MAJOR ARTICLE

Herd Protection by a Bivalent Killed Whole-Cell Oral Cholera Vaccine in the Slums of Kolkata, India

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Background. We evaluated the herd protection conferred by an oral cholera vaccine using 2 approaches: cluster design and geographic information system (GIS) design.

Methods. Residents living in 3933 dwellings (clusters) in Kolkata, India, were cluster-randomized to receive either cholera vaccine or oral placebo. Nonpregnant residents aged ≥1 year were invited to participate in the trial. Only the first episode of cholera detected for a subject between 14 and 1095 days after a second dose was considered. In the cluster design, indirect protection was assessed by comparing the incidence of cholera among nonparticipants in vaccine clusters vs those in placebo clusters. In the GIS analysis, herd protection was assessed by evaluating association between vaccine coverage among the population residing within 250 m of the household and the occurrence of cholera in that population.

Results. Among 107 347 eligible residents, 66 990 received 2 doses of either cholera vaccine or placebo. In the cluster design, the 3-year data showed significant total protection (66% protection, 95% confidence interval [CI], 50%–78%, $P < .01$) but no evidence of indirect protection. With the GIS approach, the risk of cholera among placebo recipients was inversely related to neighborhood-level vaccine coverage, and the trend was highly significant ($P < .01$). This relationship held in multivariable models that also controlled for potentially confounding demographic variables (hazard ratio, 0.94 [95% CI, .90–.98]; $P < .01$).

Conclusions. Indirect protection was evident in analyses using the GIS approach but not the cluster design approach, likely owing to considerable transmission of cholera between clusters, which would vitiate herd protection in the cluster analyses.

Clinical Trials Registration. NCT00289224.

Keywords. cholera; herd effect; bivalent killed oral cholera vaccine; cluster randomized trial.

Herd protection is conferred by a vaccine when it decreases the force of transmission of infection due largely to the presence of vaccinees in a population who prevent transmission to their unimmunized contacts [1]. Herd protection by vaccines has been suggested for a diverse array of vaccines used in public health practice [2–9]. Interest in herd protection has increased because of the price of vaccine, which may not be affordable to many developing countries if only direct efficacy is considered. In some cases, the cost-effectiveness profile of a vaccine may become favorable if herd protective effects are considered [10]. For a cholera vaccine that confers moderate level of protection,

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the demonstration of herd protective effects may establish whether its use will be sufficient for disease control [11]. At the level of the population, the public health effects of a vaccination program may be assessed in terms of (1) indirect (herd) protection—the protection of nonvaccinated individuals in the population; (2) total protection—enhanced protection of vaccinated individuals due to reduced transmission in the community; and (3) overall protection, which is the weighted average of indirect protection of nonvaccinated individuals and total protection of vaccinated individuals [1, 12].

Clinical trials that randomize clusters of individuals can assess herd-protective effects of vaccines designed to prevent infections that are transmitted from person to person [13]. Several factors need to be considered in the design and analysis of cluster-randomized trials of vaccines [14]. For instance, the clusters must be selected in such a way that transmission of the target infection between individuals occurs within clusters and there is little transmission to the clusters from the outside. Such transmission could attenuate measured estimates of vaccine-induced herd effects. Additionally, there has to be little migration between clusters, because these migrations may affect composition of clusters with respect to vaccinees and nonvaccinees, and thereby may affect the measured herd effects.

Recent methodological developments in using a geographic information system (GIS) [15] have also enabled measurement of herd protective effects. The approach takes advantage of the fact that neighborhood-level vaccine coverage may differ among residents living in different places in the study area. If substantial heterogeneity in neighborhood level vaccine coverage is observed, vaccine herd effects can be measured by evaluating correlation of the disease incidence with the neighborhood-level vaccine coverage. However, such an approach is affected by many nonrandom factors affecting vaccine coverage levels of the neighborhoods. The analyses are observational; thus, care should be taken to adjust analyses for factors that might bias the association between levels of vaccine coverage and the disease rates [15].

We assessed the herd protection in the phase III study of the bivalent killed oral cholera vaccine (OCV) in Kolkata, using both the cluster-randomized design and the GIS approaches. The latter approach was used because of the proximate clusters in densely populated slums of Kolkata, making it likely that transmission of cholera occurred between clusters.

METHODS

The Trial

The trial was conducted in 3 wards of Kolkata, India (Figure 1) with a population of approximately 109 000 individuals residing in 3933 dwellings, locally known as premises. Details of the study design and procedures have been described in further detail elsewhere [16, 17]. In brief, a dwelling was defined as a hut (or a group of huts), or a multistory building where several households share water pipes, bathrooms, and latrines as assigned by the Kolkata Municipal Corporation; and a household was defined as a group of individuals residing together who share the same cooking pot. Residents aged ≥1 year who were not pregnant were invited to participate. Eligible residents were cluster-randomized, by dwelling, and preassigned to receive 2-dose regimens of either OCV or placebo. Enrollment and administration of the preassigned agents was performed after acquisition of written informed consent by dosing teams in vaccination centers serving the population. Individuals ≥18 years of age and parents or guardians of all 1- to 17-year-old participants provided written informed consent. Written assent was additionally obtained from children aged 12–17 years.

Selection of Neighborhood Size and Neighborhood-Level Vaccine Coverage

To define an optimal neighborhood for the vaccine coverage, we investigated different scales of neighborhood from a minimum of 0.03 km^2 (100-m radius), 2% of the size of a geographic unit, to a maximum of 0.28 km^2 (300-m radius), 15% of the size of the unit. The underlying assumption for defining an optimal neighborhood was that it should not be too small to get an unstable outcome and should not be too big where local detail is obscured. Hartley's variance ratio (F_{max}) test [18] was used with different sizes of neighborhood, which yielded 250 m as the optimum scale. The neighborhood level vaccine coverage was then calculated for each household as the number of vaccinated individuals (2-dose recipients) divided by the number of persons who were age-eligible for the trial within a 250-m radius of the household.

Definition of Cholera and Dysentery Episodes

A cholera episode was defined as a non–bloody diarrhea episode in which *Vibrio cholerae* O1 was isolated from a stool specimen [19] and a visit was made to the residence of the person to confirm that the person sought care for diarrhea on the date of presentation [16]. To ensure that the indirect protection of the vaccine is specific for cholera, we also assessed the indirect protection against dysentery episodes, which was defined as diarrhea accompanied by visible blood in stool and a fecal culture negative for *V. cholerae* O1. We assessed the risk of target outcomes (cholera or dysentery) by considering only the first episode detected for a subject during the follow-up period, defined as between 14 and 1095 days after a second dose of placebo or vaccine for the 2-dose recipients. For 1-dose or no-dose recipients, we considered the episode detected between 14 and 1095 days after the median date of the second

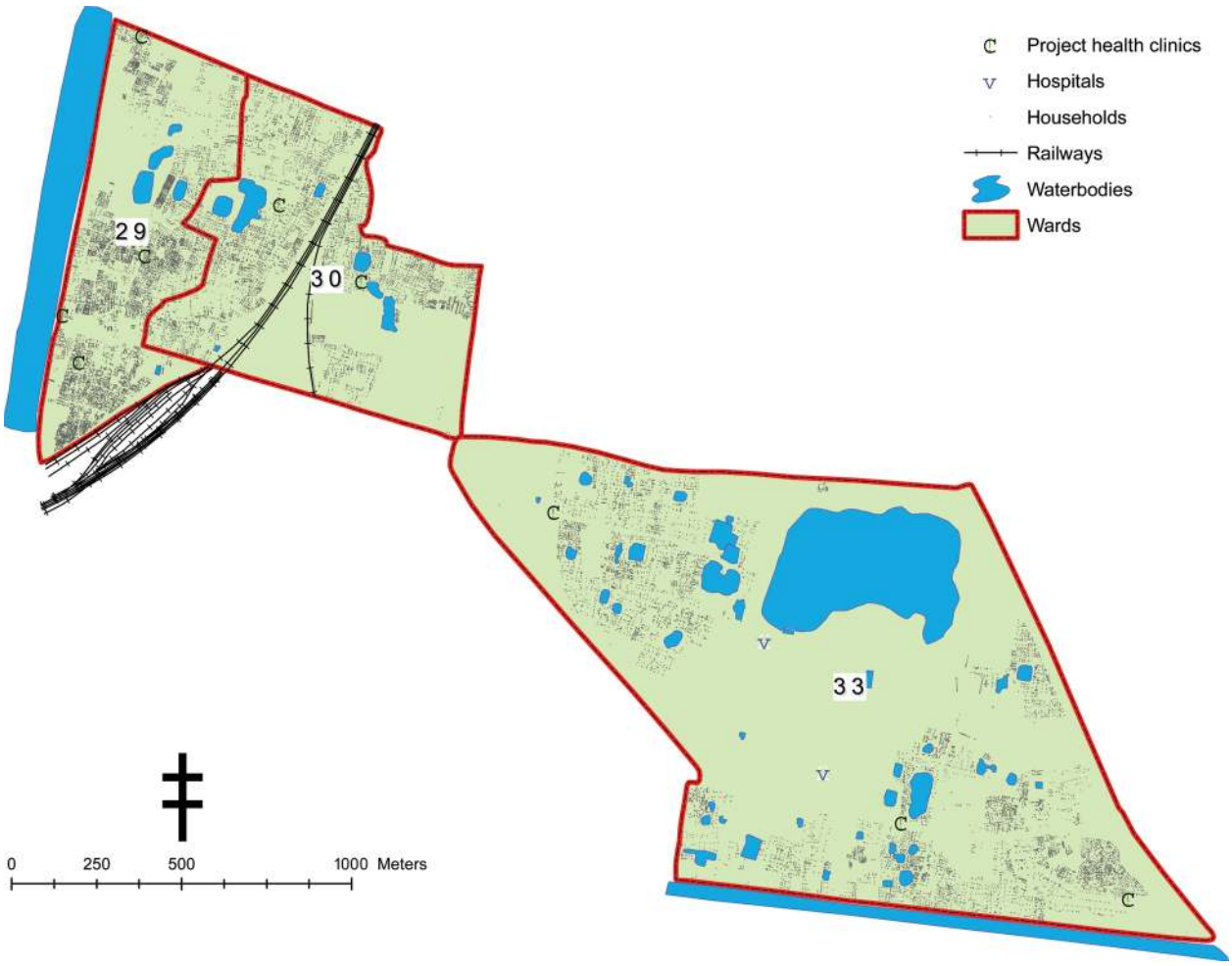

Figure 1. The study area in Kolkata, West Bengal, India (the ward numbers are given inside the ward boundaries).

dose of placebo or vaccine in the cluster the subjects were assigned to.

Analytic Strategies for Estimating Different Types of Vaccine Protection

In cluster-randomized design approach, total (direct plus indirect) vaccine protection was estimated by comparing the incidences of cholera among individuals who received 2 doses of the vaccine in vaccine clusters and the incidences among individuals who received 2 doses of placebo in the placebo clusters. Indirect protection was estimated by comparing the incidences among nonrecipients of the vaccine in vaccine clusters and the incidences among nonrecipients of placebo in the placebo clusters. Overall protection was estimated by comparing the incidences among all individuals in the vaccine clusters and the incidences among all individuals in the placebo clusters [20].

In the GIS approach, indirect protection among vaccine recipients was assessed by correlating incidence of cholera among the 2-dose recipients and neighborhood-level vaccine coverage. To evaluate vaccine indirect protection among vaccine nonrecipients, we assessed whether the incidence of cholera among 2-dose placebo recipients declined as neighborhood-level vaccine coverage increased. To evaluate overall vaccine indirect protection in the community, we assessed incidence of the target outcome among all individuals in the clusters with higher vaccine coverage to the incidence of cholera among all individuals in the neighborhoods with lower vaccine coverage.

Because the GIS-based analysis did not preserve the original randomization of clusters in the trial, it was necessary to study a bias-indicator outcome in addition to cholera. For this analysis, we selected dysentery, a syndrome that was not prevented by the vaccine but that shares many risk factors with cholera, as the bias-indicator outcome [21].

Statistical Analysis

In the cluster-randomized design approach, we used Cox proportional hazards models to evaluate vaccine protection.

Deaths, outmigrations, and internal movements were treated as censoring events. We fitted both unadjusted and covariate-adjusted models [22, 23]. Adjustment for the design effect of cluster randomization was done using a robust error variance [24]. Covariates were adjusted for factors used to stratify the randomization (cluster size and ward of residence), as well as individual-level variables that were found to be associated with risk for cholera in our previous analyses [16, 17].

In the GIS approach, the subjects were divided into quintiles according to the level of vaccine coverage. We calculated the protective efficacy (PE) by quintiles using the formula $(1 - \text{relative risk}) \times 100$ and assessed whether there was an inverse relationship between the level of vaccine coverage in the neighborhood around an individual (coded directly as a percentage) and the occurrence of disease in the individual by using the Cochran-Armitage trend test [25]. For more rigorous analyses of the association between level of vaccine coverage and disease incidence, we also controlled for the same variables that were used to analyze effectiveness using the cluster design approach described above. All statistical tests were interpreted in a 2-tailed fashion.

Ethical Considerations

The study protocol was approved by the ethics committee of the National Institute of Cholera and Enteric Diseases, the Health Ministry Screening Committee of India, and the International Vaccine Institute Institutional Review Board.

RESULTS

Among 108 777 residents in the study area, 107 347 were age eligible (≥1 year) for the trial; 66 900 persons received 2 doses of either cholera vaccine or placebo, yielding a 62% coverage rate (Figure 2). There were 245 first episodes of cholera in the entire population and 166 first episodes of cholera among the 2-dose recipients during the 3-year follow-up period. Seventy-four cases of cholera were observed among 39 091 subjects who did not receive any dose (absentees, refusals, pregnant women, and children <1 year of age). Five cases occurred among 1-dose recipients, who were excluded in this analysis. There were 657 first episodes of dysentery among the entire population; of these, 271 cases were observed among 2-dose vaccine recipients and 252 cases among 2-dose placebo recipients during the 3 years of follow-up.

Analysis using the cluster design approach demonstrated significant total protection (66%, 95% confidence interval [CI], 50%–78%, $P < .01$) by the cholera vaccine against cholera diarrhea after adjustment for the design effect of the cluster randomization and potential risk factors for cholera (Table 1). In the cluster design analysis there was no indirect vaccine protection; however, there was statistically significant overall protection against cholera (49% [95% CI, 29%–63%], $P < .01$).

The results of the GIS approach showed that the risk of cholera among placebo recipients was inversely related to the neighborhood-level vaccine coverage in a simple analysis, with a trend that is statistically significant ($P < .01$; Table 2). A similar trend was not apparent among the recipients of the cholera vaccines. When analyzing the data on dysentery, we observed no such relationship between the risk of dysentery and the neighborhood level of cholera vaccine coverage. In the simple analysis, a positive significant relationship ($P < .01$) was observed between the neighborhood level of cholera vaccine coverage and the risk for dysentery among cholera vaccine recipients (Table 3); however, after controlling for the risk factors (age, individuals living in larger cluster specified in the stratification, wards, monthly per capita expenditure of the household, individuals living in a household always wash hands with soap and water after defecation, individuals living in their own house, individuals living in a household owning at least 1 luxury item, and distance from the household to the nearest health clinic) in the Cox proportional hazards model, the hazard ratio (HR) was 1.03 (95% CI, .99–1.06, $P = .10$).

Because the inverse relationship between vaccine coverage and the risk of cholera was more pronounced for placebo recipients than for vaccinees (Table 2), it was of interest to explore the implications of high levels of vaccine coverage for the measurement of vaccine PE. Table 2 shows that the PE remained relatively stable (74%–77%) among residents in the lower level of coverage (≤28%), but declined rapidly with the increase of coverage showing no significant protection among residents living in areas with higher level of vaccine coverage.

In the model that considered vaccine 2-dose recipients, the higher level of vaccine coverage did not show any added benefit to the vaccine recipients apart from vaccine-induced direct protection (Table 4). However, we observed a significant inverse relationship between the level of vaccine coverage and individuals' risk for cholera in the model considering placebo recipients and 3 years of follow-up (HR, 0.94 [95% CI, .90–.98], $P < .01$), indicating an indirect effect of the cholera vaccine against cholera diarrhea (Table 4). This result is similar when analyzing the data with the 2 years of follow-up (HR, 0.94 [95% CI, .90–.99], $P = .01$). Among placebo recipients, the herd protection was found to be significantly higher in the second year of follow-up (HR, 0.91 [95% CI, .85–.96], $P < .01$) than that for the other years, and a moderate level of herd protection was observed in the third year of follow-up (HR, 0.94 [95% CI, .87–1.01], $P = .06$). The data of the first year of follow-up did not show indirect protection of the vaccine. When we fitted the model by different level of coverage as shown in Table 2, herd effects were seen at coverage levels of at least 28%, but did not increase much with higher

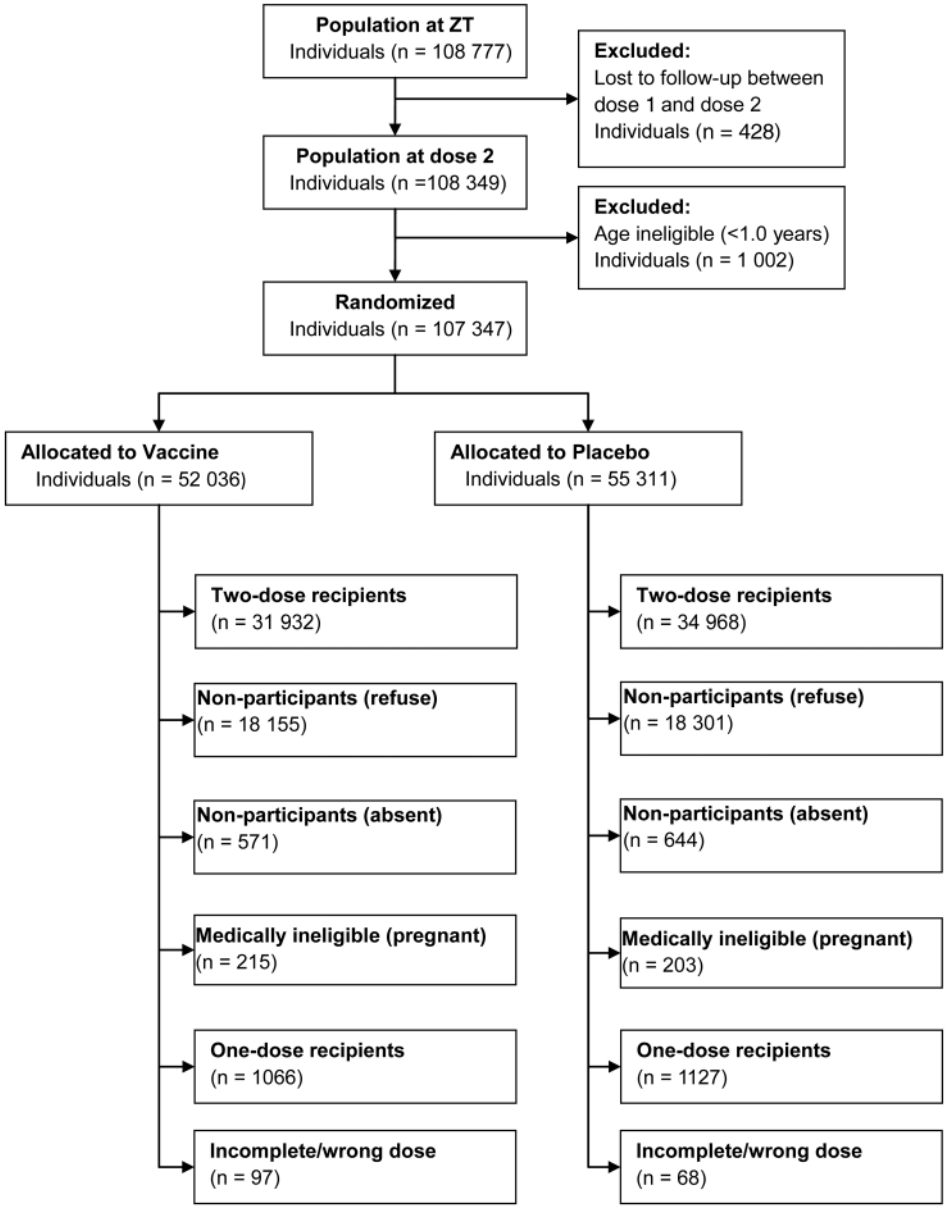

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) diagram for the flow of subjects in the oral cholera vaccines in Kolkata, India. Abbreviation: ZT; zero-time.

levels of coverage (Table 5). A model that took into account all individuals (overall effect) shows a significant overall protection when the level of coverage goes beyond 34%.

DISCUSSION

This is the first report of the herd protection conferred by the bivalent killed whole-cell OCV in an urban slum setting. The findings confirm the herd protective effect of killed whole-cell OCVs demonstrated in an earlier work by Ali et al [15], in a retrospective analysis of a trial conducted >2 decades ago of killed OCVs in a rural area of Bangladesh [26]. Moreover, our analysis includes data from 3 years of surveillance indicating that herd protection may be sustained for 3 years after receipt of the vaccine.

The results of the cluster design analysis reaffirm that the bivalent killed whole-cell OCV offers a similar level of total (direct plus indirect) protection (66%) against cholera infections in the third year as in the second year [16]. The cluster design approach, however, failed to show any indirect protection. This could be due to a high level of transmission of cholera across clusters. To evaluate the herd effect of a vaccine

Table 1. Total, Indirect, and Overall Vaccine Protection Using the Design Approach, Kolkata, India, 2007–2009

	Total (n = 66 900)		Indirect (n = 39 091)		Overall (N = 108 349)	
	Vaccine Arm	Placebo Arm	Vaccine Arm	Placebo Arm	Vaccine Arm	Placebo Arm
Subjects, No.	31 932	34 968	19 420	19 671	52 515	55 834
Cholera episodes detected in follow-up, No.	38	128	34	40	76	169
Person-days of follow-up	32 387 004	35 432 997	18 442 159	18 596 485	51 965 506	55 188 643
Incidence, per 100 000 person-days	0.12	0.36	0.18	0.22	0.15	0.31
Protection (95% CI; *P* value)						
Unadjusted analysis	68% (52%–78%; <.01)		14% (–25% to 41%; 0.42)		52% (34%–65%; <.01)	
Adjusted analysis[a]	66% (50%–78%; <.01)		0% (–59% to 37%; 0.99)		49% (29%–63%; <.01)	

Abbreviation: CI, confidence interval.

[a] Adjusted for the design effect of cluster randomization, cluster size, wards of residence, age, living in a household where residents always wash hands with soap and water after defecation, living in a house owned by the residents, living in a household owning at least 1 luxury item, monthly per capita expenditure of the household (Indian rupees), and distance (meters) from the household to the nearest health clinic.

in a cluster-randomized trial, one must ensure minimal transmission of the target pathogens across clusters. In this study, the densely populated dwellings (clusters) were closely connected, sewers were open, some people openly defecated, and water pipes were shared among dwellings. Thus, transmission of the target pathogens across clusters was likely.

The results of the GIS approach demonstrated that higher neighborhood level cholera vaccine coverage was linked with lower risk of cholera among the household residents, in particular among placebo recipients, for whom a strong inverse relationship was observed. The higher coverage level, presumably by reducing transmission in the area, resulted in a herd effect, leading to a low incidence in the unimmunized segment [27]. The results also suggest that when the vaccine coverage is >28%, there is a substantial reduction in the disease risk for nonvaccinees. Data from the first year of follow-up were not adequately powered to assess the indirect effect of the bivalent killed whole-cell OCV, as was seen in the earlier analysis for the total effect [16].

The herd effect among vaccine recipients is not as pronounced as it was observed in the 1985 cholera trial in Matlab [15]. This could be due to the fact that it was a cluster randomized trial, and the clusters artificially divided the densely populated Kolkata slums into units in which close contact among residents allowed easy contamination across clusters. However, the results of the GIS approach indicate that the risk of cholera among vaccinated and unvaccinated individuals is significantly lower in a high-vaccine-coverage area compared

Table 2. Risk of Cholera and Protective Efficacy of the Cholera Vaccine Among Persons Who Received Cholera Vaccine or Placebo, by Level of Cholera Vaccine Coverage, During 3 Years of Follow-up, Kolkata, India

	Vaccinees			Placebo Recipients					
Level of Vaccine Coverage[a]	No.	Cases	Risk per 1000 Persons[b]	No.	Cases	Risk per 1000 Persons[c]	PE[d] (%)	95% CI (%)	*P* Value
0.00–25.00	4687	6	1.28	7219	40	5.54	77	49–90	<.01
25.01–28.00	6086	9	1.48	7805	44	5.64	74	47–87	<.01
28.01–31.00	6905	7	1.01	6038	15	2.48	59	–5 to 84	.06
31.01–34.00	6208	6	0.97	6662	15	2.25	57	–14 to 84	.09
≥34.01	8046	10	1.24	7244	14	1.93	36	–55 to 73	.33
Total	31 932	38	1.19	34 968	128	3.66	68	52–78	<.01

Abbreviations: CI, confidence interval; PE, protective efficacy.

[a] Cholera vaccine coverage in a neighborhood of 250 m around the household. All age-eligible people within 250 m were included in the calculation. The level of vaccine coverage is based on the quintiles of the 2-dose recipients of either cholera vaccine or placebo.

[b] Cochran-Armitage trend test for vaccinees, $P = .71$.

[c] Cochran-Armitage trend test for placebo recipients, $P < .01$.

[d] The PE is calculated as (1 – relative risk) × 100.

Table 3. Risk of Dysentery Among 2-Dose Recipients of the Assigned Agents, by Neighborhood Level of Cholera Vaccine Coverage, During 3 Years of Follow-up, Kolkata, India

	Vaccine Group			Placebo Group		
Level of Vaccine Coverage (%)[a]	Recipients of 2 Doses	No. of Cases	Risk per 1000 Persons	Recipients of 2 Doses	No. of Cases	Risk per 1000 Persons
0.00–25.00	4687	29	6.19	7219	39	5.40
25.01–28.00	6086	35	5.75	7805	51	6.53
28.01–31.00	6905	56	8.11	6038	56	9.27
31.01–34.00	6208	73	11.76	6662	53	7.96
≥34.01	8046	78	9.69	7244	53	7.32
Total	31 932	271	8.49	34 968	252	7.21
	Cochran-Armitage trend test, $P < .01$			Cochran-Armitage trend test, $P = .10$		

[a] Cholera vaccine coverage in a neighborhood of 250 m around the household. All age-eligible people within 250 m were included in the calculation. The level of vaccine coverage is classified in every 4% keeping close to quintile classification of the 2-dose recipients of either cholera vaccine or placebo.

to that in a low-coverage area, confirming both direct and indirect benefits of the vaccine. The markedly reduced level of cholera vaccine protective efficacy, also observed in the Matlab study [15], confirms that high levels of vaccine coverage in an area may bias the estimates of efficacy downward.

The GIS approach differs substantially from the cluster-randomized approach. In the latter, the unit at risk was the dwelling units of individuals, vaccine coverage was classified dichotomously, and the validity of the analysis was dependent on the assumption that there was little intercluster transmission of cholera. In the GIS approach, the unit at risk was a single individual rather than a cluster of individuals, so that the approach was not as susceptible to problems of intercluster transmission. Vaccine coverage, classified on a dimensional scale, referred to coverage of a population residing within a relatively wide radius around the individual. This latter feature may have enabled the GIS approach to overcome the distortions introduced by intercluster transmission of cholera in the cluster-randomized analysis.

One limitation in the GIS approach is that the levels of vaccine coverage influenced by the cluster design were not distributed at random geographically. For this reason, we controlled for known demographic determinants of cholera in the multivariable models. Because the expected risk of cholera may differ between persons who volunteer to participate in a trial vs those who do not [28], we restricted the analysis to persons who received 2 doses of either vaccine or placebo. The inverse relationship between neighborhood level of coverage of the household with cholera vaccine and an individual's risk of cholera remained intact despite these analytic adjustments and restrictions, making both confounding bias and selection bias implausible explanations for our findings. Also suggesting that the GIS approach did not yield biased results is the observation that the bias indicator condition, dysentery, did

Table 4. Hazard Ratios for the Neighborhood Level of Vaccine Coverage Among Recipients and Nonrecipients of the Cholera Vaccine by Year of Follow-up, Kolkata, India

	Recipients of 2 Doses of Vaccine (n = 31 932)			Recipients of 2 Doses of Placebo (n = 34 968)			All Participants (N = 108 349)		
Year of Follow-up	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value
1st year (ZT to ZT + 365 days)	1.22	.94–1.57	.13	1.00	.93–1.08	.99	1.02	.94–1.10	.68
2nd year (ZT + 366 days to ZT + 730 days)	1.07	.91–1.25	.42	0.91	.85–.96	<.01	0.93	.88–.98	<.01
3rd year (ZT + 731 days to ZT + 1095 days)	1.01	.91–1.12	.85	0.94	.87–1.01	.06	0.96	.91–1.00	.07
Two years (ZT to ZT + 730 days)	1.12	.97–1.30	.13	0.94	.90–.99	.01	0.96	.92–1.00	.06
Three years (ZT to ZT + 1095 days)	1.07	.97–1.19	.18	0.94	.90–.98	<.01	0.96	.93–.99	.01

Abbreviations: CI, confidence interval; HR, hazard ratio; ZT, zero-time.

[a] Adjusted for cluster, age, individuals living in larger cluster specified in the stratification, wards, monthly per capita expenditure of the household, individuals living in a household who always wash hands with soap and water after defecation, individuals living in their own house, individuals living in a household owning at least 1 luxury item, and distance from the household to the nearest health clinic.

Table 5. Hazard Ratios by Different Levels of Neighborhood Vaccine Coverage Among Recipients and Nonrecipients of the Cholera Vaccine in the 3 Years (Zero-Time [ZT] to ZT + 1095 days) of Follow-up, Kolkata, India

Level of Vaccine Coverage (%)	Recipients of 2 Doses of Vaccine (n = 31 932)			Recipients of 2 Doses of Placebo (n = 34 968)			All Participants (N = 108 349)		
	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value
0.00–25.00[b]	1.00	…	…	1.00	…	…	1.00	…	…
25.01–28.00	1.23	.43–3.48	.69	0.95	.57–1.58	.85	1.01	.68–1.48	.95
28.01–31.00	1.20	.39–3.67	.74	0.50	.26–.94	.03	0.68	.44–1.06	.09
31.01–34.00	1.01	.30–3.37	.98	0.48	.25–.90	.02	0.64	.40–1.00	.05
≥34.01	1.58	.43–5.69	.48	0.35	.15–.78	.01	0.46	.26–.82	.01

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Hazard ratio adjusted for the design effect of cluster randomization, age, individuals living in larger cluster specified in the stratification, wards, monthly per capita expenditure of the household, individuals living in a household who always wash hands with soap and water after defecation, individuals living in their own house, individuals living in a household own at least 1 luxury item, distance from the household to the nearest health clinic.

[b] Reference category.

not reveal evidence of vaccine herd effects. The study was conducted in a densely populated urban area. However, the GIS methodology is equally applicable in the less densely populated setting, as it has been applied elsewhere [29].

On the basis of our experiences, we believe that 50% coverage can be achieved in mass vaccination programs of the 2-dose oral cholera vaccine [16, 21, 26, 29]. Mathematical models suggest that with 50% vaccination coverage, cholera can be controlled in endemic areas [11]. A recent study conducted in Zanzibar [29] supports this finding where, with 50% vaccination coverage, no cholera cases were observed after the mass vaccination except an outbreak during the period September 2009–April 2010.

The recent devastating cholera outbreaks in Haiti and Zimbabwe underscore the need for improved public health responses for its control. The World Health Organization recently prequalified the low-cost reformulated bivalent killed whole-cell OCV used in this study. Since then the vaccine has been used in Guinea [30] and Haiti [31] as additional tools in cholera control. Our findings confirm that killed OCVs—and more specifically, the reformulated bivalent OCV—confer significant herd protection beyond the first year following vaccination. The robustness of our findings adds plausibility to the assertion that the herd effects of killed oral cholera vaccines may account for a large portion of their public health value and reinforces recent recommendations for the use of killed OCVs by WHO [32].

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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