Examining the Role of Social Networks and Herd Immunity in a Cholera Vaccine Trial in Bangladesh

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Abstract

Recent work showed that in a field trial for a killed oral cholera vaccine in Matlab, Bangladesh, the vaccine conferred herd protection to non-vaccinated individuals based on the levels of coverage in their spatially-defined neighborhood. Indirect protection was more pronounced for placebo recipients, suggesting herd immunity. However, as in traditional vaccine trials, the study assumed equal contact amongst all individuals. To further expand on this work, this research develops social networks based on demographic data from the vaccine trial population and evaluates whether or not these networks of contacts confer the same protection as levels of neighborhood vaccine coverage. We calculated levels of coverage in the social networks of individuals who participated in the trial, receiving either the vaccine or the placebo, and measured risk by level of coverage within the entire social network as well as in networks bounded by spatial neighborhoods. Levels of coverage were associated with decreased cholera risk in all participants, but the effect was stronger in vaccine recipients than in placebo recipients. Our results suggest that social networks have protective effects and may be useful for future vaccine research.

Introduction

The objectives of this research are to develop new theory and methodologies for geographic vaccine trials. Generally, the underlying assumption in conventional vaccine trial methods is that the effect of the vaccine is the same throughout the trial area. A previously conducted study tested whether this assumption is true for an oral cholera vaccine trial using a spatially referenced database (Ali et al., 2005, Ali et al., 2008, Emch et al., 2006, and Emch et al., 2007). The results illustrated that the protective efficacy of oral cholera vaccines varies in space (Emch et al., 2007) and that the variation is inversely related to vaccine coverage (i.e., % of people vaccinated in an area) after adjusting for several ecological factors (Emch et al., 2006). Higher levels of neighborhood vaccine coverage are linked to lower risk of cholera among residents (Ali

et al., 2005 and Ali et al., 2008). These findings show that higher levels of vaccine coverage can lead to higher levels of indirect protection of non-vaccinees, and may also lead to higher levels of total protection, i.e., indirect protection combined with direct protection of vaccines (Ali et al., 2005). We coined the term "ecological vaccine trials" because such an approach includes neighborhood-level variables in addition to conventional individual-level variables commonly used in vaccine evaluation. Most recently, the definition of what classifies as a neighborhood was further developed by considering environmental connectivity, or the extent to which people are connected by water bodies. Findings indicated that indirect protection is positively linked to levels of vaccination in environmental neighborhoods as well (Emch et al., 2009).

The previous work is extended here by integrating an additional social component that has thus far not been considered. More specifically, we account for the social networks that individuals belong to and how these networks offer indirect protection regarding vaccine efficacy. Conventional vaccine evaluation may be biased because of spatial variation in neighborhood-level vaccine coverage and different community-level characteristics. While previous geographic analysis of the vaccine data provided profound new insights into the incorporation of spatial theory and methods into vaccine trials, potentially important social factors were not considered. Namely, the initial model assumed that all people are just as likely to come into contact with one another within a given Euclidean neighborhood size, when in fact, realistically, individuals are more likely to interact with other individuals to whom they are connected through kin or social relations. While a spatially-defined neighborhood can be used to calculate potential fecal-oral contact, social proximity is also likely to control contamination. Indirect protection may thus be affected by levels of coverage not only in spatial and environmental neighborhoods, but also social networks. This study extends the previous research by testing indirect protection when data on vaccination levels in networks is integrated into our original model. We test this using information not only for the entire network but also for local-level connections, or those that occur within certain distances. We do this because despite being socially connected, individuals who live further away from one another may have less frequent contact and thus less of an effect on indirect protection outcomes.

We use three datasets including: (1) a cholera vaccine trial database, (2) a longitudinal demographic database of the rural population from which the vaccine trial participants were

selected, and (3) a household-level spatial database of the same study area. These databases provide a unique opportunity to develop and test new vaccine trial methods. The cholera vaccine trial is one of the largest in history with approximately 49,336 two or three dose vaccinees, and the longitudinal demographic database of the study area is known to be the most comprehensive in the developing world. All vital demographic events in a population of approximately 200,000 people were noted every two weeks through an extensive community-based data collection system. A corresponding household-level GIS database allows us to identify the household location of all individuals who took part in the trial as well as the household location of each person in the demographic surveillance system (i.e., the background population). This spatial database, in conjunction with the demographic and vaccine datasets, facilitates adding an integrated, comprehensive, and accurate spatial component to all of the datasets. The datasets are also contemporaneous; the demographic and vaccine datasets were collected during the same time period, and the GIS database of households was created later but the locations of the houses did not change.

Our main objective is to introduce methods for future vaccine trials that consider the dynamics of vaccine coverage not only in space, but also in social networks. We accomplish this by measuring relationships between vaccinee and placebo incidence based on the levels of vaccine coverage within the social network to which individuals belong, while also considering potentially confounding ecological variables. We hypothesize that higher levels of vaccine coverage will lead to higher levels of indirect protection of non-vaccinees, similar to the findings by Ali et al. (2005) and Emch et al. (2009) in terms of neighborhood-level coverage. We also hypothesize this protective effect is greater when considering only those socially connected individuals within a certain distance, as we assume frequency of interaction with those actors is greater.

Background and Data

In 1985, a community-based individually randomized oral cholera vaccine trial was conducted in Matlab, Bangladesh, the research site for the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B). This double-blind trial measured the efficacy of two vaccines, the B subunit-killed whole cell (BS-WC) and the killed whole cell only (WC). The

control agent was *Escherichia coli* K12 strain. Females aged 15 years and older and children aged 2–15 were the target group. Three vaccine doses were given in six-week intervals. The vaccine trial used a passive surveillance system to identify cholera cases from the study area. The surveillance took place at one hospital and two community-based treatment centers. During 5 years of follow-up, the protective efficacy was 49% for the BS-WC group ($P < 0.001$) and 47% for the WC group ($P < 0.001$). Protection was lower in children who were vaccinated at 2–5 years than in older persons. For children in this age group, protection waned after 4–6 months and was not evident at all during the third year. Vaccinated persons older than 5 years of age were protected even in the third year of follow-up (Clemens, Sack, Harris, et al., 1990).

The research site for the ICDDR,B and for this project is called Matlab because the Centre's hospital is located in Matlab Town. Matlab is in south-central Bangladesh, approximately 50 km southeast of Dhaka, adjacent to where the Ganges River meets the Meghna River forming the Lower Meghna River. A demographic surveillance system (DSS) has recorded all vital events of the study area population since 1966; the study area population has been approximately 200,000 since that time. The database is the most comprehensive longitudinal demographic database of a large population in the developing world. The residents of the study area live in clusters of patrilineally related groups of households called *baris*. A GIS database of the Matlab field research area has been created to facilitate spatial analysis (Ali et al., 2001; Emch, 1999). Features in digital format include *baris*, rivers, and health facilities. Figure 1 shows the GIS database at three different scales. The map view on the far right has the individual *bari* identification numbers visible. The *baris* are all identified by an ICDDR,B DSS census number, a unique number assigned to all individuals in the study area, within the structure of the GIS database. In turn, demographic data, disease incidence, or vaccine status data can be linked to specific *bari* locations. The Matlab field research center has in- and out-patient services, a medical laboratory, and research facilities. One-hundred twenty community health workers visit each household area every two weeks to collect demographic, morbidity, and other data.

This study uses retrospective vaccine trial data collected in Matlab from 1985 to 1990 (Clemens et al., 1987; Clemens et al., 1988a; Clemens et al., 1988b; Clemens et al., 1991; Clemens et al., 1992; Clemens et al., 1989; Clemens et al., 1986; Clemens et al., 1986; Clemens et al., 1989; Clemens et al., 1990; Clemens et al., 1990; Clemens et al., 1988; Clemens et al., 1988; Clemens

et al., 1989; Durham et al., 1998; van Loon et al., 1996; and Sack et al., 1991). The objective of this randomized double-blind, placebo controlled trial was to determine whether three doses of BS-WC and WC vaccines reduce the incidence of laboratory confirmed cholera in 2–5-year-old children and females over 15. The target group was individually randomized based on a simple random sampling scheme derived from DSS records. The Matlab GIS database includes an accurate *bari* location for all individuals living in the study area including all vaccinees, controls, people who refused vaccines, and everyone else living in the study area who was not part of the study. The GIS database also includes the locations of the treatment facilities that were used in the passive surveillance system for the vaccine trial. We have linked the individual-level data from the vaccine trial to *bari* locations via the ICDDR,B DSS census identification number. The GIS thus facilitates the identification of the dwelling locations of individuals who participated in the clinical trial, as well as the entire population distribution of the Matlab study area.

Social network analysis methods are used to measure relationships between social entities (Wasserman & Faust, 1994; Hanneman, 2001). They are particularly useful for measuring social relationships that influence disease outcomes or health interventions (Morris, 2004). In this study, we identify and consider social relationships between *bari*s and use these to define social networks at the individual level. Specifically, the actors in our network are people with some kinship relationship that will foster movement between physical residences, and thus the relationships that we will measure are based on family connections. Kinship networks are an important part of social interactions, especially in rural communities (Guest and Chamratrithirong, 1992) and in lower socio-economic settings (Hollinger and Haller, 1990). While individuals in our study area certainly interact with others to whom they are not related, many of the more prolonged social interactions such as visits between households and shared meals are likely to include kin. We then integrate vaccine coverage and disease data into this network for the purpose of evaluating the relationship between levels of coverage in the network and disease incidence. Research on the spread of epidemics across networks has shown that successful immunization strategies should take such relationships into account in order to be most effective (Pastor-Satorras and Vespignani, 2002; Eubank et al, 2004). Much of this research, however, is usually based on simulated models of disease diffusion, while our work

analyzes placebo incidence and vaccine coverage across a social network using existing vaccine trial data.

Methods

We first used demographic and migration data from the time period during which the vaccine trial was conducted to create a social network showing linkages between *baris*, representing the network that existed in the beginning phases of the vaccine trial. This was done using individual-level identification codes which are related to the *bari*s in which a person has lived or currently lives. Each person in the Matlab study area and within the vaccine trial population has two unique identifiers, a Current ID (CID) and Registration ID (RID). The CID and RID are assigned upon birth or in-migration to Matlab and the RID is retained throughout the duration of the individual's time of residence in the study area. The CID, however, changes when an individual moves to a new *bari*. Both CID and RID are based on *bari* identification codes and therefore one can use them to determine the current or original *bari* of residence.

These inter-*bari* migrations are usually based on kinship, such as marriage into a different family. We assume here that when an individual moves, he or she maintains interaction with the previous *bari* of residence due to existing kinship relations. Though the original migration is directional, the resulting interaction between the two *bari*s is mutual; therefore the social connections are non-directional. Using individual RIDs and CIDs, we determined the last *bari* of residence for each individual if he or she had migrated, at some point, to their current *bari*. This created an individual-to-*bari* linkage, which we aggregated to a *bari*-to-*bari* linkage, or a linkage between the individual's previous and current *bari*.

We then created a node list containing each *bari* and every *bari* that it was presumed to be socially connected to, via the migration of individuals. Out of 6,423 *bari*s used in the trial, 233 were socially isolated, meaning they had no connections. For the 6,190 *bari*s that did have social ties, the average degree centrality was 4.71 ties and the median number of ties was 2.5. When adding the isolated *bari*s, the average degree centrality was 4.53 ties and the median number of ties was 2. The highest number of connections any *bari* had was forty.

Using the total number of vaccines in the network over the total targeted population in the network, we calculated the rate of vaccine coverage for the social network of every *bari*, which included the respective populations within the ego *bari* as well. We used the following model:

$$C_i = \left[\frac{v_i}{t_i}\left(\frac{\sum_{j=1}^{k} v_j}{\sum_{j=1}^{k} t_j}\right)\right] \times 100$$

Equation 1: Method for calculating bar-level social network vaccine coverage

Where C_i is the rate of vaccine coverage within the social network of *bari i*; v_i and t_i are the sum of the vaccinees and the target population, respectively, in *bari i*; v_j is the sum of the vaccinees in *bari*s *j* through *k* socially connected to *bari i*; and t_j is the sum of the target population in *bari*s *j* through *k* socially connected to *bari i*.

For each individual, we assigned a rate of vaccine coverage within his or her social network, based on the social network of his or her *bari* of residence at the beginning of the vaccine trial:

$$C_{p,i} = \left[\frac{v_i}{t_i}\left(\frac{\sum_{j=1}^{k} v_j}{\sum_{j=1}^{k} t_j}\right)\right] \times 100$$

Equation 2: Method for calculating individual-level social network vaccine coverage

Where $C_{p,i}$ is the rate of vaccine coverage within the social network of individual p, within *bari i*. The remaining elements are as described above in Equation 1.

We then repeated the process of creating a social network as described above including only those socially connected *bari*s that also fell within a 500 meter and 1,000 meter (one kilometer) neighborhood of the ego *bari* (Figure 2). These *bari*s were then integrated into Equations 1 and 2. The resulting coverage variable was assigned to each individual, representing the level of vaccine coverage in his or her social network within 500 meters and one kilometer. We chose a 500 meter neighborhood because that was the distance used by both Ali et al. (2005) and Emch et al. (2009), but extended this to one kilometer as well for comparison purposes. We hypothesized that individuals interact more frequently with those in their social network who live

at a closer distance, and thus indirect protection conferred by the level of vaccine coverage in one's neighborhood-bounded social network would have a stronger effect.

In order to analyze the relationship between vaccine coverage in one's social network and disease incidence, we built logistic regression models using generalized estimating equations with a logit link function to control for *bari*-level clustering. The dependent variable unit was the individual and the main independent variables of interest were level of vaccine coverage within his or her 1) entire social network, 2) social network within 500 meters, and 3) social network within one kilometer. The models also controlled for potential confounding variables (age, sex, religion, distance to nearest river, distance to nearest treatment center, and dysentery incidence). Coefficients of independent variables in the models were exponentiated to estimate the odds ratio of cholera associated with different levels of coverage. Standard errors for the coefficients were used to estimate *P* values and associated 95% confidence intervals for the odds ratios.

Results

Among the vaccine trial target population living in the villages that were mapped with geographic information systems in 1994, there were 49,336 vaccine recipients and 24,667 placebo recipients. Within a year of vaccination, 204 cholera cases were detected, 96 (47%) of whom had been vaccinated. Of the vaccine recipients, the average level of vaccine coverage in the social network was 44.7%. The average level of coverage for placebo recipients was 43.6%, and the average level across both populations was 44.3%.

Table 1 shows the relationship between an individual's risk of cholera and levels of vaccine coverage in his or her entire social network, in models that used generalized estimating equations with the logit link function and that controlled for potential confounding variables known to be associated with the risk of cholera in the study area. In these models, we also controlled for whether an individual had experienced dysentery during follow-up to adjust for confounding effects not captured by the other variables in the models. Three separate models were built for (1) both vaccine and placebo recipients, (2) vaccine recipients only, and (3) placebo recipients only. In the combined model, vaccination of the individual and the level of vaccine coverage

measured through the social network were each shown to have independent protective effects on cholera risk ($P<0.0001$ and $P=0.0002$, respectively). Models 2 and 3 show that the inverse relation between cholera risk and the level of vaccine coverage was more pronounced for vaccinees (odds ratio of 0.97, $P = 0.003$) than for placebo recipients (odds ratio of 0.98, $P = 0.008$) while controlling for other known risk factors of cholera.

Tables 2 and 3 show the results of the same model as used above, but using only those social contacts within a 500-meter and 1-kilometer neighborhood to calculate vaccine coverage. Similarly to the entire social network, vaccination and levels of vaccine coverage within the neighborhood-level social network had a protective effect for all recipients ($P<0.0001$ and $P=0.003$, respectively, for 500 meters; $P<0.0001$ and $P=0.002$, respectively, for one kilometer), but the protective effects of the social networks were not as pronounced as with the entire network. The same pattern remains regarding levels of coverage and relative risk in the total population and vaccine versus placebo recipients; that is, levels of vaccine coverage in the neighborhood-level social network displayed a stronger protective effect for vaccine recipients ($P=0.02$) than for placebo recipients ($P=0.03$). Figure 3 illustrates the differences between risk for the three populations within the three types of networks, and compares it to results from Ali et al. (2005) which used levels of vaccine coverage in the population within a 500-meter Euclidian distance.

Discussion

Previous work shows that indirect protection conferred by a cholera vaccine is related to higher levels of vaccine coverage in spatial neighborhoods. However, this method assumes that all individuals within such neighborhoods are equally likely to come into contact with one another. Developing measures to define who an individual is more likely to interact with is useful for understanding the nature of indirect protection and herd immunity in ecological vaccine trials, particularly if herd immunity is indeed related to contact with vaccinees.

In this research, we seek to develop additional methods for vaccine trials by using levels of vaccine coverage in social networks as an independent variable predicting cholera risk. As we

hypothesized, our results show that individuals are in fact indirectly protected if rates of coverage in their social network are higher. This applies when considering both the entire network as well as networks at the neighborhood scale, and when controlling for various ecological effect modifiers. Overall, these results are consistent with the previous work of Ali et al. (2005) and Emch et al. (2009), which examined risk related to levels of coverage within spatial and environmental neighborhoods. However, these two studies found a stronger effect for placebo recipients, while our results identified a stronger effect for those who had received the vaccine. Furthermore, vaccine coverage in social networks bounded by distances of 500 meters and one kilometer was less protective than coverage within the entire network. These results were unexpected given our original hypotheses, raising interesting questions regarding the nature of indirect protection and herd immunity as related to environmental versus population variables. There are certainly multiple processes that affect vaccine efficacy, and social networks are only one of them. An improved analysis would integrate both social and environmental components is the subject of our future research program.

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Supplemental Materials

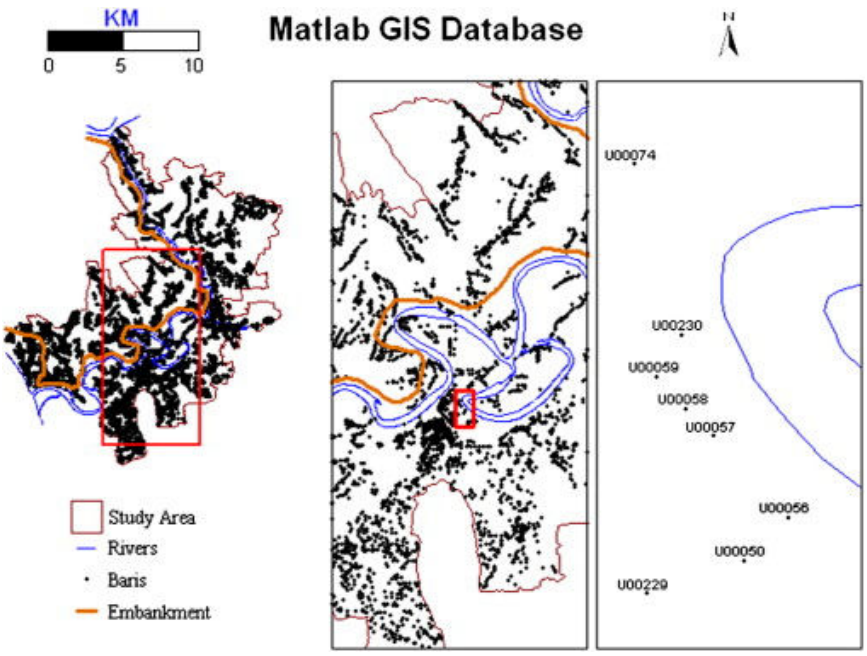

Figure 1: The Matlab GIS at three different scales

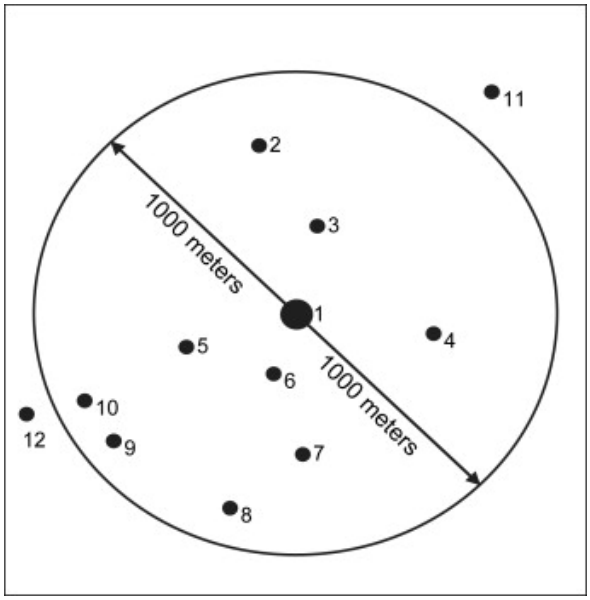

Figure 2: Example of a 1000-meter neighborhood

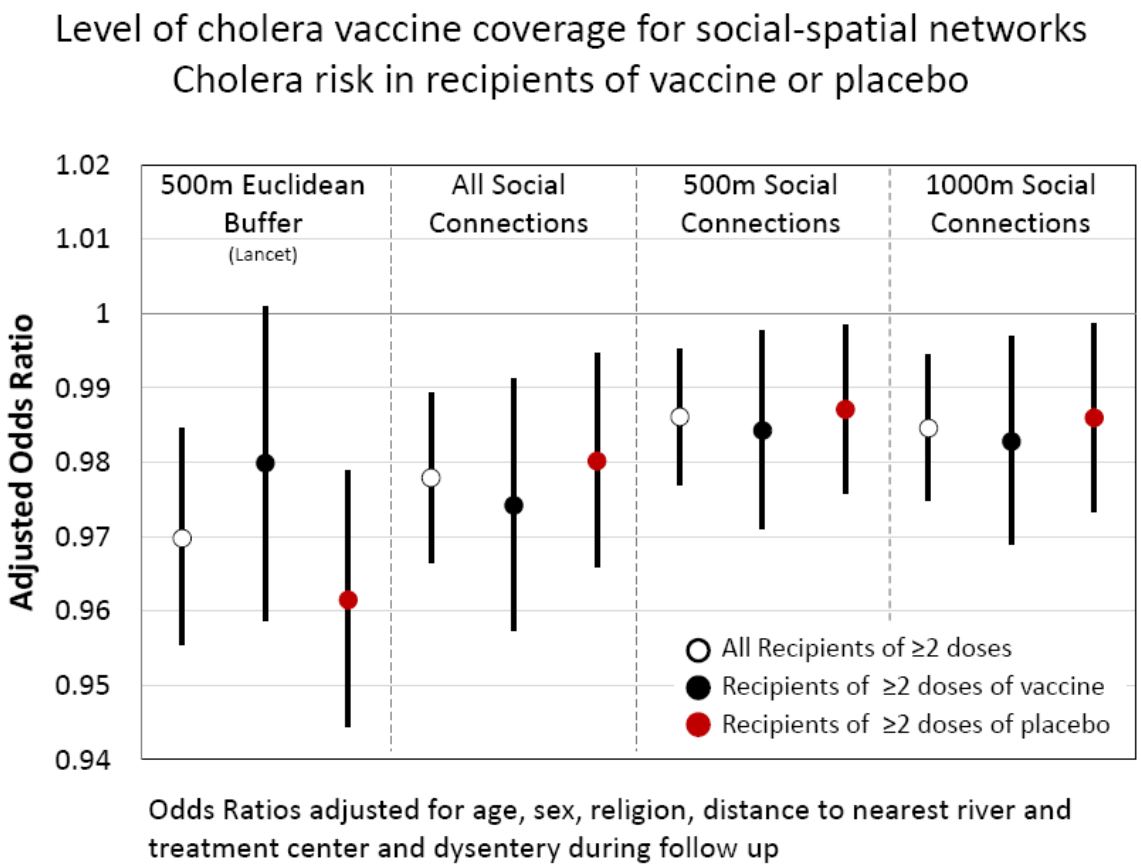

Figure 3: Cholera risk in all recipients and vaccine vs. placebo recipients considering levels of vaccine coverage in a) the entire population within a 500-meter Euclidian buffer (from Ali et al, 2005); b) the individual's entire social network; c) the individual's social network within 500 meters, and d) the individual's social network within one kilometer.

	Model 1: All recipients of ≥2 doses (n=74 003)			Model 2: Recipients of ≥2 of vaccine (n=49 336)			Model 3: Recipients of ≥2 doses of placebo (n=24 667)		
	OR*	**95% CI**	**p**	**OR***	**95% CI**	**p**	**OR***	**95% CI**	**p**
Age (years)	0.98	0.97-0.99	0.0008	0.95	0.92-0.98	0.003	0.99	0.98-1.0	0.2
Sex (female vs. male)	1.14	0.83-1.55	0.43	1.18	0.77-1.80	0.45	1.05	0.68-1.62	0.81
Religion (Hindu vs. non-Hindu)	1.1	0.70-1.74	0.0036	1.19	0.62-2.29	0.6	1.05	0.58-1.93	0.86
Distance from *bari* to nearest river (km)	0.88	0.76-1.01	0.66	0.86	0.71-1.03	0.10	0.91	0.75-1.10	0.32
Distance from *bari* to nearest treatment center (km)	1.13	1.04-1.21	0.06	1.14	1.03-1.26	0.009	1.11	0.99-1.24	0.06
Experienced dysentery during follow-up (yes/no)	4.63	1.41-15.14	0.0113	6.12	1.51-24.81	0.011	3.17	0.46-21.87	0.24
Received >=2 doses (vaccine vs. placebo)	0.46	0.35-0.6	<0.0001	-	-	-	-	-	-
Level of vaccine coverage in social network (%)	0.98	0.97-0.99	0.0002	0.97	0.96-0.99	0.003	0.98	0.97-0.99	0.008

Table 1: Predictors of cholera risk among vaccine and placebo recipients.

*Multivariate odds ratio for the cited variable, adjusted for all other variables in the table, in a model using generalized estimating equations (GEE) with the logit link function.

	Model 1: All recipients of ≥2 doses (n=74 003)			Model 2: Recipients of ≥2 of vaccine (n=49 336)			Model 3: Recipients of ≥2 doses of placebo (n=24 667)		
	OR*	**95% CI**	**p**	**OR***	**95% CI**	**p**	**OR***	**95% CI**	**p**
Age (years)	0.98	0.96-0.99	0.001	0.95	0.92-0.98	0.003	0.99	0.98-1.0	0.2
Sex (female vs. male)	1.14	0.83-1.55	0.43	1.18	0.77-1.80	0.45	1.05	0.68-1.62	0.82
Religion (Hindu vs. non-Hindu)	1.09	0.69-1.72	0.72	1.17	0.61-2.24	0.6	1.04	0.57-1.91	0.89
Distance from *bari* to nearest river (km)	0.87	0.76-0.99	0.04	0.84	0.70-1.01	0.07	0.90	0.75-1.08	0.26
Distance from *bari* to nearest treatment center (km)	1.12	1.03-1.21	0.01	1.14	1.03-1.26	0.01	1.10	0.99-1.23	0.08
Experienced dysentery during follow-up (yes/no)	4.67	1.42-15.33	0.01	6.17	1.51-25.21	0.01	3.20	0.46-22.16	0.24
Received >=2 doses (vaccine vs. placebo)	0.46	0.35-0.61	<0.0001	-	-	-	-	-	-
Level of vaccine coverage in social network within 500m (%)	0.99	0.99-1.0	0.003	0.98	0.97-1.0	0.02	0.99	0.98-1.0	0.03

Table 2: Predictors of cholera risk among vaccine and placebo recipients, using a 500-meter neighborhood.

*Multivariate odds ratio for the cited variable, adjusted for all other variables in the table, in a model using generalized estimating equations (GEE) with the logit link function.

	Model 1: All recipients of ≥2 doses (n=74 003)			Model 2: Recipients of ≥2 of vaccine (n=49 336)			Model 3: Recipients of ≥2 doses of placebo (n=24 667)		
	OR*	**95% CI**	**p**	**OR***	**95% CI**	**p**	**OR***	**95% CI**	**p**
Age (years)	0.98	0.96-0.99	0.001	0.95	0.92-0.98	0.0027	0.99	0.98-1.0	0.2
Sex (female vs. male)	1.13	0.83-1.55	0.43	1.18	0.77-1.80	0.45	1.05	0.68-1.62	0.82
Religion (Hindu vs. non-Hindu)	1.08	0.69-1.71	0.73	1.15	0.60-2.22	0.66	1.04	0.57-1.91	0.90
Distance from *bari* to nearest river (km)	0.87	0.76-1.0	0.05	0.85	0.71-1.02	0.08	0.90	0.75-1.09	0.28
Distance from *bari* to nearest treatment center (km)	1.12	1.04-1.21	0.004	1.14	1.03-1.26	0.01	1.11	0.99-1.23	0.07
Experienced dysentery during follow-up (yes/no)	4.62	1.41-15.16	0.01	6.13	1.5-25.1	0.0116	3.17	0.46-21.82	0.24
Received >=2 doses (vaccine vs. placebo)	0.46	0.35-0.6	<0.0001	-	-	-	-	-	-
Level of vaccine coverage in social network within 1 km(%)	0.98	0.97-0.99	0.002	0.98	0.97-1.0	0.0169	0.99	0.97-1.0	0.0314

Table 3: Predictors of cholera risk among vaccine and placebo recipients, using a one-kilometer neighborhood.

*Multivariate odds ratio for the cited variable, adjusted for all other variables in the table, in a model using generalized estimating equations (GEE) with the logit link function.