e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2024; 16(9); 39-45

Original Research Article

Etiological Spectrum of Acute Diarrheal Diseases among Children of Under 5 Years Age Group Following Introduction of Rotavirus Vaccine in National Immunization Programme in a Tertiary Care Center of West Bengal

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Received: 01-06-2024 Revised: 15-07-2024 / Accepted: 21-08-2024

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Conflict of interest: Nil

Abstract

Introduction: Despite a significant improvement in diarrheal disease management by early initiation of inexpensive oral replacement therapy, mass education and improved generalized sanitation, still diarrhea is the second leading cause of death among children aged less than 5 years.

Aims: Changes in the epidemiology and etiology of diarrheal diseases among children aged less than 5 years in the post vaccination period and alterations in pathogenic rotavirus strains.

Materials and Method: This study provides comprehensive data on the changes in clinical-epidemiological conditions associated with acute diarrhea among children aged less than 5 years since the introduction of the rotavirus vaccine in the National Immunization Program from September 2019.

Result: Four children (1.1%) died—all of them were malnourished and had comorbidities such as Congenital heart disease (1), postadenovirus bronchiolitis obliterens (1) and undiagnosed congenital anomalies (2). The detected enteropathogens among the 4 succumbed children were adenovirus, rotavirus and mixed infections of E. coli and Salmonella. On nutritional assessment of admitted children, 364 (95.8%) were appropriate for age, 11 (2.9%) had moderate malnutrition, and 5 (1.3%) had severe malnutrition (SAM), of which 4 children died.

Conclusion: The decline in rotaviral diarrhea among children in the post immunization period is evident in almost all the studies. The simultaneous emergence of newer viruses, such as norovirus and adenovirus, for which we have no vaccines, creating a new burden on the public health system necessitates continuous monitoring in both hospital and community settings. This database will aid health authorities in identifying appropriate preventive strategies to lower the incidence of pediatric diarrhea and death.

Keywords: Acute diarrheal diseases, Rotavirus vaccine, Gastroenteritis and Pathogen shift.

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Introduction

Despite a significant improvement in diarrheal disease management by early initiation of inexpensive oral replacement therapy, mass education and improved generalized sanitation, still diarrhea is the second leading cause of death among children aged less than 5 years. [1] Diarrhea is an important component of the vicious cycle of intercurrent infection, failure to thrive, and severe malnutrition (SAM) leading to pediatric death. It is more challenging in developing countries such as India, where the prevalence of diarrhea was 9.2% during the study period (2016-2020) according to the NFHS. [2] The pathogens mostly isolated from stool samples of children suffering from watery diarrhea are Rotavirus, E. coli (EIEC) Shigella, and Campylobacter jejuni. [3,4,5,6] Among all the

enteropathogens, rotavirus is globally recognized as the leading cause of moderate to severe watery diarrhea among children younger than 5 years.[7] In India, the rotavirus disease burden is high, contributing 40% of the total hospitalization of children under 5 years of age and approximately 78,000 deaths annually.[8,9]

Rotaviruses have a dual classification system based on immunological reactions and two external structural proteins, VP4 and VP7. There are 15G and 26P genotypes, of which the G1P [8], G2P[4], G3P[8], G3P[8] and G9P[8] are the most common strains causing viral diarrhea among children prior to the onset of rotavirus immunization.[10] However, with the introduction of large-scale rotavirus vaccination at both the governmental and private levels, it is expected that there will be changes in rotavirus serotype prevalence over time and the emergence of newer serotypes that were less pathogenic earlier. As of now in India, 4 types of rotavirus vaccines are available, 2 of which are monovalent (Rotarix and Rotavac) and 2 of which are pentavalent (Rotasiil and Rotatec), with differences in genotypic strain composition. All of these vaccines unitedly have caused significant success in reducing the diarrhea disease burden.[11] However, this approach has also changed the etiological spectrum of diarrheal diseases among children both in terms of emergence of newer viruses and newer strains of the rotavirus family. Other pathogens, such as bacteria and parasites also got reshuffled in terms of their prevalence for diarrheal diseases with the changing immunological status of children in the post vaccination era. Our study aimed to determine the changes in the epidemiology and etiology of diarrheal diseases among children aged less than 5 years in the post vaccination period and alterations in pathogenic rotavirus strains.

Materials and Methods

A prospective observational study was conducted at a tertiary care fully dedicated pediatric hospital in Kolkata from January 2023 to September 2023. Ethical clearance was obtained from the institutional ethics committee, and subjects were included after getting informed consent from their parents. All pediatric patients aged 4 months to 5 years who were hospitalized for acute diarrhea with severe dehydration or other complications and who successfully completed all 3 doses of the rotavirus vaccine were included in our study. We excluded children with known malabsorption syndrome, congenital diarrhea, inborn error of metabolism, or immunodeficiency to minimize bias. Acute diarrhea was defined as ≥ 3 liquid stools in a 24-hour period or a substantial change in stool consistency (bloody, very loose, or watery) following at least 7 days of diarrhea-free days. Diarrhea severity was measured by the Vesikari score (≤7 mild, 7-10 moderate, ≥11 severe).[12] At admission, nutritional status was assessed by the World Health Organization (WHO) child growth standards, and nutritional status was determined by calculating z scores for weight-for–height to determine wasting and height-for–age for stunting. The severity of malnutrition was classified as normal (>1), mild (-1 to -1.99), moderate (-2 to -2.99) or severe (≤ 3).[13]

Children aged 4 months to 5 years and admitted with diarrhea requiring IV fluids and medications were enrolled in our study after getting consent from their parents. Demographic and clinical details were recorded in structured case sheets, and immunization cards were checked for all subjects. Two stool samples were collected within 24 hours of admission and stored at the appropriate temperature (-4 degree) ; subsequently, one was sent to the Microbiology Department of our Institute for bacteriological analysis, and the other was sent to the Virology Department of our extended campus National Institute of Cholera and Enteric Diseases (NICED, Kolkata) for viral analysis. At the NICED, Kolkata nucleic acid was extracted from clarified viral suspensions using a Purelink Viral RNA/DNA Mini Kit from Invitrogen. The extracted genetic material was subjected to one-step reverse transcriptase polymerase chain reaction (PCR) for the detection of enteroviruses. The rotavirus genotypes were identified by primers targeting the VP7 (G) and VP4 (P) viral proteins, and when a genotype combination could not be identified, the strains were considered untypable. For bacterial analysis, a GN card was used; for MIC detection, AST cards 280 and 281 were used in the Vitek system. Standard case management was used for all patients, and observation continued until discharge.

For statistical analysis, the data were entered into a Microsoft Excel spreadsheet and subsequently analyzed by SPSS (version 27.0; SPSS, Inc., Chicago, IL, USA) and Graph Pad Prism version 5. The data are presented as the means and standard deviations for numerical variables and as counts and percentages for categorical variables. A chi-squared test ($\chi 2$ test) was used for any statistical hypothesis test wherein the sampling distribution of the test statistic was a chi-squared distribution when the null hypothesis was true. Without other qualifications, the chi-square test is often used for Pearson's chi-square test. Unpaired proportions were compared by the chi-square test or Fisher's exact test, as appropriate.

Explicit expressions that can be used to carry out various t tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a t-distribution under the null hypothesis is given. Additionally, the appropriate degrees of freedom are given in each

case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test.

Once a t value is determined, a p value can be found using a table of values from Student's t distribution. If the calculated p value is less than the threshold chosen for statistical significance (usually 0.10, 0.05, or 0.01), then the null hypothesis is rejected in favor of the alternative hypothesis.

A P value ≤ 0.05 was considered to indicate statistical significance.

Results

A total of 380 children with acute diarrhea and severe dehydration requiring hospitalization during our study period from January 2023 until the end of September 2023 were enrolled after satisfying the inclusion and exclusion criteria and providing consent. The mean age of the individuals in the cohort was 2 years (SD: ±1.23), with the lowest recorded age being 5 months and the highest being 5 years (Table 1). The most common age group was 1-5 years (78.9%), and the rest were infants (21.15%). In our study, male children (n=207) outnumbered female (n=173) children, and the mean duration of hospital stay was 4.5 days, with a maximum recorded duration of 12 days, as few children developed complications. The majority of the children (n=364: 95.8%) had uneventful clinical courses and required fluid replacement, probiotics, and zinc ± antibiotics; however, 16 children (4.3%) entered a complicated clinical course with PICU admission for 12 children (3.2%) due to AKI subsequently to delayed presentation, and 4 children (1.1%) were transferred to the surgical ward for intussusception (Table 2). Four children (1.1%) died—all of them are malnourished and had comorbidities such as Congenital heart disease (1), postadenovirus bronchiolitis obliterens (1) and undiagnosed congenital anomalies (2). The detected enteropathogens among the 4 succumbed children were adenovirus, rotavirus and mixed infections of E. coli and Salmonella. On nutritional assessment of admitted children, 364 (95.8%) were appropriate for age, 11 (2.9%) had moderate malnutrition, and 5 (1.3%) had severe malnutrition (SAM), of which 4 children died.

By analyzing the stool samples of our subjects admitted with acute diarrhea with severe dehydration, we detected one or more microorganisms in 222 (58.4%) candidates and no enteropathogens in the stool samples of the remaining 158 (41.6%) children. Nineteen children had mixed infections involving viruses/viruses and viruses/bacteria. The most commonly detected enteropathogens were rotavirus (22.9%), norovirus (10.5%), and adenovirus (7.1%) from the virus family, and E. coli was the most frequently detected bacteria (3.4%), followed by Shigella (2.9%) and Salmonella (1.6%). Among the stool samples from patients with mixed infections (n=19 :: 5%), rotavirus and norovirus were the most common offending agents (2.6%), followed by rotavirus and adenoviral agents (1.1%), and less than 1% had mixed bacterial and viral infections (Table 3).

We found that viral diarrhea was more common among infants than among toddlers, and both rotavirus and adenovirus caused a prolonged hospital stay (>5 days: 26.8%) compared to norovirus, which was associated with shorter hospitalization in most children (Table 3). Children of both sexes were equally affected by viral diarrhea, which was more common among healthy children. Among all the subjects, adenovirus-affected children had a stormy course, and norovirus carries minimum risk and good prognosis.

A genotypic study of all rotavirus-affected stool samples revealed that G3 [P8] was the most common genotype (32%), followed by G2 [P4] (19.8%), G3 [P4] (16%) and G1 [P8], which were the most common serotypes in the prerotavirus vaccination era and now had a prevalence of 8%. Sixteen percent of the samples were untypable (Table 4).

Discussion

This study provides comprehensive data on the changes in clinical-epidemiological conditions associated with acute diarrhea among children aged less than 5 years since the introduction of the rotavirus vaccine in the National Immunization Program from September 2019.[11] Our study showed a decrease in the incidence of diarrhea-related admission by 6.45% in comparison to last 3 years average admission data. In our study, the most common age group was 1-5 years (78.9%), and the remaining (21.15%) were infants. A marked change in rotavirus serotype diversity was noted in our study; for example, G3[P8] emerged as the most common serotype (32.1%), followed by G2[P4] (19.8%) and G3[P4] (16%), whereas G1[P8], which was the most common serotype in the prevaccination era, currently has a strikingly low prevalence of 7.5% among all rotaviral diarrheal cases.[23] The majority of our children (95.8%) had uneventful outcomes, and few of them had complicated clinical courses due to delayed arrival at the hospital. We recorded the deaths of 4 children (1.1%), all of whom had a failure to thrive (FTT) and had comorbidities.

A systematic review and meta-analysis of randomized controlled trials (RCTs) revealed that following rotavirus vaccination, there was a 31% reduction in the risk of rotavirus diarrhea and a

23% reduction in all-type of diarrhea.[14] In a study in Mexico, Richardson et al. reported that rotavirus vaccination was associated with a 36% reduction in hospitalization for diarrheal diseases.[15] An analysis of the National Health Survey-5 by Dhalaria et al. revealed an overall decrease in diarrhea incidence of 17% after 3 doses of rotavirus vaccine were administered.[16] As most of these are community-based studies, so the decreasing impact of rotavirus vaccination both on the incidence of diarrheal events and on the rate of hospitalization was greater than that in our study, as our cohort consisted of only hospitalized children. A change in age distribution from the prevaccination era was evident where infants were the most affected by diarrheal diseases after 6 months of life once the protection of breast milk disappeared, followed by a lower prevalence in the older age group. This can be explained by the fact that older adults develop immunity against rotavirus through repeated episodes of infection, as mentioned by Girish Kumar et al. in their multicenter study prior to rotavirus vaccine introduction. [17,18,19,20] Both Rotavac and Rotasiil, the flagship vaccines for national immunization program showed reduced protective antibody titer in second year of life (48.9%) compared to first year of life (56.3%).[21,22] Thus a waning immunity as years passes post immunization. We found that rotavirus was the most common (22.9%) organism causing acute watery diarrhea among children aged less than 5 years, followed by norovirus (10.5%) and adenovirus (7.1%).

This prevalence is significantly lower than the prevalence of rotaviral diarrheal diseases (33-44%) prior to the introduction of rotavirus vaccine, as reported by Girish Kumar et al. in their multicentric ICMR-funded study where NICED-Kolkata was one of the centers.[17] There were differences in the incidence of rotavirus infection across geographical regions of India, with the lowest burden occurring in southern India (33.8%), followed by northern states (37.7%), and the highest caseloads occurring in eastern India (39.8%). Following mass immunization, the rate of reduction in rotavirus infection also differs from region to region, as mentioned by Varghese et al. in their study; the maximum reduction in rotavirus diarrhea was noted in Tirupati (72.1%), and the minimum was observed in Vellore (32.45%). Varghese et al. found in their multicentric community-based surveillance study of 8499 children during the post vaccine period that G3 [P8] was the most common serotype (44.3%), followed by G1 [P8] (15.4%), G2 [P4] (7.4%), and G1 [P6] (3.7%). These results are comparable to our study reports; however, being a multicentric study, they could document the geographic and temporal trends of rotavirus strains across India.[23,24,25,26,27] An increase in the G3 [P8] strain was also evident in the USA after the introduction of the rotavirus (Rotatec) vaccine.[28,29] However, a study in Kenya showed no changes in the rotavirus serotype pattern after the introduction of rotavirus (Rotarix), whereas a Brazilian study detected few changes in rotavirus serotype distributions, such as G2[P4], which is the major strain.[28,30] We detected no new serotypes, possibly due to the small sample size compared to those of larger multicentric studies, and 17% of rotavirus cases are untypable. We found that the next most important viruses for acute diarrhea were norovirus (10.5%) and adenovirus (7.1%), which were also found in a few overseas studies, such as one at Nicaragua, where norovirus was the most common agent (20.4%), followed by sapovirus (16.6%). As India has experienced adenovirus epidemics among children both before and after the COVID-19 pandemic, a higher percentage of adenoviruses may be found in stool samples.[31] This is a completely changing scenario compared to the Global Enteric Multicenter Study (GEMS) and Malnutrition and Enteric Disease Study (MAL-ED), which was performed prior to rotavirus vaccine introduction, where the most common organisms causing acute diarrhea in children were rotavirus, Cryptosporidium, Shigella, and E. coli (ETEC).[32,33] Among bacterial agents we found E.Coli the commonest (4%) cause of diarrhea both isolate and mixed infection with other viruses followed by Shigella, Salmonella which was similar to Becker-Dreps et al. study at Nicaragua [31] and all this raises the concern of increased incidence of HUS. We did not detect Campylobacter jejuni in our study, which may be due to annual variation in transmission, as we skipped the autumn season. A lower percentage of mixed bacterial-viral diarrhea may be due to the early use of antibiotics, improved sanitation, and easy access to purified water.

The strength of our study was the detailed analysis of etiological agents causing acute diarrhea in children under 5 years of age who presented with severe dehydration and required hospitalization during the post vaccination period. There are few limitations to our study, such as its small sample size, single-center nature, inability to demonstrate variable responses to different types of rotavirus vaccines available on the market and further serotyping of norovirus. We dropped parasitic study because single microscopy cannot distinguish E. histolytica, a pathogen, from E. dispar, which is a commensal in the large gut.

Conclusion

The decline in rotaviral diarrhea among children in the postimmunization period is evident in almost all the studies. The simultaneous emergence of newer viruses, such as norovirus and adenovirus,

for which we have no vaccines, creating a new burden on the public health system necessitates continuous monitoring in both hospital and community settings. This database will aid health authorities in identifying appropriate preventive strategies to lower the incidence of pediatric diarrhea and death.

Take home message: It's time to develop newer vaccines to cover emerging lethal diarrheal viruses to reduce pediatric diarrheal mortality and morbidity.

Acknowledgment: The authors thank the Department of Microbiology and Virology, NICED, Kolkata, for the viral analysis of our samples. The authors would like to thank the Diarrheal Training Unit (DTU) and Microbiology Department of DR BC ROY PGIPS, especially Dr. Jayshree Konar, Assistant Professor, for her contribution to the study.

Author contributions:

SSB made substantial contributions to the concept, design of work, manuscript writing, interpretation of data, results and discussion: MM in data collection, analysis, statistical analysis, review and manuscript writing; SM in data collection, provides inputs to the study, statistical analysis; AC in data collection, and reference drafting; MC in virological analysis and interpretation , critically analysis and finalized the manuscript. All the authors approved the manuscript. SSB will act as a guarantor for this paper.

Declarations:

The study was conducted with the approval of the Ethics Committee of DR BC ROY PGIPS, **BCH/ME/PR/2369.**

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