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Use of oral cholera vaccine as a vaccine probe to define the geographical dimensions of person-to-person transmission of cholera

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ABSTRACT

Background: Cholera is known to be transmitted from person to person, and inactivated oral cholera vaccines (OCVs) have been shown to confer herd protection via interruption of this transmission. However, the geographic dimensions of chains of person-to-person transmission of cholera are uncertain. The ability of OCVs to confer herd protection was used to define these dimensions in two cholera-endemic settings, one in rural Bangladesh and the other in urban India.

Methods: Two large randomized, placebo-controlled trials of inactivated OCVs, one in rural Matlab, Bangladesh and the other in urban Kolkata, India, were reanalyzed. Vaccine herd protection was evaluated by relating the risk of cholera in placebo recipients to vaccine coverage of surrounding residents residing within concentric rings. In Matlab, concentric rings in 100-m increments up to 700 m were evaluated; in Kolkata, 50-m increments up to 350 m were evaluated.

Results: One hundred and eight cholera cases among 24 667 placebo recipients were detected during 1 year of post-vaccination follow-up at Matlab; 128 cholera cases among 34 968 placebo recipients were detected during 3 years of follow-up in Kolkata. Consistent inverse relationships were observed between vaccine coverage of the ring and the risk of cholera in the central placebo recipient for rings with radii up to 500 m in Matlab and up to 150 m in Kolkata.

Conclusions: These results suggest that the dimensions of chains of person-to-person transmission in endemic settings can be quite large and may differ substantially from setting to setting. Using OCVs as 'probes' to define these dimensions can inform geographical targeting strategies for the deployment of these vaccines in endemic settings.

Introduction

Killed oral cholera vaccines (OCVs) are now stockpiled by the World Health Organization (WHO) and are recommended public health tools for the control of cholera outbreaks (Martin et al., 2012). It is generally accepted that the rational use of such vaccines, either for epidemic or endemic cholera, will require that vaccination be targeted to geographically circumscribed populations at greatest risk of cholera. Knowledge of the geographic dimensions of chains of person-to-person cholera transmission will be important for effective geographic targeting, as OCVs have been demonstrated to confer both direct protection to vaccinees and herd protection to populations, the latter operating via interruption of person-to-person transmission.

The geographic dimensions of chains of person-to-person cholera transmission were estimated in this study. A geographic information system (GIS)-based method that has been employed previously to evaluate whether OCVs confer vaccine herd protection was used (Ali et al., 2005). It was reasoned that because vaccine herd protection results from interruption of person-to-

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person cholera transmission, delineation of the dimensions of OCV herd protection should demarcate the dimensions of chains of person-to-person transmission.

Methods

Overview

The vaccine herd protective effects of inactivated OCVs were analyzed in two randomized, placebo-controlled trials, one in Matlab, Bangladesh (Clemens et al., 1990) and the other in Kolkata, India (Sur et al., 2009), using a GIS-based method (Ali et al., 2005; Ali et al., 2013). In this approach, a 'virtual cluster' is defined as persons whose residences are within a specified radius of the residence of each person under analysis (termed the 'focal person'), and the risk of cholera for each focal person under analysis is related to the vaccine coverage in surrounding virtual clusters. An inverse relationship suggests vaccine herd protection, and when the focal person under analysis has received placebo, indirect vaccine protection is measured (Ali et al., 2005; Ali et al., 2013; Clemens et al., 2011). Conceptually, the maximum radius in which indirect vaccine protection is demonstrated should demarcate the geographical size of a surrounding population that puts an unimmunized individual at risk of becoming infected via person-to-person transmission. In this study, the indirect OCV protection of each focal person (placebo recipient) by vaccination in successive rings of persons in surrounding residences was analyzed, thus identifying the dimensions of chains of person-to-person cholera transmission in the two study settings.

OCV trials under analysis

The two randomized, placebo-controlled trials analyzed in this study were conducted in rural Matlab, Bangladesh, an area bisected by the Dhonagoda River, and in urban Kolkata, India, comprising wards 29, 30, and 33 (Figure 1); these trials have been described in detail elsewhere (Clemens et al., 1990; Sur et al., 2009; Clemens et al., 1986). Dosing with inactivated OCV or placebo was conducted in 1985 in Matlab and in 2006 in Kolkata. In Matlab, children aged 2–14 years and non-pregnant female adults (≥15 years) were eligible to participate in the trial. In Kolkata, non-pregnant persons aged ≥1 year were eligible. In Matlab, eligible persons were individually randomized to a three-dose regimen of an oral cholera toxin B subunit-killed whole cell (BS-WC) vaccine, oral killed whole cell (WC)-only vaccine, or oral placebo. In Kolkata, eligible persons were randomized by residential dwelling to a two-dose regimen of an oral killed WC-only vaccine or oral placebo.

Diarrhea surveillance

In Matlab, surveillance was conducted for all diarrheal patients from the study area who attended either the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) Matlab hospital or two community-operated treatment centers. Diarrhea was defined as the presence of at least three loose or liquid motions in the 24 h before presentation, or one to two or an indeterminate number of loose or liquid stools in the 24 h before presentation with at least two signs of dehydration (poor skin turgor, sunken eyes, dry mucous membranes, weakened radial pulse) on presentation. Stools or rectal swabs were collected from these patients and were tested for *Vibrio cholerae* O1 using conventional microbiological methods (Bopp et al., 1999).

In Kolkata, diarrhea surveillance was conducted in nine project health clinics and two governmental hospitals. Diarrhea was defined as having three or more loose stools in the 24 h before presentation, or one to two or an indeterminate number of loose or liquid stools in the 24 h before presentation together with moderate or severe dehydration, according to WHO criteria, on presentation (WHO, 2005). Rectal swabs were collected from all diarrheal patients and tested in the project laboratory for *V. cholerae* O1 and *V. cholerae* O139 using conventional methods (Bopp et al., 1999).

In both studies, cholera was defined as non-bloody diarrhea in which *V. cholerae* O1 was isolated. *V. cholerae* O139 was not isolated in the Kolkata trial. In the present analyses, cholera cases occurring during 1 year after the time of vaccination in Matlab and during 3 years after the time of vaccination in Kolkata were considered;

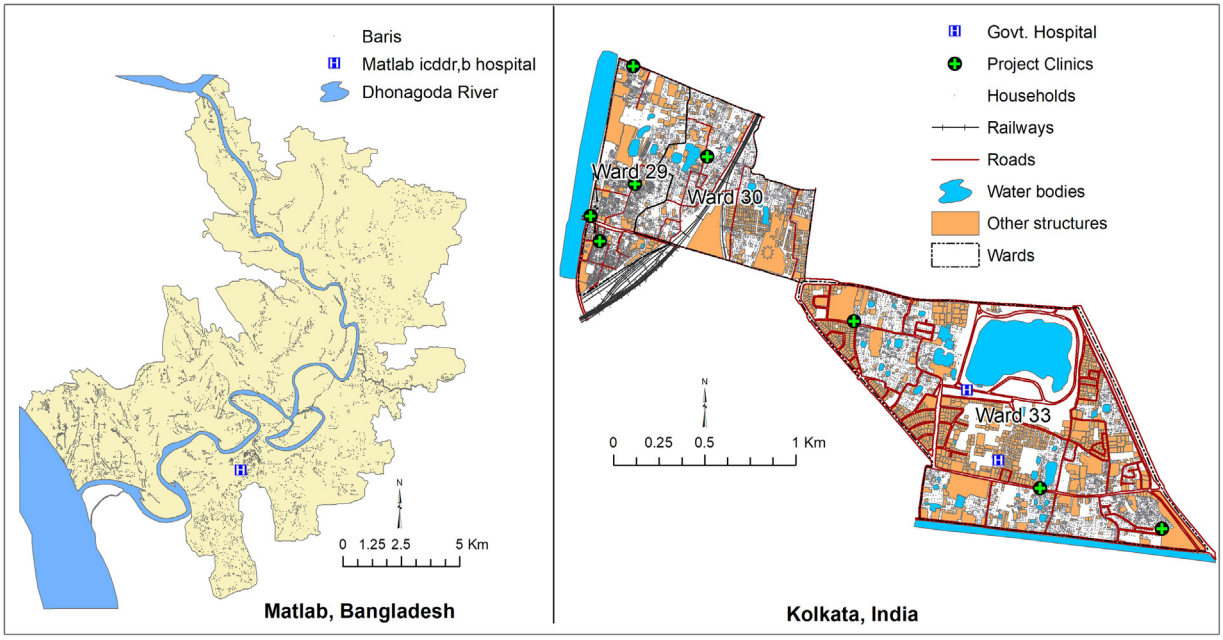

Figure 1. The study areas.

these were both intervals in which indirect herd OCV protection was demonstrated in the earlier analyses (Ali et al., 2005; Ali et al., 2013).

Defining virtual clusters

In the earlier published analyses of these trials (Ali et al., 2005; Ali et al., 2013), a statistical criterion was used to define the radius around each placebo recipient to demarcate the virtual cluster of people for determination of vaccine coverage. This criterion was related to the variability of the variances of vaccine coverage across virtual clusters, and was not based on whether vaccine coverage was inversely related to the risk of cholera. This criterion yielded a radius of 500 m for Matlab and 250 m for Kolkata.

In the present analyses, virtual clusters were defined a priori as concentric rings of residential populations in 100-m increments up to 700 m (seven rings centering each placebo recipient) in Matlab, and in 50-m increments up to 350 m (also seven rings centering each placebo recipient) in Kolkata. The difference in the size of increments was related to the dispersed population in Matlab versus the congested urban setting in Kolkata. Vaccine coverage in each ring was computed as the number of recipients of at least two doses of vaccine divided by the number of all eligible residents at the time of the first dose.

Statistical analysis

The earlier analyses found no design effect due to the residence-based allocation in Kolkata; therefore this trial was analyzed as if it had been individually randomized (Sur et al., 2009). Indirect vaccine protection was assessed by relating the risk of cholera in recipients of at least two doses of placebo (focal persons) to vaccine coverage of the defined rings around these recipients. In crude analyses the relationship for each ring between the quintile of vaccine coverage around each focal person (quintiles were ascertained from the distribution of coverages for all rings of the same radius) and the risk of cholera in the focal person, was evaluated, and this relationship was assessed with the Cochran–Armitage test for trend. In multivariable logistic regression models, the relationship between the levels of vaccine coverage of the defined ring (expressed dimensionally and fitted as an independent variable) and the occurrence of cholera for each focal person (the dependent variable) was assessed, controlling for potentially confounding variables. Based on the findings of the earlier work, candidate variables for inclusion as covariates in the models for Matlab were age at the date of first dose, distance to the icddr,b hospital in Matlab, and distance to the Dhonagoda River. Age at date of first dose, sex, owning at least one luxury item, per-capita household expenditure, washing hands with soap and water after defecation, and living in an owned house were considered as candidate covariates in the Kolkata models. To select the covariates for the final models, those candidate variables found to be associated with the risk of cholera at $p < 0.10$ in the bivariate models were included, and these were retained in the final model if they remained significant at $p < 0.20$ in a backward elimination process. Multivariable odds ratios (OR) relating each percentage increase in vaccine coverage to the occurrence of cholera were estimated by exponentiation of the coefficient for the vaccine coverage variable in the models; p-values and 95% confidence intervals (CI) for these OR were estimated using the standard errors of these coefficients. All p-values and 95% CI were two-sided.

Ethics

The project in Matlab was approved by the Ethical Review Committees of the icddr,b, Dhaka, Bangladesh and WHO (Geneva). The project in Kolkata was approved by the ethics committees of the National Institute of Cholera and Enteric Diseases (NICED) and the Health Ministry Screening Committee of India, and the International Vaccine Institute Institutional Review Board. Informed consent was obtained from all participants in these studies.

Results

There were 124 035 individuals eligible for vaccination in Matlab and 107 774 individuals eligible for vaccination in Kolkata. Among these populations, 108 cholera cases occurred among 24 667 recipients of at least two doses of placebo during the 1 year of follow-up in Matlab; 128 cholera cases occurred among 34 968 two-dose placebo recipients during the 3 years of follow-up in Kolkata.

The previously published reports that evaluated vaccine coverage from 0 m to 500 m around placebo recipients in Matlab (Ali et al., 2005) and from 0 m to 250 m around placebo recipients in Kolkata (Ali et al., 2013) each found significant inverse relationships between vaccine coverage and the risk of cholera in placebo recipients (Table 1).

Cholera vaccine coverage for each concentric ring in the present analysis is presented in Table 2. Average vaccine coverage in each ring ranged from 41% to 45% in Matlab and from 26% to 30% in Kolkata. In the crude analyses in Matlab, a consistent inverse relationship between the quintile of vaccine coverage within the concentric ring and the risk of cholera in the focal person at the center of the ring was observed for all rings with radii up to 500 m. However, such a relationship was observed only for rings with radii up to 200 m for focal persons in Kolkata (Table 3).

The backward elimination process for selecting covariates for the final model resulted in no covariates retained for Matlab and only age retained for Kolkata. Multivariable logistic regression models showed a significant association between OCV coverage in the ring and the risk of cholera in focal persons for rings with radii up to 500 m in Matlab and up to 150 m for placebo recipients in

Table 1
Relationships between inactivated oral cholera vaccine coverage and the risk of cholera in placebo recipients in earlier published analyses (Ali et al., 2005; Ali et al., 2013).

	Kolkata			Matlab		
	HR[a]	p-Value	95% CI	OR[b]	p-Value	95% CI
Cluster level cholera vaccine coverage	0.97	<0.0001	0.96–0.98	0.96	<0.0001	0.94–0.98

HR, hazard ratio; CI, confidence interval; OR, odds ratio.

[a] Hazard ratio for the relative reduction in the risk of cholera for each percentage increase in vaccine coverage. Adjusted for age, sex, religion, distance from household to nearest river, distance from household to nearest treatment center (kilometers), and experienced dysentery during follow-up.

[b] Odds ratio for the relative reduction in the rate of cholera for each percentage increase in vaccine coverage. Adjusted for age, individuals living in a larger cluster specified in the stratification, wards, monthly per-capita expenditure of the household, individuals living in a household always washing hands with soap and water after defecation, individuals living in their own house, individuals living in a household owning at least one luxury item, and distance from the household to the nearest health clinic.

Table 2
Descriptive statistics for inactivated oral cholera vaccine coverage of populations residing in the different concentric rings surrounding placebo recipients in the Matlab (Bangladesh) and Kolkata (India) trials.

Ring size (meters)	Mean %	Median %	Minimum %	Maximum %
Matlab, Bangladesh				
0–100	45.35	46.60	0	85.71
101–200	43.01	45.08	0	100.00
201–300	42.26	44.85	0	100.00
301–400	43.04	44.87	0	100.00
401–500	42.32	44.74	0	100.00
501–600	41.98	44.32	0	80.00
601–700	42.25	44.42	0	82.35
Kolkata, India				
0–50	26.55	26.69	0	71.47
51–100	29.72	29.19	0	62.62
101–150	30.01	29.27	0	68.92
151–200	30.70	29.76	0	60.67
201–250	31.05	30.03	0	74.42
250–300	30.83	29.48	0	80.00
301–350	30.02	29.55	12.17	68.18

Kolkata (Table 4). To assess whether the relationships between OCV coverage and cholera risk in focal persons, by distance from the focal person, could be explained simply by variations in population density, population density was added as a covariate in these models. Models that included population density as a covariate again showed significant inverse associations between OCV coverage and the risk of cholera in focal persons for distances up to 500 m in Matlab and 150 m in Kolkata.

Discussion

Using analyses of the indirect herd protection conferred by OCVs as a probe to define the geographical dimensions of chains of person-to-person transmission of cholera in Matlab, a rural site, and Kolkata, an urban site, an inverse relationship was found between vaccine coverage of the surrounding population and the risk of cholera for placebo recipients for virtual clusters with radii up to 500 m in Matlab and up to 150 m in Kolkata. These results suggest that the dimensions of chains of person-to-person transmission in endemic settings can be quite large and may differ substantially from setting to setting.

Cholera has long been known to occur in geographic clusters. Early studies of space–time clustering of cholera noted clustering of cases within the same household or within small groups of nearby households (Craig, 1988; Glass et al., 1983; Sugimoto et al., 2014; Giebultowicz et al., 2011; Mosley et al., 1965; Philippines Cholera Committee, 1970; Tamayo et al., 1965), leading to the conventional wisdom that the person-to-person spread of cholera is usually limited to household transmission. More recently, two analyses performed in Matlab and Kolkata found an increased risk of clinically significant cholera shortly after the detection of index cases for populations within 450 m of the residence of index cases in Matlab, and within 50 m of residences of index cases in Kolkata (Ali et al., 2016; Debes et al., 2016).

It is interesting to compare the present study estimates with those of these more recent estimates, particularly since the present study and the earlier studies were done at the same study sites (Ali et al., 2016; Debes et al., 2016). All three analyses identified surrounding populations much larger than the immediate household or clusters of households as being relevant to cholera transmission, and all identified substantially larger zones in the rural Bangladesh site than in the urban India site. However, in contrast to the two earlier analyses in Matlab and Kolkata, which evaluated the population at risk for clinically significant cholera around identified cholera cases, regardless of the type of transmission, the present study analyses specifically addressed the size of surrounding zones in which the use of OCVs had a demonstrable effect on person-to-person transmission.

Whether a simple proxy measure – population density – might serve in lieu of analyses of OCV herd protection to define the geographic dimensions of person-to-person transmission was examined. However, inclusion of population density as an additional covariate in the multivariable models failed to erase the relationships between vaccine coverage and cholera risk in focal persons, by distance from the focal person, indicating that population density cannot be used as a simple proxy measure for estimating the geographical dimensions of chains of person-to-person transmission.

Several potential limitations of this analysis require discussion. First, the impact of vaccine coverage calculated at the time that vaccine doses were given was analyzed, rather than vaccine coverage during post-vaccination follow-up, which would have changed over time due to population births, deaths, and migrations. Such misclassification of coverage over time would most likely have been non-differential with respect to the risk of cholera and would have tended to make the estimates of the radii of persons contributing to person-to-person transmission of cholera conservative. Second, in the analyses the ORs were in the range of 0.974–0.999 for Matlab and 0.949–0.996 for Kolkata, which may seem modest in magnitude. However, it should be appreciated that these ORs reflect relative reductions of risk of cholera per one percentage increase in vaccine coverage. Third, for simplicity, the analyses considered concentric circular geographic rings of populations. It may be that zones of person-to-person transmission in the two settings did not conform geometrically to circles.

Fourth, although randomized clinical trials were analyzed, the present analyses of herd protection were observational in design and were subject to the limitations of such a non-randomized design. Fifth, the maximum radius for herd protection may vary not only from site to site, but also from vaccine to vaccine; had the studies been performed with other cholera vaccines, the results may have been different, depending on the capacity of the vaccines studied to interrupt transmission. Nonetheless, the present analyses are of relevance to the deployment of inactivated OCVs, which are currently stockpiled by the WHO for deployment in cholera-affected settings. Sixth, the analyses addressed cholera occurring in endemic settings, in which the population has some level of natural immunity; whether the findings can be generalized to epidemic settings in immunologically naïve populations, where the global OCV stockpile is occasionally deployed, is uncertain and constitutes an important subject for future research. Finally, caution should be exercised in generalizing the different geographical dimensions of person-to-person transmission in Kolkata versus Dhaka to other urban versus rural areas. The Matlab and Kolkata sites differed in multiple ways, not all of which were related to their urban versus rural contexts.

This study has both theoretical and practical implications. The maximum size of virtual clusters for which indirect vaccine protection was detected in the two trials differed from the sizes of virtual clusters that were analyzed in the earlier published analyses of the trials, in which a radius for virtual clusters was determined with an arbitrary statistical criterion (Ali et al., 2005; Ali et al., 2013). This discrepancy suggests that work is required to improve the earlier method for sizing virtual clusters in analyzing vaccine herd protection. On the other hand, it was reassuring that the present study analyses showed a pattern of declining vaccine herd protection with increasing distance of the vaccinated population from the central placebo recipient under analysis,

Table 3
Risk of cholera among placebo recipients by quintile of vaccine coverage for each concentric ring around the placebo recipients in the Matlab (Bangladesh) and Kolkata (India) trials.

Matlab				Kolkata			
% coverage by distance	Placebo recipients	Cases	Risk/1000	% coverage by distance	Placebo recipients	Cases	Risk/1000
0–100 m				0–50 m			
≤36.36	5389	30	5.57	≤21.38	10 633	44	4.14
36.37–44.23	5089	25	4.91	21.39–27.33	7641	36	4.71
44.24–50.59	5057	24	4.75	27.34–32.55	6613	27	4.08
50.60–57.22	4841	19	3.92	32.56–40.49	5711	15	2.63
≥57.23	4291	10	2.33	≥40.50	4370	6	1.37
Z-statistic	2.43				2.81		
(*p*-Value)[a]	(0.0158)				(0.0049)		
101–200 m				51–100 m			
≤32.35	4911	30	6.11	≤23.13	7059	38	5.38
32.36–41.67	4968	29	5.84	23.14–27.18	7410	35	4.72
41.68–48.51	4919	22	4.47	27.19–32.03	6995	22	3.15
48.52–55.42	5001	15	3.00	32.04–37.89	6755	21	3.11
≥55.43	4868	12	2.47	≥37.90	6749	12	1.78
Z-statistic	3.40				3.85		
(*p*-Value)[a]	(0.0007)				(0.0001)		
201–300 m				101–150 m			
≤30.86	4891	34	6.95	≤24.65	7410	37	4.99
30.87–41.03	4978	24	4.82	24.66–28.04	7430	34	4.58
41.04–47.98	4962	15	3.02	28.05–31.57	7116	25	3.51
47.99–55.00	4962	25	5.04	31.58–36.05	6453	19	2.94
≥55.01	4874	10	2.05	≥36.06	6559	13	1.98
Z-statistic	3.20				3.34		
(*p*-Value)[a]	(0.0014)				(0.0008)		
301–400 m				151–200 m			
≤32.79	4882	27	5.53	≤24.87	6900	40	5.80
32.80–41.51	4922	26	5.28	24.88–28.32	7332	24	3.27
41.52–47.97	4975	20	4.02	28.33–31.71	7066	19	2.69
47.98–54.48	4945	26	5.26	31.72–36.34	6519	22	3.37
≥54.49	4943	9	1.82	≥36.35	7151	23	3.22
Z-statistic	2.50				2.18		
(*p*-Value)[a]	(0.0125)				(0.0292)		
401–500 m				201–250 m			
≤32.77	4966	29	5.84	≤25.26	6284	26	4.14
32.78–41.71	4968	27	5.43	25.27–28.10	7039	28	3.98
41.72–47.34	4940	25	5.06	28.11–31.21	6225	24	3.86
47.35–53.37	4952	17	3.43	31.22–35.35	7493	25	3.34
≥53.38	4841	10	2.07	≥35.36	7927	25	3.15
Z-statistic	3.20				1.16		
(*p*-Value)[a]	(0.0014)				(0.24)		
501–600 m				251–300 m			
≤32.39	4862	28	5.76	≤25.70	6547	29	4.43
32.40–41.30	4923	14	2.84	25.71–28.23	7293	25	3.43
41.31–46.69	4940	18	3.64	28.24–30.86	6899	30	4.35
46.70–52.43	4927	29	5.89	30.87–35.12	6833	21	3.07
≥52.44	5015	19	3.79	≥35.13	7396	23	3.11
Z-statistic	0.30				1.28		
(*p*-Value)[a]	(0.78)				(0.20)		
601–700 m				301–350 m			
≤32.34	4827	21	4.35	≤25.43	7134	23	3.22
32.35–41.27	5019	25	4.98	25.44–28.29	6827	22	3.22
41.28–47.01	4985	27	5.42	28.30–30.88	6887	29	4.21
47.02–52.99	4886	20	4.09	30.89–34.19	6881	30	4.36
≥53.00	4950	15	3.03	≥34.20	7239	24	3.32
Z-statistic	1.20				−0.56		
(*p*-Value)[a]	(0.24)				(0.57)		

[a] The *Z*-statistics and *p*-values were derived using the Cochran–Armitage trend test, as described in the Methods section.

providing evidence of the construct validity of the method. From a practical perspective, the approach used herein may provide guidance to geographically targeted OCV strategies for the control of outbreaks of cholera occurring in endemic settings.

In summary, the results of this study suggest that the dimensions of chains of person-to-person transmission in endemic settings can be quite large and may differ substantially from setting to setting. Using OCVs as 'probes' to define these dimensions can

Table 4
Odds ratios relating the risk of cholera in placebo recipients to inactivated oral cholera vaccine coverage in successive concentric rings of populations in the Matlab (Bangladesh) and Kolkata (India) trials.

Matlab				Kolkata			
Ring size (meters)	OR[a]	95% CI	*p*-Value	Ring size (meters)	OR[a]	95% CI	*p*-Value
0–100	0.985	0.971–0.999	0.0330	0–50	0.984	0.970–0.999	0.0315
101–200	0.984	0.973–0.996	0.0076	51–100	0.974	0.957–0.993	0.0062
201–300	0.984	0.973–0.996	0.0070	101–150	0.972	0.949–0.996	0.0223
301–400	0.985	0.973–0.997	0.0182	151–200	0.989	0.965–1.013	0.3673
401–500	0.986	0.974–0.999	0.0283	201–250	1.002	0.978–1.028	0.8496
501–600	0.999	0.985–1.013	0.8695	251–300	0.979	0.951–1.007	0.1383
601–700	0.995	0.981–1.008	0.4343	301–350	1.004	0.973–1.035	0.8184

OR, odds ratio; CI, confidence interval.
[a] Adjusted for age at the date of first dose.

inform geographical targeting strategies for the deployment of these vaccines in endemic settings.

Contributors

MA and JC contributed to the study design. MA, DS, SK, SD, FM, SKB, and JC contributed to the implementation and supervision of the study. MA, BM, and DRK analyzed the data and took responsibility for the accuracy of the data analysis. All authors participated in the writing of the manuscript and approved the final version of the manuscript.

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Conflict of interest

None declared.

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