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Epidemiology of Cholera in Bangladesh: Findings From Nationwide Hospital-based Surveillance, 2014–2018

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(See the Editorial Commentary by Harris and LaRocque on pages 1643–4.)

Background. Despite advances in prevention, detection, and treatment, cholera remains a major public health problem in Bangladesh and little is known about cholera outside of limited historical sentinel surveillance sites. In Bangladesh, a comprehensive national cholera control plan is essential, although national data are needed to better understand the magnitude and geographic distribution of cholera.

Methods. We conducted systematic hospital-based cholera surveillance among diarrhea patients in 22 sites throughout Bangladesh from 2014 to 2018. Stool specimens were collected and tested for *Vibrio cholerae* by microbiological culture. Participants' socioeconomic status and clinical, sanitation, and food history were recorded. We used generalized estimating equations to identify the factors associated with cholera among diarrhea patients.

Results. Among 26 221 diarrhea patients enrolled, 6.2% (n = 1604) cases were *V. cholerae* O1. The proportion of diarrhea patients positive for cholera in children <5 years was 2.1% and in patients ≥5 years was 9.5%. The proportion of cholera in Dhaka and Chittagong Division was consistently high. We observed biannual seasonal peaks (pre- and postmonsoon) for cholera across the country, with higher cholera positivity during the postmonsoon in western regions and during the pre–monsoon season in eastern regions. Cholera risk increased with age, occupation, and recent history of diarrhea among household members.

Conclusions. Cholera occurs throughout a large part of Bangladesh. Cholera-prone areas should be prioritized to control the disease by implementation of targeted interventions. These findings can help strengthen the cholera-control program and serve as the basis for future studies for tracking the impact of cholera-control interventions in Bangladesh.

Keywords. cholera; diarrhea; surveillance; Bangladesh.

The incidence of diarrhea remains high globally, although mortality has declined due to life-saving interventions such as oral rehydration solution. Despite the successes, the Global Burden of Disease Study ranked diarrheal diseases as the ninth leading cause of death globally, and the fourth leading cause in children under 5 years of age [1]. In South Asia and sub-Saharan Africa, diarrheal illness accounts for at least 10% of deaths in children [2].

The Global Task Force on Cholera Control (GTFCC) has recently launched ambitious goals for reducing cholera deaths by 90% by 2030 and eliminating cholera from at least 20 of the 47 high-burden countries, including Bangladesh [3]. To achieve these objectives, the World Health Organization (WHO) has recommended the use of oral cholera vaccines (OCVs) together with other cholera prevention and control strategies. To ensure access to OCV for cholera-affected countries, a global OCV stockpile was created in 2013. However, the current global OCV supplies are too low for targeting all individuals living in countries at risk [4]. Thus, countries with cholera need to identify and focus control efforts in high-risk populations.

In Bangladesh, located in the heart of the Ganges Delta and considered to be the ancestral home of cholera [5], the disease remains a significant public health problem [6]. People live in high-risk, densely populated environments with poor access to safe water and sanitation [7]. It is suggested that 66 million people are at risk of cholera in Bangladesh, with an incidence rate of 1.64/1000 population, 100 000 cases, and 4500 deaths annually [4]. These estimates were only obtained from population-based published studies to estimate the annual number of cases. Bangladesh is developing a national cholera-control plan in order to meet objectives set forth in the GTFCC Roadmap. It was therefore crucial to determine the magnitude of cholera to obtain information on seasonality and location of prevalent areas in Bangladesh. Based on this need, a nationwide enteric disease surveillance with laboratory confirmation was initiated in 2014, which covered all divisions across the country. The objective was to understand the epidemiology of cholera throughout Bangladesh.

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METHODS

Ethics Statement

Informed consent was obtained from participants. For children younger than 18 years, informed consent was taken from participants/legal guardians. The surveillance protocol was approved by the Research Review Committee and Ethical Review Committee of International Centre for Diarrheal Disease Research, Bangladesh (icddr,b).

Study Site

Surveillance was conducted in administrative areas (currently 8) designated as "Divisions" (Bibhag) with a total of 64 districts (Zilla) and 492 subdistricts (Upazila). In May 2014, the icddr,b and the Institute of Epidemiology, Disease Control, and Research (IEDCR) collaboratively started the diarrheal disease surveillance in 10 hospitals. Surveillance was interrupted between January and May 2016 due to a gap in funding. From May 2016, surveillance was expanded to additional 12 facilities focusing on cholera surveillance. A total of 22 surveillance sites (13 districts, 6 subdistricts, 2 tertiary-level hospitals, and the Bangladesh Institute of Tropical and Infectious Disease [BITID]) were established across 21 different districts (Figure 1). We selected sentinel surveillance sites based on reports of acute watery diarrhea and cholera (including analyses of data from the national District Health Information Software v2 database) from the Directorate General of Health Services and previously published cholera surveillance studies [6].

Diarrhea Case Definition

Surveillance was carried out in all age groups; however, different case definitions for those under 2 months of age and those older than or equal to 2 months are as follows:

- Diarrhea cases (age <2 months): Changed stool habit from usual pattern in terms of frequency (more than the usual number of purgings) or nature of stool (more water than fecal matter).

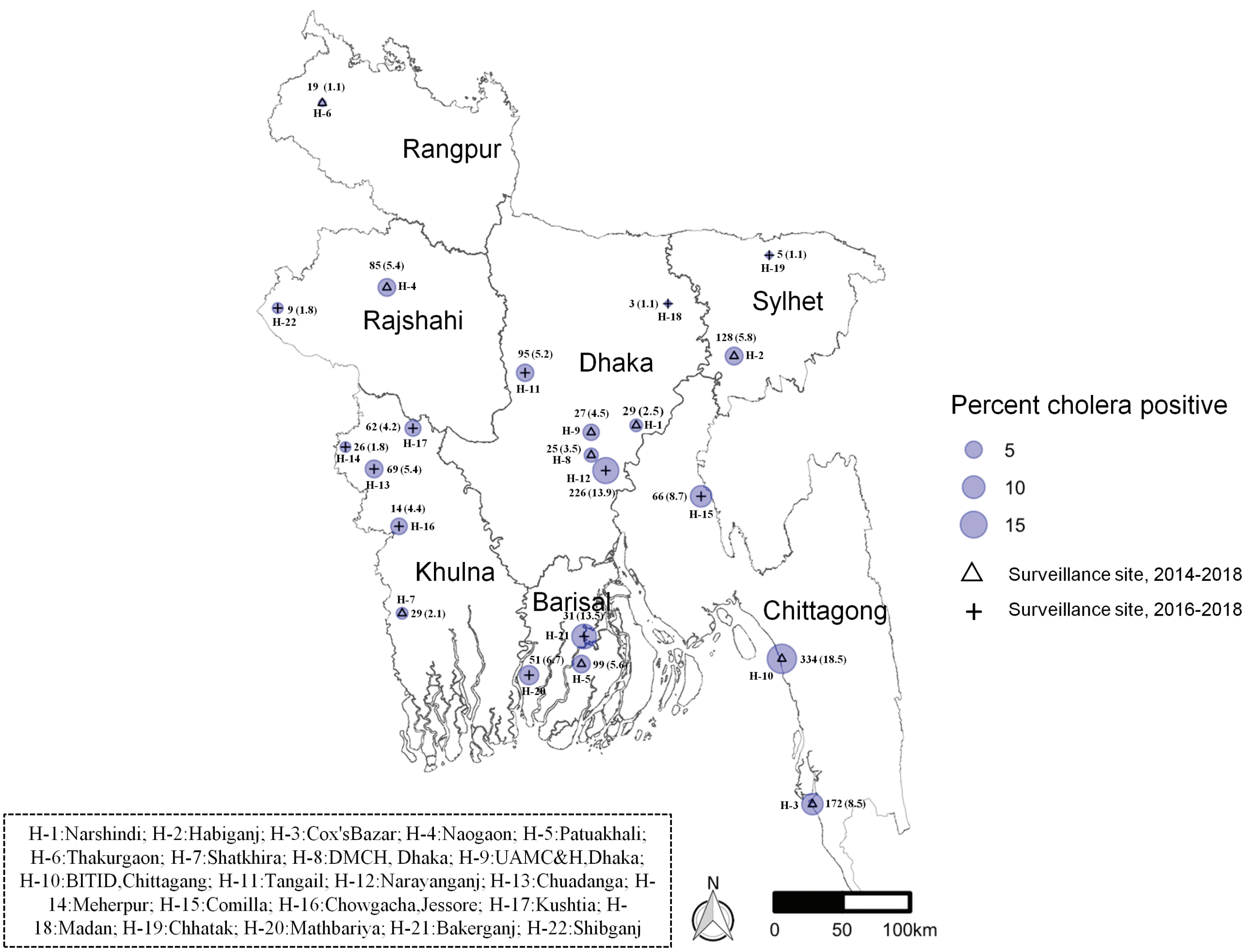

Figure 1. Map of nationwide study surveillance sites in Bangladesh, May 2014–June 2018, showing the percentage of culture-positive *Vibrio cholerae* among the enrolled cases with acute watery diarrhea. The map was created by R (v. 3.4.2, R Foundation for Statistical Computing, Vienna, Austria) and Arc GIS v10.6 (http://www.esri.com/software/arcgis/arcgis-for-desktop). Abbreviations: BITID, Bangladesh Institute of Tropical and Infectious Disease; DMCH,Dhaka Medical College and Hospital; UAMC&H, Uttara Adhunik Medical College and Hospital.

- Diarrhea cases (age ≥2 months): Any patient attending hospital with 3 or more loose or liquid stools within 24 hours or 3 loose/liquid stools or fewer causing dehydration in the last 24 hours.

Surveillance

Surveillance teams were established with a physician, a nurse, a medical technologist, and a trained field attendant. At each site, an assigned nurse prepared a daily list of patients with diarrhea (both inpatient and outpatient). Four patients with diarrhea who met the case definition and had no other severe comorbidity (eg, severe acute respiratory illness, acute cardiovascular symptoms, or severe acute neurological disorder) were enrolled by the physician from Saturday to Wednesday each week. Two patients with diarrhea aged less than 5 years old and 2 patients aged 5 years or older were enrolled each day; if the target number of patients in a particular age group was not met, we overenrolled in the other group to meet the target of 4 patients. Upon receiving consent, the physician collected the patient's sociodemographic characteristics such as age, gender, profession (eg, service holders such as those working in banks, schools, public or private organizations or workers paid/contracted on a daily basis involved in manual labor, construction, or agriculture), diet history, medical history (including assessment of dehydration status), sanitation, and hygiene information; and a stool sample was collected for testing. The specimens were transported in Cary-Blair transport media within 15 days to the laboratories in Dhaka at the icddr,b, and IEDCR. Specimens were immediately processed in the laboratory.

Stool samples were analyzed for detection of bacterial causes of acute watery diarrhea. From the first 10 surveillance sites, we tested for *Vibrio cholerae* O1/O139, enterotoxigenic *Escherichia coli* (ETEC), and *Salmonella* spp. For the remaining 12 surveillance sites, we only tested stool specimens for *V. cholerae* O1/O139.

Laboratory Procedures

For the identification of *V. cholerae*, specimens were streaked onto taurocholate-tellurite gelatin agar (TTGA) and incubated overnight at 37°C. Specimens were also inoculated in alkaline peptone water for enrichment and incubated for an additional 18–24 hours [8] and plated on TTGA. Suspected colonies were serotyped with monoclonal antibody specific to *V. cholerae* O1 (Ogawa and Inaba) and O139 serogroups [9, 10]. For the detection of ETEC, stool specimens were spread on MacConkey agar and incubated overnight at 37°C. Enterotoxigenic *E. coli* was confirmed by multiplex polymerase chain reaction (PCR) targeting the gene targets for ETEC toxin LT and ST [11]. For the detection of *Salmonella*, specimens were streaked onto Salmonella-Shigella agar and then incubated overnight at 37°C, followed by systematic biochemical and serological testing methods (Denka Seiken).

Data Management and Analysis

The demographic, clinical, and associated factors are described for cholera cases and all enrolled diarrhea cases. We also compared data from patients with cholera with non–cholera cases by a 2-sample test of proportions. We estimated risk ratios for different potential factors associated with cholera assumed as clusters using log-binomial regression with generalized estimating equations (GEEs) accounting for robust standard errors. For the GEE models, we used an independent correlation structure, accounting for individual clustering within each site. A univariate analysis was conducted using GEE to examine the risk of cholera for factors including age, gender, and exposure histories. Based on previous literature review, we then constructed a multivariable log-binomial regression model and performed inference with GEEs.

For the geographic location of cholera in Bangladesh, we selected geographic midpoints in the country and defined 4 zones: Northeast (NE), Northwest (NW), Southeast (SE), and Southwest (SW). Within each zone, we reported the percentage of cholera-positive cases among the patients with diarrhea. To describe the catchment area of the sentinel sites and healthcare-seeking behavior of the patients with diarrhea, we calculated the distance of each enrolled patient's home location to the hospital. We then calculated the cumulative probability distribution of attending a sentinel site by distance in kilometers (km) for cholera and non–cholera cases and also by disease severity based on dehydration status.

RESULTS

Between 4 May 2014 and 31 June 2018, we captured a total of 210 679 cases of diarrhea and 26 221 were enrolled; 46% were female. Among children under 5 years of age (45.6% of those tested), 86.7% (10 374/11 968) were younger than 2 years and 13.3% (1594/11 968) were aged 2–4 years old. Of children 5 years and older in age (54.4% of those tested), 9.5% (1350/14 253) were 5–17 years, 63.5% (9044/14 253) were 18–45 years, and 27% (3859/14 253) were 46 years or older. Of those enrolled, 62.8% had no formal schooling, which included children and those who did not complete primary school (class 5); 23% of patients were housewives and 8.6% were service holders; among those who were older (≥15 years), 45% were housewives and 17% were service holders. The majority of patients reported some (63.9%) or severe (14.2%) dehydration. Vomiting (67.3%), abdominal cramps (61.6%), and fever (60.5%) were also reported. Twenty-eight percent of patients had eaten food from roadside vendors, 11% had eaten food in large gatherings, and 14% had neighbors with diarrhea in the week prior to illness (Supplementary Table 1).

We detected *V. cholerae* O1 in stool of 6.2% (1604/25 958) of patients. Among those younger than 5 years, 2.1% (253/11 968) of diarrheal cases were positive for cholera, with 72.3% (183/253) of cases occurring in the under-2-year age and 27.7% (70/253) in 2–4-year age group. Among those who were older, 9.5% (1351/14 253) of cases were positive for cholera, of which 13.4% (181/1351) were aged 5–17 years, 67.4% (910/1351) were 18–45 years, and 19.2% (260/1351) were 46 years or older. The age distribution of cholera cases was qualitatively similar among the different Divisions and 53% were male. The majority (82.4%) of cholera cases had primary or no formal schooling (which included children and those who did not complete primary school). Most cholera cases had some or severe dehydration (78%), vomiting (75%), and abdominal cramps (71%). Approximately 30% had eaten food from roadside vendors, 14% had eaten food in large gatherings, while 17.5% had neighbors with diarrhea in the week prior to illness (Table 1).

Most of the *V. cholerae* isolates (70%) were Inaba serotype. Ogawa predominated between 2014 and 2015. During 2016–2017, the serotype profile switched; Inaba almost replaced the Ogawa serotype across the country. In 2018, the serotype started to shift back from Inaba to Ogawa and 45.8% were Ogawa isolates.

Approximately 3.1% of patients with diarrhea were ETEC positive and 2.7% were *Salmonella* spp. positive from the 10 surveillance sites in which multiple pathogens were tested. Only 0.34% of patients with diarrhea were coinfected with both ETEC and *V. cholerae*, and 0.06% were coinfected with *Salmonella* spp. and *V. cholerae*.

Table 1. Distribution of Demographic, Clinical Factors and History of Exposures of *Vibrio cholerae* Culture Positives by Divisions, May 2014–June 2018, Bangladesh

	Divisions							
Characteristics	Overall (N = 1604)	Dhaka (N = 405)	Chittagong (N = 572)	Barisal (N = 181)	Sylhet (N = 133)	Khulna (N = 200)	Rajshahi (N = 94)	Rangpur (N = 19)
Age (years)								
<5	253 (15.8)	48 (11.9)	63 (11.0)	40 (22.1)	37 (27.8)	35 (17.5)	15 (15.9)	15 (78.9)
5–17	181 (11.3)	48 (11.8)	70 (12.2)	19 (10.5)	20 (15.0)	17 (8.5)	7 (7.5)	0 (0.0)
18–45	910 (56.7)	237 (58.5)	346 (60.5)	94 (51.9)	61 (45.9)	117 (58.5)	52 (55.3)	3 (15.8)
>46	260 (16.3)	72 (17.8)	93 (16.3)	28 (15.5)	15 (11.3)	31 (15.5)	20 (21.3)	1 (5.3)
Sex (male)	853 (53.2)	227 (55.9)	295 (51.6)	84 (46.4)	71 (53.4)	105 (52.5)	58 (61.7)	13 (68.4)
Education status								
No formal schooling (child, did not complete primary)	630 (39.3)	138 (34.1)	208 (36.4)	70 (38.7)	78 (58.7)	93 (46.5)	28 (29.8)	15 (78.9)
Primary	691 (43.1)	191 (47.2)	281 (49.1)	60 (33.2)	50 (37.6)	64 (32.0)	43 (45.7)	2 (10.5)
Secondary and above	28 (17.6)	76 (18.8)	83 (14.5)	51 (28.2)	5 (3.8)	43 (21.5)	23 (24.5)	2 (10.5)
Occupation								
Service holder	290 (18.1)	127 (31.3)	130 (22.7)	8 (4.4)	4 (3.0)	13 (6.5)	7 (7.5)	1 (5.3)
Agricultural worker	84 (5.2)	12 (2.9)	14 (2.5)	8 (4.4)	16 (12.0)	24 (12.0)	10 (10.6)	0 (0.0)
Businessman	104 (6.5)	26 (6.4)	35 (6.1)	12 (6.6)	3 (2.3)	14 (7.0)	13 (13.8)	1 (5.3)
Housewife	456 (28.4)	96 (23.7)	156 (27.3)	72 (39.8)	33 (24.8)	72 (36.0)	26 (27.7)	1 (5.3)
Day laborer	131 (8.2)	32 (7.9)	70 (12.2)	5 (2.8)	8 (6.0)	6 (3.0)	10 (10.6)	0 (0.0)
Students and unemployed	254 (15.8)	51 (12.6)	94 (16.4)	36 (19.9)	28 (21.1)	32 (16.0)	12 (12.8)	1 (5.3)
Infant/child (≤10 years)	275 (17.1)	55 (13.6)	73 (12.8)	40 (22.1)	39 (29.3)	37 (18.5)	16 (17.0)	15 (78.9)
Others	10 (0.6)	6 (1.5)	0 (0.0)	0 (0.0)	2 (1.5)	2 (1.0)	0 (0.0)	0 (0.0)
Clinical characteristics								
Fever	804 (50.1)	293 (72.4)	235 (41.1)	49 (27.1)	81 (61.0)	106 (53.0)	30 (31.6)	10 (52.6)
Vomiting	1207 (75.3)	363 (89.6)	414 (72.4)	139 (76.8)	72 (54.1)	133 (66.5)	72 (76.6)	14 (73.7)
Dehydration status								
None	358 (22.3)	26 (6.4)	197 (34.4)	48 (26.5)	41 (30.8)	21 (10.5)	24 (26.5)	1 (5.3)
Some	875 (54.6)	170 (41.9)	280 (48.9)	118 (65.2)	79 (59.4)	161 (80.5)	62 (65.9)	5 (26.3)
Severe	371 (23.1)	209 (51.6)	95 (16.6)	15 (8.3)	13 (9.8)	18 (9.0)	8 (8.5)	13 (68.4)
Abdominal cramp	1141 (71.2)	352 (86.9)	366 (63.9)	152 (83.9)	75 (56.4)	121 (60.5)	72 (76.6)	3 (15.8)
Behavioral exposures								
Water treatment habit (boiled)	130 (8.1)	67 (16.5)	49 (8.6)	7 (3.9)	1 (0.8)	2 (1.0)	4 (4.3)	0 (0.0)
Consumed food from roadside vendors	485 (30.2)	68 (16.8)	216 (37.8)	48 (26.5)	35 (26.3)	75 (37.5)	43 (45.7)	0 (0.0)
Consumed food from large gatherings	226 (14.1)	21 (5.2)	132 (23.1)	12 (6.6)	17 (12.8)	27 (13.5)	17 (18.1)	0 (0.0)
Household members suffered from diarrhea during last week	158 (9.9)	21 (5.2)	92 (16.1)	13 (7.2)	4 (3.0)	15 (7.5)	13 (13.8)	0 (0.0)
Neighbors had diarrhea during last week	280 (17.5)	18 (4.4)	132 (23.1)	90 (49.7)	14 (10.5)	18 (9.0)	7 (7.5)	1 (5.3)

Data are presented as n (%).

The proportion of cases positive for cholera varied widely in the different surveillance sites, ranging from 1.1% to 18.3%. The Cox's Bazar (8.4%), BITID (18.3%) in Chittagong Division, and Narayanganj (13.9%) sites in Dhaka Division consistently had the highest number of cholera cases. In contrast, rates in Sylhet, Rajshahi, Khulna, and Rangpur ranged from 1.1% to 5.8% (Figure 1).

Although the numbers of patients with diarrhea were generally constant over time, there was a distinct pattern in the seasonality of cholera (Figure 2A). A biannual cholera peak was present across all sites in the pre–monsoon (March–June) and post–monsoon (September–October) seasons (Figure 2B). In the NW and SW regions, we observed higher cholera positivity during the postmonsoon peak, while in the NE and SE regions the premonsoon seasonal peak predominated (Figure 2C).

Cholera-associated Factors

In the GEE, we found that the risk of cholera among patients with diarrhea younger than 5 years of age was lower than in other age groups, with 5- to 17-year-olds having a 5.1-fold increased risk of cholera (95% confidence interval [CI], 2.9–8.8), 18- to 45-year-olds having a 3.8-fold increased risk of cholera (95% CI, 2.1–6.7), and those aged 46 years or older having a 2.7-fold increased risk of cholera (95% CI, 1.5–4.9) compared with those less than 5 years of age. Being an agricultural worker, businessman, housewife, or student was significantly associated with a decreased risk of being a confirmed cholera case compared with being a service holder. Patients with diarrhea who had neighbors with diarrhea in the week prior to illness had a 1.6 times greater risk of cholera (95% CI, 1.2–2.1) (Table 2).

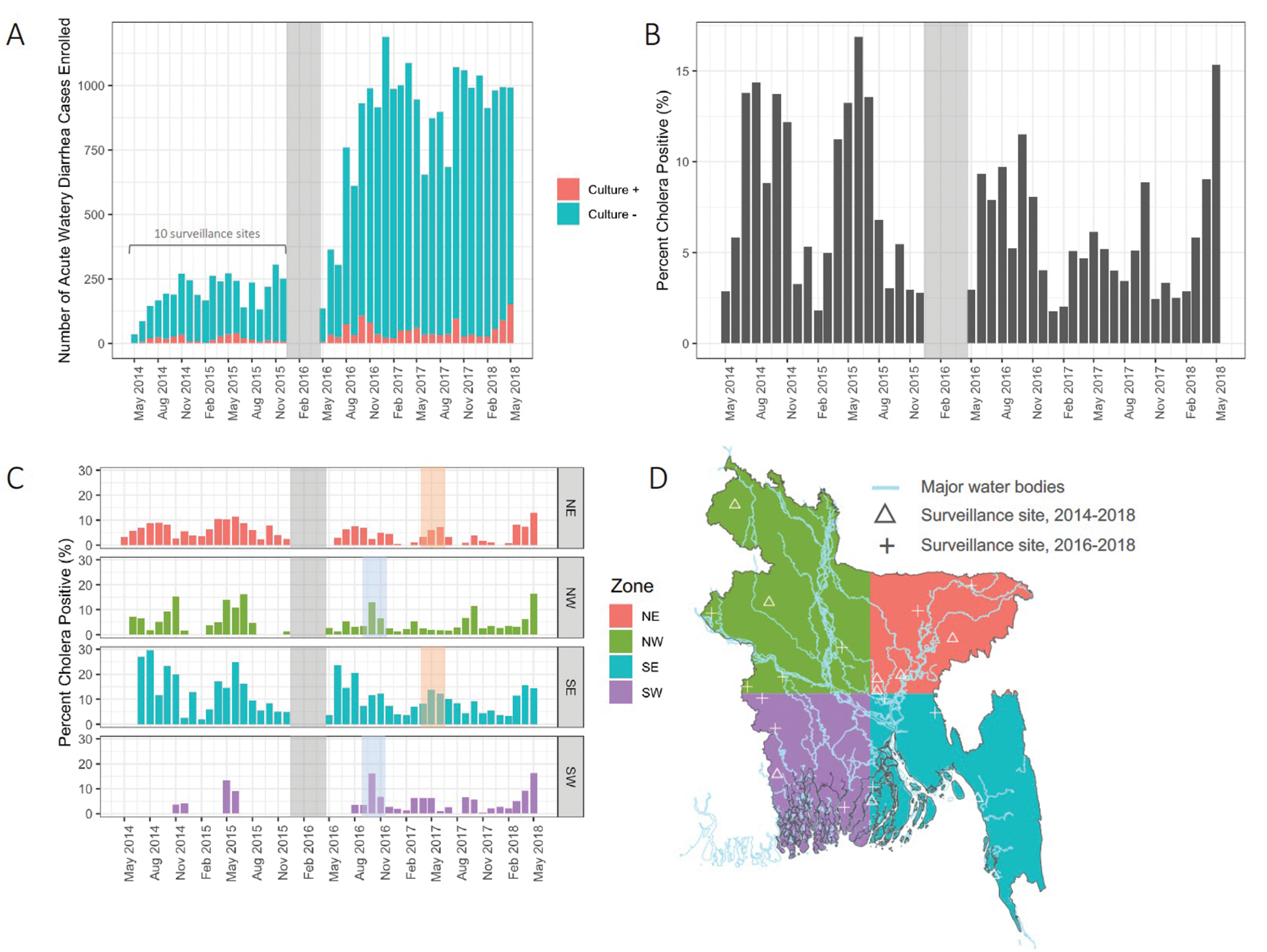

Figure 2. *A*, The number of acute watery diarrhea cases enrolled in the surveillance system across the study period (May 2014–December 2015 and May 2016–June 2018) by *Vibrio cholerae* culture–positive and –negative status. The gray-shaded area indicates when surveillance was interrupted (January 2016–May 2016). *B*, The percentage of *V. cholerae*–positive cases among all patients with acute watery diarrhea enrolled across the study period. *C*, The percentage of *V. cholerae*–positive cases among all patients with acute watery diarrhea enrolled across the study period by geographic zone: NE, NW, SE, and SW. *D*, Map of Bangladesh identifying the 22 surveillance sites and 4 geographic zones (NE, NW, SE, SW) with colors corresponding to panel *C*. Abbreviations: NE, Northeast; NW, Northwest; SE, Southeast; SW, Southwest.

Table 2. Analysis of Behaviors and Exposure Risk Factors of Confirmed *Vibrio cholerae* Culture–Positive Cases Using a Generalized Estimation Equation for All Surveillance Sites

Characteristics	cRR (95% CI)	aRR (95% CI)
Age (years)		
<5 (ref)	1.0	1.0
5–17	6.3 (4.6, 8.8)	5.1 (2.9, 8.8)
18–45	4.7 (3.7, 6.2)	3.8 (2.1, 6.7)
>46	3.2 (2.4, 4.2)	2.7 (1.5, 4.9)
Sex (male)[a]	.9 (.9, 1.1)	…
Education		
No formal schooling (child, did not complete primary) (ref)	1.0	1.0
Primary	2.7 (2.2, 3.4))	1.1 (.9, 1.3)
Secondary and above	2.4 (1.8, 3.1)	0.9 (.7, 1.1)
Occupation		
Service holder (ref)	1.0	1.0
Agricultural worker	.5 (.4, .8)	0.6 (.4, 0.8)
Businessman	.7 (.5, .9)	0.7 (.6, 0.9)
Housewife	.6 (.5, .8)	0.6 (.5, 0.7)
Day laborer	1.2 (.9, 1.6)	1.2 (.9, 1.5)
Students and unemployed	.8 (.6, 1.0)	0.7 (.5, .9)
Infant/child (≤10 years)	.2 (.1, .3)	0.6 (.3, .9)
Others	.5 (.2, 1.1)	0.5 (.2, 1.1)
Behavioral exposures[a]		
Water treatment habit (boiled)	1.0 (.8, 1.4)	1.2 (.9, 1.5)
Consumed food from roadside vendors	1.1 (.9, 1.5)	.9 (.8, 1.1)
Consumed food from large gatherings	1.3 (1.0, 1.8)	1.0 (.8, 1.2)
Household members suffered from diarrhea during last week	1.6 (1.2, 2.1)	1.2 (.9, 1.5)
Neighbors had diarrhea during last week	1.3 (.9, 1.9)	1.6 (1.2, 2.1)

Independence correlation structured assumed; 95% CIs were calculated using robust standard errors.

Abbreviations: aRR, adjusted risk ratio; CI, confidence interval; cRR, crude risk ratio; ref, reference.

[a]All "no exposure"s and female as reference.

Hospital Catchment Area

Eighty percent of both cholera and noncholera patients with diarrhea came from a distance of up to 50 km (median, 12.2 km; interquartile range [IQR], 4.9–34 km) of their homes for seeking treatment at a surveillance hospital. However, 55% of severe cholera cases (defined by dehydration status) traveled from within a 50-km distance of the hospital facility for treatment (median, 26.1 km; IQR, 9.3–251 km). Approximately 70% of noncholera patients with severe diarrhea also traveled within 50 km of a hospital site (median, 18.8 km; IQR, 9.3–251 km) (Supplementary Figure 1). To understand how care-seeking behaviors may influence our results, we conducted an analysis which restricted data to only diarrhea cases within 10 km of each clinic and found that the proportion of diarrheal cases with cholera was similar to the main findings, with the exception of a few health centers (Supplementary Table 2).

DISCUSSION

This study describes the nationwide enteric disease sentinel surveillance system, with an emphasis on cholera in Bangladesh. We show that cholera is pervasive throughout the country, with substantial heterogeneities within and between geographic areas. Among all Divisions, the sites in Chittagong had the highest proportion of cholera among cases with acute watery diarrhea (AWD) (>12%) followed by Dhaka and Barisal (6.5%). The highest cholera positivity (>18%) was documented in the BITID site in the Chittagong Division, although this may be due to the fact that BITID is a well-known referral hospital in the area (Table 1, Figure 1).

In the Dhaka Division, 9% of patients with diarrhea in the Narayanganj District were *V. cholerae* positive every year during the study period. Of note, the icddr,b diarrheal hospital, a renowned cholera hospital with over 60 years of activity, is well known to people living in Dhaka. On average, up to 22% of hospitalized patients with diarrhea are annually found to be cholera positive at the icddr,b hospital [12]. Given that the icddr,b hospital attracts people from far away and is also a referral hospital for diarrhea, we did not include this site in our surveillance network due to potential biases in extrapolating findings to the general population. The presence of this hospital may have led to underestimates of the prevalence of cholera among diarrhea cases in other clinics in Dhaka. However, based on the Diarrheal Disease Surveillance System data of the icddr,b, Dhaka Division can be extrapolated to be the area with the highest rates of cholera. In the Barisal Division, the highest burden was observed in Bakerganj, a subdistrict, which is supported by previous studies conducted by the icddr,b in the same area earlier [5].

Analysis of the demographic characteristics of patients showed that the case distribution was approximately equal by sex, which is comparable to other studies conducted in Bangladesh as well as other cholera-endemic countries [13, 14]. Children less than 5 years old, and especially those less than 2 years old (n = 183; 1.8%), had a higher proportion of noncholera diarrheal episodes (the majority may have been be due to rotavirus) than those in older age groups (Table 1, Supplementary Table 1). This is consistent with findings from previous studies [15, 16]. In an earlier analysis carried out at the icddr,b diarrheal hospital in Dhaka [17] and other surveillance sites in Bangladesh, the diarrheal rates were found to be higher in older children and adults than in the younger age group [6, 18]. Our observations also show a lower prevalence of cholera in children under 2 years of age, although 40% of cases of diarrhea are seen in this age group. This observation also lends support to the GTFCC 2017 recommendations that cholera should be suspected among persons aged 2 years and older, with AWD and severe dehydration or dying of AWD in areas where a cholera outbreak has not been declared.

Our sentinel surveillance shows that cholera is endemic in Bangladesh, with a distinct seasonality across the country. We observed different seasonality for cholera in the sites, especially between the eastern and western regions of Bangladesh. This observation is similar to those in previously conducted studies reported from Bangladesh [19, 20]. This variation may be related to local ecology, such as the location of the major rivers, which requires further evaluation.

The primary catchment area was approximately 50 km from each surveillance site, where 80% of the patients with diarrhea resided. Cases with severe cholera traveled farther distances seeking treatment compared with non–severe cholera cases and other patients with severe diarrhea; only 55% of cases with severe cholera traveled within 50 km of a hospital site. It is important to note that our observation is limited by the fact that the majority of sentinel sites are referral hospitals in the area, and we cannot exclude the possibility that patients were referred to a surveillance hospital by the closest treatment facility. Healthcare-seeking behavior for other severe illnesses, however, shows that patients travel far distances to attend a healthcare facility [21].

Due to funding constraints, the study was limited to 22 sentinel sites, which may not fully reflect the diversity of cholera epidemiology within the country. Establishing a higher-density surveillance network at all levels of the healthcare system, and across areas that we expect to have both high and low cholera incidence, may allow for more detailed insights. Another major limitation was that the data were from a facility-based surveillance system for which the exact catchment area (eg, the denominator) and the sensitivity of detecting all cholera cases in the catchment area are unknown. In future expansions of this surveillance system, healthcare utilization surveys and possibly cross-sectional serological surveys may help improve our ability to estimate the true incidence of cholera disease and *V. cholerae* O1 infection [22].

Furthermore, the patients enrolled were not followed up after treatment or discharge; therefore, data on clinical consequences and mortality are lacking. Finally, for the confirmation of cholera cases, this study used a conventional culture method and not PCR, which may improve the sensitivity, especially in the presence of antibiotics [23, 24].

This nationwide hospital-based surveillance shows the presence of cholera in all geographical regions in Bangladesh that were under surveillance. Although describing cholera epidemiology is complex in Bangladesh, we show that different frequencies of disease exist across this small geographical area. Our study identified at least 8 geographical areas (health facilities of district and subdistrict levels) where cholera was consistently higher over the reporting period. Dhaka remains as one of the areas with a moderate-to-high prevalence of cholera among cases of diarrhea in accordance with data from the icddr,b systematic surveillance system (where 2% of all diarrhea cases are tested for *V. cholerae* and other pathogens) [22]. Given the population size, the absolute impact of controlling cholera in Dhaka would be substantial, both within the city and likely elsewhere in the country.

One of the most immediate ways to protect populations against cholera is to provide OCV. Given our findings, large OCV campaigns are justified in at least a subset of the surveillance areas. While there is no well-defined threshold of cholera incidence or prevalence (among diarrhea cases), targeting areas with a high prevalence may be a reasonable place to start. Based on the data, it would be judicious to plan for OCV campaigns around Comilla, BITID, Cox's Bazar, and Narayanganj, as well as Bakerganj. Since Dhaka city itself has a high burden of cholera based on icddr,b cholera surveillance data, it should also be targeted for OCV rollout to control epidemics of cholera.

The study provides critical insights for the Bangladesh National Cholera Control Plan and points towards key geographic areas within the country where cholera- prevention and -control activities, including vaccination, should be prioritized. For long-term control of cholera, massive investments in sustainable water and sanitation infrastructure are needed, although universal access may be years, if not decades, away. Continued, and expanded, national disease surveillance will be critical in the years to come to monitor progress on the road to elimination and to quantify the impact of interventions like OCV. The multisectoral support of different ministries of the government of Bangladesh and international partners for the improvement of water and sanitation measures, strengthening the national health systems, and targeted use of OCV will be critical to meeting the WHO-backed goal of ending cholera by 2030 in Bangladesh.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Gill CJ, Thea DM, Hibberd P. Diarrhoeal disease trends in the GBD 2015 study: optimism tempered by scepticism. Lancet Infect Dis **2017**; 17:884–5.
2. UNICEF. Committing to child survival: a promise renewed. UNICEF Levels & Trends in Child Mortality, Report **2015**.
3. Legros D; Partners of the Global Task Force on Cholera Control. Global cholera epidemiology: opportunities to reduce the burden of cholera by 2030. J Infect Dis **2018**; 218(Suppl_3):S137–40.
4. Ali M, Nelson AR, Lopez AL, Sack DA. Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis **2015**; 9:e0003832.

5. Barua D. History of cholera. In: Barua D, Greenough WB, eds. Cholera. Boston, MA: Springer USA, **1992**:1–36.
6. Sack RB, Siddique AK, Longini IM Jr, et al. A 4-year study of the epidemiology of Vibrio cholerae in four rural areas of Bangladesh. J Infect Dis **2003**; 187:96–101.
7. Islam MT, Clemens JD, Qadri F. Cholera control and prevention in Bangladesh: an evaluation of the situation and solutions. J Infect Dis **2018**; 218:171–2.
8. Bwire G, Orach CG, Abdallah D, et al. Alkaline peptone water enrichment with a dipstick test to quickly detect and monitor cholera outbreaks. BMC Infect Dis **2017**; 17:726.
9. Rahman M, Sack DA, Mahmood S, Hossain A. Rapid diagnosis of cholera by coagglutination test using 4-h fecal enrichment cultures. J Clin Microbiol **1987**; 25:2204–6.
10. Chowdhury F, Mather AE, Begum YA, et al. Vibrio cholerae serogroup O139: isolation from cholera patients and asymptomatic household family members in Bangladesh between 2013 and 2014. PLoS Negl Trop Dis **2015**; 9:e0004183.
11. Qadri F, Das SK, Faruque AS, et al. Prevalence of toxin types and colonization factors in enterotoxigenic *Escherichia coli* isolated during a 2-year period from diarrheal patients in Bangladesh. J Clin Microbiol **2000**; 38:27–31.
12. Andrews JR, Leung DT, Ahmed S, et al. Determinants of severe dehydration from diarrheal disease at hospital presentation: evidence from 22 years of admissions in Bangladesh. PLoS Negl Trop Dis **2017**; 11:e0005512.
13. Sarker AR, Islam Z, Khan IA, et al. Cost of illness for cholera in a high risk urban area in Bangladesh: an analysis from household perspective. BMC Infect Dis **2013**; 13:518.
14. Deepthi R, Sandeep SR, Rajini M, Rajeshwari H, Shetty A. Cholera outbreak in a village in South India—timely action saved lives. J Infect Public Health **2013**; 6:35–40.
15. Desai SN, Cravioto A, Sur D, Kanungo S. Maximizing protection from use of oral cholera vaccines in developing country settings: an immunological review of oral cholera vaccines. Hum Vaccin Immunother **2014**; 10:1457–65.
16. Khan AI, Levin A, Chao DL, et al. The impact and cost-effectiveness of controlling cholera through the use of oral cholera vaccines in urban Bangladesh: a disease modeling and economic analysis. PLoS Negl Trop Dis **2018**; 12:e0006652.
17. Qadri F, Ali M, Chowdhury F, et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. Lancet **2015**; 386:1362–71.
18. Chowdhury F, Rahman MA, Begum YA, et al. Impact of rapid urbanization on the rates of infection by Vibrio cholerae O1 and enterotoxigenic Escherichia coli in Dhaka, Bangladesh. PLoS Negl Trop Dis **2011**; 5:e999.
19. Paul RC, Faruque AS, Alam M, et al. Incidence of severe diarrhoea due to Vibrio cholerae in the catchment area of six surveillance hospitals in Bangladesh. Epidemiol Infect **2016**; 144:927–39.
20. Alam M, Islam A, Bhuiyan NA, et al. Clonal transmission, dual peak, and off-season cholera in Bangladesh. Infect Ecol Epidemiol **2011**; 1:7273. doi: 10.3402/iee.v1i0.7273.
21. Hegde ST, Salje H, Sazzad HMS, et al. Using healthcare-seeking behaviour to estimate the number of Nipah outbreaks missed by hospital-based surveillance in Bangladesh. Int J Epidemiol **2019**; 48:1219–27.
22. Azman AS, Lessler J, Luquero FJ, et al. Estimating cholera incidence with cross-sectional serology. Sci Trans Med **2019**; 11:eaau6242.
23. Alam M, Hasan NA, Sultana M, et al. Diagnostic limitations to accurate diagnosis of cholera. J Clin Microbiol **2010**; 48:3918–22.
24. Faruque SM, Biswas K, Udden SM, et al. Transmissibility of cholera: in vivo-formed biofilms and their relationship to infectivity and persistence in the environment. Proc Natl Acad Sci USA **2006**; 103:6350–5.