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Original Research Article

Norovirus gastroenteritis in children under-five years hospitalized for diarrhea in two cities of northeast India: A retrospective study

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ABSTRACT

Purpose: Norovirus gastroenteritis, known to cause 'winter vomiting disease' is increasingly being identified as a major cause of viral gastroenteritis worldwide. The impact and prevalence of this viral disease are lacking in many parts of India including northeast India. This study aimed to determine the prevalence and association of *norovirus* gastroenteritis among under-five-year-old hospitalized children in two cities in northeast India (Dibrugarh in Assam & Dimapur in Nagaland).

Materials and methods: A retrospective analysis of 407 randomly selected diarrheal stool samples was conducted using a commercial multiplex probed-based real-time RT-PCR assay capable of detecting six-viral gastroenteritis pathogens including *Norovirus GI, Norovirus GII, Rotavirus, Human Adenovirus, Human Astrovirus,* and *Sapovirus*.

Results: Results showed that *norovirus* was detected in 18.4% of the samples (75/407; 95% CI: 14.8%–22.5%), with *norovirus* genogroup II being the predominant group in 97.3% of *norovirus* cases. A significant association of *norovirus* diarrhea was found with seasonality, with higher prevalence in colder months compared to warmer months (22.4% vs 9.1%, p-value:0.002). Additionally, 66.7% (50/75) of cases of *norovirus* gastroenteritis had reported vomiting as the major symptom and had a shorter duration of diarrhea (p-value 0.03). Co-infections with other viral pathogens were seen in 45.9% (187/407) of the cases. The detection of *rotavirus* was 67.1% (273/407), human *adenovirus* (45.9%; 187/407), *sapovirus* and *astrovirus* (5.9%, 24/407 each), and *norovirus* GI (0.5%, 2/407) among the cases.

Conclusion: This study reports the prevalence of *norovirus* gastroenteritis in northeast India and further highlights that *norovirus* gastroenteritis is responsible for substantial cases of hospitalization of under-five years children in the region.

1. Introduction

Norovirus (NoV) is a small single-stranded non-enveloped RNA virus that belongs to the family *Calciviridae* that causes viral acute gastroenteritis outbreaks worldwide [1,2]. It was first discovered in 1968 and is the second most common cause of viral acute gastroenteritis (AGE) in children under 5 years of age, after *rotavirus* [3,4]. *Norovirus* has a 7.6 kb genome that has three open reading frames that encode six non-structural proteins and two capsid proteins (VP1 & VP2) [4,5]. Noroviruses have been classified into 10 different genogroups and are further divided into 48 genotypes and 60 P types based on the major capsid protein sequence and the RNA-dependent RNA polymerase (RdRp) [6]. Genogroup II genotype 4 (GII.4) is the major cause of *norovirus* outbreaks worldwide [7].

Noroviruses are highly contagious, being transmitted mainly through the fecal-oral route, including through direct contact, contaminated food, and water. The virus is more resistant to chlorine than *rotavirus* and

Abbreviations: AGE, Acute gastroenteritis; CI, Confidence Interval; ELISA, Enzyme-linked immunosorbent assay; NoV, Norovirus; QRT-PCR, Real-time Reverse transcription polymerase chain reaction; RT-PCR, Reverse transcription polymerase chain reaction; SPSS, Statistical Package for the Social Sciences; U5, Under 5 years.

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poliovirus [8]. The incidence of *norovirus* is highest in young children and more common in low-income countries. A person can experience an average of three to eight episodes of *norovirus* illness in their lifetime, with at least one occurring by the age of five [9]. Despite better hygiene and sanitation, *norovirus* remains a main cause of sporadic outbreaks of AGE in developed countries. The virus was first detected in stool specimens during an outbreak of gastroenteritis in Norwalk, Ohio, and was originally known as the Norwalk virus. It was described as a "winter vomiting disease" due to its seasonal association and the predominant symptom of vomiting [3,7].

Norovirus can easily spread and cause outbreaks in various settings such as hospitals, nursing homes, schools, and day-care centers due to its high contagiousness and low infectious dose [10]. The genetic and antigenic diversity of this group of viruses presents grave challenges both for creating largely sensitive diagnostic tools and as well as an immunogenic vaccine. Diagnosis of norovirus infection can be done by reverse transcription polymerase chain reaction (RT-PCR), or antigen-based detection assays like ELISA and immunochromatography (IC). With no specific vaccines or medicines available to treat norovirus infection, care is mainly focused on preventing and managing dehydration [11].

A literature review covering 185,000 cases of acute gastroenteritis found that *norovirus* is responsible for 18% (95% CI: 17–20%) of cases worldwide [12]. However, data on *norovirus*-associated diarrhea in India, particularly in northeast India, is limited. Studies from India have reported a prevalence of 1.4%–44% [10,13–16]. A recent study from Kolkata, India reported a 6% prevalence of *norovirus* in under-five (U5) children with diarrhea [14]. With increased awareness, reports of outbreaks of *norovirus* gastroenteritis among school children from the state of Kerala, India in January 2023 had made National news [17]. This study aimed to determine the prevalence of *norovirus* diarrhea in U5 children hospitalized with acute gastroenteritis in two regions of northeast India.

2. Methods & materials

The study was performed on archival stool samples collected between January 2014 to December 2016, (as a part of the National Hospital-based *rotavirus* surveillance network conducted in Assam Medical College & Hospital, Dibrugarh, Assam & District Hospital, Dimapur, Nagaland). All personal information has been anonymized and it is described in our previous study performed on the same samples [18]. The inclusion criteria included U5 children hospitalized for AGE with the passage of loose stools three or more times with or without vomiting in any 24 h prior to admission, and written & informed consent from parents for inclusion in the study. Exclusion criteria included parents or guardians refusing consent, those above the age of 59 months, and outpatient subjects. As described earlier, the use of archival samples was approved by the institutional ethics committee in 2017. Informed and written consent for future use of leftover stool samples for research purposes was taken at the time of subject enrolment.

2.1. Sample collection

In brief, a systematic randomized representative 407 out of 1407 archival stool samples stored at −80°C, were selected for the present study. The age range of the subjects was from 3 to 59 months requiring hospitalizations for acute gastroenteritis (≥ passage of three loose motions in 24 h).

2.2. Nucleic acid extraction

Nucleic acid was extracted from processed stool samples diluted at a 1:4 ratio with phosphate-buffered saline, using a commercial spin-column-based nucleic acid extraction kit based on the manufacturer's protocol (RTP Pathogen kit, Stratec Molecular, Berlin, Germany).

2.3. Norovirus QRT-PCR assay

A CE-IVD-approved commercial viral gastroenteritis panel (FTD Viral gastroenteritis kit, Fast-Track Diagnostics, Luxembourg), that can simultaneously detect six viral pathogens including *Norovirus GI, Norovirus GII, Rotavirus, Human Adenovirus, Human Astrovirus,* and *Sapovirus,* was used which is based on a TaqMan probe-based multiplex Real time-PCR assay. Tests were performed in an ABI 7500 Real-time PCR equipment (ABI 7500, ThermoFisher, Scientific, Waltham, USA) available at the institute. Each run included positive controls, negative controls, and internal controls as per the manufacturer's instructions.

2.4. Statistical analysis

All data were entered in statistical software (IBM SPSS statistics version 26, Armonk, New York, USA). The association of demographic/clinical and other variables with *norovirus* gastroenteritis was examined in SPSS using descriptive statistics, Pearson's Chi-square test for significance (p-value ≤0.05), and odds ratios, and their 95% confidence intervals were used to record the magnitude and direction of associations.

3. Results

The study examined a total of 407 archival samples from two hospitals in Northeast India (201 cases from Assam Medical College & Hospital, Dibrugarh Assam, and 206 cases from District Hospital, Dimapur, Nagaland).

3.1. Norovirus prevalence with demographic variables

The age range of the subjects was from 3 to 59 months with a median age of 20 months (SD ± 11.7) and 265/407 (65.1%) of subjects were within 2 years of age. The majority of the enrolled cases, 251/407 (61.7%) were males (Table 1). The mean duration of hospital stay of the enrolled subjects was 2.6 days (SD ± 1.7). The overall prevalence of *norovirus* (GI &GII) was found to be 18.4% (75/407; 95% CI: 14.8%–22.5%). Both the hospitals in Assam and Nagaland had similar prevalence rates i.e. 17.9% (36/201) vs 18.9% (39/206) respectively (p-value:0.79).

The majority of the *norovirus* diarrhea cases 73/75 (97.3%) were of genogroup II whereas only two cases of genogroup I were detected. Both the genogroup I cases were from the state of Nagaland. The prevalence was similar among male and female cases (17.9%, 45/251 in males compared to 19.2%, 30/156 in females, p-value: 0.74). A slightly higher prevalence of 20.4% (29/142) vs 17.4% (46/265) of *norovirus* diarrhea was seen among those above 24 months compared to those under 2 years, however, it was not significant statistically (p-value: 0.44). The most significant association of *norovirus* diarrhea was found with seasonality with a higher prevalence in colder months compared to warmer months (22.4% vs 9.1% respectively, p-value:0.002) (Table 1). Though all the cases analyzed in our study were hospitalized cases of diarrhea, it was however observed that *norovirus* diarrhea had a slightly milder diarrheal event based on the number of episodes of loose motion, duration of diarrhea, and fever (Table 1). Overall, *norovirus* gastroenteritis cases had a significantly shorter duration of diarrhea i.e. three or fewer days compared to non-*norovirus* diarrhea (p-value: 0.03) (**Table 1**). Also, it was observed that *norovirus* diarrhea was associated with a higher frequency of vomiting, as 50/75 (66.7%) of the cases with *norovirus* had reported vomiting.

3.2. Norovirus diarrhea with other viral gastroenteritis pathogens

Other viral gastroenteritis pathogens were also screened for 407 samples, and it was found that *Rotavirus* with 273/407 (67.1%) was the major diarrheal pathogen in the U5 age group. It was followed by human *adenovirus* with 187/407 (45.9%), *norovirus* GII with 73/407 (17.9%),

Table 1
Norovirus G1 & G2 diarrhea in U5 hospitalized children: Distribution & association with demographic and clinical variables (N = 407).

Variables	Total frequency (N)	*Norovirus G1 & G2* Positive frequency (%)	Odds-Ratio (OR)	95% CI of OR	p-value
1. **Geographical region**					0.79
a) Dibrugarh, Assam	201	36 (17.9%)	1		
b) Dimapur, Nagaland	206	39 (18.9%)	1.07	0.65–1.76	
2. **Gender**					0.74
a) Male	251	45 (17.9%)	1		
b) Female	156	30 (19.2%)	1.09	0.65–1.8	
3. **Age**					0.44
a) upto 24 months	265	46 (17.4%)	1		
b) Above 24 months but less than 60 months	142	29 (20.4%)	1.22	0.72–2.05	
4. **Severity of Diarrhea**					**0.04**
a) upto 6 episodes of loose motion in any 24 h	195	44 (22.6%)	1		
b) More than 6 episodes of loose motion in any 24 h	212	31 (14.6%)	0.6	0.35–0.97	
5. Vomiting					0.14
a) No	166	25 (15.1%)	1		
b) Yes	241	50 (20.7%)	1.47	0.87–2.5	
6. Duration of diarrhea					**0.03**
a) upto 3 days	242	53 (21.9%)	1		
b) more than 3 days	165	22 (13.3%)	0.55	0.32–0.94	
7. Fever					**0.013**
a) No	207	48 (23.2%)	1		
b) Yes	198	27 (13.6%)	0.52	0.31–0.88	
8. Lethargy					0.2
a) No	206	33 (16.0%)	1		
b) Yes	201	42 (20.9%)	1.38	0.83–2.3	
9. Restless					0.53
a) No	338	64 (18.9%)	1		
b) Yes	69	11 (15.9%)	0.81	0.4–1.63	
10. Seasonality					**0.002**
a) Colder months (Nov–April)	286	64 (22.4%)	1		
b) Warmer months (May–Oct)	121	11 (9.1%)	0.34	0.17–0.68	

Table 2
Prevalence of viral gastroenteritis pathogens in Dibrugarh, Assam, and Dimapur, Nagaland in U5 hospitalized children (N = 407).

Variables	Total frequency (N)	*Norovirus G1* Positive frequency (%)	*Norovirus G2* Positive frequency (%)	*Rotavirus* Positive frequency (%)	*Astrovirus* Positive frequency (%)	Human *Adenovirus* Positive frequency (%)	*Sapovirus* Positive frequency (%)	*Co-infection of Norovirus G2 and Rotavirus* Positive (%)
Geographical region								
Dibrugarh, Assam	201	0 (0%)	36 (17.9%)	134 (66.7%)	10 (5%)	93 (46.3%)	4 (2%)	24 (11.9%)
Dimapur, Nagaland	206	2 (1%)	37 (18.0%)	139 (67.5%)	14 (6.8%)	94 (45.6%)	20 (9.7%)	18 (8.7%)

sapovirus with 24/407 (5.9%), *astrovirus* with 24/407 (5.9%) and *norovirus* GI with 2/407 (0.5%) (Table 2). The prevalence of *sapovirus* was 9.7% (20/206) in Dimapur, Nagaland compared to 2% (4/201) in Dibrugarh, Assam which was statistically significant (p-value:0.003). Further, it was observed that 10.3% of the subjects (42/407) had coinfection of *norovirus* with *rotavirus*, while 45.9% (187/407) had a coinfection with any of the six-viral pathogens studied including 37.8% (154/407) of the cases with dual infection, 7.9% (32/407) had a triple infection and one case (0.2%, 1/407) had a quadruple infection. Both *norovirus* and *rotavirus* were found to have a significantly higher prevalence in the colder months, while *adenovirus* had shown a peak in the warmer months (Fig. 1). Typical amplification plot of the multiplex RT-PCR is shown in Fig. 2.

4. Discussion

Diarrhea is a leading cause of death in children under five, causing 525,000 deaths annually worldwide. The disease is caused by various pathogens including viruses, bacteria, and parasites. Just one or two days of diarrhea can cause severe dehydration and electrolyte imbalances in children [9]. *Rotaviruses* were once the main cause of acute gastroenteritis in children, but as *rotavirus* vaccinations improve and better diagnostic methods become available, a shift towards caliciviruses like *norovirus* and *sapovirus* may be seen [19]. *Norovirus* is increasingly recognized as a common cause of sporadic acute gastroenteritis in children and is a leading cause of viral outbreaks in all age groups worldwide [9].

The present study of hospitalized children under five, found the overall prevalence of *norovirus* to be 18.4%. The study result is in line with a large systematic review estimating an 18% prevalence of *norovirus* in all diarrhea cases worldwide [12]. In another recent study from western Maharashtra India, norovirus was detected in 17.7% of U5 children with diarrhea, similar to the prevalence of the present study [20]. Other studies have reported different prevalence rates, with *norovirus* found in 41.2% in a study from Mumbai, India, a prevalence of 6.3–12.6% in children <7 yrs of age in Western India, and 10.3% of symptomatic cases in Hyderabad, India [15,16,21]. Some studies have reported a lower prevalence of 1.4%–2.3% as well [13,22]. The prevalence of *norovirus* was recorded at 9.3% in Tunisia and 25% in China [23, 24].

The present study found that 73/75 (97.3%) of *norovirus* cases were of genogroup GII, with only two cases belonging to GI. This is in line with the global trend, as GII is the predominant genogroup causing diarrhea in India and globally [16]. Several studies conducted in India found GII to be the most common genogroup. Studies from South India reported 72.5%–82.5% of *norovirus* cases were GII [4,15], while from Western Maharashtra India, showed 100% of cases detected were of GII [20]. However, some studies, such as those from South Mumbai, India, found that GI was the predominant genogroup among children [16].

In the present study, *norovirus* cases were evenly distributed between male (17.9%) and female children (19.2%). Other studies also found no significant difference in *norovirus* positivity between male and female patients. For instance, a study in Chennai, India found slightly more male

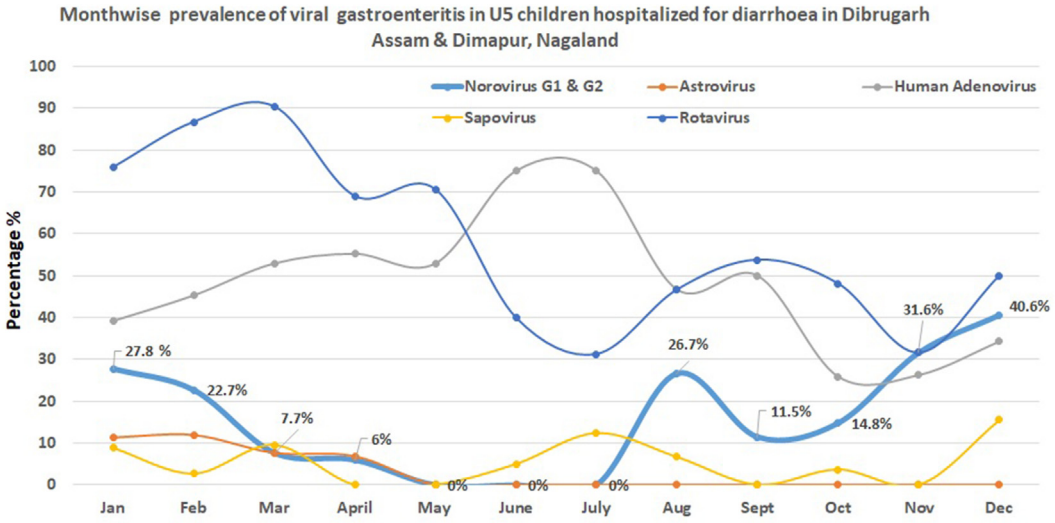

Fig. 1. Shows the month-wise prevalence of different viral gastroenteritis pathogens. Norovirus GI & GII is shown in bold blue line which displays a significantly higher prevalence in the winter months compared to the summer months.

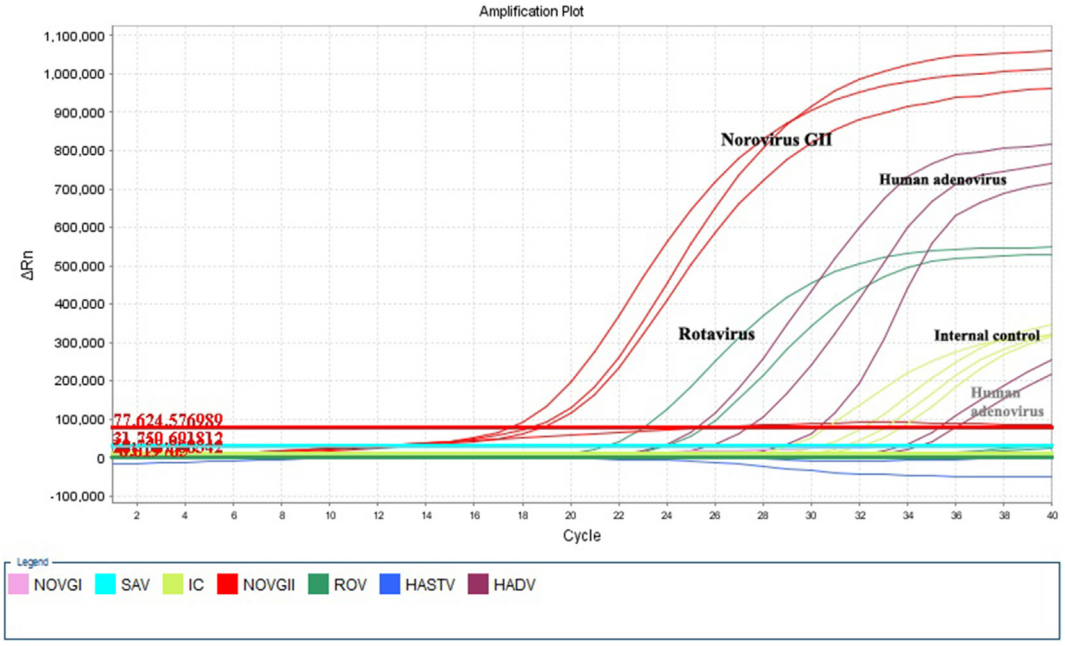

Fig. 2. Displays the typical amplification plot of multiplex TaqMan based real-time RT-PCR. The amplification curve of *Norovirus GII* is shown in red while *Rotavirus* is shown in dark green, *Human adenovirus* is shown in maroon and internal controls are shown in light green color.

patients infected with *norovirus*, but the difference was not statistically significant [9]. In a decade-long study on *norovirus* AGE in Ghanaian children, there were slightly more cases in male children, but the infection was not gendered dependent [25]. However, a multi-county birth cohort study across eight different geographical locations, found a higher prevalence among females [26].

The present study found a higher prevalence of *norovirus* diarrhea in children older than 24 months, unlike some other studies that reported maximum *norovirus* positivity in children under 2 years of age. For example, studies from South and Central India found maximum *norovirus* positivity among children ≤2 years of age, [16,20,21]. Studies from Himachal Pradesh and Delhi also found *norovirus* infection to be more common in children under 2 years of age [13,27]. In a study from South India, the median age of *norovirus* GI and GII was less than 6 months and 8 months, respectively [4].

Norovirus is a seasonal disease, often referred to as "winter vomiting disease" due to its higher incidence in colder months and vomiting being its primary symptom [28]. Outbreaks of *norovirus* are reported year-round, but there is a surge in cases during winter months in temperate climates [29,30]. However, studies have also reported spring and summer peaks in *norovirus* outbreaks in children under 5 years of age, as well as seasonal outbreaks in other regions such as India and Taiwan [6,16,27,30]. The symptoms of *norovirus* include vomiting, diarrhea, dehydration, and fever [25,30]. In our study, the majority of *norovirus* cases had a mild illness, but other studies have reported moderate to severe illness in those infected with the virus [10,31]. In addition to *norovirus*, other viral pathogens causing gastroenteritis such as *rotavirus*, human *adenovirus*, *sapovirus*, and *astrovirus* were detected in this study using multiplex TaqMan assay-based RT-PCR. The prevalence of *sapovirus* was found to be statistically higher from the study site in Nagaland

(9.7%) compared to the site in Assam (2%), and coinfections with other viruses were also noted, with *rotavirus* being the most common co-pathogen in 10.3% of Norovirus cases. Furthermore, it was observed that 37.8% had a dual infection, 7.9% had a triple infection and one case (0.2%) had a quadruple infection among the six viruses studied. A recent study from Assam, India reported that Norovirus was the most common co-infection detected with adenovirus in 20.4% of U5 diarrhea cases [32]. Mixed infections with other pathogens were seen in 27% of diarrheal cases in a study from South India, while the study from Assam recorded 21.7% coinfection of viral pathogens [4,32], as compared to ~46% coinfection in this present study.

5. Conclusion

This study highlights the impact of *norovirus* on gastroenteritis in U5 children in two states of northeastern India. Despite advances in combatting diarrheal diseases, accurately identifying the causative agents remains a challenge. *Norovirus* is a leading cause of severe acute viral gastroenteritis and diarrhea-related deaths globally, second only to *rotavirus*. Due to its potential for harm, especially in vulnerable populations, and difficulties in controlling it, vaccines may be the best solution. Knowing the prevalent strains of *norovirus* can be crucial in controlling it in the community.

Source of support

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Ethical approval

The study was approved by the institutional ethics committee of ICMR RMRC, Dibrugarh in 2012 and 2017, to perform anonymous testing of archival stool samples for which initial consent from participants was taken to use leftover samples for future research.

Contribution of each author

BB conceptualized, designed, and acquired funds for the study. NKB & BB drafted and analyzed the manuscript. AJ and RH performed the laboratory test. TT and MG recruited the clinical subjects and collected data. HK reviewed and edited the manuscript. All the authors have revised the manuscript and accepts it in its present form.

Conflict of interest

None.

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