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Characteristics of Rotavirus, ETEC, and *Vibrio Cholerae* Among Under 2-year Children Attending an Urban Diarrheal Disease Hospital in Bangladesh

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Abstract

Background: Information on comparative clinical and host characteristics of under-2 children with watery diarrhea caused by rotavirus, *Enterotoxigenic Escherichia coli* (ETEC), and *Vibrio cholerae* as single pathogens is lacking. We sought to investigate the sociodemographic, clinical, and host characteristics of under-2 children hospitalized due to these pathogens. **Methodology:** We conducted a hospital-based case-control study using the icddr,b Diarrheal Diseases Surveillance System. Children of either sex, <2 years with diarrhea, who attended the hospital during 2014 to 2018, constituted the study population. Stool specimens having a single pathogen like rotavirus, ETEC, or *Vibrio cholerae* constituted the cases and stool specimens having no detectable common enteropathogens comprised the controls. Multinomial logistic regression analysis was done where control was the reference group. **Results:** A total of 14 889 patients were enrolled, 6939 of whom were under-2 children, and 5245 (76%) constituted our study population. Among them 48% (n = 2532), 3% (n = 148) and 1% (n = 49) had rotavirus, ETEC, and *Vibrio cholera*, respectively. A control group (diarrhea without these 3 or *Shigella*, *Salmonella*, *Aeromonas*) accounted for 48% (n = 2516). In multinomial regression model, children with rotavirus (adjusted odds ratio [aOR], 1.36; 95% confidence interval [95% CI], 1.19-1.55) less often presented with dehydrating diarrhea compared to those with ETEC (aOR, 1.54; 95% CI, 1.05-2.26) and cholera (aOR, 2.25; 95% CI, 1.11-4.57). Rotavirus diarrhea was associated (aOR, 1.25; 95% CI, 1.07-1.46) with those who received antimicrobials prior to hospital admission and protectively associated with drinking tap water (aOR, 0.84; 95% CI, 0.73-0.95); however, ETEC diarrhea had protective association (aOR, 0.62; 95% CI, 0.43-0.92) with children who received antimicrobials prior to hospital admission and was associated with drinking tap water (aOR, 1.78; 95% CI, 1.19-2.66). Use of intravenous fluid was associated with cholera (aOR, 10.36; 95% CI, 4.85-22.16) and had protective association with rotavirus episodes (aOR, 0.64; 95% CI, 0.45-0.91). **Conclusions:** Clinical presentations and host characteristics of rotavirus, ETEC, and *Vibrio cholerae* diarrhea differed from each other and the information may be helpful for clinicians for better understanding and proper management of these children.

Keywords

Bangladesh, diarrhea, rotavirus, Vibrio cholerae, Enterotoxigenic Escherichia coli, less than 2 years

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Introduction

Diarrheal disease remains in the top 5 causes of childhood mortality globally,[1] with 72% of deaths associated with diarrhea occurring during the first 2 years of life.[2] Considering the etiology, rotavirus is the most common cause of acute watery diarrhea globally with about 39% of diarrhea hospitalizations and 199 000 deaths each year, mostly in children under the age of 2 years[3]; unfortunately, 85% of them occur in low-income countries.[4] In Bangladesh, rotavirus incidence in under-5 children was estimated to be 10 000 cases per 100 000 children prior to vaccination, with 1850 deaths every year[5]; and the burden

of rotavirus is particularly high in children under 2 years of age.[6] Next to rotavirus, Enterotoxigenic *Escherichia coli* (ETEC) has been estimated to have caused 42 000 deaths of children under 5 years of age in 2013.[7] ETEC causes significant diarrheal morbidity and mortality in children in resource-poor settings such as Bangladesh.[8] ETEC can quickly dehydrate young infants, leading to death unless appropriate rehydration is introduced immediately.[9] On the other hand, *Vibrio cholerae* causes an estimated 11 million cholera cases worldwide every year among children below the age of 5 years and most often identified in fatal cases over a 2-year period.[10] Bangladesh is one of the world's most cholera-endemic countries. Annually, Dhaka hospital and Mirpur treatment center of icddr,b reported 15 000 to 20 000 cases of cholera.[11] Cholera is present throughout the year, with a peak prior to and during the monsoon season, and it can be devastating during flood months.[12]

Although all 3 pathogens present with features of acute watery diarrhea, each of them may differ in their manifestations and severity, evidence based comparative information on which is limited. A Diarrheal Disease Surveillance System (DDSS) has been in place since 1979, at the International Centre for Diarrheal Disease Research, Bangladesh (icddr,b), which systematically enrolls 2% (every 50th) of its patients irrespective of age, sex, disease severity, and socio-economic status with the aim of collecting clinical, epidemiological, and etiological information on diarrheal illnesses due to common enteropathogens. Thus, the present study aimed to review comparative differences in patient characteristics (socio-demographic, host, and clinical) among children below the age of 2 years infected with any single pathogen of the 3 studied pathogens (rotavirus, ETEC, and *Vibrio cholerae*) in urban Bangladesh.

Methodology

Study Site

icddr,b is an international health research organization that addresses some of the world's most pressing health issues by translating research findings into treatment, training, and policy advocacy. Established in 1962 in Dhaka, the capital city of Bangladesh, Dhaka Hospital of icddr,b delivers quality care and treatment to people with diarrheal diseases mostly from urban and peri-urban Dhaka. The vast majority of them are from poor socio-economic backgrounds. The hospital also conducts research on enteric infections caused by common pathogens including rotavirus, ETEC, *Vibrio cholerae*, and *Shigella*; as well as acute respiratory infections and malnutrition.[13] The DDSS collects information on the clinical, epidemiological and demographic characteristics, feeding practices, particularly of infants and young children, housing and environment as well as nutritional status by administering a structured questionnaire. A trained research assistant interviews either the patient or the caregiver in the case of young children, following the same questionnaire.[14-16]

Study Design, Sampling Technique, and Eligibility Criteria

The case-control study was conducted in Dhaka hospital of icddr,b and the study extracted information regarding the enrolled children from the DDSS database. The duration of the present study was 5 years; January 2014 to December 2018. Children of either sex, below the age of 2 years with diarrhea, who attended the hospital between January 2014 to December 2018, constituted the study population; where stool specimens having a single pathogen like rotavirus, ETEC or *Vibrio cholerae* comprised the cases and stool specimens having no detectable common enteropathogens (rotavirus, ETEC, *Vibrio cholerae*, *Shigella* spp., *Salmonella* spp., *Aeromonas*) constituted the controls (Figure 1). We excluded all children from our study if rotavirus, ETEC, and *Vibrio cholera* had co-infection with other pathogens or if they had identified *Shigella* spp., *Salmonella* spp., *Aeromonas*.

Laboratory Method

A 2% sub sample from the surveillance patients of Dhaka Hospital are examined in the central laboratory of icddr,b in Dhaka. Each specimen is aliquoted into 3 serial containers and submitted to the respective laboratory for routine screening of common enteric pathogens such as rotavirus, ETEC, and *Vibrio cholerae*.[17-20] Detection of Group A rotavirus-specific VP6 antigen is done from the stool specimens by using solid phase sandwich-type enzyme immunoassay modeled according to the commercial kit (UTF-8 ProSpecT Rotavirus Microplate Assay

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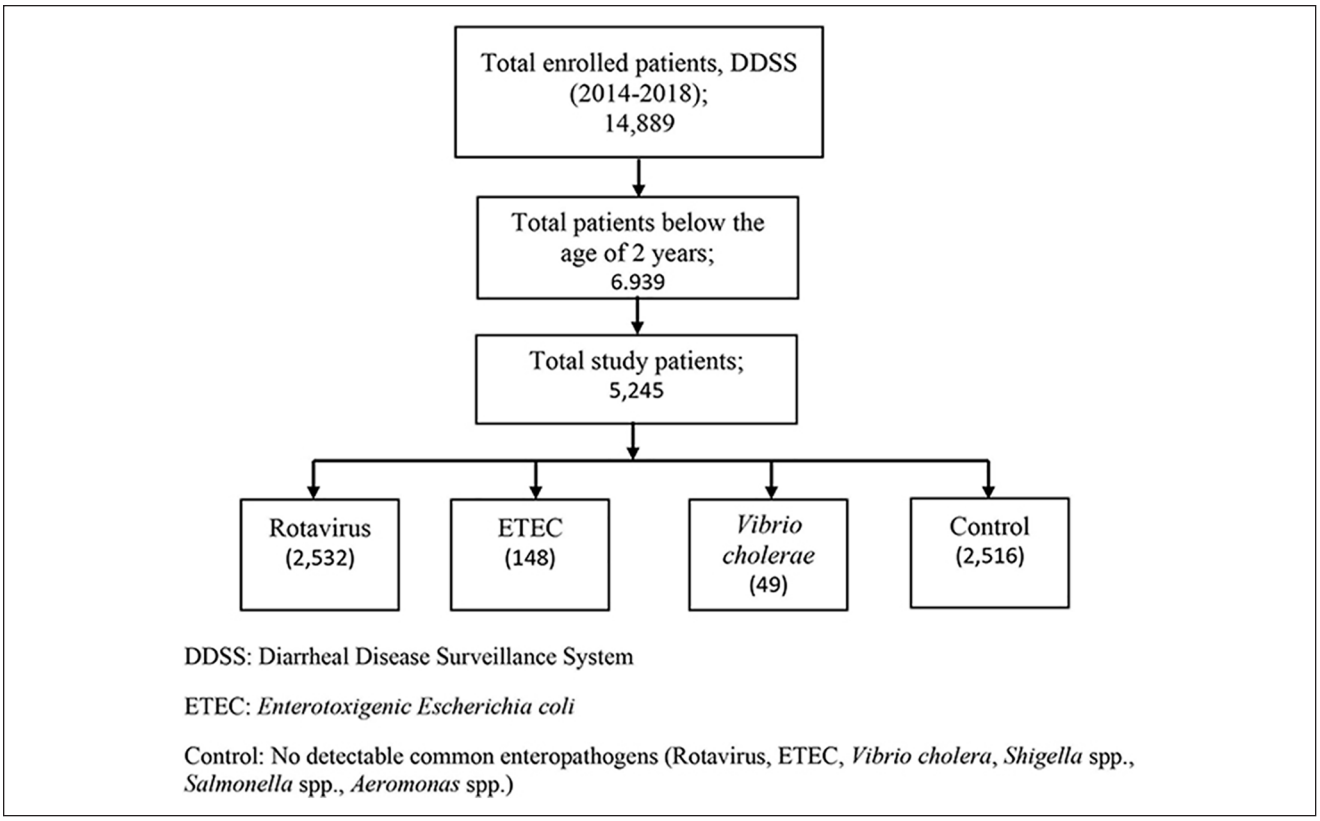

Figure 1. Sample framing.

[Oxoid Ltd, Basingstoke, UK]). Positive and negative controls are included, and quality control of the enzyme-linked immune assay (EIA) test is routinely performed using rotavirus positive samples with known optical density (OD) values.[17,20] For ETEC, stool samples are plated onto MacConkey agar, and the plates are incubated at 37°C for 18 h, and 6 lactose-fermenting individual colonies, morphologically resembling *E. coli*, are tested immediately after isolation for the presence of toxins and Colonization Factors (CFs).[20,21] For isolation of *Vibrio cholerae*, stool samples are plated on taurocholate-tellurite-gelatin agar and gelatin agar (Difco, Detroit, USA); after overnight incubation of plates, serological confirmation of suspected *Vibrio* spp. colonies is carried out by slide agglutination.[20,22,23]

Definition

Diarrhea was defined as passage of 3 or more abnormally loose or liquid stools during the previous 24 h.[24] However, malnutrition (underweight, stunting, and wasting) was defined as individual with weight-for-age *z*-score (WAZ), height-for-age *z*-score (HAZ), and weight-for-height *z*-score (WHZ) <-2.00 SD,respectively.[24,25]

Data Analysis

Statistical Package for Social Sciences (SPSS), Windows (Version 15.2; CPSS Inc) and Epi Info (Version 6.0, USD, Stone Mountain, GA, USA) were used for data analyses. Chi-square test was performed in 2×4 table for estimation of a probability (P) of $<.05$ (type I error) considered as statistically significant. Finally, multinomial logistic regression analysis was done between the control and cases, where detection of no pathogen (control) was the reference group (control = 0, rotavirus = 1, ETEC = 2, and *Vibrio cholerae* = 3). Variables used in the model included: age (0-5 months [reference], 6-11 months, 12-23 months), sex (male [reference], female), maternal literacy (illiterate [reference], literate), drinking tap water (no [reference], yes), use of boiled drinking water (no [reference], yes), duration of diarrhea (>1 day [reference], ≤ 1 day), frequency of stool (≤ 10 times/24 h [reference], >10 times/24 h), use of antimicrobial at home (no [reference], yes), history of vomiting (no [reference], yes), abdominal pain (no [reference], yes), dehydration (no sign of dehydration [reference], some or severe dehydration), use of intravenous fluid (no [reference], yes), hospital stay (<24 h [reference], ≥ 24 h), underweight (no [reference], yes), stunting (no [reference], yes) and wasting (no [reference],

yes). Child's age was categorized into 3 stratums, 0 to 5 months (early infancy), 6 to 11 months (late infancy), and 12 to 23 months (childhood).

Ethical Statement

DDSS (Ref No.: 1992-011) of icddr,b is a routine ongoing activity of the Dhaka hospital, which has been approved by the Research Review Committee (RRC) and Ethical Review Committee (ERC) of icddr,b. At the time of enrollment, verbal consent was obtained from the caregivers or guardians on behalf of the child. The information was stored in the hospital database and often used for conducting researches. The patient's or caregivers' verbal consent was documented by a check mark on the questionnaire, which was subsequently showed and finally a copy of the document provided to them. Parents or guardians are assured about the non-disclosure of information collected from them, and are also informed about the use of data for analysis and further use of the results for improving patient care activities as well as publications without disclosing the name or identity of their children. ERC is satisfied with the voluntary participation, maintenance of the rights of the participants and confidential handling of personal information by the hospital physicians and has approved this consenting procedure.[26]

Results

A total of 14 889 patients were enrolled into the DDSS. Of them, 6939 (47%) were children below the age of 2 years with diarrhea. Of that cohort, 5245 were the study population; and among them 2729 (52%) represented the cases and 2516 (48%) served as the control group. Prevalence of rotavirus, ETEC, and *Vibrio cholerae* as single pathogen was 48% (n = 2532), 3% (n = 148) and 1% (n = 49) respectively among study children below the age of 2 years. Comparison of socio-demographic, clinical, and host contexts in univariate analysis showed that all the variables of interest significantly differed from each other except female gender, duration of diarrhea <1 day, abdominal pain, and wasting (Table 1).

Multinomial logistic regression analysis reported that in children aged 6 to 11 months, frequency of stool >10 times/24 h, use of antimicrobial prior to hospital admission, history of vomiting, some or severe dehydration, and hospital stay ≥ 24 h had significant association with rotavirus diarrhea. On the other hand, tap water drinking, use of boiled drinking water and use of intravenous fluid had protective association with rotavirus diarrhea (Table 1).

For ETEC diarrhea, significant association was observed for tap water drinking and some or severe dehydration; however, use of antimicrobial prior to hospital admission had protective association with ETEC diarrhea among children less than 2 years old (Table 1).

Similarly, for children of 12 to 23 months old, some or severe dehydration and use of intravenous fluid had significant association with *Vibrio cholerae*. Conversely, none of the variables had protective association with this enteric pathogen (Table 1).

Moreover, female, maternal literacy, duration of diarrhea <1 day, abdominal pain, underweight, stunting, and wasting were not associated with any of the 3 enteric diarrhea pathogens of interest.

Discussion

All 3 pathogens, rotavirus, ETEC, and *Vibrio cholerae*, are responsible for acute watery diarrhea; the present comparison however, indicated that the features of their infections significantly differed from each other with regard to socio-demographic, clinical, and host characteristics. The present study documented the use of a higher proportion of antimicrobials at home for rotavirus diarrheal illnesses compared to *Vibrio cholerae* and ETEC diarrhea, despite lack of evidence on the positive role of antibiotics.[27] This might be due to the high frequency of stool as well as vomiting and fever in children with rotavirus diarrhea making their parents anxious and warranting them to visit unlicensed health care providers where over use of antimicrobials is not an uncommon practice. The study also noted that drinking tap water has a protective effect for rotavirus diarrhea while it is a risk factor for ETEC diarrhea; however, there is lack of any significant association between drinking tap water and cholera. This finding is consistent with the study results of Islam et al.[28] who reported a high coliform count at the use of raw water, and that consumption of boiled drinking water was safe for each of the responsible pathogens.

Clinical presentations such as dehydrating diarrhea were more often observed in cases of cholera rather than rotavirus and ETEC diarrhea. High frequency of vomiting, loss of stool volume and excess serum concentration of bicarbonate causes dehydration and metabolic acidosis in cholera leading to such clinical presentations.[29] This observation also correlates with higher use of intravenous saline for management of acute dehydrating cholera compared to rotavirus diarrheas. Conversely, longer duration of hospital stay for rotavirus patients might be due to longer natural remission time compared to their counterparts.

Higher proportions of rotavirus diarrhea were recorded for older infants, just after the period of exclusive breast feeding, suggesting a protective immune response for that age group.[4] However, cholera cases were more common during childhood (12-23 months) and thereafter, suggesting the protective effect of breast feeding, and other factors such as lack of exposure in infancy and short-lived transplacental immunity at that age.[14] Cholera is more frequent among malnourished children due to potential less production of hydrochloric acid in the stomach among those who

Table 1. Socio-demographic, host and clinical characteristics of rotavirus, ETEC and *Vibrio cholerae* (2014-18).

Variables	Rotavirus *n* = 2532 (%)	ETEC *n* = 148 (%)	*Vibrio cholerae* n = 49 (%)	No pathogen *n* = 2516 (%)	#*P* Value	##Rotavirus aOR (95% CI) p	##ETEC aOR (95% CI) p	##*V. cholera* aOR (95% CI) p
Age								
0-5 months	285 (11)	17 (11)	6 (12)	368 (15)	1	1	1	1
6-11 months	1303 (52)	65 (44)	15 (31)	1133 (45)	<.001	1.45 (1.21-1.74)*	1.39 (0.80-2.43)	1.36 (0.49-3.74)
12-23 months	944 (37)	66 (45)	28 (57)	1015 (40)	.003	1.16 (0.96-1.40)	1.55 (0.89-2.71)	1.02 (1.06-7.04)*
Female	983 (39)	65 (44)	22 (45)	1023 (41)	.342	0.92 (0.82-1.04)	1.10 (0.78-1.54)	1.23 (0.68-2.22)
Mother literacy	2326 (92)	129 (87)	41 (84)	2316 (92)	.033	0.97 (0.78-1.97)	0.67 (0.40-1.13)	0.78 (0.34-1.80)
Drinking tap water	1255 (49)	104 (70)	33 (67)	1480 (59)	<.001	0.84 (0.73-0.95)*	1.78 (1.19-2.66)*	1.51 (0.76-3.01)
Boiled drinking water	665 (26)	51 (34)	19 (39)	844 (33)	<.001	0.83 (0.72-0.95)*	0.82 (0.56-1.21)	1.04 (0.53-2.03)
Duration of diarrhea <1 day	617 (25)	41 (28)	16 (33)	683 (27)	.087	0.94 (0.82-1.08)	0.83 (0.56-1.21)	0.90 (0.46-1.76)
Frequency of stool >10 times/24 h	1800 (71)	81 (55)	34 (69)	1479 (59)	<.001	1.51 (1.34-1.71)*	0.82 (0.59-1.16)	1.37 (0.72-2.61)
Use of antimicrobial prior to hospital admission	2126 (84)	103 (70)	31 (63)	1999 (80)	<.001	1.25 (1.07-1.46)*	0.62 (0.43-0.92)*	0.59 (0.31-1.14)
Vomiting	1996 (79)	114 (77)	42 (86)	1816 (72)	<.001	1.33 (1.16-1.52)*	1.23 (0.83-1.84)	1.65 (0.72-3.82)
Abdominal pain	1187 (47)	68 (46)	19 (39)	1126 (45)	.351	1.04 (0.93-1.17)	1.02 (0.73-1.43)	0.75 (0.41-1.38)
Some or severe dehydration	859 (34)	53 (36)	31(63)	616 (24)	<.001	1.36 (1.19-1.55)*	1.54 (1.05-2.26)*	2.25 (1.11-4.57)*
Use of intravenous fluid	78 (3)	10 (7)	19 (39)	71 (3)	<.001	0.64 (0.45-0.91)*	1.79 (0.85-3.76)	10.36 (4.85-22.16)*
Hospital stay ≥24 h	801 (32)	29 (20)	18 (37)	386 (15)	<.001	2.31 (1.99-2.67)*	1.19 (0.76-1.87)	1.38 (0.68-2.78)
Underweight	482 (19)	32 (22)	19 (39)	524 (21)	.003	0.85 (0.70-1.03)	0.92 (0.53-1.58)	1.18 (0.50-2.79)
Stunting	421 (17)	27 (18)	17 (35)	483 (19)	.001	–	–	–
Wasting	431 (17)	27 (18)	12 (24)	418 (17)	.499	–	–	–

*$P < .05$; ETEC- Enterotoxigenic *Escherichia coli*; aOR- adjusted odds ratio.
#All statistical values are equated from univariate analysis (2 × 4 table).
##All statistical values are equated from multinomial logistic regression.
Dependent variable: Presence of pathogens where no pathogens considered as reference group (no pathogen = 0, rotavirus = 1, ETEC = 2, *Vibrio cholerae* = 3).
Reference categories for independent variable were: (0-5 months, male sex, maternal illiteracy, not drinking tap water, unboiled drinking water, duration of diarrhea >1 day, frequency of stool ≤10 times/24 h, not used antimicrobial at home, no vomiting, no abdominal pain, no sign of dehydration, not use of intravenous fluid, hospital stay <24 h, normal weight [weight-for-age ≥ −2.00]).

are at greater risk of death, as reported elsewhere[30]; however, our study did not indicate a significant association between childhood malnutrition (underweight) and diarrhea caused by the pathogens that were examined.

Limitation

We do not know whether single pathogens are truly single since we had a limited number of pathogens isolated in the DDSS. Metagenomics' analysis which includes more pathogens would be required to identify true single pathogens and also to describe the role of additional pathogens in diarrheal diseases. We could not exclude other pathogens such as other viral diarrhea (norovirus, adenovirus, sapovirus) and other pathogens causing watery diarrhea like cryptosporidium, diarrheagenic *E.coli* other than ETEC due to lack of information. However, recent studies for rural Bangladesh and other countries revealed that such pathogens were also prevalent among asymptomatic healthy controls thus their role in pathogenicity needs to be further explored.[31] Healthy children below the age of 2 years would have been ideal for the control group, but since Dhaka hospital focuses on clinical management of diarrheal illnesses caused by common pathogens, no healthy control group could be included. We tried to exclude all the pathogens identified by the DDSS (rotavirus, ETEC, *Vibrio cholera*, *Shigella* spp., *Salmonella* spp., *Aeromonas*) in considering this group as control. Thus, there might be a chance of co-infection with other causative pathogens, however, a recent study also showed very low prevalence of such co-infection.[31] However, the unbiased systematic sampling method to enroll patients, use of a large data set, and quality laboratory performance helped the study to identify the diarrheal pathogens and thus, contributed to the strengths of the current analyses.

Conclusion

The results of this study may provide a better understanding of the differences related to socio-demographic and clinical characteristics in children below the age of 2 years suffering from rotavirus, ETEC, and *Vibrio cholerae* diarrhea that may further help for the clinical diagnosis and management of such children in resource-poor settings.

Declaration of Conflicting Interests

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