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FACTORS ASSOCIATED WITH ROTA VIRUS DIARRHEA IN THE POST VACCINE PERIOD AS SEEN AT MOI TEACHING AND REFERRAL HOSPITAL, KENYA:
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ABSTRACT

Objectives: **To describe the prevalence and factors associated with rotavirus diarrhea in the post vaccine era.**
Design: **Cross-sectional study.**
Setting: **Moi Teaching and referral Hospital, Pediatric Emergency Department.**
Participants: **Children ≤2 years with acute diarrhea illness. Data was collected onto an interviewer administered questionnaire and a Certest® rapid rotavirus stool antigen test done. Main outcome measures: Socio-demographic and clinical characteristics including: Age, Gender, Rotavirus antigen test results, level of dehydration and anthropometric measurements.**
Results: **311 participants with acute diarrhea were recruited, with 55.6% (173/311) being rotavirus positive. On bivariate analysis, age appropriate completion of routine vaccination (p=0.030), two doses of rotavirus vaccination (p=0.005) and nutrition status (p=0.009) were associated with a positive rotavirus test. On logistic regression, mild wasting (OR 2.581; CI 95% 1.068-6.236;p=0.035) and moderate wasting (OR 3.424; CI 95% 1.221-9.604;p=0.019) were associated with rotavirus positive diarrhea. Receiving two rotavirus vaccines (OR 0.151; CI 95% 0.032-0.709;p=0.017) and age appropriate completion of routine vaccination (OR 0.478; CI 95% 0.256-0.892;p=0.003) was protective. The peak rotavirus prevalence was during the dry season. Receiving one rotavirus vaccine, severe malnutrition and socio-demographic characteristics e.g. age, the child's primary caregiver, overcrowding were not statistically significant. Although majority of the children with rotavirus positive diarrhea had non-severe dehydration (63%, 109/173) this was also not significant (OR 1.066; CI 95% 0.6695-1.699;p=0.786).**
Conclusion: **Prevalence of Rotavirus diarrhea is still high among the under twos in our set up. Two rotavirus vaccines are needed for full protection. Advocacy and public health interventions should intensify to improve the vaccine coverage**

INTRODUCTION

Diarrhea still carries a high morbidity and mortality rate in Sub-Saharan Africa and Kenya. Globally diarrhea affects 2 billion people annually, 1.9 million of whom are children aged five years and below[1]. The mortality rate is however higher for the under-fives at 18%. This translates to 5,000 deaths daily. Up to 90% of these deaths are in Africa and Asia [1]. In this group, most deaths occur among those under two years of age, [2].

Diarrhea can be bacterial, viral or parasitic, but viral diarrhea is the most predominant. The prevalence of diarrheas is almost equal across socio- economic classes[1].Studies over the last 30 years have consistently shown that rotavirus is the most important cause of infantile gastroenteritis worldwide [3].

The most recent African Rotavirus Surveillance Network publication (2009) involving 15 countries in Africa , reported a rotavirus prevalence rate between 30% to 41% in East Africa. Central and western parts of Africa reported a prevalence range of 21% to 59%. [4]. Africa accounts for half of all deaths globally from Rotavirus associated diarrhea. Kenya has documented that Group A Rotavirus accounts for 14% to 39 % of rotavirus infection among children with acute diarrheal illnesses in hospitals [5]. Rotavirus vaccination was identified in 2013 by the World Health Organization (WHO) as a key strategy in reduction of rotavirus diarrhea burden.

Rotavirus vaccination has been shown to decrease the prevalence, disease severity and mortality. It is part of a comprehensive strategy that includes both preventive and protective measures against diarrhea with a goal of preventing avoidable deaths by the year 2025.

The measures specifically aimed towards diarrhea include: vitamin A supplementation; Rotavirus vaccination; safe water and improved sanitation and continued feeding. Management of children with diarrhea using Low osmolarity ORS and zinc has also been advocated for in this action plan [6].

MATERIALS AND METHODS:

This was a cross-sectional study describing the factors associated with Rotavirus diarrhea at Moi Teaching and Referral Hospital, Pediatric Emergency Department, Eldoret, Kenya.

The target populations were children aged 2 years and below presenting with acute diarrheal illness between the months of November 2015 and June 2016. We approached every 5th child presenting with acute diarrheal illness at the center every day from 8 am for screening for eligibility for the study and consenting for the study period.Upon recruitment, we conducted a questionnaire-guided interview to the caregivers of these children seeking their socio-demographics, did a clinical examination on the children and took a stool sample for testing using a rapid rotavirus stool antigen test, Certest®.

Children excluded from the study if they had prior diagnosis of malabsorptive diarrhea, poison ingestion or if they were unable to provide a stool sample during the time of interaction. Data was entered into an MS Access® database and analyzed using Stata® version 13.1. Bivariate and multivariate analyses were carried out to test for associations at 95% confidence interval and p values ≤0.05 were considered statistically significant.

RESULTS

A total of 311 children were recruited into the study. The majority (60%, 186) were males their median age was 12 months (IQR 8,19). 81% had a parent as the primary caregiver followed by house help at 14%. The prevalence of rotavirus was55.6% (173/311) (Table 1) .

Table 1

Showing the socio-demographic factors associated with Rotavirus Antigen test positivity:

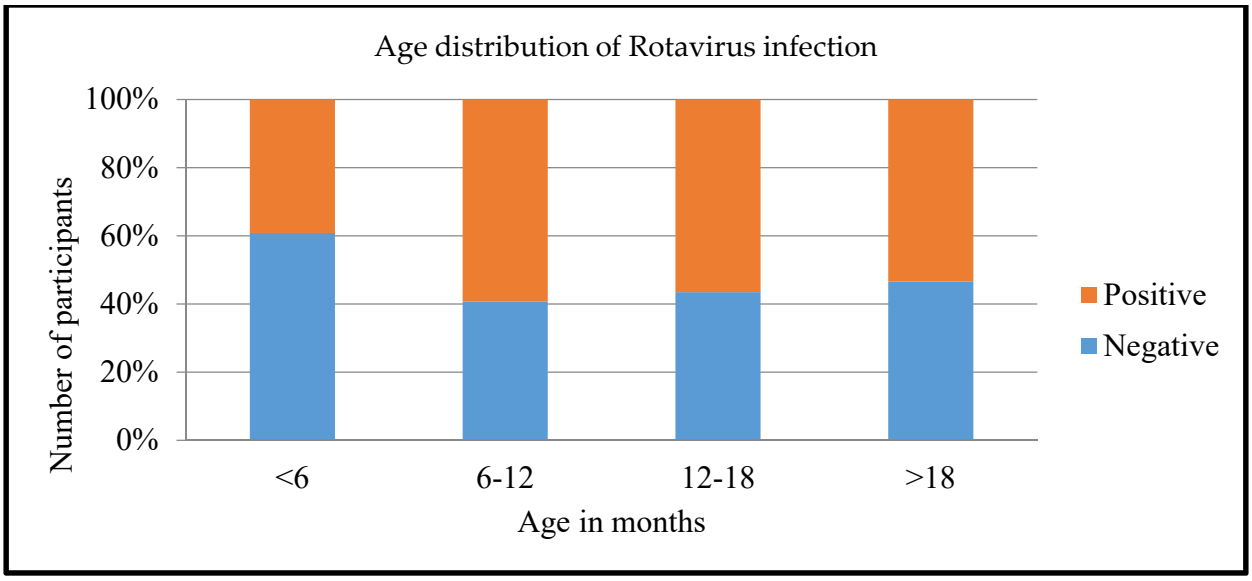
Parameter:	Number of participants: (n=311)	Rotavirus Negative	Rotavirus Positive	P value
Age Distribution				
< 6 months	45(14.5%)	26 (57.7%)	19 (42.2%)	0.244
6 – 12 months	109(35%)	45 (41.3%)	64 (58.7%)	
12 – 18 months	69(22.2%)	28 (40.6%)	41 (59.4%)	
>18 months	88(28.3%)	38 (43.2%)	50 (56.8%)	
Gender				
Female	125(40.2%)	56 (44.8%)	69 (55.2%)	0.901
Male	186(59.8%)	82 (44.1%)	104 (55.9%)	
Primary Caregiver				
Parent	251(80.7%)	109 (43.4%)	142 (56.6%)	0.783
House help	43(13.8%)	21 (48.8%)	22 (51.2%)	
Others	17(5.5%)	8 (47.1%)	9 (52.9%)	

Although the overall incidence of diarrhea increased gradually from January to May, rotavirus associated diarrhea was more prevalent during the months of February and March and then subsequently reduced. The month of February had the lowest amount of rainfall in the study period as recorded by the Kenya Meteorological department in Eldoret. (Figure 1)

Distribution of rotavirus infection

Figure 1

Bar graph showing age related prevalence of rotavirus diarrhea among the children with diarrhea.



Children aged between six and twelve months of age had the highest proportion of rotavirus infection while those aged below six months of age had the lowest proportion of infection. After infancy, rotavirus positivity decreased progressively.

CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

Majority (83.3%) of the children were up-to-date with their vaccination and 85% had received two rotavirus vaccine doses. The children who had received age appropriate vitamin A at least once were 73.3% (228/300). The measles vaccine coverage was at 93.2% (205/220). 36 % of the children had severe dehydration while 15.1% (47/311) had WHZ score ≤-3 (severe wasting). 84% (261/311) of the children had Bristol stool ype 6-7.

Table 2

Showing Clinical factors associated with Rotavirus antigen test positive

Parameter	Participants (n = 311)	Rotavirus Negative	Rotavirus Positive	P value
Vaccination Status				
Up to date	259(83.3%)	122 (47.1%)	137 (52.9%)	0.03
Not up to date	52(16.7%)	16 (30.8%)	36 (69.2%)	
Rotavirus Vaccination				
None	30(9.6%)	5 (16.7%)	25 (83.3%)	0.005
Missed second dose	6(1.9%)	2 (33.3%)	4 (66.7%)	
Received two doses	265(85.2%)	124 (46.8%)	141 (53.2%)	
Not applicable	10(3.3%)	7 (70.0%)	3 (30.0%)	
Dehydration Level				
Severe dehydration	113(36.3%)	49(43.4%)	64(56.6%)	0.786
Non-severe dehydration	198(63.7%)	89(39%)	109(61%)	
HIV* Status				
Positive	11	8 (72.7%)	3 (27.3%)	0.146[1]
Negative	291	126 (43.3%)	165 (56.7%)	
Sero-exposed	9	3 (33.3%)	6 (66.7%)	
Temperature [2]				
Low	72	31 (43.1%)	41 (56.9%)	0.089
Normal	131	67 (51.1%)	64 (48.9%)	
High	108	40 (37%)	68 (63%)	
Nutrition status n=301[3] (WHO WLZ score) 706				
Undernourished (Z score <-1)	109(38.9%)	40(36.7%)	69(63.3%)	0.009
Mild	-	*10 (27.8%)*	*26 (72.2%)*	
Moderate	-	*6 (22.2%)*	*21 (77.8%)*	
Severe	-	*24 (52.2%)*	*22 (47.8%)*	
Over-nourished (Z score > 1)	90(%)	48 (53.3%)	42 (46.7%)	
Normal (Z score 1 to -1)	102(%)	46 (45.1%)	56 (54.9%)	

Human Immunodeficiency Virus infection status on Determine® test.

1.Fischer's exact test
2.Normal ranges (36.5 to 37.5OC)
3.Weight for Length Z Score according to the World Health Organization

Nutritional status was associated with rotavirus infection, with increasing proportion of positivity when normal nutritional status children were compared to undernourished children. The duration of exclusive breastfeeding and breastfeeding status showed no statistical significance

DISCUSSION

Two years after the introduction of rotavirus vaccination in the regular vaccination schedule, the burden of diarrhea is still high and of unknown etiology. While the vaccine has largely been successful in the high income countries, it is necessary to establish whether rotavirus is still a leading cause of diarrhea in the Low-Middle income countries and to describe its clinical pattern of presentation, to advice on targets that can further reduce the burden of diarrhea among children.

Rotavirus diarrhea has age dependent susceptibility and the children under two have been most affected in the pre-vaccination period. [7, 8, 9]. Rotavirus prevalence has however varied greatly for both the pre-vaccine and post-vaccine periods. In a systematic review in the pre-vaccination period, the prevalence varied from 16% to 61% in various North African (Algeria, Egypt, Morocco and Tunisia) and Asian countries (Bahrain, Qatar, Syria, United Arab Emirites and Yemen).

The highest prevalence was in Syria at 61% while the lowest was in Saudi Arabia at 16% [10] A report by the rotavirus surveillance network in 2014 showed a pre-vaccine prevalence of 40.7% (35.6% to 49.1%) in 34 sentinel sites in twenty Africa countries [11]. Findings in Kenya have shown prevalence as high as 53.4% at Kenyatta National Hospital, prior to introduction of rotavirus vaccination [12].The post-vaccination period has been characterized by a decline in prevalence of rotavirus infection, though at varying proportions. In Ghana, there was a decline from 49.7% to 27.8% [7].

In Malawi the post-vaccine prevalence was 31% from 50% previously [13]. Zambia also reported a decline from 40.1% to 24.7%% rotavirus positivity [14]. These three countries are +among the pacesetters in prevention of acute diarrheal illness by rotavirus vaccination in Africa.Our study showed a rotavirus prevalence of 55.6%, a value higher than studies carried out in the post and pre vaccination period in other hospital based studies. The high prevalence in this study, can be attributed to differences in methodology this study compared to previous studies.

These study differences include include age of participants, site of the study, population studied among others. The prevalence of Rotavirus diarrhea is higher when only children aged two years and below are included in the study compared to when older children are also included. For instance, the prevalence rose from 15% and 22.7% in Cameroon and Kenya respectively to 42.8% and 44.7% [9] [15].This explains the relatively high prevalence in our study. Age dependent susceptibility in children below two years is due to inadequate immunity which is gained from exposure to the virus. These hospital based studies have shown a higher prevalence compared to population based studies that have showed as low prevalence as 10-15% [15, 16].

This is due to study population biases since the hospitalized children have diarrheal illness at recruitment while population based studies include asymptomatic children. The prevalence also varies from hospital to hospital even in multicenter studies within one country such as

that seen in Cameroon where they had a range of 33.9% to 46.5%[9] . The variation from one hospital to the other is attributed to the differences in catchment populations that increase their risk of rotavirus infection. Urban centers have higher prevalence of rotavirus diarrhea compared to rural areas due to the high population density and poor sanitation.

High prevalence of rotavirus even after introduction of the vaccine in other African countries, has been hypothesized to be due to various reasons. These include lower vaccine efficacy in high burden countries as seen in Zambia and Malawi[13,14]. This has been studied further in other high burden countries and various probable reasons behind the lower vaccine efficacy put forward.

There have been studies that show that variability in gut microbiota causes reduced vaccine efficacy, Bacteroides predominance in the gut is associated with poorer vaccine response compared to Streptococcus bov is [17]. Also, variations in Rotavirus serotype and re-emergence of strains following the introduction of the vaccine have been attributed to poorer vaccine response.

In a study in Kenya there was documented re-emergence of genotypes not covered by the vaccine such as G[9] and G[12] strains [8]. Breast milk antigens have been shown lower vaccine seroconversion in high burden-low income countries where breastfeeding rates are high. The antirotavirus specific IgA in breastmilk is high especially in high burden countries.

There is also a chance that these children have had exposure to wild type rotavirus prior to vaccination, hence the response to vaccination will be poor due to preformed antibodies against rotavirus [18]. This study showed that mild and moderate malnutrition increased the risk of rotavirus infection (OR 2.581;CI 95% 1.068–6.236; p=0.035) and (OR 3.424; CI 95% 1.221 – 9.604; p=0.019) respectively, while severe malnutrition had no association with the infection (OR 0.795; CI95% 0.373, 1.692; p=0.552). However, the relationship between malnutrition and rotavirus infection is still unclear. Under-nutrition has been associated with increased prevalence and worsening severity of rotavirus diarrhea and lower vaccine efficacy [13]. This is thought to result from the lower immunity in under-nutrition and villous blunting.

Severe malnutrition on the other hand was not associated with rotavirus infection in our study. Our findings of high rotavirus infection prevalence could further be explained by high number of mild and moderately malnourished children among the participants. There have been some contradictory studies that showed malnutrition having been protective against rotavirus infection [19]. The pre-vaccine studies in Kenya showed a higher prevalence among those of normal nutritional status [8].

In the post-vaccine period, vaccine evaluation studies have demonstrated a decline in hospitalization and severity of rotavirus infection. The rotavirus vaccine functions to decrease severity of illness in terms of dehydration level and hospitalization rates [20]. There has however been some hospital based studies showing a decline in prevalence of rotavirus after introduction of the vaccine [7]. There have been no reports to the contrary.

The rotavirus positivity and disease severity has been shown to decrease on an incremental proportion every year after introduction of vaccination. The total percentage improvement in the burden has increased progressively [7,13,14]. While we did not set out to carry out a vaccine evaluation, this study found that rotavirus vaccination is protective against rotavirus infection especially when given in two doses. One dose of rotavirus vaccine conferred some protection but was not statistically significant.

The vaccine coverage was however lower in this study than the World Health Organization recommended level required for public health protection of 90% [6].

CONCLUSION

The prevalence of rotavirus associated diarrhea in our setup is high with malnourished children being most at risk. Complete vaccination against rotavirus is protective against rotavirus diarrhea. We recommend a multifaceted approach towards prevention of rotavirus diarrhea by vaccination and nutrition support of the children under two years of age.

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