Risk Factors for Household Transmission of *Vibrio cholerae* in Dhaka, Bangladesh (CHoBI7 Trial)

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Abstract. Household contacts of cholera patients are at a 100 times higher risk of a *Vibrio cholerae* infection than the general population. To examine risk factors for *V. cholerae* infections and investigate intervention strategies among this population, we followed household contacts of cholera patients for the 1-week high-risk period after the index patient obtained care. This study was nested within a randomized controlled trial of the Cholera-Hospital-Based-Intervention-for-7-days (CHoBI7), a handwashing with soap and water treatment intervention in Dhaka, Bangladesh. Rectal swab results were available from 320 household contacts of cholera patients at five time points over a 1-week period. Fecal and water samples were analyzed for *V. cholerae* by bacterial culture. All analyses were stratified by study arm. Within the intervention arm, stored household drinking water with a median free chlorine concentration below 0.5 mg/L was associated with a three times higher odds of a cholera infection (odds ratio [OR]: 3.0; 95% confidence interval [CI]: 1.32, 6.63). In the control arm, having *V. cholerae* in stored water was associated with a significantly higher odds of a symptomatic cholera infection (OR: 8.66; 95% CI: 2.11, 35.48). No association was found between observed handwashing with soap at food and stool-related events and *V. cholerae* infections. Stored household drinking water with detectable *V. cholerae* and chlorine concentrations below the World Health Organization guideline were found to be important risk factors for cholera infection among household contacts of cholera patients. These findings emphasize the need for water treatment interventions targeting this high risk population.

INTRODUCTION

The World Health Organization (WHO) estimates that there are 3–5 million cholera cases worldwide per year resulting in more than 100,000 deaths.^{1,2} Previous studies have identified multiple risk factors for becoming infected with cholera such as drinking street-vended water,³ placing one's hands into stored household water,⁴ bathing in a river,^{4,5} eating left-over food,⁶ eating food prepared by a recently ill food handler,⁷ not washing hands with soap before eating food,⁸ and being a first degree relative of a cholera case.⁹ These findings indicate that water and food borne contamination are the main transmission routes for cholera infection.

Household contacts of cholera patients are at a 100 times higher risk of becoming infected with cholera compared with the general population during the 1-week period after the index cholera patient obtained care at a health facility.^{9–12} These high rates of infection among household members are likely attributed to sharing contaminated environmental sources or secondary transmission through poor hygiene practices.¹³ Currently in Bangladesh, administration of oral rehydration solution is the recommended standard of care for recovering cholera patients after they are discharged from health-care facilities. However, there is no standard of care for highly susceptible household contacts of cholera patients.

In an effort to initiate a low cost standard of care for this high-risk population, our research group developed the Cholera Hospital-Based Intervention for 7 days (CHoBI7). This hospital-based water, sanitation, and hygiene (WASH) intervention is delivered by health promoters to cholera

patients and their household members over the 7-day high-risk period for this vulnerable population. Chobi means picture in Bangla for the pictorial WASH module that is delivered as part of the intervention. The CHoBI7 intervention includes: 1) a pictorial module describing cholera transmission routes and prevention, and 2) a cholera prevention package that contains chlorine tablets for treatment of stored water (Aquatabs sodium dichloroisocyanurate; Medentech, Wexford, Ireland, UK), a soapy water bottle (detergent powder and water), a handwashing station, and a sealed water vessel that is used for safe storage of household water.

The CHoBI7 intervention resulted in a significant reduction in the incidence of symptomatic cholera, and a 47% percent reduction in the incidence of overall cholera infections among household contacts of cholera patients in our recent randomized controlled trial conducted in Dhaka, Bangladesh.¹³ Furthermore, we observed significantly higher water quality and handwashing with soap practices in the intervention arm compared with the control arm 6–12 months after the intervention was delivered. These findings demonstrated that the 1-week CHoBI7 intervention presents an effective approach to reduce cholera infection in a high-risk population, which leads to sustained uptake of the promoted handwashing with soap and water treatment behaviors over time, and increased cholera awareness.^{13–15}

In this prospective cohort study, we investigate environmental and individual risk factors for cholera infections in urban Dhaka, Bangladesh. This study is nested within our recent randomized controlled trial of the CHoBI7 intervention, thereby providing the unique opportunity to evaluate how risk factors change within a population with the implementation of a WASH intervention in comparison to a control group.

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TABLE 1
Individual and household risk factors for cholera infection among household contacts of cholera patients (visits 1–5), urban Bangladesh

Characteristics	Control arm (N = 160)							CHoBi7 intervention arm (N = 160)						
	Characteristic, % (N)							Characteristic, % (N)						
	Total contacts	Contacts, % (N)	Cholera positive	OR*	Lower CI	Upper CI	P value	Total contacts	Contacts	Cholera Positive	OR*	Lower CI	Upper CI	P value
Cholera-infected household contacts†	160	20 (32)						160	19 (30)					
Individual characteristics														
Female	160	62 (99)	18 (18)	0.82	0.37	1.82	0.62	160	59 (94)	21 (20)	1.56	0.72	3.4	0.26
Age (years) mean ± SD (min–max)	160	18 ± 15 (1–67)		0.97	0.93	1	0.06	160	18 ± 15 (0.75–75)		0.98	0.95	1.01	0.22
0–5 years	160	16 (26)	27 (7)	2.2	0.72	6.73	0.17	160	21 (34)	32 (11)	1.44	1.18	7.67	0.02
5–14 years	160	40 (64)	23 (15)	1.83	0.8	4.19	0.15	160	32 (51)	16 (8)	1.23	0.56	2.71	0.6
Greater than 14 years (reference)	160	44 (70)	14 (10)	–	–	–	–	160	47 (75)	15 (11)	–	–	–	–
Individuals that reported consuming food outside of the household during the surveillance period	160	98 (156)	21 (32)	0	\$	\$	0.58	160	81 (129)	17 (22)	1.23	0.13	11.72	0.86
Spent any time outside the home during the study period	160	90 (144)	19 (28)	1.87	0.48	7.2	0.36	160	94 (150)	19 (29)	0.49	0.07	3.36	0.47
Did not practice handwashing with soap at a key event during structured observation‡	82	77 (63)	21 (13)	0.7	0.18	2.76	0.61	86	14 (12)	8 (1)	2.93	0.27	31.42	0.37
Household characteristics														
Number of households	83							82						
Source water with detectable <i>Vibrio cholerae</i> during the surveillance period	160	27 (43)	30 (13)	2.13	0.83		0.11	160	34 (54)	24 (13)	1.61	0.71	3.66	0.26
Stored water with detectable <i>V. cholerae</i> during the surveillance period	160	14 (22)	36 (8)	2.96	0.97	9.03	0.06	160	7 (11)	9 (1)	0.39	0.07	2.09	0.27
Median household free chlorine concentration during the surveillance period (mg/L) (mean ± SD, min–max)	160	0.02 ± 0.008 (0.01–0.04)		2.00E+10	9.27 E–4	4.35 E+23	0.13	160	0.97 ± 0.49 (0.11–1.97)		1.95	1.22	3.11	0.0048
Household with a median free available chlorine concentration less than 0.5 mg/L cutoff	160	100 (160)	20 (32)	N/A	N/A	N/A	N/A		20 (32)	34 (11)	2.95	1.32	6.63	0.0086

CI = confidence interval; N/A = not applicable; OR = odds ratio; SD = standard deviation.

*Generalized estimating equations were used to account for clustering within a household.

†Includes both symptomatic and asymptomatic cholera. Symptomatic cholera was defined as a cholera infection with diarrhea and/or vomiting in the past 48 hours.

‡Key events are before eating or preparing food and after using the toilet or cleaning a child's anus. § No cholera infections in one of the categories therefore confidence intervals could not be calculated.

METHODS

Informed consent was obtained from all study participants (household contacts and index cholera cases), which included an adult participant (> 18 years of age) signing an informed consent and/or parental consent form and children between the ages of 12 and 17 years signing an assent form. All study procedures were approved by the research Ethical Review Committee of the International Center for Diarrheal Disease Research, Bangladesh (icddr,b) and institutional review board of the Johns Hopkins Bloomberg School of Public Health.

The CHoBI7 randomized controlled trial in Dhaka, Bangladesh, was conducted from June 2013 to November 2014. A detailed description of the intervention provided is described elsewhere.¹³ Suspected cholera patients, defined as patients presenting at the icddr,b Dhaka hospital with acute watery diarrhea (three or more loose stools over a 24-hour period) and moderate to severe dehydration using the WHO definition, were screened for the presence of *Vibrio cholerae* in their stool using the Crystal VC Rapid Dipstick test (Span Diagnostics, Surat, India).^{13,16–20} All positive findings by dipstick were confirmed by bacterial culture. Suspected cholera patients admitted to icddr,b Dhaka hospital residing within a police station (thana) of Dhaka city were screened for eligibility for the CHoBI7 trial. Cholera patients were defined as suspected cholera patients with a stool bacterial culture result positive for *V. cholerae*. Cholera patients were excluded from the study if they had a household contact already enrolled (currently or previously), or if they had received cholera vaccine, to avoid confounding from an ongoing vaccine trial. Household contacts were defined as individuals sharing the same cooking pot as the index cholera patient for the past 3 days. To be eligible for the study, household contacts had to plan to reside in the household of the index patient for the next week. Eligible household contacts present in the hospital at the time of patient enrollment were invited to participate, and a household visit was made to recruit household contacts within 36 hours of patient enrollment. A cluster was defined as the index cholera patient and their corresponding household contacts.

Patient households were visited at days 1, 3, 5, 7, and 9 (visits 1–5) after the presentation of the cholera patient at icddr,b Dhaka Hospital for clinical and environmental surveillance. For clinical surveillance, household contacts were asked if they had diarrhea (three or more loose stools over a 24-hour period) or vomiting in the past 48 hours, and a rectal swab sample was collected from willing household contacts at each household visit to test for the presence of *V. cholerae* in stool by bacterial culture according to previous published methods.¹³ For environmental surveillance, a water sample was collected from the household's water source and stored drinking water in the home at each household visit to test for the presence of *V. cholerae* by bacterial culture and to measure free available chlorine concentrations, using a digital colorimeter (Hach, Loveland, CO).¹³ The WHO recommended cut-off for free available chlorine of a minimum of 0.5 mg/L present in piped drinking water supplies was used.²⁰ A questionnaire was also administered to household members to collect information on individual and household demographic characteristics.

To observe handwashing with soap practices, a 5-hour structured observation substudy was conducted in all households recruited from October 2013 to November 2014 (59 intervention and 56 control) on surveillance days 5, 6, or 7. Handwashing practices were recorded at the following key events promoted in CHoBI7: 1) after using the toilet, 2) after cleaning a child's anus, 3) before eating, and 4) before preparing food.

Statistical analysis. To investigate environmental, demographic, and behavioral risk factors for cholera infections among household contacts of cholera patients, we compared individual and household characteristics within intervention and control arm households enrolled in the one week CHoBI7 trial. The two primary outcomes were 1) incidence of *V. cholerae*-infected household contacts (any cholera infection: asymptomatic or symptomatic), which was defined by a culture-positive result for *V. cholerae*, and 2) the incidence of symptomatic *V. cholerae* infection, which was by a culture-positive result for *V. cholerae* and reported diarrhea or vomiting in the past 48 hours.^{5,10,13} Symptomatic *V. cholerae* infection was only investigated in the control group, as the intervention arm of this study had no symptomatic cholera infections during the intervention period.¹³

Bivariate logistic regression analysis was performed stratified by study arm using the household contact information summarized for visits 1–5 to investigate, which risk factors were significant predictors of overall and symptomatic cholera infection. Generalized estimating equations were used for regression models to account for clustering at the household level and approximate 95% confidence intervals (CI).²¹ Where no cholera infections occurred in a specific category a Fisher's exact test was performed to calculate the *P* values for these variables. All analyses described above were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC)

RESULTS

Four hundred and thirty-nine household contacts were enrolled in the CHoBI7 study from 165 cholera patient households (220 control contacts and 219 intervention contacts). Bacterial culture results for *V. cholerae* were available for 320 (73%) of the total 439 household contacts (160 intervention contacts and 160 control contacts) for visits 1–5 and these contacts were used to perform the statistical analysis. There were no significant differences in age, gender, or presence of diarrhea or vomiting during the surveillance period between enrolled household contacts with or without rectal swab culture results available.¹³ Nineteen percent (62/320) of household contacts developed cholera infections during the surveillance period. Thirty percent of households (49/165) had detectable *V. cholerae* in source water used for drinking during the surveillance period. All clinical strains isolated were *V. cholerae* O1 Ogawa.

Risk factors for a cholera infection (asymptomatic and symptomatic). Within the intervention arm, a household median free chlorine concentration below 0.5 mg/L was associated with a three times higher odds of a cholera infection (odds ratio [OR]: 3.0; 95% CI: 1.32, 6.63), and each 0.5 mg/L decrease in free chlorine was associated with a 1.95 times higher odds of a cholera infection (95% CI: 1.2–3.1) (Table 1). Additionally, in the intervention arm,

individuals 0–5 years had an increased odds of having a cholera infection compared with those individuals 14 years of age or older (OR: 1.44; 95% CI: 1.18–7.67). The 0–5 age group also had a significantly lower proportion of individuals that spent time outside the home during the surveillance period (78%) compared to individuals 5–14 years (94%) and individuals 14 years or greater (96%) ($P < 0.0001$). No association was found between observed handwashing with soap at food and stool-related events during structured observation or detectable *V. cholerae* in source and stored water and cholera infections.

Risk factors for a symptomatic cholera infection. In the control arm, having *V. cholerae* in stored household water was associated with a significantly higher odds of a symptomatic cholera infection (OR: 8.66; 95% CI: 2.11, 35.48) (Table 2). In addition, individuals 5–14 years of age had an increased odds of having a symptomatic cholera infection compared with those individuals 14 years of age or older (OR: 3.25; 95% CI: 1.01–10.48). There was no significant difference in time spent outside the home by age category among individuals in the control arm. No other significant risk factors were identified.

DISCUSSION

We conducted a prospective evaluation of risk factors for cholera infections among household contacts of cholera

patients in urban Dhaka, Bangladesh. We found stored household drinking water with detectable *V. cholerae* and chlorine concentrations below the WHO guideline to be important risk factors for overall and symptomatic cholera infections among this high-risk population. This result is consistent with the main findings from our recent randomized controlled trial of the CHoBI7 intervention, which found that distribution of chlorine tablets and a sealed water vessel in combination with a handwashing with soap intervention resulted in a significant reduction in symptomatic cholera infections among household members of cholera patients.¹³ Our study findings are also consistent with our recent laboratory experiments which found chlorine tablets (Aquatabs sodium dichloroisocyanurate) to be highly effective in deactivating *V. cholerae* O1,²² and consistent with the WHO guideline of 0.5 mg/L of free available chlorine for piped water supply to ensure water is microbiologically safe.²⁴ Unexpectedly, lack of handwashing with soap at food and stool-related events were not significant risk factors of cholera infection. Overall, our findings suggest contaminated drinking water may be the predominant route for cholera infections in this susceptible population.

Our finding that household stored drinking water was an important transmission route for cholera among household contacts is consistent with earlier studies by Spira and others and Hughes and others in rural Bangladesh.^{5,10} In the study by Spira and others, the rates of cholera infection

TABLE 2

Individual and household risk factors for symptomatic cholera infection among household contacts of cholera patients (visits 1–5), urban Bangladesh

	Total contacts	Control arm (N = 160)					
		Characteristic, % (N)		OR*	Lower CI	Upper CI	P value
		Contacts	Symptomatic cholera				
Cholera-infected symptomatic household contacts†	160	8 (13)					
Individual characteristics							
Female	160	62 (99)	9 (9)	1.53	0.31	7.46	0.6
Age (years) mean ± SD (min–max)	160	18.22 ± 15.26 (1–67)		0.98	0.94	1.02	0.33
0–5 years	160	16 (26)	4 (1)	0.96	0.15	6.13	0.97
5–14 years	160	40 (64)	14 (9)	3.25	1.01	10.48	0.048
Greater than 14 years (reference)	160	44 (70)	4 (3)	1			
Individuals that reported consuming food outside of the household during the surveillance period	160	98 (156)	8 (13)	Infinity	§	§	1
Spent any time outside the home during the study period	160	90 (144)	9 (13)	Infinity	§	§	0.37
Did not practice handwashing with soap at a key event during structured observation‡	82	77 (63)	10 (6)	0.35	0.02	7.71	0.51
Household characteristics							
Number of households	83						
Source water with detectable <i>Vibrio cholerae</i> during the surveillance period	160	27 (43)	5 (2)	1.7	0.45	6.38	0.43
Stored water with detectable <i>V. cholerae</i> during the surveillance period	160	14 (22)	14 (3)	8.66	2.11	35.48	0.003
Median household free chlorine concentration during the surveillance period (mg/L) (concentration, SD [min–max])	160	0.02 ± 0.008 (0.01–0.04)		5.28E + 10	1.17E – 07	2.39E + 28	0.23
Household with a median free available chlorine concentration less than 0.5 mg/L cutoff	160	100 (160)	3 (4)	¶	¶	¶	¶

CI = confidence interval; N/A = not applicable; OR = odds ratio; SD = standard deviation.

*Generalized Estimating Equations were used to account for clustering within a household.

†Symptomatic cholera was defined as a cholera infection with diarrhea and/or vomiting in the past 48 hours.

‡Key events are before eating or preparing food and after using the toilet or cleaning a child's anus. § No symptomatic cholera infections in a category therefore confidence intervals could not be calculated. A Fisher exact test was used to calculate the P value.

¶No households had greater than 0.5 mg/L free available chlorine.

were significantly higher in cholera patient households with stored and source water with detectable *V. cholerae*. Furthermore, neighborhoods that were classified as "Cholera Positive" (based on the presence of cholera patients) had 26% of source water sampled positive for *V. cholerae*, compared with 2.1% in "Cholera-Negative" neighborhoods. In these same "Cholera-Positive" neighborhoods, 23% of household stored water sampled was positive for contamination, compared with 0% in "Cholera-Negative" neighborhoods.¹⁰ In the study by Hughes and others, the rates of cholera infection were higher in cholera patient households with source water with detectable *V. cholerae*. In neighborhoods with a cholera patient, 44% had detectable *V. cholerae* in source water compared with 2% in control neighborhoods.⁵

We found that household contacts 0–5 years in the intervention arm were at significantly higher odds of becoming infected with cholera compared to contacts 14 years of age or older. In addition in the control arm, the odds of cholera infection for the 0–5 year age group was 2.2, however, this result was not statistically significant. This is consistent with previous studies which have found younger children to be at higher risk for cholera infection.^{2,5} In the study by Weil and others conducted in Dhaka, Bangladesh, household contacts of cholera patients less than or equal to 14 years of age were at an increased risk of cholera infections.² In the study by Hughes and others, children 5–9 years of age were at an increased risk of cholera infection.⁵ In the study by Glass and others, children 2–9 years of age were most commonly hospitalized for cholera infections.²⁴ This finding is likely attributed to young children lacking the naturally acquired immunity to cholera found in older individuals that have been previously exposed. The reason for symptomatic cholera infections only being significantly higher in the 5–14 year age group is unclear, and should be investigated in future studies.

Lack of handwashing with soap at food and stool-related events during structured observation was not a significant risk factor for cholera infection. This is in contrast to previous studies which have found lack of handwashing with soap to be a significant risk factor for cholera.^{8,25} One potential explanation is that contamination of drinking water with *V. cholerae* had a larger relative contribution to cholera infections than individual hygiene practices. Alternatively, our small sample size for this variable may have limited our ability to detect a significant association. This finding needs to be further investigated in future studies.

Our study has several limitations. First, structured observation data and fecal samples were not available for all enrolled household contacts. Future studies should investigate risk factors for cholera infections among household contacts of cholera patients using a larger sample size. Second, we did not conduct microbiological analysis of food consumed in the household to test for the presence of *V. cholerae*, nor did we measure pathogen load on the hands of study participants using hand rinses.²⁶ These additional measures should be used in future studies. Third, the CHoBI7 intervention combined both chlorination of drinking water and handwashing with soap, therefore, we cannot evaluate potential risk factors for cholera infection when each intervention is delivered alone. Fourth, we did not assess the blood type or initial vibriocidal antibody titers present in the blood of our study participants. Both

blood group Type O and low initial vibriocidal titers have been found to be risk factors for developing cholera symptoms from *V. cholerae* O1 and O139.² These risk factors should be further investigated in future studies.

This study also had several strengths. The first strength was environmental surveillance of household water sources and stored water over the 1-week high-risk period for this population. The second was structured observation being conducted to observe handwashing with soap practices at stool- and food-related events. Third was the intensive clinical surveillance which was conducted at five time points over the 1-week high-risk period for household contacts of cholera patients. Fourth was including a control and intervention group which allowed us to investigate how risk factors changed within a population with the implementation of a WASH intervention in comparison to a control group. Fifth was investigating risk factors for overall cholera infections and symptomatic cholera infections.

Household water quality and water treatment practices were found to be significant risk factors for cholera infection among household contacts of cholera patients. These findings emphasize the need for water treatment and safe water storage interventions targeting this high-risk population.

Received November 4, 2016. Accepted for publication February 6, 2017.

Published online March 27, 2017.

Acknowledgments: We thank the study participants and the following research assistants who conducted the field work for this study: Ismat Minhaz Uddin, Rafiqul Islam, Al-Mamun, Maynul Hasan, Kalpona Akhter, Khandokar Fazilatunnessa, Sadia Afrin Ananya, Akhi Sultana, Sohag Sarker, Jahed Masud, Abul Sikder, Shirin Akter, Lubna Tani, and Laki Das.

Financial support: This research was supported by the Center for Global Health at Johns Hopkins University and the National Institute of Allergy and Infectious Diseases, National Institutes of Health, the Rangpur Medical College Hospital, and icddr,b. Thanks to the governments of Australia, Bangladesh, Canada, Sweden, and United Kingdom for providing core/unrestricted support.

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