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A Cluster-Randomized Effectiveness Trial of Vi Typhoid Vaccine in India

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ABSTRACT

BACKGROUND

Typhoid fever remains an important cause of illness and death in the developing world. Uncertainties about the protective effect of Vi polysaccharide vaccine in children under the age of 5 years and about the vaccine's effect under programmatic conditions have inhibited its use in developing countries.

METHODS

We conducted a phase 4 effectiveness trial in which slum-dwelling residents of Kolkata, India, who were 2 years of age or older were randomly assigned to receive a single dose of either Vi vaccine or inactivated hepatitis A vaccine, according to geographic clusters, with 40 clusters in each study group. The subjects were then followed for 2 years.

RESULTS

A total of 37,673 subjects received a dose of a study vaccine. The mean rate of vaccine coverage was 61% for the Vi vaccine clusters and 60% for the hepatitis A vaccine clusters. Typhoid fever was diagnosed in 96 subjects in the hepatitis A vaccine group, as compared with 34 in the Vi vaccine group, with no subject having more than one episode. The level of protective effectiveness for the Vi vaccine was 61% (95% confidence interval [CI], 41 to 75; P<0.001 for the comparison with the hepatitis A vaccine group). Children who were vaccinated between the ages of 2 and 5 years had a level of protection of 80% (95% CI, 53 to 91). Among unvaccinated members of the Vi vaccine clusters, the level of protection was 44% (95% CI, 2 to 69). The overall level of protection among all residents of Vi vaccine clusters was 57% (95% CI, 37 to 71). No serious adverse events that were attributed to either vaccine were observed during the month after vaccination.

CONCLUSIONS

The Vi vaccine was effective in young children and protected unvaccinated neighbors of Vi vaccinees. The potential for combined direct and indirect protection by Vi vaccine should be considered in future deliberations about introducing this vaccine in areas where typhoid fever is endemic. (ClinicalTrials.gov number, NCT00125008.)

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Typhoid fever, caused by *Salmonella enterica* serotype Typhi (*S.* Typhi), results in an estimated 216,000 to 600,000 deaths annually, almost all in developing countries.[1,2] Among licensed, newer-generation typhoid vaccines, the injectable Vi polysaccharide vaccine has several characteristics that make it attractive for use in developing countries. Given in a single dose, the Vi vaccine is sold at prices as low as 50 cents per dose. Moreover, the Vi vaccine is produced by two international manufacturers and several manufacturers in developing countries, which have licensed it for persons 2 years of age or older.[3-5]

Despite a World Health Organization (WHO) recommendation for its use, the Vi vaccine has been administered only sparsely in public health programs in developing countries.[6] The limited use of the Vi vaccine in these settings has been partly due to doubts about the programmatic feasibility and effect of Vi vaccination in public health programs, as well as questions about whether the vaccine is protective in children between the ages of 2 and 5 years and whether it can confer herd protection.[7,8] To address these uncertainties, we conducted a large-scale, cluster-randomized effectiveness trial in Kolkata, India, where typhoid fever is endemic.

Methods

Study Site

We conducted the trial in a contiguous area encompassing most of Ward 29 and all of Ward 30 in Eastern Kolkata, a legally registered urban slum with a population of about 60,000 residents. Before vaccination, a census of the population enumerated all households and persons in the study area and characterized the socioeconomic status, water source, and hygiene status of each household. Each household and person in the census were assigned a unique study identification number. The census, together with geographic mapping, was used to define 80 contiguous geographic clusters that served as the units of randomization (Fig. 1). The mean (±SD) total population of each cluster was 777±136 persons for the group receiving the Vi polysaccharide vaccine (Vi vaccine group) and 792±142 for the group receiving the hepatitis A vaccine (hepatitis A vaccine group).

Primary and Secondary Outcomes

The primary outcome was the level of total vaccine protection, which was calculated by comparing rates of typhoid fever in the Vi vaccine group with those in the hepatitis A vaccine group. The secondary outcomes were the level of indirect vaccine protection, which was calculated by comparing the rates of typhoid fever among nonvaccinees in the Vi vaccine clusters with those in the hepatitis A vaccine clusters, and the level of overall vaccine protection, which was calculated by comparing the rates of typhoid fever among all residents of the Vi vaccine clusters with those among all residents in the hepatitis A vaccine clusters (for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org).[9]

Vaccines

Each dose of Vi vaccine (Typherix, GlaxoSmithKline) contained 25 μg of Vi polysaccharide. The control vaccine, inactivated hepatitis A vaccine (Havrix, GlaxoSmithKline), contained 720 IU of inactivated hepatitis A virus for children between the ages of 2 and 18 years and 1440 IU for adults. Each vaccine was administered by intramuscular injection. The Vi vaccine was provided in single-dose syringes, and the hepatitis A vaccine was provided in single-dose vials. The vaccines were labeled only by a code letter. Two codes, one for each vaccine, were used for vaccines given to children between the ages of 2 and 18 years, and two different codes were used for vaccines given to adults.

Randomization of Clusters

The clusters were stratified according to ward and the number of residents who were 18 years of age or younger (<200 vs. ≥200 persons) and the number of residents who were older than 18 years (<500 vs. ≥500 persons), resulting in eight strata. For each stratum, a statistician who was unaware of the study-group assignments used a table of random numbers to assign half the 80 clusters to each vaccine.

Administration of Vaccines

The vaccines were administered between November 27 and December 31, 2004. All cluster residents were eligible to receive a study vaccine if they were 24 months of age or older, had no reported

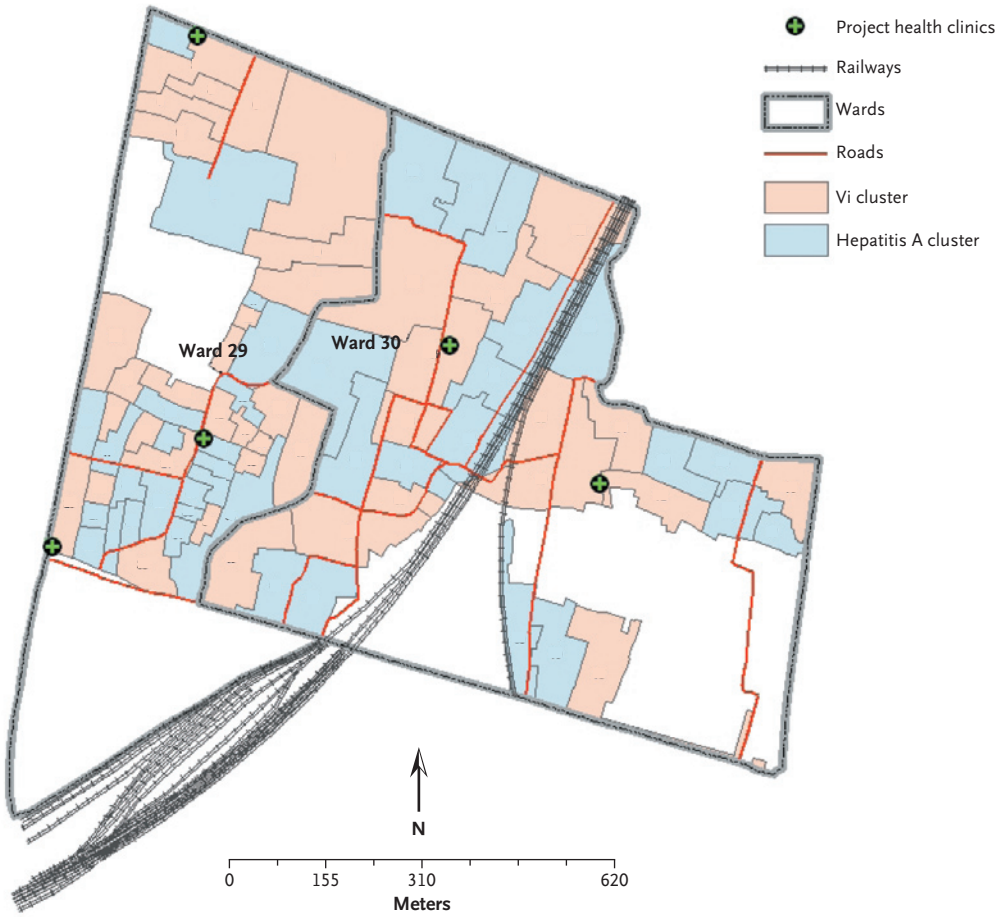

Figure 1. Geographic Clusters in Kolkata, India.

fever or had an axillary temperature of no more than 37.5°C at the time of administration, and were not pregnant or lactating. All subjects or their guardians provided written informed consent. Vaccination was performed by 20 teams in special vaccination centers set up for each cluster. Each team was assigned to administer only one of the vaccines during the entire study period. After the close of the trial, age-eligible residents of clusters were offered the vaccine that was provided to the other study group.

SURVEILLANCE FOR ADVERSE EVENTS

All subjects were observed for 30 minutes after vaccination. A subgroup of 320 subjects — 2 subjects assigned to each code letter for each cluster — was randomly selected for home follow-up for 3 consecutive days after vaccination to detect common, short-latency adverse events. Of these subjects, 202 (63%) consented to participate in the follow-up. Passive surveillance for adverse events was implemented for 1 month after vaccination at all study clinics and hospitals. Serious adverse events[10] were evaluated by a local clinical monitor and promptly transmitted to the data and safety monitoring board, the study secretariat at the International Vaccine Institute, and the vaccine manufacturer.

SURVEILLANCE FOR ENTERIC FEVER

Follow-up extended through December 30, 2006. Five study clinics (three in Ward 29 and two in Ward 30) were established to conduct surveillance for febrile illnesses and refer patients with severe disease for hospital care. Private medical providers in the two study wards were encour-

aged to refer febrile patients to these study clinics. In addition, emergency rooms, outpatient clinics, and inpatient wards of the two hospitals serving the study area monitored patients presenting with febrile illnesses. Subjects from the study area who presented with a history of fever for at least 3 days were examined by a study physician. At that time, data on the subject's history and physical findings were systematically recorded. After oral informed consent was provided, a blood specimen was obtained for culture with the use of Bactec Plus Aerobic/F medium for persons 13 years of age or older and Bactec Peds Plus medium for those under the age of 13 years (Becton Dickinson). Standard biochemical and serologic methods were used to identify *S.* Typhi and *Salmonella enterica* serotype Paratyphi (*S.* Paratyphi).[11] Susceptibility to antibiotic drugs was tested with the use of the Kirby–Bauer disk-diffusion method on Mueller–Hinton agar with standard antibiotic disks (Becton Dickinson).

Patients were identified in the surveillance sites with the assistance of study-census identification cards that were distributed to all subjects, as well as a computerized census located at each site. If a blood culture yielded either *S.* Typhi or *S.* Paratyphi, a study team was dispatched to the home of the patient within 7 days to verify that he or she had indeed visited the treatment site for care on the date noted during surveillance. WHO guidelines were followed for the antibiotic treatment of enteric fever, taking into account antibiotic-susceptibility results.[12]

SURVEILLANCE FOR DEMOGRAPHIC EVENTS

After vaccination, two censuses were carried out to identify subjects who had left the study area, those who had moved to another cluster in the study area, and those who had died. The first census was carried out in October and November 2005, and the second in January and February 2007. In addition, deaths were documented during monthly visits by community health workers to each household. To assign a cause of death, a study physician interviewed family members within 3 months after the death to obtain historical information on the events leading to death and reviewed the clinical records.

SEROLOGIC SURVEILLANCE

To assess serum IgG anti-Vi antibody responses to vaccination, study physicians selected two subjects who had been assigned to each of the two study codes for each cluster to undergo blood testing. Because of the age-related stratification of the codes, two subjects between the ages of 2 and 18 years and two older subjects were targeted for testing in each cluster. During testing, a 5-ml sample of blood was obtained by venipuncture from subjects after they had provided written informed consent. Among the 320 persons who were preselected for blood testing, samples were obtained just before vaccination from 170 subjects, 6 weeks after vaccination from 159 subjects, and 2 years after vaccination from 130 subjects. After undergoing separation, frozen serum samples were coded and sent to GlaxoSmithKline Vaccines for testing for IgG anti-Vi antibody titers with the use of an enzyme-linked immunosorbent assay (ELISA).[13] As in studies performed for licensure of the Vi vaccine, an antibody level of 150 ELISA units (EU) per milliliter or more was considered to be a seropositive result.

DEFINITIONS

Several definitions were formulated a priori. A household consisted of all persons residing together and sharing the same cooking pot. Baseline was defined as the date of vaccination or, for nonvaccinees, the date at which 50% of vaccinees in the cluster had been vaccinated. If a patient reported more than once to a treatment center with fever and if the onset of fever for one visit was within 14 days after the date of presentation for the previous visit, the visits were grouped into a single febrile episode. An episode of typhoid fever, the primary end point for the trial, was a febrile episode in which *S.* Typhi was isolated from at least one blood culture. An episode of paratyphoid fever, a secondary end point for the trial, was a febrile episode in which *S.* Paratyphi was isolated from at least one blood culture but *S.* Typhi was not isolated. The onset of an episode of typhoid or paratyphoid fever was considered to be the date of onset of fever that was reported during the first treatment visit for the episode.

STUDY OVERSIGHT

The institutional review boards at the International Vaccine Institute, the National Institute of Cholera and Enteric Diseases, and the Indian Council of Medical Research approved the protocol and monitored the progress of the study. All authors vouch for the completeness and accuracy of the

data presented. There were no agreements regarding confidentiality of the data among donors, the study sponsor (the International Vaccine Institute), the vaccine manufacturer, and the investigators. The vaccine manufacturer conducted serologic assays in a blinded manner but played no role in the design of the study, in data analysis, or in the preparation of the manuscript.

STATISTICAL ANALYSIS

We assumed that the risk of typhoid in the control group would be approximately 2 cases per 1000 subjects and that the coefficient of variation among the clusters would be 0.5. We calculated that two groups, each with approximately 20,000 subjects and 40 clusters, would be sufficient to detect total vaccine protection of at least 60% with a power of 80% at a two-sided significance level of 0.05.[14]

For the comparison of individual-level variables, we used generalized estimating equations to adjust for membership in the randomized clusters, with the logit-link function for dichotomous variables and the identity-link function for continuous variables.[15] We compared cluster-level variables using Student's t-test for continuous variables and the chi-square test for categorical variables. For the analyses of vaccine protection, we used Cox proportional-hazards regression models.[16-18] Hazard ratios were estimated by exponentiation of the coefficient for the vaccine variable in these models, and the protective effectiveness of vaccination was estimated as ([1 − hazard ratio] × 100%). Analyses that were adjusted only for the design effect of cluster randomization were termed simple analyses. Those that were additionally adjusted for other baseline covariates were termed adjusted analyses. All P values and 95% confidence intervals were calculated with two-tailed tests (see the Supplementary Appendix for details).

RESULTS

STUDY SUBJECTS

At baseline, there were 62,756 residents in the 80 trial clusters, of whom 61,280 were eligible, according to age criteria for participation in the trial (Fig. 1 in the Supplementary Appendix). A total of 37,673 subjects were vaccinated: 18,869 in the Vi vaccine group and 18,804 in the hepatitis A vaccine group. During 2 years of follow-up, 2549 vaccinees (7%) died or migrated out of the study area, and 44 vaccinees (0.1%) migrated to another cluster within the study area.

All vaccinees received the correct cluster-assigned vaccine. The two study groups were well balanced at both the individual and cluster levels with respect to a variety of demographic, socioeconomic, water-source, and hygiene characteristics (Table 1). The mean rate of vaccine coverage of clusters that were assigned to the Vi vaccine group (61%) was similar to that for clusters assigned to the hepatitis A vaccine group (60%).

TOTAL PROTECTION

Cases of typhoid fever occurred throughout the follow-up period (Fig. 2 in the Supplementary Appendix). No deaths or severe complications from typhoid were identified. Typhoid fever was diagnosed in 34 subjects in the Vi vaccine group, as compared with 96 subjects in the hepatitis A vaccine group, resulting in a level of protective effectiveness for the Vi vaccine of 61% (95% confidence interval [CI], 41 to 75; P<0.001 in adjusted models) (Table 2). All episodes occurred at least 4 weeks after vaccination.

None of the 130 typhoid isolates had multidrug resistance to first-line antibiotics (chloramphenicol, ampicillin, and trimethoprim–sulfamethoxazole) or resistance to fluoroquinolones; 64 isolates (49%) were resistant to nalidixic acid, with similar proportions of resistant typhoid isolates in the Vi vaccine group (59%) and the hepatitis A vaccine group (46%, P=0.19). All strains were found to express Vi capsular polysaccharide.

None of the a priori subgroup analyses revealed significant differences in vaccine protection according to subgroup. When evaluated according to age at vaccination in adjusted models, the rate of protective effectiveness for the Vi vaccine was 80% (95% CI, 53 to 91) among children who were vaccinated at ages under 5 years, 56% (95% CI, 18 to 77) among children vaccinated between the ages of 5 and 14 years, and 46% (95% CI, −43 to 79) among persons vaccinated at older ages (Table 3).

Paratyphoid fever was diagnosed in 54 subjects in the Vi vaccine group, as compared with 49 subjects in the hepatitis A vaccine group, resulting in a level of protective effectiveness for the Vi vaccine of −10% (95% CI, −65 to 27; P=0.66) in the simple analysis and of −15% (95% CI, −70 to 22; P=0.47) in the adjusted analysis.

Table 1. Baseline Characteristics of the Subjects and Clusters.*

Variable	Vi Vaccine (N=18,869)	Hepatitis A Vaccine (N=18,804)
Subjects		
Age — yr	28.5±18.0	27.9±17.8
Male sex — no. (%)	9,876 (52)	9,920 (53)
Hindu religion — no. (%)	12,335 (65)	10,825 (58)
No. of members in household	7.1±3.9	7.0±3.7
Ability of head of household to read and write — no. (%)	13,980 (74)	13,099 (70)
Monthly household per capita expenditure above the median of 500 rupees — no. (%)†	7,795 (41)	7,636 (41)
Ownership of at least one luxury item in household — no. (%)‡	4,131 (22)	3,918 (21)
Tube-well or faucet source of drinking water in household — no. (%)§	2,711 (14)	1,824 (10)
Flush toilet in household — no. (%)¶	905 (5)	577 (3)
Access to a specific place for waste disposal in household — no. (%)‖	18,547 (98)	18,429 (98)
Household farther from treatment center than median distance — no. (%)**	8,900 (47)	9,935 (53)
Clusters		
Age		
Group — no./cluster		
2–18 yr	256±118	273±115
>18 yr	503±84	500±93
All residents per cluster — yr	29.0±5.0	28.5±4.6
Households — no./cluster	142±27	146±36
Vaccinated subjects — no./cluster	472±103	470±104
Cases of typhoid fever during year before study — no./1000 cluster residents	1.54±1.40	1.38±1.38
Population density — no. of residents/100 m^2/cluster	18.4±17.8	22.2±20.1
Vaccine coverage of persons ≥2 yr of age — %	61±11	60±12

* Plus–minus values are means ±SD. P>0.05 for all comparisons between the two study groups.
† The median of 500 rupees ($12.50 in 2004 U.S. dollars) is for the subjects in the study.
‡ A luxury item was defined as a refrigerator, motorbike, or washing machine.
§ Data regarding the source of water were available for 18,862 subjects in the Vi vaccine group and 18,803 in the hepatitis A vaccine group.
¶ Data regarding flush toilets were available for 18,831 subjects in the Vi vaccine group and 18,737 in the hepatitis A vaccine group.
‖ Data regarding access to a specific place for waste disposal were available for 18,821 subjects in the Vi vaccine group and 18,790 in the hepatitis A vaccine group.
** This category refers to a subject living in a household with a distance to the nearest treatment center (one of the five study clinics or the two hospitals used for surveillance) that was longer than the median distance for the entire study population (147.3 m).

INDIRECT AND OVERALL PROTECTION

In an adjusted model, the Vi vaccine provided significant indirect protection against typhoid fever among unvaccinated residents in Vi vaccine clusters, with a level of protective effectiveness of 44% (95% CI, 2 to 69; P=0.04) (Table 4). In addition, an adjusted model showed a level of overall protection against typhoid of 57% among residents of the Vi vaccine clusters, regardless of whether they had been vaccinated (95% CI, 37 to 71; P<0.001).

SEROLOGIC RESPONSES

At baseline, subjects in the two study groups had similar geometric mean titers of serum IgG anti-Vi antibodies: 118 EU per milliliter in the Vi vaccine group and 111 EU per milliliter in the hepatitis A vaccine group (P=0.64) (Table 5, and the

Table 2. Occurrence of Typhoid Fever at 2 Years and Protective Effectiveness of Vi Vaccine.

Variable	Vi Vaccine (N=18,869)	Hepatitis A Vaccine (N=18,804)	Protective Effectiveness of Vi Vaccine (95% CI)*	
			Simple Analysis	Adjusted Analysis†
			percent	
Subjects with typhoid fever — no.	34	96		
Person-days of follow-up — no.	13,309,337	13,214,761		
Incidence of typhoid fever — no. of cases/100,000 person-days	0.26	0.73	65 (42–79)	61 (41–75)

* P<0.001 for the comparison between the Vi vaccine group and the hepatitis A vaccine group.
† Protective effectiveness was adjusted for the variables used to stratify the clusters for randomization, as well as age, religion, living in a household with a monthly per capita expenditure above the median, and living in a household with a specific place for waste disposal. The model for the adjusted analysis was derived from 128 cases of typhoid fever among 37,164 subjects for whom complete data were available on all variables.

Table 3. Cases of Typhoid Fever at 2 Years, According to Age Group at Baseline, and Protective Effectiveness of Vi Vaccine.*

Age at Baseline	Vi Vaccine	Hepatitis A Vaccine	Protective Effectiveness of Vi Vaccine (95% CI)	
			Simple Analysis	Adjusted Analysis
	no./total no. (no./100,000 person-days)		*percent*	
2.0 to 4.9 yr	5/1097 (0.64)	27/1095 (3.54)	82 (58 to 92)	80 (53 to 91)†
5.0 to 14.9 yr	21/4282 (0.69)	54/4584 (1.67)	59 (18 to 79)	56 (18 to 77)‡
≥15.0 yr	8/13,490 (0.08)	15/13,125 (0.16)	48 (–44 to 81)	46 (–43 to 79)§

* Protective effectiveness was adjusted for the variables used to stratify the clusters for randomization, as well as religion and living in a household with a monthly per capita expenditure above the median (for subjects between the ages of 2.0 and 4.9 years) and religion and living in a household with a specific place for waste disposal (for subjects between the ages of 5.0 and 14.9 years). For subjects who were 15.0 years of age or older, no additional covariates were selected by means of the backward-selection procedure described in the text.
† The model for subjects between the ages of 2.0 and 4.9 years was derived from 32 cases of typhoid fever among 2174 subjects for whom data on all variables were complete.
‡ The model for subjects between the ages of 5.0 and 14.9 years was derived from 75 cases of typhoid fever among 8848 subjects for whom data on all variables were complete.
§ The model for subjects 15.0 years of age or older was derived from 23 cases of typhoid fever among 26,615 subjects for whom data on all variables were complete.

Supplementary Appendix). Geometric mean titers in the hepatitis A vaccine group remained stable on subsequent blood testing at 6 weeks and 2 years, whereas in the Vi vaccine group, the geometric mean titer was 2505 EU per milliliter 6 weeks after vaccination and 843 EU per milliliter 2 years after vaccination (P<0.001 for the between-group comparisons at both time points). Meaningful analysis of samples from young children was precluded by the small number of subjects under the age of 5 years who underwent blood testing after vaccination: five subjects at 6 weeks of follow-up and three subjects at 2 years of follow-up. The proportions of subjects in the Vi vaccine group who had post-vaccination antibody titers of 150 EU per milliliter or more were similar for subjects between the ages of 5 and 14 years and for those who were 15 years of age or older (100% and 92%, respectively, at 6 weeks, and 91% and 88%, respectively, at 2 years).

ADVERSE EVENTS

During the first 30 minutes after injection, three events were noted in the Vi vaccine group and one in the hepatitis A vaccine group. All were syncopal episodes or vertigo, and none were judged to be serious adverse events. A total of 92 subjects in the Vi vaccine group and 110 subjects in the hepatitis A vaccine group were followed actively for 3 days after vaccination. All but one of the

Table 4. Cases of Typhoid Fever in Analyses of Indirect and Overall Protection at 2 Years and Protective Effectiveness of Vi Vaccine.

Type of Protection	Vi Vaccine	Hepatitis A Vaccine	Protective Effectiveness of Vi Vaccine (95% CI)	
			Simple Analysis	Adjusted Analysis*
			percent	
Indirect protection				
Subjects with typhoid fever — no./total no.	16/12,206	31/12,877		
Incidence of typhoid fever — no. of cases/100,000 person-days	0.19	0.35	45 (1–70)†	44 (2–69)†‡
Overall protection				
Subjects with typhoid fever — no./total no.	50/31,075	127/31,681		
Incidence of typhoid fever — no. of cases/100,000 person-days	0.23	0.58	60 (39–74)§	57 (37–71)§¶

* Protective effectiveness was adjusted for the variables used to stratify the clusters for randomization, as well as age and living in a household with a longer distance to the nearest treatment center (in the analysis of indirect protection) and age, religion, living in a household with a monthly per capita expenditure above the median, and living in a household with a longer distance to the nearest treatment center than the median (in the analysis of overall protection).
† P=0.04.
‡ This model was derived from 47 cases of typhoid in 25,083 subjects for whom data on all variables were complete.
§ P<0.001.
¶ This model was derived from 177 cases of typhoid among 61,996 subjects for whom data on all variables were complete.

subjects were examined on each of the follow-up days. Events that were significantly more common in the hepatitis A vaccine group than in the Vi vaccine group included local erythema (in 22% of subjects vs. 4%, P<0.001), pain at the injection site (55% vs. 18%, P<0.001), an axillary temperature of at least 37.5°C (7% vs. 1%, P=0.04), and fatigue (18% vs. 4%, P=0.04). No signs or symptoms were significantly more common in the Vi vaccine group.

During the first 30 days after vaccination, there were 18 deaths (10 in the Vi vaccine group and 8 in the hepatitis A vaccine group) and 1 nonfatal serious adverse event (subarachnoid hemorrhage in the hepatitis A vaccine group). Eleven deaths were due to cardiovascular causes and one each to diabetes, burns, malaria, poisoning, tuberculosis, and upper gastrointestinal bleeding; the cause of one death was unknown. None of the events were judged to be causally related to vaccination.

DISCUSSION

The Vi polysaccharide vaccine conferred 61% total protection against typhoid fever in a general population in Kolkata, India, and was associated with minimal side effects, findings that are consistent with the results of other studies.[19-21] Children under the age of 5 years had a notably high level of protection (80%). This protection for children under the age of 5 years is important because this age group has been shown to be at high risk for typhoid fever in many areas where the disease is endemic.[22-24] Furthermore, our data show that Vi vaccination confers significant herd protection to nonvaccinees. Although it has been suggested that the use of Vi vaccine might set the stage for an increase in the rate of paratyphoid fever, our data provide little support for this hypothesis.[25] Among breakthrough cases of typhoid in the Vi vaccine group, there was no evidence of either increased antibiotic resistance or selection of Vi-negative strains.

Our study had some important limitations, including the fact that the two vaccines were not packaged in an identical fashion. We attempted to minimize the effect of this difference by not identifying the vaccines other than by code, by not informing local research staff members about how the two vaccines were packaged, and by assigning each vaccination team to only one vaccine. Moreover, the Vi vaccine conferred no protection against paratyphoid fever, making it unlikely that

bias affected the findings of the trial. Because of logistical considerations, it was necessary to create adjacent geographic clusters between which there may have been substantial transmission of typhoid. This compromise probably diluted the herd effects of vaccination that were measured in the trial and should make our estimates of all three measures of vaccine protection conservative. Finally, the trial was not powered to detect differences between subgroups in rates of protective effectiveness. Thus, although the difference in the level of protection between young children and older persons was not significant, it is possible that young children were better protected.

Baseline titers of serum IgG anti-Vi antibodies were similar in the two study groups, which suggests that the indirect protection observed in the Vi vaccine clusters could not have been attributed to imbalances in baseline anti-Vi antibody titers. Although the small number of subjects precluded an assessment of serologic IgG anti-Vi antibody responses to receipt of the Vi vaccine in children under the age of 5 years, short-term and long-term seropositive response rates in older subjects were similar to those reported in earlier studies of the same Vi vaccine.[13,26,27]

Logistically and programmatically, it is possible to deliver the low-cost Vi vaccine in diverse settings in developing countries.[28-32] The fact that the adjusted level of overall protection (57%) was similar to the adjusted level of total protection among vaccinees (61%), despite vaccine coverage of only about 60% of the subjects, underscores the importance of herd protection by the Vi vaccine and the need for consideration of herd protective effects in future deliberations about the use of this vaccine in developing countries.

Table 5. Serum IgG Anti-Vi Antibody Titers at Baseline and 6 Weeks and 2 Years after Vaccination.*

Measures	Vi Vaccine	Hepatitis A Vaccine
At baseline		
Geometric mean titer — EU/ml	118.2±2.2	111.4±2.4
Seropositivity — no./total no. (%)†	22/79 (28)	21/91 (23)
At 6 wk		
Geometric mean titer — EU/ml	2505.3±4.2‡	107.4±2.5
Seropositivity — no./total no. (%)†	74/78 (95)‡	14/81 (17)
At 2 yr		
Geometric mean titer — EU/ml	842.6±4.3‡	105.8±2.3
Seropositivity — no./total no. (%)†	55/63 (87)‡	13/67 (19)

* Plus–minus values are geometric mean titers ± the antilogarithm of the standard deviation of logarithm titers.
† Seropositivity was defined as a titer of 150 ELISA units (EU) per milliliter or more.
‡ P<0.001 for the comparison between the Vi vaccine group and the hepatitis A vaccine group, after adjustment for the cluster randomization.

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