MAJOR ARTICLE

Clinical Outcomes in Household Contacts of Patients with Cholera in Bangladesh

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Background. Multiple *Vibrio cholerae* infections in 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 samples for culture for a period of 21 days after presentation of the index case.

Results. One-half (460 of 944) of all contacts reported diarrhea during the study period, and symptoms most frequently began 2 days after presentation of the index case. Antibiotics were used by 199 (43%) of 460 contacts with diarrhea. Results of rectal swab cultures for *V. cholerae* were positive for 202 (21%) of 944 contacts, and 148 (73%) 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 among household contacts of patients with cholera is higher than was 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. Re-evaluation of targeted chemoprophylaxis for household contacts of patients with cholera may be warranted.

The etiologic agent of cholera, *Vibrio cholerae*, causes 3–5 million cases of secretory diarrhea and >100,000 deaths annually [1]. Strains of *V. cholerae* can be differentiated serologically by the O-side chain of the lipopolysaccharide component of the outer membrane. Although >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 [2–5].

Multiple *Vibrio cholerae* infections in the same household are common. These may occur simultaneously through shared sources of contaminated food and water or through fecal-oral transmission in households. In 2 large prospective cohorts of contacts of patients with cholera in Bangladesh, rectal swab–positive infections occurred in 78 (15%) of 506 household contacts of patients with cholera caused by *V. cholerae* O1 biotype classical [6] and in 476 (29%) of 1658 household contacts of patients with cholera caused by *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 patients with cholera are at high risk of infection, even in areas where cholera is endemic.

To identify factors associated with susceptibility to *V. cholerae* in the present era, we prospectively observed a cohort of household contacts of patients with severe cholera in Dhaka, Bangladesh. Previously, we described

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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 >100,000 patients with diarrheal illness and associated comorbid conditions annually, including >20,000 patients with cholera. Index patients ⩾6 months of age who presented to the ICDDR,B with acute secretory diarrhea, a stool culture positive for *V. cholerae* O1 or O139, and no significant comorbid 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 3 days. Contacts were excluded if they were enrolled in other studies or if they had received care at the ICDDR,B during the preceding 2 months. A field team discussed enrollment with household members within 6 h after index case presentation, and consenting contacts without significant comorbid disease were enrolled in the study.

Contacts were observed prospectively for a 21-day period, beginning on the date of stool culture confirmation of the index case and enrollment of contacts (day 2). Collection of rectal swab samples and clinical data occurred during home visits on consecutive study days 2–7 and on days 14–21. Study personnel obtained clinical histories from the preceding week on study days 2, 14, and 21. Blood samples were collected from contacts at the ICDDR,B on days 2, 7, and 21. Persons who did not complete 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 US Department of Health and Human Services were followed during the conduct of this research.

Microbiological and serological assays. A stool sample from the index patient was cultured overnight on taurocholate-tellurite-gelatin agar (TTGA), and suspect colonies were confirmed using the slide agglutination method with use of specific monoclonal antibodies [10, 11]. Rectal swab samples 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 were incubated overnight. Colony identification was performed after plating on TTGA. Vibriocidal antibody assays were conducted 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), as described elsewhere [9, 13]. Contacts were not routinely tested for other pathogens.

Clinical management and outcomes. Diarrhea was defined as ⩾3 loose stools during a 24-h period. Contacts with a rectal swab culture positive for *V. cholerae* were considered to be infected. Dehydration was defined according to standardized ICDDR,B criteria, with moderate dehydration defined as any of the 2 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 and/or irregularity of the radial pulse. *V. cholerae* shedding duration was defined as the period between the positive rectal swab culture results, including days when a negative rectal swab culture result was obtained, or weekly periods during which no rectal swab sample was obtained between positive culture results.

Contacts who reported loose bowel movements received oral rehydration solution 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 with use of the aforementioned criteria. If dehydration was present, contacts were given oral rehydration solution and were 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 rectal swab culture positive 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 g) or azithromycin (1 g) was used. Children <18 years of age were treated with erythromycin (30–50 mg/kg/day for 3 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 patients with cholera, although self-prescribed antibiotic use by household contacts was common and recorded in the clinical history.

Statistical analysis. Data were analyzed using Stata, version 9.0 (Stata). Student's *t* test was used to compare mean values, with a predetermined cutoff of $P \leqslant .05$ indicating a statistically significant difference. A multivariate analysis of risk factors for

Table 1. Demographic, Microbiological, and Clinical Characteristics of Household Contacts

Characteristic	All contacts (n = 944)	Contacts with negative culture results (n = 742)	Contacts with positive culture results (n = 202)
Age, mean years	21	22	18[a]
Female sex	471 (50)	371 (50)	100 (50)
Diarrhea[b]	460 (49)	312 (42)	148 (73)[a]
Vomiting[b]	124 (13)	78 (11)	46 (22)[a]
Received antibiotics	271 (29)	127 (17)	144 (71)[a]
Received oral rehydration solution	366 (39)	241 (32)	125 (62)[a]
Developed dehydration	26 (3)	10 (1)	16 (8)[a]
Required intravenous fluids	16 (2)	6 (<1)	10 (5)[a]

NOTE. Data are no. (%) of contacts, unless otherwise indicated. Student's t test was used to compare mean values.

[a] There was a statistically significant difference between uninfected contacts and infected contacts ($P < .001$).

[b] Symptoms reported during the week before case presentation, in addition to during the follow-up period.

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 a predetermined cutoff of $P \leqslant .2$ for inclusion in the model. Odds ratios (ORs) with 95% confidence intervals (95% CIs) are reported in the text and tables. All reported P values are 2-tailed.

RESULTS

Household characteristics. From January 2001 through May 2006, we enrolled 1077 contacts of 399 patients with cholera. Nine hundred forty-four contacts completed the 21-day observation period. The median age of index patients 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 a mean of 2.7 contacts per case. Nuclear family members of the index patient made up 94% of household contacts. Parents of the index patient 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 sample collection among contacts who completed the 21 days of observation was >95%.

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

The use of oral rehydration solution and antibiotics were common among household contacts of patients with cholera. Most contacts (303 [83%] of 366) who developed diarrhea and/or vomiting during the follow-up period (after the enrollment of the index patient) used oral rehydration solution. Antibiotics were taken by 120 (83%) of 144 contacts with symptomatic *V. cholerae* infection. Among all 460 contacts who reported diarrhea, 199 (43%) used antibiotics, including 79 contacts with diarrhea and rectal swab culture negative for *V. cholerae.* 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 cultures positive for *V. cholerae* over the period of observation. Index patients presented to the ICDDR,B a mean duration (± standard deviation) of 17 ± 3.7 h after the onset of diarrhea. Two-thirds of contacts (302 [66%] of 460) who reported diarrhea developed symptoms after

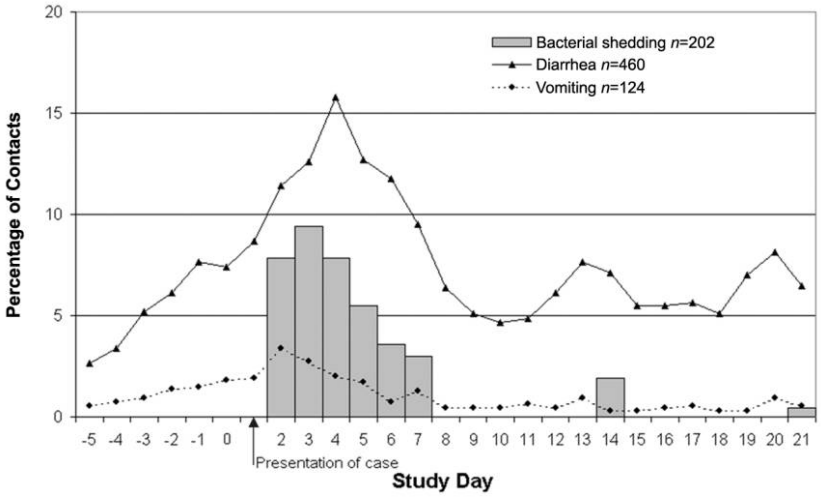

Figure 1. Clinical symptoms and *Vibrio cholerae* shedding in household contacts relative to the presentation of the index patient. The day of presentation of the index patient to the International Centre for Diarrhoeal Disease Research, Bangladesh hospital is denoted day 1 (a mean of 17 h after the onset of symptoms). Contacts were enrolled on day 2, the day of culture confirmation of the index case.

case presentation. Diarrhea developed in half of these contacts (152 [50%] 302) within 4 days after the hospitalization of the index patient; the most common day of diarrhea onset was 2 days after presentation of the index patient. Vomiting in contacts generally began immediately before the onset of diarrhea. Similarly, 121 (60%) of 202 household contacts who developed rectal swab–positive infection did so by day 4 after infection, with a peak in the proportion of *V. cholerae*–positive contacts on day 3 after enrollment of the index patient. By day 5 of the follow-up period, 145 (72%) 202 contacts who developed infection during the 21-day follow-up period had tested positive for *V. cholerae*.

Dehydration developed in 26 contacts (3 had severe dehydration, and 23 had moderate dehydration), and 16 of these contacts tested positive for *V. cholerae* by rectal swab culture. An additional 3 contacts with dehydration had a ⩾4-fold change in serum vibriocidal antibody titer during the follow-up period. Most dehydrated contacts (16 [62%] 26) were identified on the day after presentation of the index patient.

Age, sex, relationship to index patient, and development of clinical illness in contacts of patients with cholera. Contacts aged ⩽14 years were more likely to develop diarrhea, vomiting, and culture-positive infection and were more likely to use antibiotics and oral rehydration solution than were older contacts (Table 2). As noted in previous studies [9], sex was not associated with increased susceptibility to infection ($P = .91$). Infection was not significantly more likely in contacts who were parents than in contacts who were children of the index patient, although as we previously reported, first-degree relatives of an index patient had a higher risk of infection than did nonrelated household contacts [9].

Risk factors for dehydration. To examine risk factors for dehydration and to investigate potential confounding, we performed stepwise multivariate logistic regression for contacts with rectal swab-positive diarrhea (Table 3). In this analysis, vomiting was the most significant predictor of the development of significant dehydration in *V. cholerae*–infected patients. Although only one-fourth (42 of 148) of the contacts positive for *V. cholerae* by culture who had diarrhea reported vomiting, the majority of contacts (16 [84%] of 19) with *V. cholerae* infection and dehydration experienced vomiting. All 3 patients who received a diagnosis of 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 duration of 2 days and a maximum duration of 12 days. There was no significant relationship between duration of shedding and symptoms. Half of the contacts who shed for ⩾7 days were asymptomatic, including the 2 contacts who shed for the longest periods (1 each for 11 and 12 days). There was no significant relationship between prolonged shedding (⩾4 days of shedding) and age (OR, 0.99; 95% CI, 0.99–1.0; $P = .66$) or blood group O status (OR, 0.60; 95% CI, 0.25–1.4; $P = .23$). Sixty contacts shared a household with a prolonged shedder, and these persons were more likely to become infected than were contacts living with individuals who shed *V. cholerae* for <4 days (OR, 2.1; 95% CI, 1.1–4.2; $P = .03$).

Table 2. Clinical Course in Household Contacts of *Vibrio cholerae*–Infected Patients

Variable	No. (%) of contacts ≤14 years of age (n = 399)	No. (%) of contacts >14 years of age (n = 545)	P[a]
Culture-positive infection	105 (26)	97 (18)	.002
Diarrhea[b]	239 (60)	221 (41)	<.001
Vomiting[b]	69 (17)	55 (10)	.001
Received antibiotics	146 (37)	125 (23)	<.001
Received oral rehydration solution	176 (44)	190 (35)	.004
Developed dehydration	15 (4)	11 (3)	.11
Required intravenous fluids	10 (3)	6 (1)	.10

[a] Student's t test was used to compare means values between contacts aged ≤14 years and contacts aged >14 years.
[b] Symptoms reported during the week before case presentation, in addition to during the follow-up period.

DISCUSSION

We performed a prospective evaluation of household contacts of patients with cholera in urban Bangladesh. Consistent with previous studies, we observed a high incidence of *V. cholerae* infection among household contacts. More than 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 patients with *V. cholerae* O1 El Tor infection. The reasons that a higher incidence of symptomatic disease among patients who had a culture positive for *V. cholerae* O1 El Tor was observed in our study, compared with 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 [16, 17].

We also observed that a substantial number of contacts with negative serial culture results 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 and/or vomiting developed a ≥4-fold 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 who developed moderate to severe dehydration tested negative for *V. cholerae* by culture and serologic testing. These results demonstrate that the burden of diarrheal illness among 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. Although 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 efforts 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 among household contacts of patients with cholera suggests that interventions at the time of the index patient'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 for epidemic cholera has been associated with the widespread acquisition of antibiotic resistance [18, 19].

Table 3. Multivariate Analysis of Risk Factors for Dehydration in 136 Infected Household Contacts with Diarrhea

Risk factor	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
Vomiting	15 (4.0–60)	<.001	14 (3.1–64)	.001
Additional day of diarrhea	1.2 (1.0–1.3)	.010	1.2 (1.0–1.3)	.030
Blood group O	3.2 (1.1–9.1)	.003	3.5 (1.1–12)	.040
Age ≤14 years	2.2 (0.71–6.9)	.17	3.2 (0.76–13)	.11

In contrast to mass chemoprophylaxis, some trials of targeted chemoprophylaxis in household contacts of patients with cholera have demonstrated efficacy in reducing the incidence of *V. cholerae* infection [20–22]. Most notably, in Bangladesh, McCormack et al [21] demonstrated that a 5-day course of tetracycline reduced the incidence of infection from 12.6% to 0.3% among household members of patients with cholera followed up for 10 days, although a single dose of tetracycline only reduced the incidence of infection to 8%. More recently, in a controlled trial, single-dose ciprofloxacin significantly reduced the incidence of severe diarrhea among household contacts of patients with cholera who had a positive culture result at the time of enrollment of the index patient [23]; 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 to children and adults with cholera, azithromycin has not been assessed for potential use as household-based chemoprophylaxis for cholera [24].

Several observations from our study support an evaluation of targeted prophylaxis for household contacts in areas of endemicity. First, the majority of symptomatic culture-positive contacts presented shortly after identification of the index patient. In addition, our observations suggest that the burden of symptomatic disease among household contacts may be greater than was previously reported. Lastly, we observed that antibiotics, which are readily available without a prescription in Bangladesh, are often used in this context by self-prescription. In general, treatment of watery diarrhea with antibiotics is frequent in Bangladesh, particularly when recommended by unlicensed pharmacy workers in the heavily used informal drug sector [25, 26]. Thus, a targeted antibiotic prophylaxis program for strictly defined household contacts of patients with cholera 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 for 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 period when there was high risk for development of infection and provided counseling and prompt medical therapy. These interventions may have resulted in an underestimate of the magnitude and severity of infection, compared with a nonobserved cohort of household contacts. Second, although the 2004 flood-associated epidemic of cholera in Dhaka occurred during our study period, enrollment was temporarily suspended to maximize clinical efforts; therefore, how flooding might affect the dynamics of *V. cholerae* infection in households of index patients in Bangladesh remains unknown [27]. Finally, it should be emphasized that, because our definition of household contacts included only individuals who shared a common food source for at least 3 days before presentation of the index patient, our results are not likely to be applicable to more-casual or transient contacts of patients with cholera.

Overall, our study underscores the burden of diarrheal disease among household contacts of patients with cholera and demonstrates risk factors for dehydration in 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 patients with cholera should be carefully reevaluated in clinical trials with several defined end points, including prevention of infection in the household, prevention of morbidity and complications, and the effects on antimicrobial-resistance patterns.

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