ORIGINAL ARTICLE

Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh

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ABSTRACT

BACKGROUND

A single-dose regimen of the current killed oral cholera vaccines that have been prequalified by the World Health Organization would make them more attractive for use against endemic and epidemic cholera. We conducted an efficacy trial of a single dose of the killed oral cholera vaccine Shanchol, which is currently given in a two-dose schedule, in an urban area in which cholera is highly endemic.

METHODS

Nonpregnant residents of Dhaka, Bangladesh, who were 1 year of age or older were randomly assigned to receive a single dose of oral cholera vaccine or oral placebo. The primary outcome was vaccine protective efficacy against culture-confirmed cholera occurring 7 to 180 days after dosing. Prespecified secondary outcomes included protective efficacy against severely dehydrating culture-confirmed cholera during the same interval, against cholera and severe cholera occurring 7 to 90 versus 91 to 180 days after dosing, and against cholera and severe cholera according to age at baseline.

RESULTS

A total of 101 episodes of cholera, 37 associated with severe dehydration, were detected among the 204,700 persons who received one dose of vaccine or placebo. The vaccine protective efficacy was 40% (95% confidence interval [CI], 11 to 60%; 0.37 cases per 1000 vaccine recipients vs. 0.62 cases per 1000 placebo recipients) against all cholera episodes, 63% (95% CI, 24 to 82%; 0.10 vs. 0.26 cases per 1000 recipients) against severely dehydrating cholera episodes, and 63% (95% CI, −39 to 90%), 56% (95% CI, 16 to 77%), and 16% (95% CI, −49% to 53%) against all cholera episodes among persons vaccinated at the age of 5 to 14 years, 15 or more years, and 1 to 4 years, respectively, although the differences according to age were not significant (P=0.25). Adverse events occurred at similar frequencies in the two groups.

CONCLUSIONS

A single dose of the oral cholera vaccine was efficacious in older children (≥5 years of age) and in adults in a setting with a high level of cholera endemicity. (Funded by the Bill and Melinda Gates Foundation and others; ClinicalTrials.gov number, NCT02027207.)

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CHOLERA REMAINS A SERIOUS GLOBAL health problem despite advances in the understanding of its pathogenesis and treatment[1,2] and despite the placement of improved water quality and sanitation at the forefront of global development priorities.[3] Killed oral vaccines against cholera have been under active development since the 1970s. In 2009, a public–private partnership in India developed and licensed a new killed whole-cell-only oral cholera vaccine (Shanchol, Shantha Biotechnics), which was modified from an earlier oral cholera vaccine produced in Vietnam and which is currently priced affordably for the public sector, at $1.85 per dose. In a trial conducted in Kolkata, India, the currently recommended two-dose regimen of this vaccine was found to confer 65% cumulative protection at 5 years of follow-up.[4] More recently, the same regimen was found to confer 53% protection over 2 years of follow-up in Dhaka, Bangladesh.[5]

In 2013, the World Health Organization (WHO) created a global stockpile of this vaccine for use in cholera epidemics. It has been argued that this vaccine would be more useful if it could be administered as a single-dose regimen, which would be easier to administer during cholera epidemics occurring in disrupted health systems after natural disasters. Because substantial immunologic responses are observed after the first dose of the two-dose regimen of this vaccine,[6,7] we conducted a clinical trial to evaluate a single dose in an urban setting in Bangladesh in which cholera is highly endemic. Here, we report the results of this trial during the initial 6 months after vaccination.

METHODS

STUDY SITE AND PARTICIPANTS

The trial was conducted in the urban slums of Mirpur, Dhaka, where endemic cholera typically peaks during March and April and the highest rates are seen in young children.[8] The study area was at least 300 m from an area where an earlier study of oral cholera vaccine had been conducted (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[5] We conducted a census of residents according to their place of usual residence in this area from November 12, 2012, to January 29, 2013, to enumerate the regular residents and to identify the locations of households with the use of a geographic information system.[9] This census was updated immediately before the initiation of vaccine administration in 2014. A household was defined as a group of people living in the same structure and recognizing a common head. The census included households with one or more features that putatively placed them at higher risk for cholera, including overcrowding (defined as three or more adults per room), poor sanitation and drainage (defined as not having a flush latrine or water-sealed latrine or having a pit latrine with no direct connection to a sewer line or septic tank), or having drinking water sources, kitchens, or toilets shared with other households. Individual-level and household-level demographic and socioeconomic information was collected from an adult inhabitant of each household after oral informed consent had been obtained. A household identification (ID) card was given to each potential study participant. Births, deaths, and migrations in the population were subsequently monitored at 6-month intervals.

ETHICS, REGISTRATION, AND STUDY OVERSIGHT

The research and the ethical review committees of the icddr,b (formerly known as the International Centre for Diarrhoeal Disease Research, Bangladesh) and the institutional review board of the International Vaccine Institute, as well as a data and safety monitoring board, approved the protocol and monitored the progress of the study. Informed consent was obtained from all participants (or from parents or guardians of participants younger than 18 years of age); assent was also obtained from participants who were 11 to 17 years of age. Consent and assent were obtained either by signature or, for participants who were not literate, by thumbprint. A witness also signed each informed-consent form. The study was registered with ClinicalTrials.gov in 2013, shortly after approval was obtained from the institutional review board in 2012 but before vaccination in 2014. All authors vouch for the completeness and accuracy of the data and analyses presented.

INTERVENTIONS

The vaccine (Shanchol), which was purchased from the manufacturer for the study, and the placebo under study were presented in single-dose vials that were identical in appearance,

each containing 1.5 ml of liquid agent. Each dose of vaccine contained approximately 1.5×10^{11} inactivated *Vibrio cholerae* O1 bacteria and 5×10^{10} inactivated *V. cholerae* O139 bacteria, as described previously.[10] Placebo vials contained 1.5 ml of identical-appearing liquid that contained only the inert constituents starch and xanthan gum. The study agents were administered between January 10 and February 4, 2014. To be eligible for participation in the trial, participants or their guardians had to provide written informed consent, and participants had to be at least 12 months of age, could not be pregnant (ascertained by self-report), could have no severe illness (defined as being too ill to leave bed), and could not have a history of previous intake of an oral cholera vaccine. At the time of the dosing, completeness of dosing was assessed and recorded by the vaccination team on study forms.

RANDOMIZATION AND BLINDING

We designed the study as an individually randomized trial to measure vaccine efficacy.[11] Each vial was labeled with a unique number, in consecutive numbers, with vaccine and placebo assembled in random order (in blocks of six) within columns of the boxes of vials (see the Supplementary Appendix). Vaccination teams were instructed to administer the vials to each consecutive eligible and consenting participant according to the numerical order of the vials in the box. At the time of dosing, the number of the administered vial was entered into a vaccination registry book.

The identities of the numbered vials were kept by the producer and two staff members of the International Vaccine Institute who were external to the trial. In addition, the on-site principal investigator had sealed envelopes containing the identity of each code number, with the provision that the envelopes should be opened only if necessary for clinical management. During the course of the trial, no envelope was opened.

OUTCOMES

Surveillance for Cholera

Surveillance for treated episodes of diarrhea was initiated on January 10, 2014, at two icddr,b hospitals and at 11 other health facilities serving the study area, constituting all major health facilities serving the study population (Fig. S1 in the Supplementary Appendix). Patients in the study area who had diarrhea were identified with

the use of their household study ID cards or by a computerized search of the census at the treatment center. Patients were examined by trained physicians, and consent for the collection of clinical data and stool was obtained. Fecal specimens were transported in Cary–Blair media to a central laboratory, where specimens were tested for *V. cholerae* according to serogroup, biotype, and serotype with the use of methods described elsewhere.[12-14] During surveillance, we detected 813 treatment-center visits for acute watery diarrhea among the study participants; all these participants consented to a fecal culture. The identity of each patient whose fecal specimen yielded *V. cholerae* O1 or O139 was confirmed by a visit, conducted within 14 days after the isolation of *V. cholerae*, to the household of the person whose name was given at the treatment center.

Age was calculated on the day on which the vaccine or placebo was received. A treatment-center visit for diarrhea was defined as a visit during which the patient reported having had three or more loose or liquid stools in the 24 hours before presentation or having had one, two, or an indeterminate number of loose or liquid stools in the 24 hours before presentation along with some sign of dehydration according to the WHO criteria.[15] Treatment-center visits for diarrhea with onset dates that were 7 or fewer days after the discharge date of the previous visit were concatenated into the same episode of diarrhea, with the onset of diarrhea for the first constituent visit being considered the onset of the episode.

An episode of cholera, the prespecified primary outcome for this trial, was defined as an episode of nonbloody diarrhea, with onset at least 7 days after the day on which the vaccine or placebo was received, in which a fecal culture yielded *V. cholerae* O1 or O139 and in which a postdischarge visit to the patient's home confirmed that the person whose name had been given at the treatment center had indeed sought care for diarrhea on the date of presentation. All other outcomes were considered to be secondary outcomes. Severe cholera, a prespecified secondary outcome, was defined as an episode of culture-confirmed cholera in which severe dehydration, ascertained according to the WHO criteria,[15] was noted during at least one constituent visit of the episode. The full details of study conduct are provided in the protocol, available at NEJM.org.

Surveillance for Adverse Events

Participants were requested to remain at the dosing site for at least 30 minutes after the dose was administered so that immediate adverse effects could be observed and treated. In passive surveillance, we requested participants to visit study physicians at designated sites if they required any kind of medical care within 28 days after dosing. At these visits, physicians systematically entered information on signs, symptoms, clinical diagnoses, and treatment offered. In active surveillance, we visited the homes of 6021 participants, selected from nine vaccination sites, on days 14 and 28 after dosing to obtain histories at 2-week intervals. An adverse event was defined as any untoward medical event with onset on or after the date of dosing, up to 28 days thereafter. A serious adverse event was defined in accordance with WHO definitions.[16] Surveillance for deaths was undertaken during demographic follow-up, and verbal autopsies were performed in the home of the deceased participant with the use of an autopsy questionnaire prepared according to WHO guidelines.[17]

Acute watery diarrhea was defined as an episode of diarrhea with onset 7 or fewer days before presentation for care and for which stools were described as liquid or watery in consistency and without visible blood; invasive diarrhea was defined as an episode of diarrhea in which blood was visible. Other signs, symptoms, and diagnoses were determined and recorded by the physician examining the patient.

STATISTICAL ANALYSIS

The primary analysis of vaccine protection was per protocol and included only first episodes of cholera with onsets of 7 to 180 days after dosing among participants who had completely ingested the assigned agent; for persons who left the study because they migrated out of the area or because they died, the last known recorded day was used. We estimated that with the inclusion of at least 102,219 participants who took one complete dose, the study would have 80% power to show the effectiveness of one dose of vaccine as compared with placebo, assuming that the risk of cholera was 0.56 episodes or higher per 1000 persons, that the vaccine protective efficacy would be 50% or higher, that the lower limit of the one-sided 95% confidence interval

for vaccine protective efficacy would be greater than 10%, and that the loss to follow-up would be 25%, at a one-tailed P value of less than 0.05.

Prespecified individual-level and community-level baseline variables that were judged to be potentially related to the risk of cholera were compared between vaccine recipients and placebo recipients with the use of the chi-square test (or Fisher's exact test) for categorical variables and Student's t-test (or the Mann–Whitney U test for variables not following a normal distribution) for dimensional variables.

In simple analyses, we estimated rate ratios of cholera episodes in vaccine recipients versus placebo recipients, using test-based methods for statistical appraisal of the ratios and calculating vaccine protective efficacy as (1−rate ratio)× 100.[18,19] We also compared the temporal pattern of cholera cases between the vaccine group and the placebo group with the use of Kaplan–Meier survival curves, evaluated with the log-rank test. In multivariable analyses, we fitted Cox regression models of time to event, including as independent variables the vaccination variable and any baseline variables that were judged to differ statistically or substantively between the two groups, and used the coefficient for the vaccination variable to estimate the hazard ratio for cholera and its standard error. To avoid overfitting the models, we used a backward elimination algorithm, set at a P value of less than 0.10, to select covariates associated with time to event.[20]

In prespecified secondary analyses of vaccine protective efficacy, we evaluated rate ratios, survival curves, and multivariable hazard ratios of initial episodes of cholera and severely dehydrating cholera during the periods 7 to 90 days and 91 to 180 days after dosing, as well as according to age at dosing (1 to 4, 5 to 14, or ≥15 years of age), creating a total of 10 prespecified secondary analyses. Vaccine protective efficacy against noncholera acute watery diarrhea was assessed in a post hoc analysis to evaluate the success of randomization in creating similar groups. For these analyses, we used statistical approaches similar to those used in the primary analyses. We assessed the heterogeneity of vaccine protective efficacy in subgroups by analyzing two-way interaction terms between the vaccination variable and subgroup variables in the models, and we assessed the heterogeneity of vaccine protec-

tive efficacy over time by evaluating fulfillment of the proportional hazards assumption for the vaccine variable.

To analyze adverse events, we compared the risk of each type of event among vaccine recipients versus the risk among placebo recipients, with methods appropriate for categorical variables, including all recipients of vaccine or placebo regardless of the amount of the agent swallowed. In these analyses, we counted only the first occurrence of an event in participants. Although one-tailed P values and 95% confi- dence intervals were prespecified for the pri- mary analysis, we cite two-tailed P values and 95% confidence intervals for all analyses to fa- cilitate interpretation of our findings.

RESULTS

STUDY PARTICIPANTS

A total of 204,700 persons (58% of the census population) underwent randomization and were included in the analysis (Fig. 1). No important differences were found in the distribution of
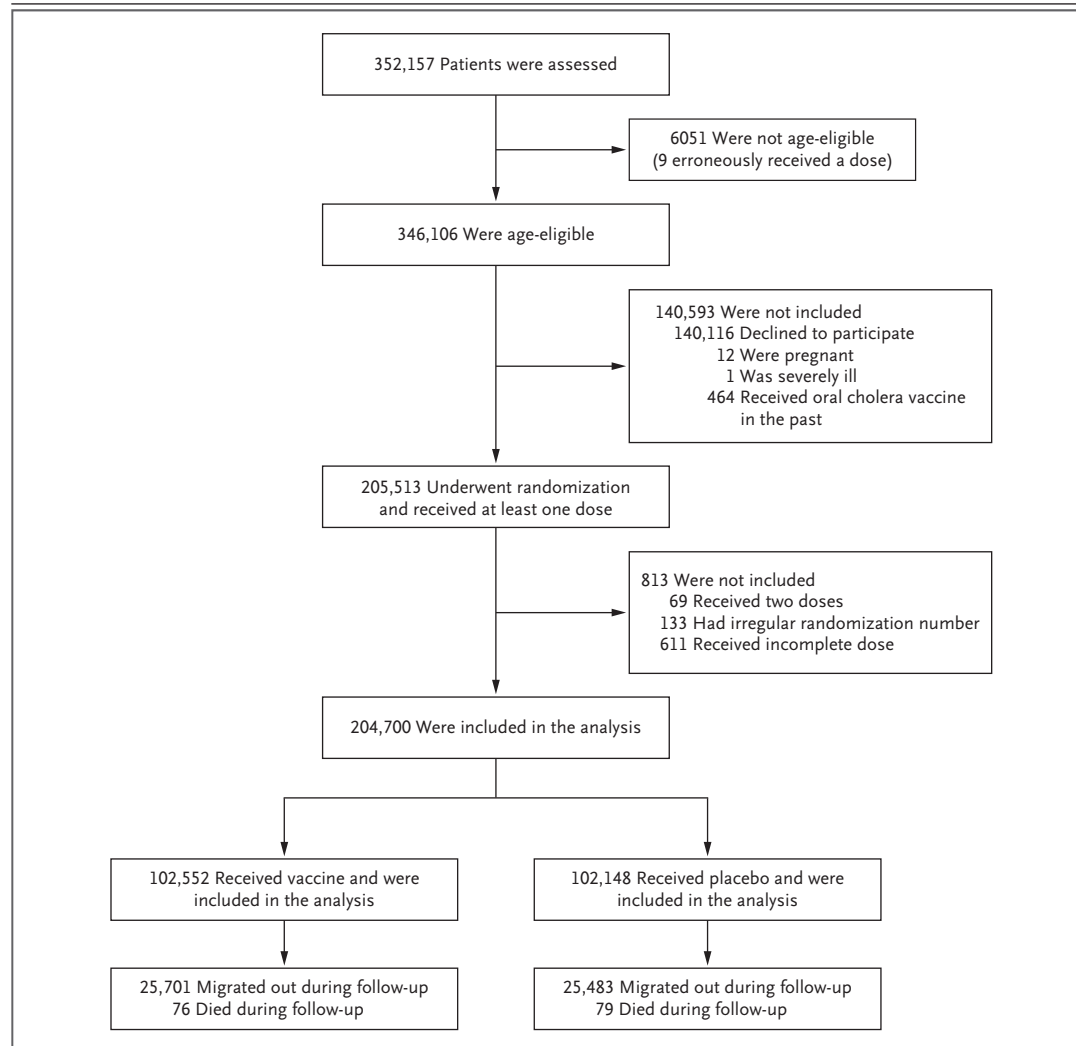
Figure 1. Enrollment and Randomization of the Population for the Analysis of the Primary Outcome.

The 12 pregnant women who were not included in the study presented for dosing at the vaccination center; most pregnant women did not present for dosing, because at the time of the census they were told not to do so. An irreg- ular randomization number refers to a duplicated randomization number on different dosing vials, an absence of a sticker number for a participant who received a dose in the vaccination register, a sticker number that was out of range (i.e., not in the range of 1 through 224,442), or two different sticker numbers on the same vial.

Table 1. Baseline Individual-Level and Community-Level Characteristics of Vaccine Recipients and Placebo Recipients Included in the Per-Protocol Analysis.*

Variable	Vaccine Recipients	Placebo Recipients	P Value†
Individual-level variables			
No. of participants	102,552	102,148	
Age on the day on which vaccine or placebo was received — yr	23.90±16.1	24.14±16.1	<0.001
Male sex — no. (%)	47,322 (46.1)	47,157 (46.2)	0.92
Diarrhea in the previous 6 months — no. (%)	10,640 (10.4)	10,501 (10.3)	0.48
No. of residents in the household	4.75±1.8	4.74±1.8	0.66
Living in own house — no. (%)	18,278 (17.8)	18,192 (17.8)	0.94
Duration living in the study area — mo	44.31±77.7	44.37±77.9	0.85
Living in household with improved water source — no. (%)‡	8,492 (8.3)	8,503 (8.3)	0.72
Living in households using treated water for drinking — no. (%)§	60,952 (59.4)	60,654 (59.4)	0.79
Living in households with sanitary toilets — no. (%)	74,572 (72.7)	73,906 (72.4)	0.06
Living in households in which residents washed hands with soap and water — no. (%)	96,483 (94.1)	96,023 (94.0)	0.45
Monthly per-capita expenditure of household — Bangladeshi taka¶	3037.57±1651.8	3022.16±1549.3	0.03
Distance from household to the nearest health facility — m	964.57±620.8	967.37±623.1	0.31
Distance from household to the previous intervention area — m‖	1474.13±766.0	1467.03±763.5	0.04
Community-level variables**			
Persons living in households using sanitary toilets — %	73.56±22.0	73.45±22.0	0.29
Persons living in households in which residents washed hands with soap and water — %	93.98±7.7	93.98±7.8	0.93
Persons living in households with an improved water source — %	8.26±11.3	8.27±11.3	0.88
Population density per 100 m²	5.56±3.2	5.56±3.2	0.67

* Plus–minus values are means ±SD.
† P values are for two-tailed comparisons between vaccine recipients and placebo recipients.
‡ An improved water source was defined as a tap, well, or hand pump.
§ Water that was boiled, filtered, or chlorinated was considered to have been treated.
¶ One U.S. dollar equals approximately 77.03 Bangladeshi taka.
‖ The previous intervention area is the area in which an oral cholera vaccine campaign was conducted in 2011.
** Community-level variables considered people living within a prespecified 100-m radius around the household, as measured with a geographic information system.

baseline characteristics between vaccine recipients and placebo recipients (Table 1). There were 101 first cholera episodes during the 6 months of follow-up, 37 with severe dehydration; the calendar timing and case load were similar to those observed during past years in this population (Fig. 2 and Table 2). All cases were *V. cholerae* O1 El Tor biotype; one isolate was Inaba serotype, and the remainder were Ogawa serotype. A total of 51,339 persons (21%) migrated out of the study area or died before completion of the 6-month follow-up; the distributions of baseline characteristics among the migrants were similar in the two groups.

VACCINE SAFETY AND PROTECTION

The occurrence of adverse events (severe and nonsevere) was similar in the two groups in both active and passive surveillance (Tables S1 and S2 in the Supplementary Appendix). During the 28-day follow-up period after dosing, no deaths associated with diarrhea occurred; no deaths or other serious adverse events were judged by personnel who were unaware of the

treatment assignments as being causally related to vaccination, nor were serious adverse events significantly more common among vaccine recipients than among placebo recipients.

The adjusted 6-month protective efficacy of the vaccine was 40% for all cholera episodes (95% confidence interval [CI], 11 to 60%; 0.37 cases per 1000 persons who received the vaccine vs. 0.62 cases per 1000 persons who receive placebo; P=0.01) and 63% for severely dehydrating cholera episodes (95% CI, 24 to 82%; 0.10 vs. 0.26 cases per 1000 persons; P=0.007) (Fig. 3 and Table 2, and Fig. S2 in the Supplementary Appendix). The vaccine protective efficacy against noncholera acute watery diarrhea was 9% (95% CI, −6 to 22%; P=0.21). We found low point estimates of vaccine protective efficacy for children vaccinated at younger than 5 years of age, both against all cholera episodes (16%; 95% CI, −49 to 53%) and against severely dehydrating cholera episodes (28%; 95% CI, −221 to 84%). In contrast, the vaccine protective efficacy against all cholera episodes was 63% (95% CI, −39 to 90%) among persons 5 to 14 years of age and 56% (95% CI, 16 to 77%) among persons 15 years of age or older. Somewhat higher values for protective efficacy against severely dehydrating diarrhea were observed in these two age groups, as compared with the youngest age group. However, the differences in vaccine protective efficacy according to age were not significant for either all cholera episodes (P=0.25) or severely dehydrating cholera episodes (P=0.49) (Table 2). There was no significant heterogeneity of vaccine protective efficacy according to duration of follow-up for all episodes of cholera (P=0.82) or for severely dehydrating cholera (P=0.38). During follow-up, there were 76 deaths in the vaccine group and 79 deaths in the placebo group; 2 deaths were associated with diarrhea and occurred in vaccine recipients. Both vaccine recipients who died were adults, one of whom had bloody diarrhea and neither of whom had a fecal culture performed because neither was seen in a study treatment center.

DISCUSSION

Our findings indicate that a single dose of the killed oral cholera vaccine provided 40% protection against all cholera for at least 6 months of
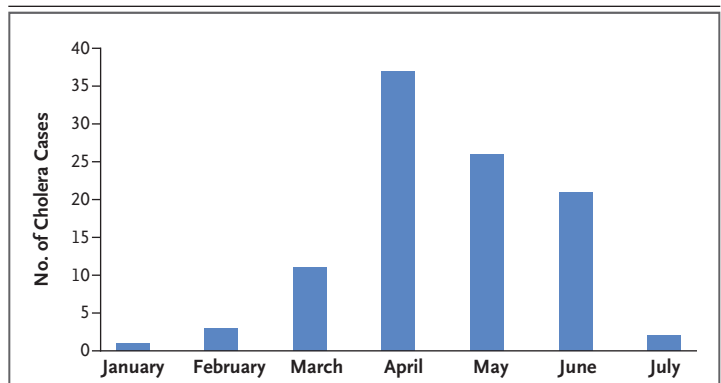
Figure 2. Numbers of Cholera Cases Included in the Analysis According to Calendar Month during the 6 Months of Follow-up in the Per-Protocol Analysis.

follow-up in a population living in an area in which cholera was highly endemic. The protection against cholera with severe dehydration was higher than that against all episodes of cholera, and vaccine protection was evident only in persons who were vaccinated as older children (≥5 years of age) or adults. Vaccine administration was not associated with a significantly higher risk of adverse events than placebo.

Several potential limitations of our trial deserve mention. First, the trial was conducted in Bangladesh, a country in which cholera is endemic and in which the population has some degree of natural immunity to cholera. Whether our findings are generalizable to populations without natural immunity to cholera can be determined only by studies performed in such populations. Second, because our study design involved individual randomization, our analyses did not capture the overall population effect of vaccination through both direct and indirect vaccine protection.[21] Third, our findings address protection only during the 6 months after vaccination.

Although our results do not rule out a small degree of oral cholera vaccine protection of young children, the suggestively lower protective efficacy seen in this age group, which is consistent with results from other trials of killed oral cholera vaccines,[5,10,22] could reflect a lesser degree of preexisting natural anticholera immunity in young children than in older persons at the time of vaccination; this age-related pat-

Table 2. Incidence Rates of All Cholera and Severe Cholera and the Protective Efficacy of the Vaccine.

Group or Subgroup	Vaccine Recipients			Placebo Recipients			Protective Efficacy*			
	No. of Participants	Cholera Episodes/Person-Days of Follow-up	Incidence per 100,000 Person-Days (95% CI)	No. of Participants	Cholera Episodes/Person-Days of Follow-up	Incidence per 100,000 Person-Days (95% CI)	Crude Estimate (95% CI) %	P Value	Adjusted Estimate (95% CI) %	P Value
All cholera										
All participants	102,552	38/15,350,665	0.25 (0.18 to 0.34)	102,148	63/15,300,389	0.41 (0.32 to 0.53)	40 (10 to 60)	0.01	40 (11 to 60)†	0.01
Age group										0.25‡
1.0 to 4.9 yr	10,221	22/1,487,919	1.48 (0.97 to 2.24)	9,765	25/1,426,827	1.75 (1.18 to 2.59)	16 (−50 to 52)		16 (−49 to 53)§	
5.0 to 14.9 yr	25,705	3/3,911,282	0.08 (0.02 to 0.24)	25,253	8/3,844,976	0.21 (0.10 to 0.42)	63 (−39 to 90)		63 (−39 to 90)¶	
≥15.0 yr	66,626	13/9,951,464	0.13 (0.07 to 0.22)	67,130	30/10,028,586	0.30 (0.21 to 0.43)	56 (16 to 77)		56 (16 to 77)‖	
Duration of follow-up										0.82**
≤90 days	102,552	16/8,105,519	0.20 (0.12 to 0.32)	102,148	24/8,075,210	0.30 (0.20 to 0.44)	34 (−25 to 65)		33 (−25 to 65)††	
91 to 180 days	83,931	22/7,245,146	0.30 (0.20 to 0.46)	83,715	39/7,225,179	0.54 (0.39 to 0.74)	44 (5.1 to 67)		44 (6.2 to 67)‡‡	
Severely dehydrating cholera										
All participants	102,552	10/15,352,684	0.06 (0.03 to 0.12)	102,148	27/15,302,545	0.18 (0.12 to 0.26)	63 (24 to 82)	0.007	63 (24 to 82)§§	0.007
Age group										0.49‡
1.0 to 4.9 yr	10,221	3/1,489,308	0.20 (0.06 to 0.62)	9,765	4/1,428,081	0.28 (0.10 to 0.75)	28 (−222 to 84)		28 (−221 to 84)¶	
5.0 to 14.9 yr	25,705	1/3,911,382	0.02 (0.00 to 0.18)	25,253	6/3,845,056	0.16 (0.07 to 0.35)	84 (36 to 98)		84 (−36 to 98)¶	
≥15.0 yr	66,626	6/9,951,994	0.06 (0.03 to 0.13)	67,130	17/10,029,408	0.17 (0.10 to 0.27)	64 (9.8 to 86)		64 (10 to 86)¶¶	
Duration of follow-up										0.38**
≤90 days	102,552	2/8,105,850	0.02 (0.01 to 0.10)	102,148	7/8,075,446	0.09 (0.04 to 0.18)	72 (−37 to 94)		72 (−37 to 94)¶	
91 to 180 days	83,944	8/7,246,834	0.11 (0.05 to 0.22)	83,730	20/7,227,099	0.28 (0.18 to 0.43)	60 (9.4 to 82)		60 (10 to 82)‖	

* Two-tailed 95% confidence intervals and P values are given for the primary analysis and for the secondary and subgroup analyses.
† The efficacy was adjusted for age, monthly per-capita expenditure of the household, and population density within 100 m of the household.
‡ The P value was calculated for the overall interaction between vaccine or placebo recipients and the subgroup variable in the model.
§ The efficacy was adjusted for age, percent of individuals using improved sanitation, and percent of individuals using improved water source.
¶ The number of outcomes was insufficient for the adjusted model.
‖ Efficacy was adjusted for age, percent of individuals using improved sanitation, and population density within 100 m of the household.
** The P value is for rejection of the null hypothesis of constancy of vaccine protection over time.
†† Efficacy was adjusted for individuals who had diarrhea in 6 months before the day of visit in the household, monthly per-capita expenditure of the household, and population density within 100 m of the household.
‡‡ Efficacy was adjusted for age, distance from household to the nearest previous intervention area, and monthly per-capita expenditure of the household.
§§ Efficacy was adjusted for distance from household to the nearest health facility and population density within 100 m of the household.
¶¶ Efficacy was adjusted for population density within 100 m of the household.
‖ Efficacy was adjusted for distance from household to the nearest previous intervention area.
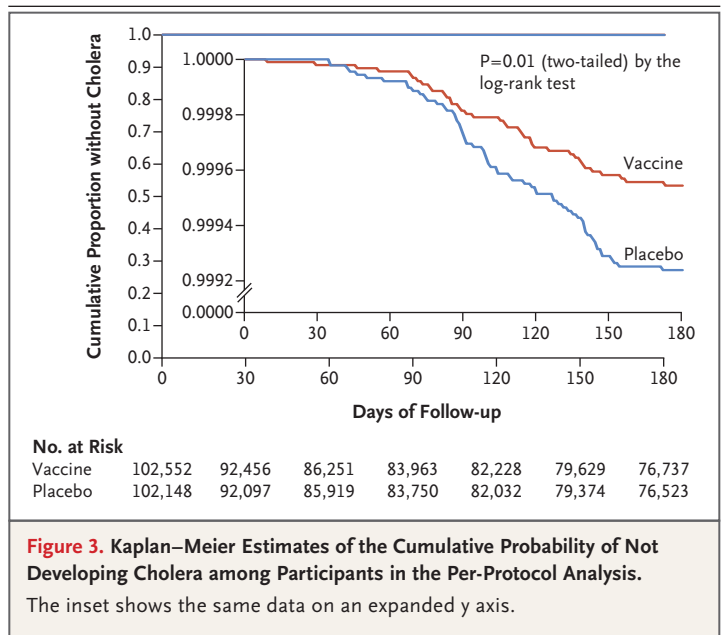
tern may be illustrated by the lower serum vibriocidal antibody titers in younger age groups in population serologic surveys.[23] The fact that serum vibriocidal antibody responses to a first dose of the oral cholera vaccine were observed in both young and older age groups in earlier studies, however, serves to emphasize that these antibodies are not correlates of vaccine efficacy.[6,7,24]

From a pragmatic perspective, our data suggest that a single dose of vaccine will not be adequate for young children who are targeted for vaccination in settings in which cholera is endemic. Whether and how a single dose might still be used in settings in which cholera is endemic is a matter for further study. At the same time, because a single dose of this vaccine seems sufficient at least for short-term protection of older children and adults, infrastructural challenges to completing a two-dose regimen need not be a consideration in the decision to use the vaccine to help contain epidemics in these settings. Similarly, our findings provide further encouragement for the use of a two-dose regimen for the routine control of endemic cholera, because some degree of protection will be provided to older children and adults who do not receive a second dose. Further follow-up in our study will be required to ascertain the duration of protection conferred by a single dose of this vaccine in older children and adults.[25]

Figure 3. Kaplan–Meier Estimates of the Cumulative Probability of Not Developing Cholera among Participants in the Per-Protocol Analysis.

The inset shows the same data on an expanded y axis.

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