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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.

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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;

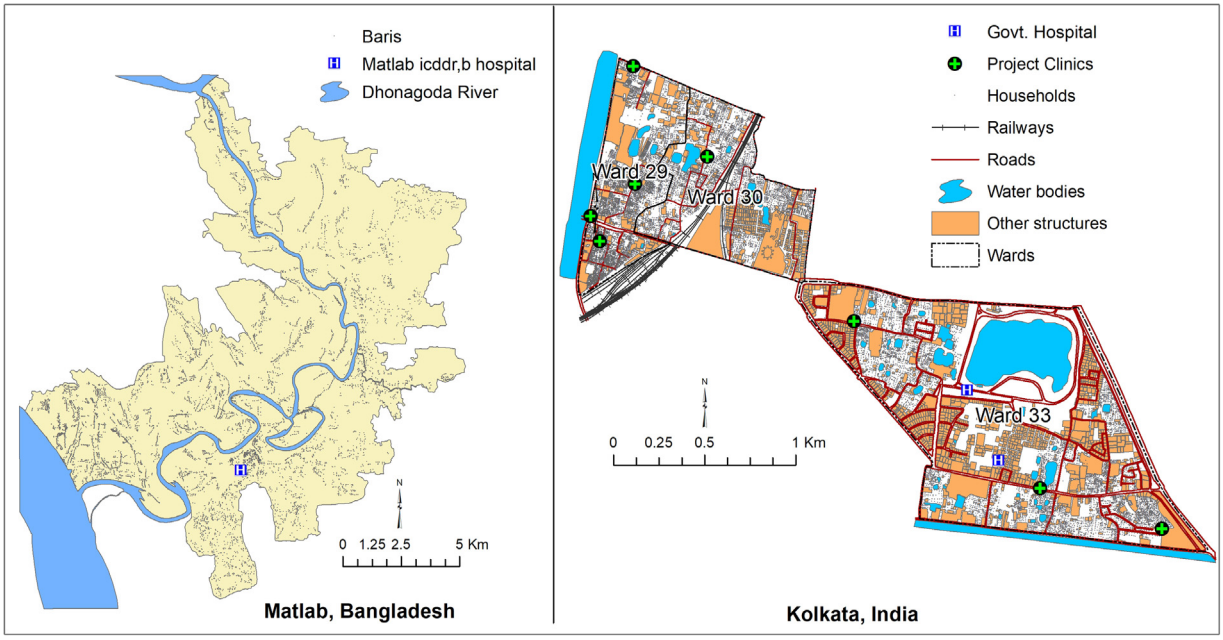

Figure 1. The study areas.

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