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Prevalence and Factors Associated with Rotavirus Infection among Vaccinated Children Hospitalized for Acute Diarrhea in Mwanza City, Tanzania: A Cross Sectional Study

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Abstract

Introduction: Rotavirus infection is a leading cause of severe diarrhea culminating to dehydration among children under five years of age. Understanding trends and factors that could assist towards devising effective preventive strategies of Rotavirus infection beyond vaccination is crucial. **Objectives:** This study was done in an attempt to determine the prevalence and associated factors of Rotavirus infection among vaccinated children aged between 6 weeks and 24 months admitted with acute diarrhea Mwanza, Tanzania. **Material and Methods:** Across sectional study involving vaccinated children aged 6 weeks to 24 months was conducted in three selected hospitals from July 2017 to January 2018. Socio-demographic and other relevant clinical information were collected using a standardized data collection tool adopted from WHO Rotavirus surveillance tool. Rotavirus infection from the stool was detected using an enzyme immunoassay. Data were analyzed using STATA version 13. **Results:** A total of 301 vaccinated children with acute diarrhea with a median age of 12 [IQR: 8 - 17] months were enrolled. Nine (3.0%) and 292 (97.0%) had received one dose and two doses of Rotavirus

vaccine, respectively. The prevalence of Rotavirus infection was 74 (24.6%) [95% CI: 20.0 - 29.8]. Independent predictors of Rotavirus infection were: dry season (OR 6.9; 95% CI: 2.9 - 16.0; $p < 0.001$), 3 ≥ children indwelling in the same house (OR 2.1; 95% CI: 1.1 - 4.2; $p = 0.043$) and vomiting (OR 3.6; 95% CI 1.1 - 12.6; $p = 0.045$). Children with Rotavirus infection had a significantly shorter hospital stay than those without Rotavirus infection (3 [2 - 4] days versus 3 [3 - 5] days; $p = 0.0297$). **Conclusions:** The prevalence of Rotavirus infection has declined among vaccinated children in Mwanza, Tanzania with significant decrease in the hospital stay. Dry seasons, three or more children indwelling in the same house and vomiting were independent predictors of Rotavirus infection. There is a need to sustain the coverage of rotavirus vaccination in low-income countries in order to significantly reduce associated morbidity and mortality.

Keywords

Rotavirus, Vaccination, Diarrhea

1. Introduction

Diarrhea remains the second most common cause of death among children below five years of age worldwide [1]. Most of these deaths are due to severe dehydration, with the majority of deaths occurring in low and middle-income countries [1]. Globally, Rotavirus is the commonest cause of severe infantile diarrhea resulting in dehydration and prolonged hospital stay among children below five years of age [2] [3]. Development of a safe and effective Rotavirus vaccine has been a priority since Rotavirus disease cannot be eliminated through the improvement of water and sanitation [4]. The World Health Organization (WHO) authorized the Rotavirus vaccine for infants to be incorporated in all national immunization programme with strong emphasis in the countries where diarrhea disease cause more than 10% of death in children below five years of age [5].

In Tanzania, Rotavirus vaccine, a live attenuated human monovalent [G1P8] vaccine (Rotarix), was introduced in the National immunization program in January 2013. Despite the Rotavirus vaccine implementation, acute diarrhea with severe dehydration cases is still reported in this setting. The prevalence of Rotavirus infection prior and after vaccine implementation has been continuously studied, however, the trends such as seasonality, severity of disease, hospital stay and associated factors of Rotavirus infection have not been adequately studied among vaccinated children [6] [7] [8]. In a view of that, this study was done to determine the prevalence of Rotavirus infection and factors associated with acute diarrhea among vaccinated children aged 6 weeks to 2 years admitted in three hospitals in the city of Mwanza. The information from this study is important in assessing the trend of Rotavirus infection in this vaccination era.

2. Material and Methods

2.1. Study Design and Settings

This was a hospital based cross sectional study involving 301 vaccinated children which was conducted from July 2017 to January 2018 in the city of Mwanza, Tanzania in three hospitals (Nyamagana District Hospital, Sekou Toure Regional Referral Hospital and Bugando Medical Centre).

2.2. Sample Size, Sampling and Inclusion Criteria

Sample size of the study was calculated using Kish Leslie formula [9] using the prevalence of 20.7% from Temu *et al.* [6]. The minimum sample size obtained was 250 children. All children who received at least one dose of Rotavirus vaccine as evidenced by RCH card aged 6 weeks to 24 months admitted for treatment of acute diarrhea within seven days duration irrespective of the other illnesses, were serially enrolled until the sample size was attained.

2.3. Variables and Outcomes

Socio-demographic data and relevant clinical information were collected using a structured pre-tested questionnaire adopted from WHO Rotavirus surveillance tool. Diarrhea was defined according to the WHO guidelines as passage of three or more loose, liquid or watery stools within 24 hours period [10]. Duration of illness, frequency of diarrhea, consistency of stool, history of fever, vomiting, history of Rotavirus vaccination were recorded followed by clinical examination to elicit hydration and nutritional status. All children were admitted and managed according to respective standard hospital guidelines. The duration of hospital stay for each child was noted.

2.4. Laboratory Procedures

All samples were collected and analyzed at the Bugando Medical Centre laboratory which is one of the WHO sentinel surveillance sites for Rotavirus gastroenteritis using enzyme-linked immunosorbent assay (The ProSpecT Rotavirus Microplate kit, Oxoid Ltd., UK) as per manufacturer's instructions.

2.5. Data Analysis

The data were analyzed using STATA software version 13. Continuous data were summarized using median with interquartile range (IQR) while categorical data were summarized using proportions. To determine the factors associated with Rotavirus infection univariable logistic regression followed by multivariable logistic regression models were performed. Factors that were statistically significant on univariable analysis were subjected to multivariable logistic regression model. Odd ratios with their respective 95% confidence interval were noted and a p value of less than 0.05 was considered statistically significant. To compare the median hospital stay after initiation of hospital management between vaccinated children with and without Rotavirus infection admitted for acute diarrhea,

two-sample Wilcoxon rank-sum (Mann-Whitney) test was used.

3. Results

3.1. Socio-Demographic Characteristics of Study Participants

A total of 301 children with acute diarrhea admitted in three hospitals were recruited in the study with a median age of 12 [IQR: 8 - 17] months, of these 40 (13.3%), 184 (61.1%) and 77 (25.6%) were from Nyamagana District Hospital, Sekou Toure Regional Referral Hospital and Bugando Medical Centre, respectively. Majority of children, 166/301 (55.2%) were males and most of the children enrolled, 285/301 (94.7%) were from urban areas (Table 1).

3.2. Clinical Findings among Vaccinated Children with Acute Diarrhea

The median duration of diarrhea was 3 [IQR: 2 - 5] days. The vaccine coverage for the first dose of Rotavirus vaccine was 100% whereas for the second dose it was 97.0% (292/301). There were 188/301 (62.7%) children with normal nutrition status. Of note, 34/301 (11.3%) and 140/301 (46.5%) children had severe dehydration and some dehydration, respectively (Table 2).

3.3. Prevalence of Rotavirus Infection among 301 Children with Acute Diarrhea

Of the 301 children with acute diarrhea investigated, 74 (24.6%) [95% CI 20.0% - 29.8%] had Rotavirus infection. The highest prevalence of Rotavirus infection was seen at Sekou Toure Regional Referral Hospital, 28.3% (52/184) followed by Nyamagana District Hospital, 27.5% (11/40) and Bugando Medical Centre, 14.3% (11/77), Figure 1.

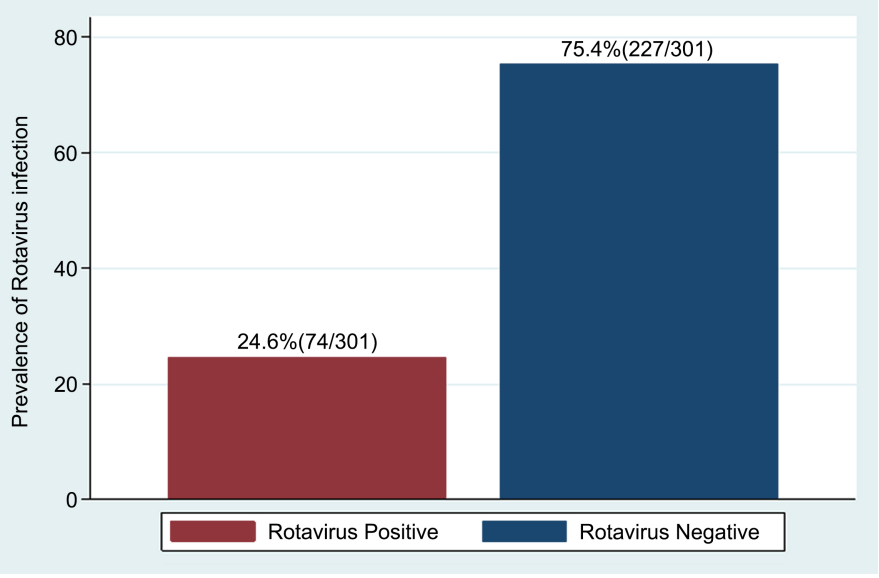

Figure 1. Distribution of Rotavirus infection among 301 vaccinated children with acute diarrhea.

Table 1. Distribution of socio-demographic data of 301 children with acute diarrhea.

Variable	Number (n)	Percent (%)
Hospital		
Nyamagana	40	13.3
Sekou-Toure	184	61.1
Bugando	77	25.6
Age of the child		
2 - 12 months	170	56.5
13 - 24 months	131	43.5
Sex of child		
Female	135	44.8
Male	166	55.2
Education of care giver		
None	34	11.3
Primary	185	61.5
Secondary	69	22.9
University	13	4.3
Employment status of care giver		
Employed	32	10.6
Petty traders	133	44.2
Non employed	136	45.2
Marital status of care giver		
Married	256	85.1
Single or widowed	45	14.9
Relationship		
Mother	279	92.7
Father	14	4.7
Guardian	8	2.7
Residence		
Urban	285	94.7
Rural	16	5.3
Weaning period		
<6 months	184	61.1
>6 months	117	38.9
Neighbour child with diarrhea		
No	232	77.1
Yes	69	22.9
Source of drinking water		
Lake	8	2.7
Tap	265	88.1
Well	28	9.3
House type		
Brick	220	73.1
Mud/Thatch	81	26.9
Number of underfive dwell in the house		
1 child	142	47.2
2 children	92	30.6
3 children	40	13.3
≥4 children	27	9.0

Table 2. Clinical findings and vaccine status of 301 children with acute diarrhea.

Variable	Number (n)	Percent (%)
Nutritional status		
Normal	188	62.7
Mild Malnutrition	67	22.3
Moderate Malnutrition	22	7.3
Severe Malnutrition	23	7.7
Dehydration status		
No dehydration	127	42.2
Some dehydration	140	46.5
Severe dehydration	34	11.3
Duration of diarrhea		
1 - 3 days	168	55.8
4 - 7 days	133	44.2
Consistency of diarrhea		
Watery	272	90.4
Watery + Mucoid	29	9.6
Number of vaccine dose		
1	9	3.0
2	292	97.0

3.4. Factors Associated with Rotavirus Infection

On univariable logistic regression analysis, the factors associated with Rotavirus infection were: being admitted to Sekou Toure hospital (OR 2.4; 95% CI 1.2 - 4.8; p = 0.018), dry season (OR 8.5; 95% CI 3.8 - 19.4; p < 0.001), three or more children indwelling in the same house (OR 2.4; 95% CI 1.2 - 4.6; p = 0.009), vomiting (OR 6.7; 95% CI 2.0 - 22.1; p = 0.002), formal education of caregiver (OR 3.7; 95% CI 1.1 - 12.6; p = 0.033). By multivariable logistic regression analysis the factors associated with Rotavirus infection were: dry season (OR 6.9; 95% CI 2.9 - 16.0; p < 0.001), three or more children indwelling in the same house (OR 2.1; 95% CI 1.1 - 4.2; p = 0.043) and vomiting (OR 3.6; 95% CI 1.1 - 12.6; p = 0.045), Table 3.

3.5. Hospital Stay of Vaccinated Children with Acute Diarrhea

Children with Rotavirus infection had a significant shorter hospital stay than those without Rotavirus infection (3 [2 - 4] days versus 3 [3 - 5] days; p = 0.0297), Table 4 and Table 5.

Table 3. Factors associated with Rotavirus infection among 301 children with acute diarrhea.

Variables	Rotavirus infection		Univariate		Multivariate	
	Positive	Negative				
	n (%)	n (%)	OR [95% CI]	p-value	OR [95% CI]	p-value
Hospital						
Bugando	11 (14.3)	66 (85.7)	1.0			
Nyamagana	11 (27.5)	29 (72.5)	2.3 [0.9 - 5.8]	0.087	1.6 [0.6 - 4.7]	0.347
Sekou-Toure	52 (28.3)	132 (71.7)	2.4 [1.2 - 4.8]	0.018	2.1 [0.9 - 4.7]	0.067
Sex of the child						
Female	28 (20.7)	107 (79.2)	1.0			
Male	46 (27.7)	120 (72.4)	1.5 [0.9 - 2.5]	0.164	-	-
Climate season						
Rainy	7 (6.1)	107 (93.9)	1.0			
Dry	67 (35.8)	120 (64.2)	8.5 [3.8 - 19.4]	<0.001	6.9 [2.9 - 16.0]	**<0.001**
Vomiting						
No	3 (5.7)	50 (93.3)	1.0			
Yes	71 (28.6)	177 (71.4)	6.7 [2.0 - 22.1]	0.002	3.6[1.1 - 12.6]	**0.045**
Dehydration						
No	29 (22.8)	98 (77.2)	1.0			
Yes	45 (25.9)	129 (74.1)	1.2 [0.7 - 2.0]	0.547	-	-
Age of the child						
13 - 24 months	34 (25.9)	97 (74.1)	1.0			
2 - 12 months	40 (23.5)	130 (76.5)	0.9 [0.5 - 1.5]	0.628	-	-
Children number in house						
1 child	27 (19.0)	115 (81.0)	1.0			
2 children	23 (25.0)	69 (75.0)	1.4 [0.8 - 2.7]	0.276	1.6 [0.8 - 3.3]	0.184
≥3 children	24 (35.8)	43 (64.2)	2.4 [1.2 - 4.6]	0.009	2.1 [1.1 - 4.2]	**0.043**
Education of care giver						
Informal	3 (8.8)	31 (91.2)	1.0			
Formal	71 (26.6)	196 (73.4)	3.7 [1.1 - 12.6]	0.033	1.3 [0.8 - 2.2]	0.314
Malnutrition						
No	44 (23.4)	144 (76.6)	1.0			
Yes	30 (26.6)	83 (73.4)	1.2 [0.7 - 2.0]	0.540	-	-
Neighbour child with diarrhea						
No	54 (23.3)	178 (76.7)	1.0			
Yes	20 (29.0)	49 (71.0)	1.3 [0.7 - 2.5]	0.335	-	-
Fever						
No	53 (27.2)	142 (72.8)	1.0			
Yes	21 (19.8)	85 (80.2)	0.7 [0.4 - 1.2]	0.158	-	-

Table 4. Distribution of hospital stay of 301 children with and without Rotavirus infection.

Rotavirus infection	Number	Median hospital stay [IQR]	p-value
Positive	74	3 [2 - 4] days	0.0297
Negative	227	3 [3 - 5] days	

Table 5. Hospital stay of vaccinated children with and without Rotavirus infection admitted for acute diarrhea during pre and post-vaccine era.

Vaccine era	Median Hospital stay [IQR]		Author, year
	Rotavirus positive	Rotavirus negative	
Pre-vaccine	3.7 days*	2.5 days*	Temu *et al.*, 2011
Pre-vaccine	4 [3 - 6] days	3 [2 - 4] days	Hokororo *et al.*, 2014
Post-vaccine	3 [2 - 4] days	3 [3 - 5] days	Present study, 2018

*Mean.

4. Discussion

This study has observed the prevalence of rotavirus infection of 24.6% which is significantly low compared to 49.4% which was observed in the same setting in pre-vaccinated era [7]. Similar findings have been realized in a recent country wide surveillance in Tanzania, in which a decline of Rotavirus infection among children below five years of age was observed. In this recent study, the decline was from 50.7% to 17.5% in Mwanza, whereas in Tanga it was from 39.2% to 15.9%. The findings on the reduction of this current surveillance are high in comparison from the prevalence obtained in our study compared to that done by Hokororo *et al.* in pre-vaccine era. This could be attributed to the differences in vaccine coverage in these regions [8]. However, a previous study by Temu *et al.* conducted in Mwanza, Tanzania among unvaccinated children in pre-vaccine years found the prevalence of Rotavirus infection of 20.7% [6], which is slightly low compared to the current study. This finding could possibly be due to the fact Temu *et al.* study used latex agglutination test to detect Rotavirus infection which has low sensitivity and specificity compared to EIA that used in this study. This study has confirmed that successfully Rotavirus vaccination can significantly reduce the prevalence of Rotavirus infection in children.

Before the introduction of Rotavirus vaccine, Rotavirus infection was more common during rainy season. Hokororo *et al.* study and a Country-wide surveillance in Tanzania, showed that in many settings Rotavirus hospitalizations before vaccine peaked during rainy season (April-July) [7] [8]. Surprisingly, this study has demonstrated that Rotavirus infection was significantly more common during dry season (July, August and September) than during the rainy season (October, November, January and February). This could be explained by the fact that during dry season there is scarcity of water supply which reduces domestic

hygiene. Similar findings on the seasonality in post-vaccine era were observed in a Country-wide surveillance in Tanzania, whereby Rotavirus infection peaked during dry season (August-September) [8]. This finding is similar to the studies done in South Asia and Northern Venezuela, in which Rotavirus infection was more common during dry season [11] [12]. These findings suggest that there is seasonal variation following the implementation of rotavirus vaccine [8].

This study showed that vomiting was significantly associated with Rotavirus infection, which is similar to the previous studies done in pre-vaccine era in rural Western Kenya, Northwestern Angola, Accra, Ghana, urban Bangladesh and Sudan [13] [14] [15] [16] [17]. This finding is attributed by the fact the virus releases enterotoxin non-structural protein-4 (NSP4) which induces the release of serotonin from human Enterochromaffin cells in the small intestines and activates serotonin receptors on the vagal abdominal afferent and hence induces activation of the nucleus tractus solitarii and area of postrema in the brain stem, which ultimately induces vomiting reflex, nausea and vomiting [18].

This study has found that vaccinated children indwelling with three or more fellow children in the same house are significantly more likely to acquire Rotavirus infection compared to those indwelling with less than three fellow children. This finding is similar to the study done in Chiapas, Mexico in which children indwelling in a house with seven or more people were significantly more likely to acquire Rotavirus infection [19]. This is attributed by the fact that the mode of spread of Rotavirus infection is largely person-to-person transmission, hence as the number of children increases in the house likewise transmission rate increases.

Studies by Temu *et al.* and Hokororo *et al.* which were done in Mwanza, Tanzania during pre-vaccine period showed that children with Rotavirus infection stayed longer in the hospital than those without Rotavirus infection [6] [7]. However, in this study, it was found that children with Rotavirus infection had a shorter hospital stay compared to those without Rotavirus infection. This observation is similar to the study done in Accra, Ghana in which children without Rotavirus stayed longer in the hospital than those with Rotavirus infection [15]. This could be explained by the fact that Rotavirus vaccination reduces the severity of diarrhea and hence children recover quickly and ultimately the length of hospital stay is shortened. This confirms that Rotavirus vaccine has reversed the trend of hospitalization.

One of the major limitations of this study is that the study was not done for entire year so the interpretation for Rotavirus seasonality is somehow limited.

5. Conclusion

Rotavirus vaccine has significantly reduced the prevalence of Rotavirus infection among vaccinated children with acute diarrhea in Mwanza, Tanzania. In addition, vaccination has reversed the trend of hospitalization among children infected with Rotavirus infection. It is recommended, that the coverage of Rotavirus vaccine should be maintained and emphasized and further studies to deter-

mine circulating genotypes of Rotavirus and other viruses causing diarrhea during this vaccination era are warranted in developing countries where rotavirus vaccination is implemented.

Ethical Approval

The ethical approval to conduct the study was sought from the joint Catholic University of Health and Allied Sciences/Bugando Medical Centre Research and Ethics Review Committee with ethical clearance number CREC/208/2017. Parental/guardian consent was obtained for each child prior recruitment.

Availability of Data and Materials

All data have been included in this manuscript.

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Author Contributions

Conceived and designed the study: DM, AH, SEM and MMM. Data collection and laboratory testing: DM, FM, DRM, ECB, ENK, AH, SEM and MMM. Analyzed the data: DM, AH, SEM and BRK. Wrote the paper: DM and DRM. Edited and reviewed critically the manuscript: AH, SEM and MMM. All authors read and approved the final manuscript.

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Competing Interest

The authors declare that there is no competing interest.

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List of Abbreviations

BMC: Bugando Medical Centre
ELISA: Enzyme Linked Immune-Sorbent Assay
CUHAS: Catholic University of Health and Allied Sciences
CI: Confidence Interval
IQR: Interquartile Range
IVDP: Immunization and Vaccination Development Programme
OR: Odds Ratio
WHO: The World Health Organization