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Clinical Outcomes in Household Contacts of Patients with Cholera in Bangladesh

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Abstract

Background—Multiple *Vibrio cholerae* infections within the same household are common. The objective of this study was to examine the incidence of *V. cholerae* infection and associated clinical symptoms in household contacts of patients with cholera, and to identify risk factors for development of severe dehydration in this cohort.

Methods—Household contacts of hospitalized patients with cholera were observed with frequent clinical assessments and collection of serum and rectal swab cultures for a period of 21 days after presentation of the index case.

Results—Half (460/944) of all contacts reported diarrhea during the study period, and symptoms most frequently began two days after presentation of the index case. Antibiotics were used by 43% (199/460) of the contacts with diarrhea. Rectal swab culture for *V. cholerae* was positive in 22% (202/944) of contacts and 73% (148) of infected contacts experienced diarrhea. Significant dehydration developed in 26 contacts; predictors of dehydration included vomiting, each additional day of diarrhea, and blood group O status.

Conclusions—In urban Bangladesh, the burden of diarrheal illness in household contacts of cholera patients is higher than previously estimated and prophylactic intervention is feasible because the majority of symptomatic cases of *V. cholerae* infection in contacts begin soon after presentation of the index case. Reconsideration of targeted chemoprophylaxis for household contacts of cholera patients may be warranted.

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Keywords

Cholera; *V. cholerae* O1/O139; gastroenteritis; household contacts; antibiotic prophylaxis

INTRODUCTION

The etiologic agent of cholera, *Vibrio cholerae*, causes 3 to 5 million cases of secretory diarrhea and over 100,000 deaths annually [1]. Strains of *V. cholerae* can be differentiated serologically by the O-side chain of the lipopolysaccharide (LPS) component of the outer membrane. Although more than 200 different serogroups have been isolated from the environment, only serogroups O1 and O139 are major causes of cholera. *V. cholerae* O1 biotype El Tor is currently the predominant cause of cholera globally and in Bangladesh.

Multiple *Vibrio cholerae* infections within the same household are common. These may occur simultaneously through shared sources of contaminated food and water, or through fecal-oral transmission within households. In two large prospective cohorts of contacts of cholera patients in Bangladesh, rectal swab positive infections occurred in 78 of 506 (17%) household contacts of patients with cholera caused by *V. cholerae* O1 biotype classical [6], and in 476 of 1658 (29%) household contacts of cholera patients infected with *V. cholerae* O1 biotype El Tor [7]. Diarrhea occurred in 50% and 35% of the rectal swab positive contacts of classical and El Tor infected index patients, respectively, with the remainder of contacts shedding *V. cholerae* without symptoms. In both studies, increasing age and increasing baseline vibriocidal antibody titers were associated with decreased risk of *V. cholerae* O1 infection in household contacts [6,7]. These studies demonstrate that household contacts of cholera patients are at high risk of infection, even in cholera endemic areas.

To identify factors associated with susceptibility to *V. cholerae* in the present era, we prospectively followed a cohort of household contacts of patients with severe cholera in Dhaka, Bangladesh. Previously, we described the genetic, immunologic, and nutritional characteristics associated with susceptibility to rectal swab culture positive *V. cholerae* infection in this cohort [8,9]. The objective of this secondary analysis was to explore the incidence and clinical outcomes of *V. cholerae* infections in household contacts of patients with cholera and to identify risk factors for development of dehydration in household contacts.

METHODS

Enrollment and study design

The Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) provides care for over 100,000 patients with diarrheal illness and associated co-morbid conditions, including over 20,000 cholera patients annually. Index patients six months of age or older presenting to the ICDDR,B with acute secretory diarrhea, a positive stool culture for *Vibrio cholerae* O1 or O139 and no significant co-morbid disease were eligible for the study. Household contacts of these patients were defined as persons sharing the same cooking pot for at least the previous three days. Contacts were excluded if enrolled in other studies or if they had received care at the ICDDR,B in the preceding two months. A field team discussed enrollment with household members within six hours of index case presentation, and consenting contacts without significant co-morbid disease were enrolled into the study.

Contacts were observed prospectively for a 21-day period, beginning on the date of index case stool culture confirmation and enrollment (referred to as day 2). Collection of rectal swabs and clinical data occurred during home visits on consecutive study days 2 through 7, and on days 14 and 21. Study personnel obtained clinical histories from the preceding week on study days

2, 14, and 21. Blood was collected from contacts at the ICDDR,B on days 2, 7 and 21. Those not completing follow-up through 21 days were excluded from the analysis.

The study was approved by the Ethical Review Committee of the ICDDR,B and the Institutional Review Board of Massachusetts General Hospital. Written informed consent was obtained from all participants or their guardians. The human experimentation guidelines of the U.S. Department of Health and Human Services were followed during the conduct of this research.

Microbiological and serological assays

Index case stool was cultured overnight on taurocholate-tellurite-gelatin agar (TTGA), and suspect colonies were confirmed with the slide agglutination method using specific monoclonal antibodies [10,11]. Rectal swabs from contacts were transported in Cary-Blair media after collection at the participant households or at the ICDDR,B. Specimens were inoculated for enrichment on alkaline bile peptone broth [12] and on TTGA and incubated overnight. Colony identification was performed after plating on TTGA. Vibriocidal antibody assays were conducted as previously described with guinea pig complement and the homologous *V. cholerae* O1 El Tor Ogawa (strain 25049), *V. cholerae* O1 El Tor Inaba (strain T-19479), or *V. cholerae* O139 (strain 4260B) [9,13]. Contacts were not routinely tested for other pathogens.

Clinical management and outcomes

Diarrhea was defined as three or more loose stools in a 24-hour period. Contacts with a positive rectal swab culture for *V. cholerae* were considered infected. Dehydration was defined according to standardized ICDDR,B criteria, with moderate dehydration defined as any two of the following features: irritability, sunken eyes, dry mucosa, thirst, or reduced skin turgor. Dehydration was classified as severe if moderate dehydration was accompanied by inability to drink, lethargy, unconsciousness, or absence/irregularity of the radial pulse. *V. cholerae* shedding duration was defined as the time period between positive rectal swab cultures, including days when a negative rectal swab culture was obtained, or during weekly periods where no rectal swab was obtained between positive cultures.

Contacts reporting loose bowel movements received oral rehydration solution (ORS) packets with instructions for home use, including information on the warning signs and symptoms of dehydration. Field staff evaluated contacts directly for signs of dehydration during each home visit using the criteria listed above. If dehydration was present, contacts were given ORS and referred to the ICDDR,B for treatment. At the ICDDR,B, intravenous fluids were used to treat patients with severe dehydration and those with moderate dehydration who could not take fluids by mouth.

Antibiotics are important adjuncts in the treatment of symptomatic *V. cholerae* infection; they reduce duration of illness, volume of diarrhea, and requirements for oral and intravenous fluid. All contacts with diarrhea and a positive rectal swab culture for *V. cholerae* received antibiotic treatment. Adults received single dose doxycycline (300 mg) until resistance became widespread in Bangladesh in 2005 [14]. Subsequently, single dose ciprofloxacin (1 gram) or azithromycin (1 gram) were used. Children under the age of 18 years were treated with erythromycin (30–50 mg /kg/day for three days) or single dose azithromycin (20 mg/kg). When indicated, antibiotics were also prescribed for *V. cholerae*-negative contacts reporting blood or mucus in the stool, or severe watery diarrhea. Study physicians did not prescribe prophylactic antibiotics for asymptomatic contacts of cholera patients, although self-prescribed antibiotic use by household contacts was common and recorded in the clinical history.

Statistical Analysis

Data was analyzed using Stata version 9.0 (Stata Corp, College Station, Texas). The Student's t-test was used to compare means, with a predetermined cutoff of $P \leq 0.05$ indicating a statistically significant difference. A multivariate analysis of risk factors for dehydration was performed with a logistic regression model using generalized estimating equations, with P values adjusted for clustering based on household [15]. The final model was based on forward selection with predetermined cutoff criteria of $P \leq 0.2$ for inclusion in the model. Odds ratios (OR) are reported in the text and tables with 95% confidence intervals. All reported P values are two-tailed.

RESULTS

Household characteristics

From January 2001 to May 2006, we enrolled 1077 contacts of 399 cholera cases. 944 contacts completed the 21-day observation period. The median age of index cases was 24 years (range 11 months to 66 years). The median age of contacts was 19 years (range 6 months to 71 years). We enrolled an average of 2.7 contacts per case. Nuclear family members of the index case made up 94% of household contacts. Parents of the index case comprised the largest group of contacts (31%), followed by sons or daughters (25%), siblings (20%) and spouses (18%). Equal numbers of men and women participated in the study. The acquisition rate for daily rectal swab collection in contacts completing the 21 days of observation was over 95%.

Clinical course in contacts of cholera patients

Table 1 compares the distribution of demographic and clinical characteristics in all 944 household contacts of cholera patients and in the 202 rectal swab positive contacts. Including the week before case presentation and the 21-day follow-up period, diarrhea was reported by 49% (460/944) of household contacts, and vomiting was reported by 13% (124/944). Daily clinical assessments after enrollment of the index case revealed moderate to severe dehydration in 3% (26/944) of household contacts overall. In contacts with a positive culture for *V. cholerae*, 73% (148/202) developed diarrhea during the observation period, and of those 86% (127/148) developed diarrhea within 72 hours of a positive culture result. As anticipated, diarrhea, vomiting and dehydration were all significantly more frequent in culture positive contacts. A large portion of symptomatic contacts with diarrhea and vomiting were not culture positive for *V. cholerae*. Of those 335 patients with diarrhea and/or vomiting and negative rectal swab cultures, 51 (15%) had a ≥ 4 fold rise in vibriocidal antibody titer during follow-up, suggesting a *V. cholerae* infection that was not detected by rectal swab culture.

The use of ORS and antibiotics were common among household contacts of cholera patients. Most contacts that developed diarrhea and/or vomiting during the follow-up period (after the enrollment of the index case) used ORS (83%, 303/366). Antibiotics were taken by 83% (120/144) of contacts with symptomatic *V. cholerae* infection. Among all contacts reporting diarrhea, 43% (199/460) took antibiotics, including 79 contacts with diarrhea and a negative *V. cholerae* rectal swab. Antibiotic use was reported by 48 uninfected contacts without diarrhea during the observation period, possibly for the treatment of other conditions or for self-prophylaxis against cholera.

Figure 1 shows the proportion of household contacts with diarrhea, vomiting and with positive *V. cholerae* cultures over the period of observation. Index cases presented to the ICDDR,B an average of 17 hours after the onset of diarrhea (SD +/− 3.7 hours). Two-thirds of contacts that reported diarrhea developed symptoms after case presentation (66%, 302/460). Diarrhea developed in half of these contacts within four days of the hospitalization of the index case (50%, 152/302); the most common day of diarrhea onset was two days following presentation

of the case. Vomiting in contacts generally began immediately before the onset of diarrhea. Similarly, 60% (121/202) of the household contacts who developed rectal swab positive infection did so by day 4 after infection, with a peak in the proportion of positive contacts on day 3 after enrollment of the index case. By day 5 of the follow-up period, 72% (145/202) of contacts who developed infection during the 21 day follow-up period had tested positive for *V. cholerae*.

Dehydration developed in 26 contacts (three severe and 23 moderate), and 16 of these contacts tested positive by rectal swab culture for *V. cholerae*. An additional three contacts with dehydration had a four-fold or greater change in serum vibriocidal antibody titer during the follow-up period. Most dehydrated contacts were identified on the day after presentation of the index case (62%,16/26).

Age, gender, and relationship to index case and development of clinical illness in contacts of cholera patients

Contacts age14 years and younger were more likely to develop diarrhea, vomiting and culture positive infection, and were more likely to use antibiotics and ORS than older contacts (Table 2). As noted in previous studies [9], gender was not associated with increased susceptibility to infection (p=0.91). Infection was not significantly more likely in contacts who were parents compared to children of the index case, although as we previously reported, first degree relatives of index cases had a higher risk of infection compared to non-related household contacts [9].

Risk factors for dehydration

In order to examine risk factors for dehydration and to investigate potential confounding, we performed stepwise multivariate logistic regression in contacts with rectal swab positive diarrhea, as shown in Table 3. In this analysis, vomiting was the most significant predictor of the development of significant dehydration in *V. cholerae* infected patients. While only one-fourth (42/148) of the *V. cholerae* culture positive contacts with diarrhea reported vomiting, the majority of contacts with *V. cholerae* infection and dehydration experienced vomiting (16/19, 84%). All three patients diagnosed with severe dehydration reported vomiting. Each additional day of diarrhea, as well as blood group O status, were independently associated with a significantly increased risk of dehydration. Although young age was associated with a significant risk of symptomatic *V. cholerae* infection, the association between younger age and risk of dehydration did not reach statistical significance in this study.

Duration of bacterial shedding

V. cholerae infected contacts shed bacteria for a mean of two days and a maximum of 12 days. There was no significant relationship between duration of shedding and symptoms. Half of the contacts shedding for seven days or more were asymptomatic, including the two contacts shedding for the longest periods (one each for 11 and 12 days). There was no significant relationship between prolonged shedding (equal to or more than four days of shedding) and age (OR 0.99, p=0.66, CI: 0.99–1.0) or blood group O (OR 0.60, p=0.23, CI: 0.25–1.4). Sixty contacts shared a household with a prolonged shedder, and these persons were more likely to become infected than contacts living with individuals who shed *V. cholerae* for less than four days (OR 2.1, p=0.03, CI: 1.1–4.2).

DISCUSSION

We performed a prospective evaluation of household contacts of cholera patients in urban Bangladesh. Consistent with previous studies, we observed a high incidence of *V. cholerae* infection among household contacts. Over 70% of rectal swab positive contacts reported

diarrhea during the observation period; this rate of symptomatic infection exceeds that observed in previous studies of household contacts of cases with *V. cholerae* O1 El Tor infection. The reasons we observed a higher incidence of symptomatic disease in patients with a positive culture for *V. cholerae* O1 El Tor compared to previous studies are unknown; this may reflect changes in the population, such as in baseline levels of immunity or population density, or changes in organism virulence. For example, the emergence of a *V. cholerae* O1 El Tor strain that produces the classical subtype of cholera toxin became widespread in Bangladesh in 2001, and may have contributed to this increase in the proportion of symptomatic cases [18,19].

We also observed that a substantial number of contacts with negative serial cultures developed symptoms consistent with acute gastroenteritis during the study period. Although it is likely that other enteric pathogens contributed to this disease burden, a substantial number of *V. cholerae* culture-negative contacts with diarrhea/vomiting developed a four-fold or greater change in vibriocidal antibody titer, suggesting that daily rectal swab cultures detected only a portion of *V. cholerae* infection. In addition, 7 of 26 contacts that developed moderate to severe dehydration tested negative for *V. cholerae* by culture and serologic testing. These results demonstrate that the burden of diarrheal illness in the household contacts of patients with severe cholera is underestimated when only *V. cholerae* culture positive cases are considered.

Vomiting and the purging of large volumes of stool are the characteristic clinical features of cholera. While self-reported stool volume and frequencies are unreliable measures of disease severity, vomiting is an easily reported clinical feature of cholera that is associated with a greatly increased risk of developing dehydration. Therefore, dehydration prevention in populations at high risk for cholera should stress to physicians and caregivers at home that patients with vomiting require closer observation and more aggressive rehydration.

The high incidence of symptomatic *V. cholerae* infection in household contacts of cholera patients suggests that interventions at the time of the index case's hospitalization might prevent significant morbidity in this population. Historically, chemoprophylaxis for *V. cholerae* infection has been controversial, and the use of population-based chemoprophylaxis strategies in epidemic cholera has been associated with the widespread acquisition of antibiotic resistance [20,21]. In contrast to mass chemoprophylaxis, some trials of targeted chemoprophylaxis in household contacts of cholera patients have demonstrated efficacy in reducing the incidence of *V. cholerae* infection [22–24]. Most notably, in Bangladesh, McCormack et al., demonstrated that a five-day course of tetracycline reduced infections from 12.6% to 0.3% in household members of cholera patients followed for ten days [23], although a single dose of tetracycline only reduced infection to 8%. More recently, in a controlled trial, single dose ciprofloxacin significantly reduced the incidence of severe diarrhea in household contacts of cholera patients with a positive culture at the time of index case enrollment [25]; however, the incidence of *V. cholerae* infection was lower than anticipated, and the authors were unable to assess the effectiveness of chemoprophylaxis in preventing *V. cholerae* infection. Although highly effective when given in a single dose for children and adults with cholera, azithromycin has not been assessed for potential use as household-based chemoprophylaxis of cholera [26].

Several observations from our study support an evaluation of targeted prophylaxis in household contacts in endemic areas. First, the majority of symptomatic culture positive contacts present shortly after identification of the index case. In addition, our observations suggest that the burden of symptomatic disease in household contacts may be greater than previously reported. Lastly, we observed that antibiotics, which are readily available without a prescription in Bangladesh, are often utilized in this setting by self-prescription. In general, treatment of watery diarrhea with antibiotics is frequent in Bangladesh, in particular when recommended by unlicensed pharmacy workers in the heavily-utilized informal drug sector [17,27]. Thus, a

targeted antibiotic prophylaxis program in strictly defined household contacts of cholera patients may encourage more judicious antibiotic use. An alternative approach may be the development of strategies for prompt care and follow-up of contacts with risk factors for dehydration. The use of prophylactic agents that are less likely to induce antimicrobial resistance and the development of rapid diagnostic testing for cholera infection may further facilitate targeted antimicrobial prophylaxis in contacts.

This study has some limitations. The generalizability of our findings may be limited by the fact that we conducted daily observation of enrolled household contacts during a high-risk period for developing infection, and provided counseling and prompt medical therapy. These interventions may have resulted in an underestimate of the magnitude and severity of infections compared to a non-observed cohort of household contacts. Second, although the 2004 flood-associated epidemic of cholera in Dhaka occurred during our study period, enrollment was temporarily suspended in order to maximize clinical efforts; it therefore remains unknown how flooding might affect the dynamics of *V. cholerae* infection within households of index patients in Bangladesh [28]. Finally, it should be emphasized that because our definition of household contacts included only individuals who shared a common food source for at least three days prior to presentation of the index case, our results are not likely to be applicable to more casual or transient contacts of cholera patients.

Overall, our study underscores the burden of diarrheal disease in household contacts of cholera patients, and demonstrates risk factors for dehydration within this population. Our data suggest that more aggressive strategies to limit household transmission may provide significant benefit, and that targeted prophylaxis for household contacts of cholera patients should be carefully re-evaluated in clinical trials with several defined endpoints, including prevention of infections in the household, prevention of morbidity and complications, and the effects on antimicrobial resistance patterns.

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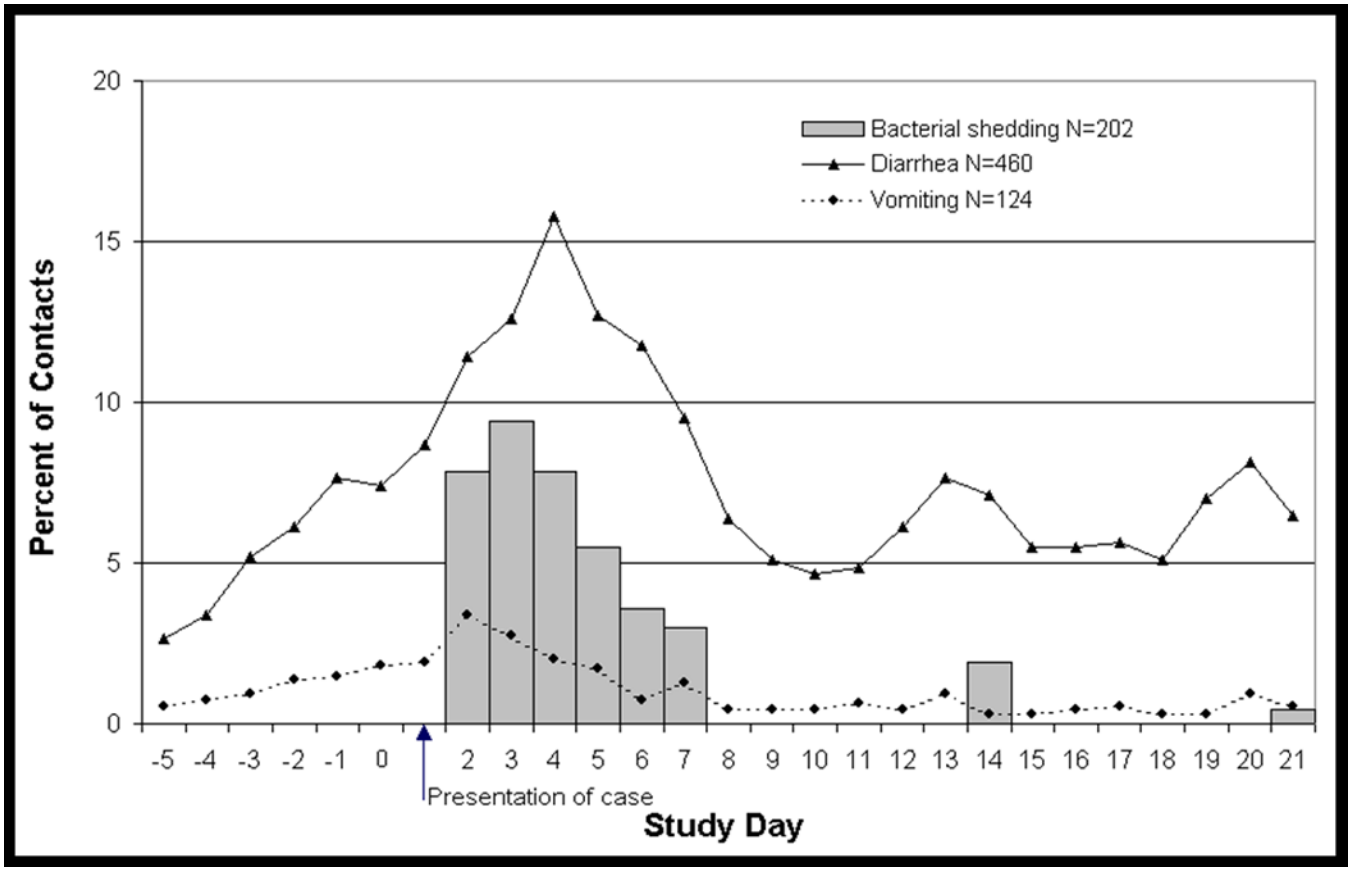

FIGURE 1.

The day of presentation of the index case to the ICDDR,B hospital is denoted day 1 (an average of 17 hours from the onset of symptoms). Contacts were enrolled on day 2, the day of culture confirmation of the index case.

Clinical symptoms and *V. cholerae* shedding in household contacts relative to the presentation of the index case.

Table 1

Demographic, microbiological, and clinical characteristics of household contacts

	All contacts (N=944)	Contacts with negative cultures (79%, N=742)	Contacts with culture positive infection (21%, N=202)
Mean age	21 years	22 years	18 years[b]
Female	471 (50%)	371 (50%)	100 (50%)
Diarrhea[a]	460 (49%)	312 (42%)	148 (73%)[b]
Vomiting[a]	124 (13%)	78 (11%)	46 (22%)[b]
Used antibiotics	271 (29%)	127 (17%)	144 (71%)[b]
Used ORS	366 (39%)	241 (32%)	125 (62%)[b]
Developed dehydration	26 (3%)	10 (1%)	16 (8%)[b]
Required IV fluids	16 (2%)	6 (<1%)	10 (5%)[b]

The Student's t-test was used to compare means.

[a] Indicates symptoms reported during the week prior to case presentation, in addition to during the follow-up period

[b] Indicates a significant difference between non-infected contacts and infected contacts ($p<0.001$)

Table 2

Clinical course in household contacts of *V. cholerae* infected patients

	Contacts 14 years and under (N=399)	Contacts over 14 years (N=545)	P value (for ≤14 years vs. >14 years)
Culture positive infection	105 (26%)	97 (18%)	0.002
Diarrhea[a]	239 (60%)	221 (41%)	<0.001
Vomiting[a]	69 (17%)	55 (10%)	0.001
Used antibiotics	146 (37%)	125 (23%)	<0.001
Used ORS	176 (44%)	190 (35%)	0.004
Developed dehydration	15 (4%)	11 (3%)	0.11
Required IV fluids	10 (3%)	6 (1%)	0.10

The Student's t-test was used to compare means.

[a] Indicates symptoms reported during the week prior to case presentation, in addition to during the follow-up period

Table 3

Multivariate analysis of risk factors for dehydration in infected household contacts with diarrhea (N=136)

	Crude Odds Ratio (95% CI)	P value	Adjusted Odds Ratio (95% CI)	P value
Vomiting	15 (4.0–60)	<0.001	14 (3.1–64)	0.001
Additional day of diarrhea	1.2 (1.0–1.3)	0.010	1.2 (1.0–1.3)	0.030
Blood group O	3.2 (1.1–9.1)	0.003	3.5 (1.1–12)	0.040
Age ≤ 14 years	2.2 (0.71–6.9)	0.17	3.2 (0.76–13)	0.11

We used a logistic regression model using generalized estimating equations, with P values adjusted for clustering based on household [15]. The final model was based on forward selection with predetermined cutoff criteria of $P \leq 0.2$ for inclusion in the model.