Since the analysis included only the first episode of invasive pneumococcal disease for each category, among HIV-infected children, the

same child may have been included in both the vaccine-serotype and non-vaccine-serotype categories if the child had multiple episodes, but the child was included only once in the category of all first episodes of invasive pneumococcal disease. The protective efficacy of the vaccine against all serotypes of invasive pneumococcal disease in all children was 50 percent. The serotypes isolated during 99 first episodes of invasive pneumococcal disease are shown in Table 3. Among vaccine-related serotypes, there was evidence of a trend toward protection from serotype 6A but not 19A.

PNEUMONIA

The rates of vaccine efficacy against radiologically confirmed first episodes of pneumonia are presented in Table 4. Among children without HIV infection, there were 169 first episodes among vaccine recipients and 212 among controls (vaccine efficacy, 20 percent; 95 percent confidence interval, 2 to 35; $P=0.03$); the efficacy of the vaccine in the entire cohort was 17 percent ($P=0.01$). In the per-protocol analysis, the efficacy of the vaccine for the primary end point of radiologically confirmed pneumonia among fully immunized children without HIV infection was 25 percent (95 percent confidence interval, 4 to 41; 158 first episodes among controls and 119 among vaccine recipients).

Table 2. First Episodes of Invasive Pneumococcal Disease.*

Variable	Vaccinated Group	Control Group	P Value	Vaccine Efficacy (95% CI)
	<i>no. of episodes</i>			<i>percent</i>
HIV-negative children				
Invasive pneumococcal disease	11	19	0.2	42 (-28 to 75)
Vaccine-serotype pneumococci	3	17	0.003	83 (39 to 97)
Non-vaccine-serotype pneumococci	4	1	0.38	-300 (-19,599 to 60)
Vaccine-related-serotype pneumococci	4	1	0.38	-300 (-19,599 to 60)
HIV-positive children				
Invasive pneumococcal disease	22	47	0.004	53 (21 to 73)
Vaccine-serotype pneumococci	9	26	0.006	65 (24 to 86)
Non-vaccine-serotype pneumococci	9	8	1	-13 (-235 to 62)
Vaccine-related-serotype pneumococci	6	16	0.05	63 (-1 to 88)
All children				
Invasive pneumococcal disease	33	66	0.001	50 (23 to 68)
Vaccine-serotype pneumococci	12	43	<0.001	72 (46 to 87)
Non-vaccine-serotype pneumococci	13	9	0.52	-44 (-283 to 43)
Vaccine-related-serotype pneumococci	10	17	0.25	41 (-36 to 75)

* Vaccine-serotype pneumococci were serotypes 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F. Vaccine-related pneumococci were serotypes 6A, 19A, and 19B. CI denotes confidence interval, and HIV human immunodeficiency virus. For HIV-positive children and for all children, the sum of episodes involving vaccine, nonvaccine, and vaccine-related serotypes exceeds the number of episodes of invasive pneumococcal disease because only the first episode of invasive disease was counted.

ANTIBIOTIC RESISTANCE

Antibiotic-resistant strains were more commonly isolated from HIV-infected children than from children without HIV infection (Table 5). In the entire group of children, the vaccine reduced the incidence of first episodes of invasive pneumococcal disease caused by penicillin-resistant pneumococci by 67 percent (95 percent confidence interval, 19 to 88; $P=0.01$). Episodes caused by pneumococci resistant to trimethoprim–sulfamethoxazole were reduced by 56 percent (95 percent confidence interval, 16 to 78; $P=0.01$), and episodes caused by pneumococci resistant to one or more selected antibiotics (penicillin, tetracycline, erythromycin, clindamycin, chloramphenicol, rifampin, or trimethoprim–sulfamethoxazole) by 56 percent (95 percent confidence interval, 21 to 77; $P=0.005$) (Table 5).

MORTALITY

The mortality rate was reduced by 5 percent among all children (229 deaths among vaccine recipients and 242 among controls, $P=0.58$) and by 6 percent among HIV-infected children (166 and 176 deaths, respectively; $P=0.63$). Among children without HIV infection, there were 36 deaths in each group. HIV status was not available for 27 vaccine recipients and 30 controls. Half the HIV-infected children who died (86 vaccine recipients and 85 controls) were not eligible for the per-protocol analysis; most were less than 18 weeks old at the time of death. Pneumonia and bronchiolitis were associated with 66 percent of deaths. There were 153 deaths attributable to pneumonia in the vaccinated group and 160 in the control group, for a reduction in mortality attributable to pneumonia of 4 percent ($P=0.73$). Nine percent of all deaths (21 in each group) were due to gastroenteritis.

SAFETY

A previous trial of the immunogenicity and safety of this vaccine in children in Soweto showed no major adverse effects.¹³ An analysis of the primary diagnoses during hospitalization of children without HIV infection in the present study revealed more viral pneumonias among vaccinated children 1 to 4 days after vaccination than among such children who were not vaccinated (18 vs. 6 cases, $P=0.02$), and this difference persisted from 1 to 8 days after vaccination (30 vs. 15 cases, $P=0.03$) but not from 1 to 31 days (83 vs. 71 cases, $P=0.37$). These cases were due primarily to respiratory syncytial virus,

Table 3. Number and Serotype of First Episodes of Invasive Pneumococcal Disease.*

Isolate	Vaccinated Group		Control Group	
	HIV-Negative	HIV-Positive	HIV-Negative	HIV-Positive
	<i>number of episodes</i>			
Vaccine serotype				
1	1		3	1
4	1		2	1
5			1	1
6B	1	1	2	7
9V		1	3	1
14		1	2	7
18C			2	
19F		2	1	3
23F		3	1	4
Total	3	8	17	25
Vaccine-related serotype				
6A	1	3		10
19A	3	2	1	3
19B				1
Total	4	5	1	14
Non-vaccine serotype				
3		1	1	
8	2			
10A		1		
12F				2
13				1
15A		1		4
15B	1			
15C		1		1
15F		1		
16F		1		
17F		1		
29		1		
34	1			
38		1		
Total	4	9	1	8
Total	11	22	19	47

* Seven subsequent episodes of invasive pneumococcal disease among children infected with human immunodeficiency virus (HIV) were excluded. In the vaccinated group there were three additional episodes due to serotype 19F after a first episode caused by 6A and one additional episode due to 6A after a first episode caused by 9V. In the control group there was one additional episode due to serotype 6A after a first episode caused by 19A, one episode due to 9V after a first episode caused by 15A, and one episode due to 19A after a first episode caused by 14.

Table 4. Efficacy of the Vaccine against First Episodes of Radiologically Confirmed Pneumonia.*

Variable	Vaccinated Group	Control Group	P Value	Vaccine Efficacy (95% CI)
	<i>no. of episodes</i>			%
HIV-negative children	169	212	0.03	20 (2 to 35)
HIV-positive children	182	209	0.19	13 (-7 to 29)
All children	356	428	0.01	17 (4 to 28)

* CI denotes confidence interval, and HIV human immunodeficiency virus.

which caused 83 percent of viral pneumonias in the vaccinated group and 80 percent in the control group, and therefore showed winter seasonality. No other potentially vaccine-associated adverse reactions were noted in the 31 days after vaccination.

During the remaining follow-up period, the vaccinated group had a higher incidence of generalized seizures (35 vs. 19 cases, $P=0.04$) but a lower incidence of “unspecified” seizures (9 vs. 21 cases, $P=0.04$). The overall rate of seizure diagnoses did not differ significantly between vaccine recipients and controls. Hyperactive-airway disease and asthma treated with bronchodilator agents were diagnosed in 59 vaccine recipients and 33 controls (relative risk, 1.79; $P=0.009$); no temporal relation to vaccination was apparent. The risk remained elevated for multiple episodes of asthma (22 cases among vaccine recipients, as compared with 12 among controls; relative risk, 1.83; 95 percent confidence interval, 0.9 to 4.1; $P=0.12$), as well as when the analysis was restricted to children who were at least 12 months of age (42 vs. 22 cases; relative risk, 1.91; 95 percent confidence interval, 1.1 to 3.4; $P=0.02$). The absolute risk of asthma was 1.66 cases per 1000 among controls and 2.96 per 1000 among vaccine recipients.

DISCUSSION

In the group of children without HIV infection, the 9-valent pneumococcal conjugate vaccine prevented 83 percent of episodes of invasive pneumococcal disease due to serotypes included in the vaccine. The results of the per-protocol and intention-to-treat analyses were similar and were in keeping with the high levels of antibody found in immunized children in Soweto after only one or two doses of vaccine.¹⁴ The immunogenicity of the vaccine, evaluated in a nested study in this trial (data not shown),

was not significantly different from that previously reported¹³ among vaccinated children in this community. The efficacy was similar to that obtained in an intention-to-treat analysis of a 7-valent pneumococcal conjugate vaccine in Navajo children (86 percent efficacy)¹⁵ and in children from northern California (94 percent efficacy).⁵ In the California study, a minority of children with bacteremia had evidence of pneumonia or meningitis, whereas the majority of children in our study had such evidence. The duration of the protective effect of the vaccine remains unknown. The level of protection observed in our study over a mean follow-up of 2.3 years was achieved without a booster dose.

Our findings extend previous observations and therefore provide evidence in support of the current U.S. recommendation to provide conjugate pneumococcal vaccine to HIV-infected children as well as children without HIV infection.¹⁶ This finding is important, given the increased incidence of invasive pneumococcal disease among HIV-infected children¹⁷ and the failure of 23-valent vaccine to prevent invasive pneumococcal disease in HIV-infected adults.¹⁸ Our data suggest that conjugate vaccine may remain useful in countries where HIV infection is the leading risk factor for invasive pneumococcal disease. We speculate that the vaccine could be further investigated in HIV-infected adults. Our study did not have sufficient statistical power to determine whether there was a significant increase in the incidence of invasive pneumococcal disease caused by serotypes that were not included in the vaccine (serotype replacement), although there was a small, nonsignificant increase in the incidence of non-vaccine-type pneumococcal infections among vaccinated children.

We found that the 9-valent conjugate vaccine offered significant protection against pneumonia. An analysis of radiologically evident pneumonia among children enrolled in the northern California trial revealed a similar level of protection against pneumonia.¹⁹ The true percentage of cases of pneumococcal pneumonia prevented by the vaccine probably exceeds 25 percent, since the specificity of alveolar consolidation as a diagnostic test of pneumococcal pneumonia is suboptimal, and thus, the use of a radiologic end point underestimates the true efficacy of a vaccine. The prevention of 25 percent of first episodes of pneumonia among children was in addition to the protection against pneumonia afforded by the *H. influenzae* type b conjugate vaccine²⁰ given to both vaccine recipients and controls.

Table 5. Efficacy of the Vaccine against Antibiotic-Resistant First Episodes of Invasive Pneumococcal Disease.*

Group of Children and Type of Antibiotic Resistance	Vaccinated Group	Control Group	Vaccine Efficacy (95% CI)	P Value
	<i>no. of episodes</i>		<i>percent</i>	
HIV-negative children				
Penicillin	0	4	100 (-52 to 100)	0.13
Trimethoprim-sulfamethoxazole	1	3	67 (-315 to 99)	0.13
Any	2	6	67 (-86 to 97)	0.29
HIV-positive children				
Penicillin	7	17	59 (-5 to 86)	0.06
Trimethoprim-sulfamethoxazole	13	29	55 (11 to 79)	0.02
Any	15	33	55 (14 to 77)	0.01
All children				
Penicillin	7	21	67 (19 to 88)	0.01
Trimethoprim-sulfamethoxazole	14	32	56 (16 to 78)	0.01
Any	17	39	56 (21 to 77)	0.005

* Penicillin-resistant strains include strains with intermediate resistance (minimal inhibitory concentration, $\geq 0.1 \mu\text{g}$ per milliliter). Strains with any resistance include strains with full or intermediate resistance, according to National Committee for Clinical Laboratory Standards criteria,¹⁰ to one or more of the following antibiotics: penicillin, tetracycline, erythromycin, clindamycin, chloramphenicol, rifampin, or trimethoprim-sulfamethoxazole. CI denotes confidence interval, and HIV human immunodeficiency virus.

Data from the Centers for Disease Control and Prevention²¹ suggest that antibiotic-resistant invasive pneumococcal disease has been decreasing among children since the introduction of conjugate vaccine. Our randomized study lends support to the existence of a causal relation between vaccination and a reduction in antibiotic-resistant invasive pneumococcal disease. Previous studies have shown a reduction in the carriage of antibiotic-resistant strains^{13,22} among vaccinated children. Reports that the incidence of invasive pneumococcal disease due to serotypes usually confined to disease in children is increasing among adults²³ and that adults who live with children attending day care are at increased risk for invasive pneumococcal disease²⁴ support the idea that vaccination of children may prevent transmission to adults.

Our finding of a transient increase in the incidence of respiratory syncytial virus pneumonia one to eight days after vaccination may represent increased susceptibility to pneumococcal pneumonia as a coinfection in children who were already colonized with pneumococci and infected with the respiratory virus. The mechanism of enhanced susceptibility may be the depletion of pneumococcal capsular-antibody-specific B cells by the vaccine before opsonophagocytic antibodies can develop.

The overall incidence of seizures in the two groups was similar, with an apparent increase in generalized seizures in the vaccinated group and a decrease in "unspecified seizures," which included

generalized seizures before admission that were not witnessed by a physician, as well as witnessed focal seizures. There is no evidence from post-marketing studies of the 7-valent vaccine to suggest that there are late increases in the incidence of seizures among vaccine recipients.

An association between vaccination and a single episode of asthma was found in some centers where children received *H. influenzae* type b conjugate vaccine, but not in others.²⁵ We did find an increase in asthma among vaccine recipients, which has not been reported to date in previous studies of the 7-valent formulation in the United States.^{5,15} An increase in asthma may be expected, given the hygiene hypothesis of decreased childhood infections.²⁶ The increased incidence of asthma among vaccinated children in our study (2.96 cases per 1000 children, vs. 1.66 per 1000 among controls) should be seen in the context of a reduction in the risk of radiologically confirmed pneumonia among vaccinated children (17.9 cases per 1000, vs. 21.5 per 1000 among controls). These data suggest that further surveillance is needed to define the risk of asthma in recipients of this vaccine. The safety analysis involved more than 1000 comparisons. Significant differences in the safety analysis at the 5 percent level are hypothesis-generating but may be due to chance.

The 9-valent pneumococcal conjugate vaccine is currently under development for licensure in both developed and developing countries but has not yet

been licensed for use. Our study provides evidence to support the wider development and use of this vaccine to prevent invasive pneumococcal disease, reduce antibiotic resistance among pneumococcal strains, and diminish the incidence of pneumonia in children.

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APPENDIX

The Vaccine Trialists Group includes the following: *International Advisory Board* — N. Pierce (chair), C. Broome, Centers for Disease Control and Prevention, Atlanta; N.E. Khomo, Department of Health, Germiston, Gauteng, South Africa; K. Mulholland, University of Melbourne, Australia; and B. Blackwelder, National Institute of Allergy and Infectious Diseases, Bethesda, Md.; *Safety Board* — S.A. Karim (chair), University of Natal, South Africa; P. Cooper, University of the Witwatersrand, Johannesburg, South Africa; B. Breiman, International Centre for Diarrheal Disease Research, Dhakar, Bangladesh; and I. Kleinschmidt, South African Medical Research Council, Durban, South Africa; *Investigators* — T. Cherian, Vaccines and Biologicals, and H. Ostensen, Diagnostic Imaging and Laboratory Technology, World Health Organization, Geneva; H. Konradsen, Statens Serum Institut, Copenhagen, Denmark; I. Chang, B. Forrest, J. Hackel, D. Madore, F. Malinoski, and G. Siber, Wyeth, Pearl River, N.Y.; H. Crewe-Brown, M. Khoosal, H. Koornhof, G. Mistry, and A. Musan-Craayenstein, University of the Witwatersrand, Johannesburg, South Africa; and S. Alekar, C. Cutland, V. Davis, L. DeGouveia, B.C. Dhladla, H. Gani, K. Ismail, A. Madhi, L. Maseko, L. Nzutha, C. O'Reilly, R. Peruman, K. Petersen, D. Pillay, V. Quan, P. Ramekgoa, N. Ramasamy, K. Shantilal, A. Singh, A. Wasas, and N. Zulu, Respiratory and Meningeal Pathogens Research Unit, Johannesburg, South Africa.

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