

Disease severity and common etiology of diarrhoea among children under-five in Mirzapur, rural Bangladesh.

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ABSTRACT

Aim: There is lack of information on the severity of diarrhoeal disease and aetiology compared to diarrhoeal illnesses with mild disease. Thus the study aimed to compare the aetiology of under-five children with moderate-to-severe disease and milder disease.

Study Design: Diarrhoeal disease surveillance.

Place and Duration of Study: Mirzapur Kumudini Hospital, Tanzail, Bangladesh, January 2010 – December 2011

Methodology: Overall; 2,324 under-5 diarrhoea children [0-11 months, 1098 (47%); 12-23 months, 789 (34%), and 24-59 months, 437 (19%)] were enrolled in the hospital and they came from the demographic surveillance system (DSS) catchment area. Whole stool samples were collected from each enrolled child to detect rotavirus, *Shigella*, ETEC and *V. cholerae*. Information on socio-demographic and clinical characteristics was collected.

Results: Rotavirus (33%) was the leading cause of diarrhoea for children less than five years, and in case of children under two years old, 90% were suffering from rotavirus diarrhoea. On the other hand, *Shigella* represented 14% of total study children and children aged 24-59 months old (45%) predominantly suffered from shigellosis. However, children with ETEC and *V. cholerae* infections represented 3% and 2% children respectively. *Shigella* was the most commonly detected pathogen (27%) among under-5 children, presented with moderate-to-severe disease followed by rotavirus (16%). In contrast to that, rotavirus was the dominant (43%) cause of diarrhoea among under-5 children reported with milder disease. Under-5 children who presented with moderate-to-severe disease were most likely to be infected with *Shigella flexneri* [OR= 9.81; 95% CI (6.38, 15.18)] and *Shigella sonnei* [6.29; (3.67, 10.87)] compared to their counterparts with milder disease.

Conclusion: *Shigella* was the leading pathogen that caused moderate-to-severe disease, whereas rotavirus often caused milder disease among children less than 5 years old in rural Bangladesh.

Keywords: Bangladesh, diarrhea, moderate-to-severe disease, rural, under-5 children.

1. INTRODUCTION

World Health Organization (WHO) ranks diarrhoeal disease as the second most common cause of under five-year childhood (<60 months) mortality in developing countries, attributing to 18% of the cumulative 10.6 million child deaths each year [1]. On an average, the morbidity rate of diarrhoeal disease accounts for 3.2 episodes per child per year in resource-poor developing countries including Bangladesh [1-3], which could be as high as 12 episodes per child per year in some settings [4]; and incidences of diarrhoeal disease is more prevalent during the first 2 years of life [5]. Poor sanitation, inadequate hygiene, unsafe drinking water, and overcrowding are the dominant risk factors for the population at risk [6] to be infected with common etiologic pathogens such as rotavirus, *Shigella* spp., ETEC and *Vibrio cholerae* [7-10]. Impairment of physical as well as mental development adds to the burden of Disability Adjusted Life Years (DALYs) (premature mortality and years of life lost due to time lived in states of less than full health) lost in addition to nutritional faltering, and breach in the productivity at adulthood [5, 11]. Although under-5 child mortality has approximately decreased by half in the past 20 years, there is no indication that the disease morbidity is decreasing [6].

Three quarters of global childhood diarrhoeal deaths occur in 15 countries only and Bangladesh is on 7th position with 50,800 annual childhood deaths [12]. A systematic surveillance in two rural health facilities between August 2005 and July 2007 among under-5 children revealed that 12-14% cases of hospitalization in rural Bangladesh were due to rotavirus infection in this age-group [13]. Moreover, prevalence of shigellosis which was 8–12% in 1980, decreased to 3% in 2008, among the diarrhoeal disease patients in a large facility in Dhaka, the capital city of Bangladesh [14].

Most of clinic-based studies were designed without considering the severity of the disease and did not categorize the degree of severity of the disease [7-9, 11, 13-15]. Thus, the present study aimed to identify the common four microbiologic etiologies (*V. cholerae*, *Shigella*, ETEC, and rotavirus) among rural children aged less than 5 years; and compare the clinical and epidemiological findings between moderate-to-severe and milder form of the disease. This study also emphasized on patterns of distribution of enteropathogens to provide definitive and comprehensive information on the etiology of moderate-to-severe disease as well as milder disease in infants and young children in rural Bangladesh. The study intends to share this information with clinicians, public health personnel, policy makers, vaccine developers and other interested parties with a view to initiate vaccine and/or public health interventions to reduce burden of disease thereby childhood mortality in rural Bangladesh.

2. MATERIALS AND METHODS

Study site

The study was conducted in the Kumudini Hospital, one of the oldest and largest tertiary hospitals in rural Mirzapur under Tangail district. It is located 60 kilometers north-west of Dhaka, the capital city. The facility has 750 beds and separate in-patient and out-patient units for cases presenting with diarrhoeal illnesses. The diarrhoeal disease surveillance system operates round the clock to obtain information and fecal specimens from the residents of Demographic Surveillance System area who are reporting with diarrhoeal illnesses regardless of disease severity.

Specimen collection and laboratory procedure

A single, fresh, whole stool specimen (at least 3 ml or grams, ideally 10 ml or grams) was collected from all children aged 0-59 months enrolled at Kumudini Hospital, Mirzapur. A faecal swab was then placed in Cary-Blair medium in a plastic screw top test tube. Stool samples were then transported to the central laboratory in Dhaka Hospital for screening common enteric pathogens such as ETEC [16], *Vibrio cholerae* [17], *Shigella* spp. [17], and rotavirus [18] maintaining standard protocols. Optimal cool temperature was strictly maintained from the point of collection of stool sample to successful submission.

Definition

Diarrhoea was defined as passage of three or more abnormally loose or watery stool in a 24-hour period. Dysentery was defined as at least one loose stool containing blood in a 24-hour period. Moderate-to-severe disease (MSD) was defined if any of the following was present - sunken eyes and/or wrinkled skin and/or visible or reported blood in stool; or a child was hospitalized with diarrhoea or dysentery; or a child needed intravenous rehydration. Children below 5 years without any signs of MSD were constituted as milder disease (MD).

Data management and analysis

For categorical variables, differences in the proportions were compared by Chi-square test and a probability of <0.05 was considered as statistically significant. Strength of association was determined by estimating odds ratio (crude OR) and its 95% confidence interval (CI). Statistical Package for Social Sciences (SPSS) Windows (Version 15.2; Chicago, IL) and Epi Info (Version 6.0, USD, Stone Mountain, GA) were used for data entry and subsequent analysis.

3. RESULTS AND DISCUSSION

Overall, infants (0-11 months) comprised 47% of all patients followed by children 12-23 months old (34%), and children 24-59 months (19%) (Table 1). Rotavirus (33%) was the leading cause of diarrhoea for children less than five years and 90% of the children under two years old. On the other hand, *Shigella* represented 14% of total isolates and children aged 24-59 months (45%) predominantly suffered from shigellosis. However, ETEC and *V. cholerae* represented 3% and 2% young childhood diarrhoeal illnesses respectively (Table 1).

Table 1. Age specific infection rate among under-5 children in rural, Mirzapur (2010-11)

Age group, n=2324 (%)	ETEC n=78 (3%)	Rotavirus n=756 (33%)	<i>Shigella</i> n=328 (14%)	<i>V. cholerae</i> n=46 (2%)
0-11 months, 1098 (47)	28 (37)	387 (51)	57 (17)	15 (33)
12-23 months, 789 (34)	37 (49)	295 (39)	122 (37)	19 (41)
24-59 months, 437 (19)	11 (14)	74 (10)	149 (45)	12 (26)

In Mirzapur, *Shigella* was the most common (27%) followed by rotavirus diarrhoea (16%) among under-5 children who presented with MSD. In contrast to that, rotavirus was the prime (43%) cause of diarrhoea among under-5 children who had reported to the facility with MD (Table 2).

Table 2. Distribution of pathogens among under-5 children with moderate-to-severe disease and mild disease in rural Mirzapur (2010-11)

Pathogen	Moderate-to-severe disease; n=904 (%)	Mild disease; n=1420 (%)	p value	Crude OR (95% CI)
Rotavirus	148 (16)	608 (43)	<.01	0.26 (0.21, 0.32)
<i>Shigella</i>	244 (27)	82 (6)	<.01	5.44 (4.14, 7.16)
ETEC	29 (3)	47 (3)	.98	0.97 (0.59, 1.59)
<i>Vibrio cholerae</i>	24 (3)	22 (2)	.09	1.73 (0.93, 3.23)

Under-5 children infected with *Shigella flexneri* and *Shigella sonnei* were more common in those under-5 children who presented with MSD compared to their counterparts with milder disease (Table 3). However, isolation rate of ETEC and *V. cholerae* was found to be similar in both MSD and MD cases.

Table 3. Distribution of *Shigella* spp. among under-5 children presenting with moderate-to-severe disease and mild disease in rural Mirzapur (2010-11)

Pathogen	Moderate-to-severe disease; n=901 (%)	Mild disease; n=1415 (%)	p value	Crude OR (95% CI)
<i>Shigella flexneri</i>	149 (17)	28 (2)	<.01	9.81 (6.38, 15.18)
<i>Shigella sonnei</i>	71 (8)	19 (1)	<.01	6.29 (3.67, 10.87)
<i>Shigella dysenteriae</i>	9 (1)	4 (<1)	.05	3.57 (1.01, 13.78)
<i>Shigella boydii</i>	15 (2)	31 (2)	<.01	0.76 (0.39, 1.46)

Information on socio-economic-demographic characteristics, sex, maternal literacy, availability of electricity, presence of cemented household floor, immunization with measles vaccine, hand washing with soap after defecation and practice of water treatment were indistinguishable among the MSD and MD cases irrespective of pathogens isolated from the stool samples (Table 4). However, clinical manifestations varied between MSD and MD. MD cases often presented with watery stool. Conversely, straining during defecation and sunken eyes were frequently reported by children with MSD infected with ETEC, rotavirus, *Shigella* and *Vibrio cholerae*. On the other hand, fever was also a common presenting feature of MSD compared to cases with MD in less than 5 years old children except children infected with *Vibrio cholerae* (Table 4).

Table 4. Socio-economic, clinical characteristics received by patients with moderate-to-severe disease and mild disease in rural Mirzapur (2010-11)

Indicators	Overall n=2324 (%)	ETEC n=76 (%)		Rotavirus n=756 (%)		<i>Shigella</i> n=328 (%)		<i>V. cholerae</i> n=46 (%)	
		MSD; n=29 (%)	MD; n=47 (%)	MSD; n=148 (%)	MD; n=608 (%)	MSD; n=246 (%)	MD; n=82 (%)	MSD; n=24 (%)	MD; n=22 (%)
Male sex	1421 (61)	16 (55)	27 (57)	95 (64)	382 (63)	143 (58)	46 (56)	11 (46)	17 (77)

Maternal literacy	2113 (89)	23 (79)	40 (85)	129 (87)	541 (89)	221 (90)	74 (90)	21 (87)	19 (86)
Electricity	1686 (73)	18 (62)	24 (51)	91 (62)	458 (75)*	174 (71)	64 (78)	17 (71)	14 (64)
Cement as predominant floor materials	585 (25)	1 (3)	4 (9)	32 (22)	175 (29)	51 (21)	26 (32)	5 (21)	6 (27)
Measles immunization (9-59 months); n=1664	1454 (87)	20 (83)	33 (87)	93 (84)	377 (85)	219 (94)	63 (91)	16 (80)	17 (100)
Use of soap after defecation	1853 (80)	21 (72)	32 (68)	115 (78)	492 (81)	186 (76)	62 (76)	7 (29)	8 (36)
Use treated water (boil/filtering)	145 (6)	3 (10)	2 (4)	12 (8)	48 (8)	6 (2)	8 (10)	0	2 (9)
Clinical characteristics									
Simple watery	1578 (68)	12 (41)	45 (96)*	117 (79)	587 (97)*	21 (9)	79 (96)*	8 (33)	21 (95)*
Sticky/mucoid	64 (3)	0	2 (4)	6 (4)*	21 (4)	5 (2)	3 (4)	0	1 (5)
Vomiting	1261 (54)	15 (52)	27 (57)	110 (74)	463 (76)	91 (37)	53 (65)*	12 (50)	12 (55)
Abdominal pain	1615 (70)	21 (72)	29 (62)	104 (70)	393 (65)	211 (86)*	54 (66)	18 (75)	11 (50)
Straining	1096 (47)	18 (62)*	15 (32)	56 (38)*	146 (24)	212 (86)*	25 (31)	14 (58)*	4 (18)
Measles (last 1mon)	129 (6)	2 (7)	2 (4)	3 (2)	44 (7)*	5 (2)	2 (2)	0	2 (9)
Eye (sunken)	208 (9)	10 (35)*	2 (4)	103 (70)*	7 (1)	27 (11)*	0	11 (46)*	0
Fever	1100 (48)	18 (62)*	17 (36)	91 (62)*	297 (49)	170 (69)*	49 (60)	16 (67)	9 (41)
Mean temperature (mean±SD)	37.2±0.8	37.4±0.9	37.2±0.7	37.3±0.9*	37.1±0.7	37.6±1.0	37.5±0.8	37.3±0.7	37.0±0.5
Respiratory rate (mean±SD)	33.8±4.8	34.8±5.5	33.8±4.8	34.4±5.8	33.6±4.3	33.4±6.0	33.2±4.1	31.1±4.0	32.5±2.8
Cough	1052 (45)	10 (35)	20 (43)	75 (51)	303 (50)	88 (36)	40 (49)	7 (29)	5 (23)
Convulsion	38 (2)	1 (3)	0	0	2 (0.3)	17 (7)	2 (2.4)	0	0

229 *Values are significant at less than 5% level (p<.05) in uni-variate model.

230

231 Rotavirus, *Shigella* spp., *Vibrio cholerae*, and ETEC are the known major etiologic agents that
232 are responsible for deaths particularly in children [7-10, 16, 19]. The present study facilitates the
233 understanding of the etiology of diarrhoea among children below 5 years visiting a large rural
234 health facility. The study revealed that most of the children presented with diarrhoea were aged
235 0-23 months and rotavirus was the leading pathogen. It has been already reported that up to 5
236 years of age, almost every child is expected to suffer from an episode of rotavirus diarrhoea [19].

Globally, rotavirus causes approximately 111 million episodes of diarrhoea and over 400,000 deaths in children <5 years of age [19]. Although mortality due to rotavirus diarrhoea decreased worldwide; however, still rotaviral diarrhoea among infant and young children remains a major public health burden due to higher hospital attendance rate [3, 19]. In present study, it was observed that children with MD were more often presented with rotavirus infection than the children with MSD. Increased use of oral rehydration fluid and zinc with improved general awareness about prompt management of diarrhoeal illnesses might have resulted in reduced severity of disease [20, 21]. At the same time, reduction of overall prevalence of malnutrition and improvement of nutrition in general among the children less than 5 years old might have caused high rate of enteric infection; as healthy and well nourished children are more likely to be infected with rotavirus [22]. Vomiting and fever, the common clinical manifestations of rotavirus were also reported in the present study [23-25], and at least 14% children presented with some-to-severe dehydration and of them, 15% children required rehydration with intravenous fluid followed by ORS [25]. Destruction of gut enterocyte and disruption of reabsorption of water and electrolytes with reduced activity of brush-border membrane bound disaccharidases likely to activate the calcium ion-dependent secretory reflexes of the enteric nervous system resulting in loss of water and electrolytes and children may present with history of frequent passage of watery stool with dehydrating diarrhoea [26].

The other pathogen, *Shigella* causing shigellosis accounted for 14% of total isolates and older children aged 24-59 months old (45%) suffered predominantly from shigellosis. A study in Pakistan reported that rate of shigellosis increased with advancing age and reached the highest point during the second year of life [27]. *Shigella* caused overall 27% of the moderate-to-severe cases among under-5 children and 7% in case of young children with milder disease in rural Mirzapur. Globally, shigellosis accounted for 69% of all episodes and 61% of all deaths attributable to shigellosis affecting children less than 5 years of age [28]. Although the proportion of shigellosis has significantly decreased over the last three decades [14], Bangladesh is still considered as an endemic zone [29]. Shigellosis is the disease of poor and insolvent people that have the lack of access to proper water and sanitation condition and do not get appropriate treatment [27]. The burden of the disease is higher in resource poor settings of developing countries and may cause as high as 167 million episodes of diarrhoea and more than a million of deaths in each year [30]. In the present study, *Shigella flexneri* and *Shigella sonnei* were the two major sero-groups that dominantly caused MSD among rural under-5 children and children with shigellosis often presented with bloody stool with fever, straining, abdominal pain, and vomiting. Findings from recent past also supported our current observations [31, 32].

The prevalence of cholera caused by *V. cholerae* was very low in rural Mirzapur among under-5 children and clinically characterized by a more sudden onset; watery diarrhoea; and associated dehydration, vomiting, muscle cramps, and abdominal pain which often lead to more severe dehydration requiring immediate hospitalization [33].

Limitations

The present study focused on the most common pathogens that cause diarrhoea among under-5 years old children. There may be other pathogens that may also cause MSD as well as MD. However, the study was able to distinguish the diversity of the severity of pathogens that were

responsible for the severity of the disease among under-5 children with an unbiased large sample size in rural resource constraint settings.

4. CONCLUSION

It has become difficult to understand the predictors that influence this diversity of enteropathogens and disease severity due to identical socio-economic-demographic characteristics that are likely to have confounding effects. Other factors like variation of host characteristics of the study children leading to severity of the disease by specific pathogens as well as virulence factors of enteric pathogens to produce the severity were inconclusive. However, the study was able to determine the disease severity specified etiology of diarrhoea among children less than 5 years old that may guide the policy makers to understand the necessity to implement interventions including vaccines.

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COMPETING INTERESTS

No competing interests exist. All authors confirm that there is no professional affiliation, financial agreement or other involvement with any company whose product figures prominently in the submitted manuscript.

ETHICAL APPROVAL

This study was approved by RRC (Research Review Committee) and ERC (Ethical Review Committee) of icddr,b (protocol number: PR-09064).

CONSENT

All individuals were enrolled and their stool specimens were collected for microbiological assessment once they gave an informed written consent.

Authors' contributions

This work was carried out in collaboration between all authors. Author SKD designed the study, performed the statistical analysis and wrote the first draft of the manuscript. Authors SA, FF, FDF managed field activities and data collection. Author MJC review and edited the manuscript.

Author KAT, MR, SN, YAB, FQ managed laboratory protocols and activity. Author TA review and edited the manuscript. Author ASGF, FQ, KAT and MR contributed to study design, development of protocol. All authors read and approved the final manuscript.

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