



## Enteric Adenovirus and Norovirus Gastroenteritis among Under-5 years Children in Owo, Ondo State, Nigeria

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### Authors' contributions

This work was carried out in collaboration between all authors. Author MOB designed the study, wrote the protocol, provided the literature searches, performed the fieldwork, the experimental and statistical analyses, and wrote the first draft of the manuscript. Author GNO designed the study, managed the analyses, read and revised the drafts of the manuscript. Author DOO provided the literature searches and revised the drafts of the manuscript. Author AOA provided logistics and managed the fieldwork. All authors read and approved the final manuscript.

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### ABSTRACT

**Aim:** Infant mortality attributable to diarrhea continue unabated, without the precise determination of the viral etiologies. Few studies exist on enteric adenoviruses and norovirus infections in infants and young children in Nigeria. This study was aimed at the detection and determination of the

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baseline prevalence of enteric adenoviruses and norovirus pathogens among under -5 years children hospitalized for acute diarrhea in Ondo state, Nigeria.

**Methods:** In a cross sectional descriptive study conducted between November 2013 and April 2014, fifty (50) fecal specimens collected from diarrheic children below 5 years and age matched non-diarrheic controls were screened for the presence of enteric adenovirus and norovirus antigens using a 4<sup>th</sup> generation quadruple Rapid Immuno- chromatographic Enzyme Immuno Assay kits.

**Results:** Adenovirus antigen was detected in 9/50 (18%) in November 2013, and February to April 2014 while norovirus was found in 4/50 (8%) of the diarrheic children, in the months of December 2013 to February 2014. The prevalent age at infection were 0-6 months for adenovirus and 31-36 months for norovirus, while the male-to-female ratio was 1.8:1. Co-infection of adenovirus with rotavirus was detected in children between 7-12 months, while co-infection of adenovirus with norovirus was detected in children between 31-36 months old at a rate of 2% respectively. There was no significant difference in the induction of diarrhea in children by each of the two viruses ( $\chi^2=1.78$ ), and no significant difference in the rate of adenovirus ( $\chi^2=0.605$ ) and norovirus infections ( $\chi^2=1.09$ ) between male and female, in the study population.

**Conclusion:** The baseline prevalence of enteric adenovirus diarrhea was 18% (occurring in November, February to April), norovirus was 8% (occurring in December to February), dual infection by adenovirus cum rotavirus, and adenovirus cum norovirus was 2% respectively, in children below 3 years in Ondo state Nigeria. The findings suggests that human enteric adenoviruses and norovirus are becoming established etiologies of infantile diarrhea in southwest Nigeria, and vaccines should be developed and vaccination implemented alongside rotavirus.

**Keywords:** Baseline prevalence; adenovirus; norovirus; diarrhea; one step Rota + Adeno+ Astro + Noro Quadruple EIA.

## 1. INTRODUCTION

Acute infective gastroenteritis is a major global health problem, which manifests as three or more watery or loose bowel evacuations with fever and vomiting in a 24 hour period that may last several days. Children under 5 years of age are particularly susceptible, and global estimates indicated a mean of between 3.5 and 7 episodes of severe diarrhea during the first 2 years of life, and the greatest burden is in the developing countries because of poor sanitation, lack of safe drinking water, and bad sanitary habits [1]. Several studies in Nigeria showed that more than 315,000 deaths of preschool age children are recorded annually as a result of diarrhea disease [2] and it remains one of the three most common causes of morbidity and mortality among children [3].

The major viral etiologies of infective diarrhea in humans include Group-A rotaviruses, astroviruses, human caliciviruses and the enteric adenoviruses [4]. In a recent study [5], rotavirus, norovirus, and adenovirus were detected in 39%, 16.2% and 6.8% respectively, in Egyptian children with gastroenteritis. Norovirus gastroenteritis was reported to be responsible for the mortality of 200,000 children in developing countries [6]. Norovirus is a single stranded RNA

virus belonging to the genus Norovirus of the family *Caliciviridae*. The virus is infectious at very low doses and transmits rapidly by the feco-oral route via contaminated food and water, causing a severe, sporadic or more than 85% of epidemic diarrhea and vomiting in all age groups [7], especially during the winter [8]. In a previous hospital based study in Lagos, the prevalence of norovirus diarrhea was 37.3% [9], while [10] reported a prevalence of 25.5% in a community based study in Osun state, Nigeria.

Human adenoviruses (HAdV) are major causes of clinical infections including respiratory diseases, gastroenteritis, and conjunctivitis [11,12]. Human *Adenovirus* belongs to the genus Mastadenovirus of the family *Adenoviridae*. The virion consists of non-enveloped, linear, dsDNA genome (26–45 kb) encapsidated in an icosahedral protein shell. There are 52 serotypes classified into six species, A-G [13,14], of which species F serotypes 40 and 41 primarily affect the gut, contributing 5%-20% of hospitalizations for childhood diarrhea [15] The incidence of infection is nearly 3 times greater in developing countries than developed ones [16]. To date, a previous study in Nigeria by Nimzig et al. [17] indicated a prevalence of 3.8% among diarrheic children in Jos. Audu et al. [18] reported a prevalence of 3% among diarrheic under-5 years

children in Lagos, while Aminu and colleagues [19] reported a rate of 8% among diarrheic children in Northwestern Nigeria. Thence, these viruses remain less investigated and there is paucity of information on the circulating viral etiologies of diarrhea in Kogi, Ondo, Kwara, Ekiti, Delta and other states of Nigeria. This present study was aimed at detecting the presence of adenovirus and norovirus enteric pathogens, using two brands of commercial rapid Enzyme Immunoassay (EIA) kits, and to determine their prevalence among under-5 years children hospitalized for diarrhea in Ondo state, Nigeria.

## **2. MATERIALS AND METHODS**

### **2.1 Study Design and Centre**

Cross sectional descriptive study, designed to detect and determine the prevalence of adenovirus and norovirus gastroenteritis among children below 5 years, admitted for diarrhea at the children emergency wards of the Federal Medical Centre Owo, Ondo State Nigeria between November 2013 and April 2014.

### **2.2 Study Population/Sampling**

Epidemiological information and clinical data associated with diarrhea were obtained using structured questionnaires, prior to collection of 50 fecal samples from infants and children below 5 years old, who sought medical care for acute diarrhea disease.

### **2.3 Criteria for Inclusion and Exclusion**

Children below 5 years who presented with loose watery stool more than 2 times in a 24 hr period, with or without vomiting, fever, dehydration, stool with mucus, and abdominal pains, were included. Children without symptoms of gastroenteritis, and those who did not grant consent, were excluded.

### **2.4 Ethical Considerations**

Ethical approval was granted before the commencement of the study. Informed consent was obtained from parents of the participating children before sample collection. Patient's anonymity was maintained, data generated were confidential, and used only for the purpose of this research.

### **2.5 Collection of Fecal Specimens**

Fecal samples were collected within 1 to 3 days after the onset of diarrhea illness into sterile universal bottles, labeled with the participant's code, date, time, and then stored frozen at -20°C prior to testing. A total of 50 fecal samples were tested during a separate parallel study for rotavirus diarrhea.

### **2.6 Sample Processing**

The reagents and the combo cassettes were removed from the pouch and labeled according to the specimen. The samples were thawed prior to addition into the stool processing diluent. 250 µl of each fecal specimen was picked using a micropipette and dispensed into the diluent tube. The tube was recapped and shaken for two minutes to ensure good sample dispersion and extraction of the antigen.

### **2.7 Detection of Adenovirus and Norovirus Antigens using Lateral Flow EIA**

The processed sample was applied to the specimen port of a fourth generation, quadruple, Rota+Adeno+Astro+Noro EIA Combo Card (Certest Biotec, S.L. Spain) and Rota/Adeno (Biocare) kits which have >99% sensitivity, and specificity respectively. Each of the tests was performed according to the manufacturer's specifications [20].

### **2.8 Statistical Analysis**

Data obtained in the study was analyzed using descriptive statistics in percentages and ratios. Infection proportions were tested for statistical significance by the use of chi-square ( $\chi^2$ ) test and used to compare groups. Differences were considered statistically significant if  $P \leq .05$ .

## **3. RESULTS**

### **3.1 Study Population and the Monthly Rates of Viruses Detected from the Samples Collected**

Fig. 1 shows the monthly distribution of the samples collected and rates of detection of adenovirus, norovirus, and co-infection of the viruses in the study participants. A total of 50 fecal samples comprising 32 (64%) from male

and 18 (36%) from female were collected from diarrheic children below 5 years of age and tested.

### 3.2 Clinical Manifestations of Adenovirus and Norovirus Gastroenteritis

General clinical features of gastroenteritis in the study participants were; watery stool, stool with mucus, fever, vomiting, abdominal pains, dehydration, comatose, and URTI (Upper Respiratory Tract Infection). Among the

participants that tested positive for adenovirus and norovirus respectively, the recorded clinical manifestations are presented in Table 1.

### 4. DISCUSSION

In this study, the clinical presentations of gastroenteritis were similar in the adenovirus and norovirus infected children except that all the norovirus cases expressed watery stools, vomiting, dehydration, fever, and non bloody stool with mucus (Table 1).

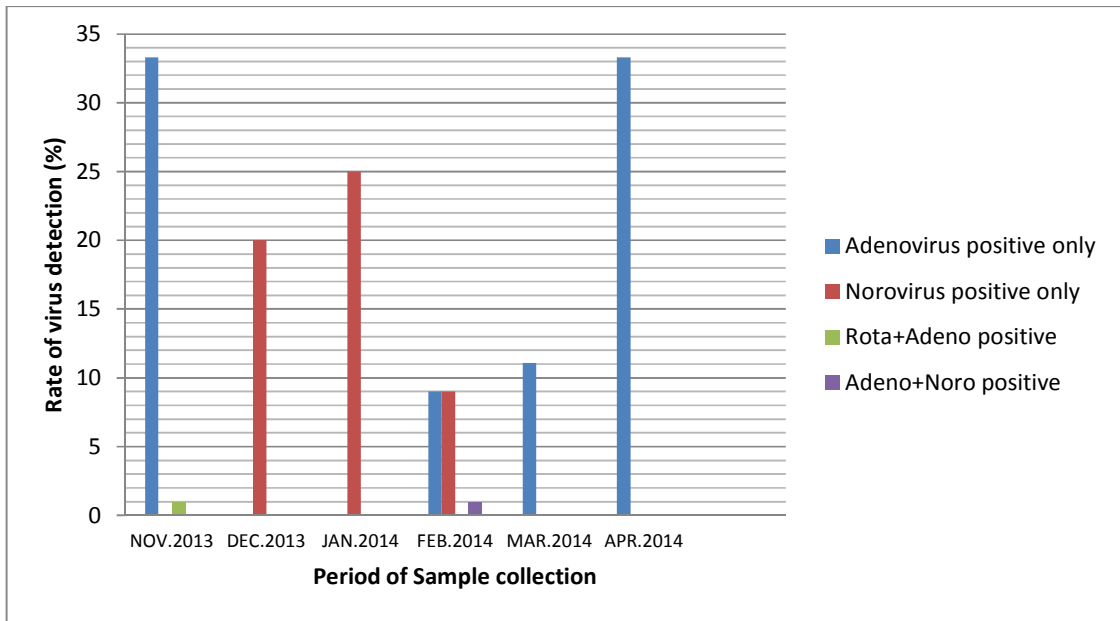


Fig. 1. Monthly rates of adenovirus, norovirus and dual virus infections among under-5 years children between November 2013 and April 2014 in Owo, Ondo state, Nigeria

Table 1. Clinical manifestations in children positive for enteric adenovirus and norovirus diarrhea among under-5 years children in Owo, Ondo State, Nigeria

Signs /symptoms	N° positive adenovirus antigen (n=9)	N° positive norovirus antigen (n=4)
Watery stool	9 (100)	4 (100)
Stool with mucus	0 (0)	2 (50)
Bloody stool	1 (11.1)	0 (0)
Fever	7 (77.8)	4 (100)
Vomiting	7 (77.8)	4 (100)
Abdominal pains	6 (66.7)	3 (75)
URTI	2 (22.2)	0 (0)
Dehydration	7 (77.8)	4 (100)

Legend: Figures in parenthesis represent percentages.

All diarrhea cases in the study participants that tested positive for the viruses presented with watery stools, and none with mucus in the adenovirus positives. However, while upper respiratory tract infection and abdominal pains was more pronounced in the adenovirus positives, dehydration and vomiting were common in the norovirus positives

Enteric adenoviruses were detected in 9/50 (18%) fecal samples of children below five years who presented with acute diarrhea at the Federal Medical Centre, Owo, Ondo state, Nigeria between November 2013 and April 2014. This rate is lower than the 22.3% for North-western Nigeria, previously reported by Aminu et al. [19]. This disparity could be due to differences in social, environmental, and climatic factors. However, contrary to the earlier reports of Avery et al. [11], that detected no enteric adenoviruses in Ibadan, southwest Nigeria, but 13.6% in a parallel study in the U.K in 1992, it is becoming evident from this present study that enteric adenoviruses are becoming an important agent of infantile gastroenteritis in southwest Nigeria. This present prevalence value is lower than the 48% reported by Al-Khafaji and colleagues [21] probably due to the challenges of war and civil strife in Iraq, but much higher than the 2.9% in Iran [22], 1.5% in Argentina [23], 6.8% in Egypt [5], and 3.0% that was reported for different studies in Korea [24], and 3.6% in Brazil [25].

Traditional diagnosis of adenoviral infections is usually by virus isolation in cell culture, by antibody studies or antigen detection by immunofluorescence, and visualization by electron microscopy [26]. These are laborious and time-consuming procedures [27] whose technologies are neither readily available in most developing countries, nor recommended for bedside point of care diagnosis. Consequently, testing and detecting viral agents of diarrhea are not investigated when a child seeks medical treatment for acute gastroenteritis. However, early rapid detection and identification of any circulating serotype is necessary for management of the disease and to limit the rapid transmission of the viruses. In addition, the prevalence studies are required in health intervention programs for prevention and control of these viral diarrhea diseases. This is the first use of the Certest quadruple Rota+ Adeno+ Astro+ Noro Immuno-chromatographic kit for one step detection of any of the four important viral agents of gastroenteritis in Nigeria. On its high specificity and sensitivity, the kits are recommended for rapid, point of care diagnosis, as a prelude to treatment and management of these viral diarrhea diseases.

Analyses by age group prevalence of adenovirus and norovirus diarrhea diseases showed that adenovirus was detected in children between 0-24 months with the highest prevalence in children 0-6 months (33.3%) old (Table 2), while

norovirus was not detected in children below 1yr but in children between 25-30 months (20%) old (Tables 3 and 4). There was no significant difference in infection of children by each of the two viruses ( $\chi^2 = 1.78$ ). The rate of norovirus infection in this study is lower than a reported prevalence of 37.3% among male children in a first hospital based study in Lagos state [9], and 25.5% among children below 12 months in a community based study in Osun state, Nigeria [10]. However the rate is higher than the reported 16.4% among Ghanaian children between 18-24 months [28]. Our study detected co-infection of adenovirus, with each of rotavirus, and norovirus in children aged between 31-36 months with a prevalence of 50% respectively (Table 4). In these older children, the observation was probably due to the clearing of the prevailing maternal antibody, the introduction of varieties of weaning diets and drink, interaction with playgroups, and exposure to various environmental contaminants during the early walking and learning processes that may predispose the children to infection. Lack of exclusive breastfeeding and contamination of weaning foods may be additional risk factors [29]. Consistent with the findings of Quyang et al. [30] and Liu et al. [31], our reports showed that gender does not play a role in adenovirus ( $\chi^2 = 0.605$ ) and norovirus ( $\chi^2 = 1.09$ ) infections as there was no significant difference in the rate of infection between the males and females. Taken together, these findings indicated that the burden of adenovirus and norovirus diarrhea exist predominantly in male and female children between 0-36 months, and this may be the prime targets for vaccination.

In this study adenovirus antigen was detected sporadically in the months of November 2013, February, March and April 2014 (Fig. 1), thereby corroborating the earlier assertion by Allard et al. [32] that the pattern of adenovirus infection may be epidemic, sporadic or endemic in all geographical regions of the world, and may occur throughout the year with little or no seasonal variation in shedding. Although we found no correlation for seasonal variation in adenovirus detection rates in this study, we observed a steady increase in prevalence of adenovirus from February to April 2014.

Considering adenovirus' resistance, persistence and effect on transmission in the environment, adenoviruses are known to be resistant to disinfectants or wastewater treatments, owing to the remarkable stability to pH, temperature, and

moisture, engendered by the double-stranded DNA genome. These contribute significantly to their persistence and carriage in the environment more than any other enteric viruses [33]. Therefore, these viruses eventually contaminate the water environment with minimal or no

reduction in their numbers and/or infectivity and elicit infection by consumption of contaminated water, particularly as the adenovirus positive participants utilized shallow wells as the sources of potable water.

**Table 2. Distribution by gender, and age group prevalences of enteric adenovirus diarrhea among under-5 years children in Owo, Ondo State, Nigeria**

Age group (month)	N° positive in male tested (%)	N° positive in female tested	Total N° positive
0-6	1/4 (25)	1/2 (50)	2/6 (33.3)
7-12	2/8 (25)	0/4 (0)	2/12 (16.6)
13-18	1/9 (11.1)	1/4 (25)	2/13 (15.4)
19-24	1/6 (16.7)	1/6 (16.7)	2/12 (16.6)
25-30	0/3 (0)	0/1 (0)	0/4 (0)
31-36	0 (0)	1/2 (50)	1/2 (50)
>36	0/1 (0)	0 (0)	0/1 (0)
Total	5/31 (16.1) <sup>a</sup>	4/19 (21) <sup>b</sup>	9/50 (18)

Legend: Figures in parenthesis represent percentages.

<sup>a, b</sup> No significant difference in the rate of adenovirus infection between male and female ( $\chi^2 = 0.605$ )

**Table 3. Distribution by age group and gender prevalences of norovirus diarrhea among under- 5 years children in Owo, Ondo State, Nigeria**

Age group (month)	N° positive in male tested	N° positive in female tested	Total N° positive
0-6	0/4 (0)	0/2 (0)	0/6 (0)
7-12	0/8 (0)	0/4 (0)	0/12 (0)
13-18	1/9 (11.1)	0/4 (0)	1/13 (7.7)
19-24	1/6 (16.6)	0/6 (0)	1/12 (8.3)
25-30	1/3 (33.3)	0/1 (0)	1/4 (20)
31-36	0/0 (0)	1/2 (50)	1/2 (50)
>36	0/1 (0)	0 (0)	0/1 (0)
Total	3/31 (9.7) <sup>a</sup>	1/19 (5.3) <sup>b</sup>	4/50 (8)

Legend: Figures in parenthesis represent percentages.

<sup>a, b</sup> No significant difference in the rate of norovirus infection between male and female ( $\chi^2 = 1.09$ ) in the studied population

**Table 4. Age distribution and prevalence of adenovirus, norovirus and dual infections among under- 5 years children in Owo, Ondo State, Nigeria**

Age group (month)	Total sample tested	Adenovirus positive	Norovirus positive	Rota + Adeno positive	Adeno + Noro Positive
0-6	6	2/6 (33.3)	0 (0)	0 (0)	0 (0)
7-12	12	2/12 (16.6)	0 (0)	1/12 (8.3)	0 (0)
13-18	13	2/13 (15.4)	1/13 (7.7)	0 (0)	0 (0)
19-24	12	1/12 (8.3)	1/12 (8.3)	0 (0)	0 (0)
25-30	4	0 (0)	1/5 (20)	0 (0)	0 (0)
31-36	2	0 (0)	0 (0)	0 (0)	1/2 (50)
>36	1	0 (0)	0 (0)	0 (0)	0 (0)
Total	50	7/50 (14)	3/50 (6)	1/50 (2)	1/50 (2)

Legend: Figures in parenthesis represent percentages.

There was no significant difference in infection of children by each of the two viruses ( $\chi^2=1.78$ ). The highest rate (33.3%) of adenovirus infection occurred in children between 0-6 months while the highest rate (20%) for norovirus occurred in children between 25-30 months. Coinfection by rotavirus and adenovirus was detected in children within the 7-12 months representing 8.3%, while adenovirus and norovirus dual infection occurred in the 31-36 months old representing 50% (Table 4)

The detected coinfection of adenovirus with rotavirus (2%) in this present study is relatively similar to the previously reported 9.1% [10] but lower than the 14.3% reported by Aminu and colleagues [19]. These findings indicated these viruses as obviously circulating in Southwest Nigeria, and may be responsible for majority of the infant morbidity and mortality associated with infective gastroenteritis that were not investigated. It is postulated that given the development of rotavirus vaccines (although tempered with drawbacks) in reducing the most globally common strains of rotaviruses, noroviruses and adenoviruses will soon take over as the leading causes of viral diarrhea in children [28]. Epidemiologically, there are risks for multistate or international outbreaks [34]. However, contrary to the findings of Ayolabi and colleagues [35], astrovirus was not detected among the study participants during the study period. To overcome the limitation of this study for a broader perspective, the sample size will have to be expanded in the future.

## 5. CONCLUSION

This present study is the third report of adenovirus gastroenteritis, occurring at a rate of 18%, and norovirus gastroenteritis at 8% respectively, in Owo Southwest Nigeria. This current paper provides a baseline data necessary for the formulation of state, National, and global health policies in mitigating the impact of viral diarrhea, an ubiquitous disease of childhood. The coinfection of adenovirus with rotavirus, and norovirus, will translate to higher severity and outcome than mono-infection in the detected cases. Further studies are required to determine the genotypes of the detected strains for molecular epidemiology and immunization purposes. Although the sample size was low at this stage, the rates were quite significant. There is need to formulate adenovirus gastroenteritis vaccine and incorporate such in the National Immunization Programme for mitigating the childhood viral diarrhea. Given the specificity and sensitivity of the quadruple, one step EIA kit utilized in this study, rapid testing and early detection of the four enteric viral agents will be achieved, for bedside management of infantile diarrhea, and preclude unnecessary administration of antibiotics.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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