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Effectiveness of monovalent rotavirus vaccine against hospital-attended rotavirus gastroenteritis among children in Uganda

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The findings and conclusions in this paper are those of the authors and do not necessarily represent the official position of the World Health Organization (WHO) or the Centers for Disease Control and Prevention (CDC).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2025.126726>.

Abstract

Background: The underlying causes for lower rotavirus vaccine effectiveness (VE) in high-child-mortality settings are not well understood. Uganda introduced the human monovalent G1P[8] rotavirus vaccine (Rotarix) in June 2018. We determined the effectiveness of Rotarix against rotavirus diarrhea requiring hospital care among Ugandan children.

Methods: We compared the vaccination status of children with laboratory-confirmed rotavirus (cases) and non-rotavirus (controls) diarrhea who were age-eligible to receive Rotarix and admitted to 3 hospitals in Uganda October 2018–December 2022. VE ($[1 - \text{odds ratio of vaccination among cases and controls}] \times 100$) was calculated using unconditional logistic regression adjusting for age, birth month-year, and hospital.

Results: Among 187 cases and 622 controls, respectively, 93 % (173/187) and 93 % (579/622) had received ≥ 1 doses of Rotarix. Adjusted full-series (2 dose) VE against rotavirus diarrhea was 29 % (95 % confidence interval: -37 %–63 %) in children 4–59 months of age. Two-dose VE was 62 % (9 %–84 %) in infants 4–11 months of age and -69 % (-401 %–43 %) in children 12–59 months of age ($P = 0.20$). VE against strains partially-heterotypic to the vaccine strain (including G3P[8], the most common circulating genotype) was 59 % (1 %–83 %).

Conclusions: Routine Rotarix vaccination was effective in preventing hospital visits for rotavirus diarrhea among Ugandan infants, although protection was not sustained after the first year of life. Protection was demonstrated against partially heterotypic rotavirus strains. These results support the continued use of rotavirus vaccines in Uganda. Additional studies are needed to understand the lower rotavirus VE seen in Uganda and other high-mortality settings.

Keywords

Diarrhea; Rotavirus; Vaccine effectiveness; Uganda

1. Introduction

Following World Health Organization (WHO) recommendations for global inclusion of rotavirus vaccines in routine immunization programs in 2009, [1] implementation of rotavirus vaccination has led to significant declines in the burden of severe diarrhea among young children in countries that have adopted these vaccines, including in Africa, [2] where a high burden of severe disease and mortality from rotavirus is concentrated. [3] Yet, both clinical trials and post-licensure evaluations have demonstrated regional variation in the performance of rotavirus vaccines, with lower vaccine efficacy and effectiveness noted in resource-limited settings of Africa and Asia (58 %–66 %), compared to that reported in high-income countries in the Americas and Europe (84 %–86 %). [4–7] The reasons for the observed disparities are not well understood and may be multifactorial. Concomitant administration of oral polio vaccines, malnutrition, interference of maternal antibodies, genetic factors, gut dysbiosis, and waning protection beyond infancy have all been purported to affect vaccine performance. Thus, measuring the effectiveness of rotavirus vaccines in settings where the burden of disease is high is important. First to demonstrate that the vaccines are working locally and help ensure continued support of national rotavirus vaccine programs. And second, because understanding the reasons for their lower performance can

inform vaccine strategies to optimize their impact; these reasons may vary from setting to setting, and some reasons may be more apparent in certain settings compared to others.

Uganda introduced a 2-dose live attenuated monovalent oral rotavirus vaccine (Rotarix, GlaxoSmithKline Biologics) into its national immunization program 26 June 2018, [8] with the first and second doses recommended at six and ten weeks of age, respectively. Vaccine uptake was fast, with 2-dose Rotarix coverage reaching 87 % by 2019. [9] We assessed the effectiveness of Rotarix against rotavirus-associated emergency department visits and hospitalization among Ugandan children aged 4–59 months under conditions of routine use.

2. Materials and methods

Data for these analyses were obtained from the ongoing WHO-coordinated Global Rotavirus Surveillance Network, a diarrhea surveillance platform that enrolls children <5 years of age using a standardized protocol. [10–12] In Uganda, surveillance is ongoing at three hospitals located in the capital city of Kampala: Mulago National Referral Hospital (initiated surveillance June 2006), Uganda Martyrs' Hospital Lubaga (initiated surveillance May 2016), and Naguru General Hospital (initiated surveillance May 2016). Children aged <5 years who underwent treatment for diarrhea in the pediatric emergency departments and wards at these hospitals are enrolled in the surveillance.

For the present evaluation we included children with acute watery diarrhea who were eligible to have received Rotarix (i.e., who were born on or after 15 May 2018 [or less than 6 weeks before vaccine introduction]) and who were at least 4 months of age at presentation (to allow sufficient time for children to receive a complete series of Rotarix). Surveillance data collected through 31 December 2022 were used. We defined acute watery diarrhea as ≥ 3 non-bloody loose or watery stools in a 24-h period lasting no more than 14 days before presentation. Stool specimens were collected within 48 h of admission and stored at 2–8 °C at each of the hospitals prior to transport to the Mulago Hospital Microbiology Laboratory, where enzyme immunoassay (EIA; ProSpecT Rotavirus Kit, Oxoid Ltd., United Kingdom) testing was performed. Specimens were then stored frozen at –20 °C in the Mulago Hospital Microbiology Laboratory. Specimens that tested positive for rotavirus by EIA and 20 % of negative samples were sent in batches to WHO's rotavirus regional reference laboratory (Sefako Makgatho Health Sciences University, The Diarrheal Pathogens Unit (DPRU), Medical Research Council, South Africa) for VP7 (G) and VP4 (P) rotavirus genotyping and quality control. Genotyping was done using reverse transcription-polymerase chain reaction (RT-PCR), as previously described. [13]

Demographic, socioeconomic, clinical, and anthropometric information were obtained through interview of parents or caregivers, physical examination, and review of medical records. We reviewed vaccination cards to record the vaccination status of the children, including dates of vaccination, and a photocopy of each child's card was obtained. Children lacking written documentation of vaccination, without EIA testing results (e.g., due to insufficient or no stool collected, or no test done), or who had stool collected >48 h after presentation were excluded.

We used a test-negative case-control study design to measure rotavirus vaccine effectiveness (VE). Cases and controls were children with acute watery diarrhea whose stool tested positive and negative for rotavirus, respectively. We calculated the odds ratio (OR) (and 95 % confidence intervals [CI]) for rotavirus vaccination among cases versus controls using unconditional logistic regression. A dose of Rotarix was counted if the dose was administered more than 14 days prior to diarrhea onset. The effectiveness of Rotarix against rotavirus associated hospitalization or emergency department visit was calculated as $(1-OR) \times 100\%$. To control for differences in age and geographic location between cases and controls, and for potential confounding due to variation in coverage since Rotarix introduction, a priori, regression models were adjusted for age in months, hospital site, and a variable for each month-year of birth. In addition, we conducted bivariate analyses to compare various demographic and socioeconomic characteristic among cases and controls. We used χ^2 tests to compare categorical variables and Wilcoxon rank sum tests to compare continuous variables, and identified sociodemographic and clinical characteristics that were different among cases and controls based on a P -value <0.2 . We included these variables (specifically, maternal education, the number of persons in the home, electricity in the home, and car ownership) as potential confounders in regression models and used hierarchical backward elimination to explore their impact on the VE results (using a significance level of 0.05 for an effect to stay in the model). Because inclusion of these variables did not induce a relative change in the 2-dose VE estimates by $>10\%$ from the a priori overall and age stratified models, here we present results from the a priori model only.

Subgroup analyses were performed to calculate VE based on age-group to assess for duration of protection (4–11 months, 12–23 months; an interaction term was included between age-group and vaccine receipt to assess this difference), disease severity (severe, very severe), undernutrition (no undernutrition, moderate or severe undernutrition), and genotypes (partially-heterotypic strains, fully-heterotypic strains). We categorized disease severity based on the 20-point clinical Vesikari scale, with a score of ≥ 11 and ≥ 15 classified as severe and very severe, respectively. Using WHO growth standards, children with a weight-for-age z score value of < -2.0 and < -3.0 were considered to be moderately and severely underweight, respectively (data for the height of enrolled children were limited, so additional parameters of undernutrition, namely height-for-age and weight-for-height, were not assessed).

Analyses were done using SAS software, version 9.4 (SAS Institute Inc). A P -value <0.05 was considered significant. This evaluation was determined to be public health non research by the US Centers for Disease Control and Prevention and was reviewed and granted exception by WHO Ethical Review Committee evaluation as part of the routine hospital-based diarrhea surveillance.

3. Results

A total of 1627 children aged ≥ 4 months met the inclusion criteria for acute watery diarrhea and were of eligible age for vaccination. Of these, a total of 818 (50 %) were excluded from the VE analyses; 30 (2 %) because stool was collected >48 h after presentation, 11 ($<1\%$) because EIA testing results were unavailable, and an additional 777 (48 %)

because documentation of rotavirus vaccination was unobtainable (Fig. 1). Demographic characteristics of children who were excluded did not differ from those included in the analyses (Table 1). However, some of the socioeconomic factors were statistically significantly different. Compared to children who were excluded, children who were included had mothers that had attained more years of education, and a higher proportion had a car, a mobile telephone, and a computer in their homes. In addition, better capture of vaccine cards was evident in Lubaga and Mulago hospitals (57 % at both sites) compared to Naguru hospital (32 %). Card ascertainment did not differ significantly by case/control status; vaccine cards could be reviewed for 187 (47 %) of 397 cases and 622 (52 %) of 1189 controls ($P=0.07$ by χ^2 test).

The final analyses included 809 children: 187 cases and 622 controls. Most children were hospitalized (791 or 98 %); the remaining 17 were treated in the emergency department (one patient's treatment location was missing). The largest number of children were enrolled in Lubaga hospital (397 or 49 %) (Table 2).

Compared to controls, cases were slightly older (median age of 11 months, range 4–39 months [cases] vs 9 months, range 4–48 months [controls]) and were less likely to live in a household that had electricity (89 % [cases] vs 94 % [controls]) or owned a car (12 % [cases] vs 20 % [controls]). Other clinical and sociodemographic characteristics were not significantly different among cases and controls.

The adjusted effectiveness of 2 vs 0 doses of Rotarix against rotavirus diarrhea hospitalization across all age-groups was 29 % (95 % CI: –37 %–63 %) (Table 3). Among infants aged 4–11 months and children aged 12–23 months, full-series VE was 62 % (95 % CI: 9 %–84 %) and –61 % (95 % CI: –392 %–47 %), respectively ($P=0.25$). Receipt of 1 dose of Rotarix was not protective against rotavirus diarrhea hospitalization in any of the age-groups examined.

One and 2-dose VE point estimates were non-significant in the subgroup analyses comparing children with normal weight-for-age versus moderately or severely underweight children, and children with severe versus very severe rotavirus disease, and confidence intervals overlapped between groups.

Genotyping was completed for 83 cases (genotyping results for the remainder of positive specimens are pending); 34 (41 %) were partly-heterotypic to the vaccine, 27 (33 %) were fully-heterotypic, three (4 %) were fully homotypic (G1P[8]), and 11 (13 %) were of mixed G or P types. Seven cases had a P type but an untypeable G type, and for one case both the G and P types were unable to be typed. The most commonly detected strain was G3P[8], found in 28 (34 %) of genotyped cases. Two-dose VE was 72 % (95 % CI: 24 %–90 %) against G3P[8], 59 % (95 % CI: 1 %–83 %) against all partially-heterotypic strains, and –53 % (95 % CI: –605 %–67 %) against all fully-heterotypic strains.

Among infants aged 4–11 months and children aged 12–59 months, full-series VE against partially-heterotypic strains was 70 % (95 % CI: 2 %–90 %) and 41 % (95 % CI: –138 %–85 %), and against fully-heterotypic strains –17 % (95 % CI: –915 %–87 %) and –201 % (95 % CI: –2714 %–68 %), respectively (Table S1).

4. Discussion

Using an established hospital-based gastroenteritis surveillance platform in Kampala, we measured the effectiveness of Rotarix against rotavirus-associated emergency department visits and hospitalization among Ugandan children during the first four years following vaccine introduction. Our 2-dose VE point estimate of 62 % in children <12 months of age is similar to the VE estimated among infants in other high-child-mortality settings mostly in Africa, 63 % (95 % CI 54 %–70 %). [4] Because rotavirus mortality peaks around 6–10 months of age, [14] our data showing that the vaccine is effective against severe disease during the first year of life is reassuring. Furthermore, although the estimated effectiveness of Rotarix in Uganda and other African countries is lower compared to that seen in the same age-group in low-mortality countries (86 % [95 % CI 81 %–90 %]), [4] the large baseline burden of diarrheal illnesses in Uganda could mean a substantial number of episodes of rotavirus gastroenteritis are being prevented by the vaccine. Continued surveillance post-vaccine introduction will be needed to evaluate the direct impact of Rotarix on the absolute number of rotavirus diarrhea hospitalizations in Uganda. One dose of Rotarix was shown not to be protective among Ugandan infants, underscoring the importance of strategies to ensure the return of children for completion of a full series of rotavirus vaccination.

We observed a sizable reduction in the effectiveness of Rotarix in the second compared to the first year of life in Uganda, although this difference was not statistically significant. Declines in the efficacy and effectiveness of the vaccine after infancy have been reported previously, primarily in high-child-mortality settings. [4,15] Although our findings could be due to waning immunity, our sample size for children older than 1 year of age was small, and the lack of effectiveness and wide confidence intervals shown could be the result of low power, so cautious interpretation is warranted. Further, the effectiveness demonstrated during the first year of life in Uganda was still lower compared to that seen in high-income settings, so waning immunity would not be the only explanation for the overall lower effectiveness of Rotarix in Uganda. Because reductions in Rotarix effectiveness during the second year life have been noted in some (Zimbabwe, Ghana, Malawi, Mozambique), but not all (Botswana, South Africa, Tanzania, Kenya) African countries, [4,16–18] more studies are needed to better understand waning of rotavirus vaccine-induced immunity in high-mortality settings. [19] Pooling of VE data from across the region to increase sample sizes could prove useful in evaluating protection at more granular time intervals since vaccination, and to examine the potential impact waning protection might have on VE, including within the first year of life. [20]

Rotarix has been shown to be cross-protective against a range of circulating rotavirus strains, [21] although slightly lower VE estimates have been noted against nonvaccine strains compared to vaccine strains; [22] these data stem mostly from middle- and high-income countries, so additional data are needed from low-income settings. We show that in Uganda Rotarix was effective against strains that were partly-heterotypic to the G1P[8] strain contained in the vaccine, and demonstrate strain-specific protection against the partially-heterotypic G3P [8], a strain that had not been previously documented to circulate in Uganda. [23] Because we found the vaccine to be effective in a narrow age-group of infants 4–11 months old, and not among older children, we were interested in disentangling the

effects of age and strain on VE, but this was not possible due to the small sample size. However, we were able to show that Rotarix was protective against G3P[8] and all partly-heterotypic strains during the first year of life. Both clinical trials and observational studies have previously shown Rotarix to be effective against G3P[8] and other partially-heterotypic strains, [24–27] but larger datasets are needed to fully evaluate whether the magnitude and duration of Rotarix protection might differ by strain. Data on any potential age differences in strain-specific effectiveness would be important in evaluating rotavirus vaccination programs as these programs mature and the burden of disease shifts to older age-groups. [25] Such data would also be key in elucidating the epitopes in vaccine strains that confer protection, as well as the pressure vaccines might exert on the genotypic diversity of rotaviruses and the emergence of novel strains. [21,25,27–29]

Prior VE analyses suggest somewhat improved protection of Rotarix against increased rotavirus illness severity, [17] and that undernutrition could be a factor influencing the decreased effectiveness of oral rotavirus vaccines in high-child-mortality settings. [30] Our analyses of the effectiveness of Rotarix by disease severity and malnutrition were limited by small sample sizes, so none of these estimates were significant, and confidence bounds were wide and overlapped. Because most rotavirus VE studies are hospital-based, they are likely capturing a higher end of the rotavirus disease severity spectrum, making analyses assessing effectiveness against disease severity challenging.

Several limitations should be considered. The main limitation of this analysis was the exclusion of close to half of the children who met the clinical case definition and who were of eligible age to receive rotavirus vaccine because of lack of adequate documentation of vaccination available at the time of the interview. Efforts to have caregivers bring the vaccination cards to the hospital while the child was admitted or at a later time were of limited success. Use of only card-confirmed vaccination status avoids any potential misclassification from verbal reports of vaccination, although if there were differences in card ascertainment between cases and controls, or in vaccination rates among included and excluded children, our VE estimates could be biased. Yet, card ascertainment was conducted without knowledge of case/control status, and the proportion of cases and controls for whom vaccine cards could be reviewed did not differ considerably. Our comparison of demographic and economic characteristics between excluded and non-excluded children revealed these indicators to be mostly similar, so one might expect vaccination rates to be similar among the groups. However, a few of the socioeconomic parameters differed statistically between the groups and might point to higher levels of card retention among households with higher levels of education and income. Relatedly, vaccine confirmation was poorest at Naguru hospital, which might be explained by differences in the populations served by the surveillance sites. Because a large proportion of enrolled children were excluded due to lack of documented vaccination available at the time of the interview, the results of this study might be representative only of Ugandan children with vaccine cards. More studies that investigate the potential impact of low card ascertainment on VE estimates are needed. Similarly, only a subset of our cases had genotype results available, so our analyses of genotype-specific effectiveness was limited to the most common genotype (G3P[8]), although we were able to demonstrate Rotarix was effective against G3P[8] and against all partially-heterotypic strains. The incomplete confirmation of vaccination status

and genotype data limited our sample size, the precision of our effectiveness estimates, and the power of our study to assess secondary endpoints. Part of the study was conducted during the COVID-19 pandemic, during which the overall burden of rotavirus might have decreased. However, both cases and controls were enrolled after seeking medical care for a diarrheal illness, so differences in their chance of being exposed to rotavirus were not expected, nor a differential impact on their odds of vaccination. Finally, the recruiting hospitals were in the capital city, which limits the generalizability of our findings, including to other settings within Uganda.

5. Conclusions

In summary, a complete series of Rotarix prevented severe rotavirus diarrhea among Ugandan infants aged 4–11 months, the age-group in which the largest burden of severe disease is focused, providing firm evidence for continued support of the rotavirus vaccination program in Uganda. Protection was also demonstrated against partially-heterotypic rotavirus strains, including against the most common genotype, G3P[8]. Rotarix effectiveness appeared to decline among children aged 12 months and older. The factors influencing the lower effectiveness of rotavirus vaccines in low-income settings are poorly understood, as is the durability of protection conferred by rotavirus vaccines in these settings, and whether the initial take of the vaccine and subsequent duration of protection differs by strains. Further studies directly evaluating these issues are needed to inform strategies to improve rotavirus vaccine performance in resource limited settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The authors do not have permission to share data.

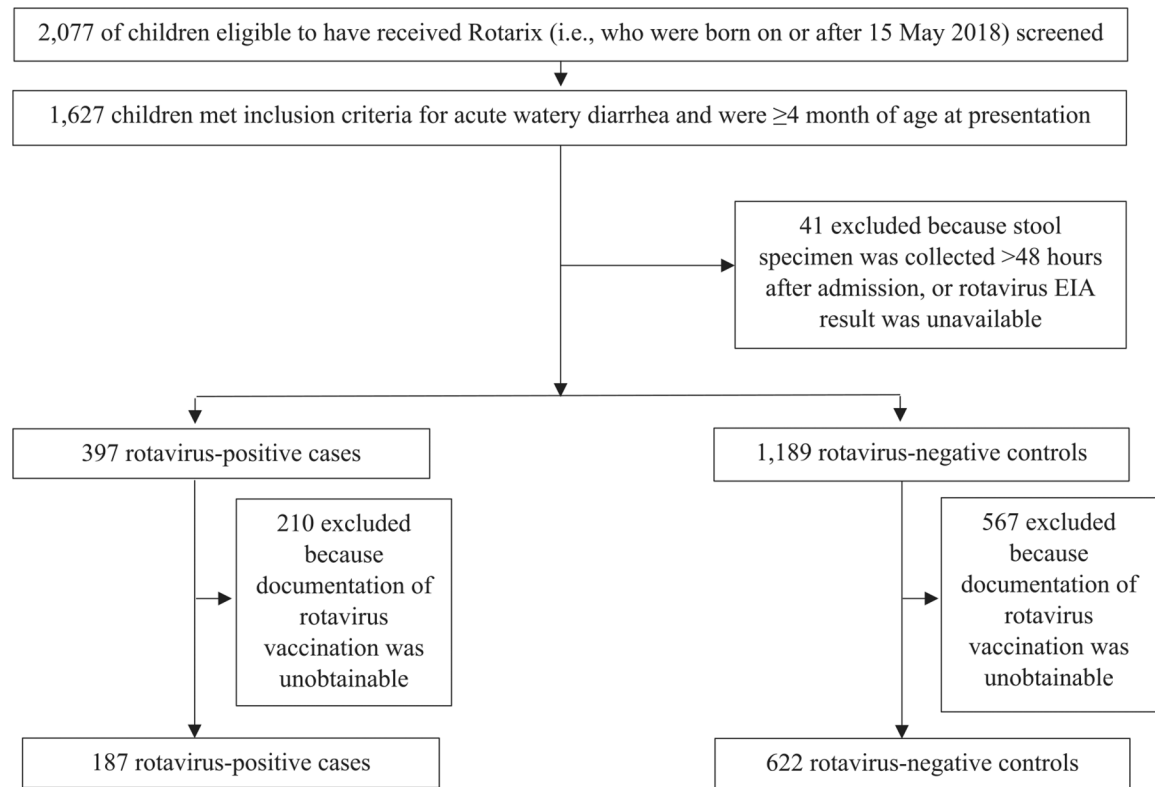
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**Fig. 1.**

Flow chart depicting enrollment of children aged 4 to 59 months evaluated for acute watery diarrhea at three hospitals in Kampala, Uganda, October 2018–December 2022.

Table 1

Comparison of Characteristics of Eligible Children with Acute Watery Diarrhea who were Included and Excluded from the Vaccine Effectiveness Analyses, Uganda, October 2018–December 2022.

Characteristic ^a	Children Included ^b (N = 809)	Children Excluded ^b (N = 818)	P-value ^c
Location			
Lubaga hospital	397 (49)	306 (37)	<0.001
Mulago hospital	279 (34)	210 (26)	
Naguru hospital	133 (16)	302 (37)	
Age, months	10 (7–14)	10 (7–15)	0.09
Age categories			
4–5 months	92 (11)	96 (12)	0.12
6–11 months	419 (52)	383 (47)	
12–23 months	255 (32)	282 (34)	
≥24 months	43 (5)	57 (7)	
Male sex	481/808 (60)	490/817 (60)	0.85
Chronic medical condition	25/788 (3)	17/793 (2)	0.20
Moderately or severely underweight^d	170/748 (23)	170/750 (23)	0.98
Maternal education			
None	18/807 (2)	27/815 (3)	0.003
Primary school	182/807 (23)	211/815 (26)	
Secondary school	398/807 (49)	407/815 (50)	
Post-secondary	144/807 (18)	127/815 (16)	
University or above	65/807 (8)	43/815 (5)	
No. of children (<5 years) in home	2 (1–2)	2 (1–2)	0.94
No. of persons in home	4 (3–5)	4 (3–6)	0.37
Socioeconomic parameters			
Electricity in home	752/808 (93)	747/815 (92)	0.28
Ownership of a car	145/806 (18)	116/815 (14)	0.04
Mobile in home	779/808 (96)	759/816 (93)	0.002
Computer in home	165/805 (21)	107/812 (13)	<0.001

^aData are median (IQR), n (%), or n/N (%).

^bMissing values were excluded in bivariate analyses and new denominators are provided for each categorical variable with missing values; comparisons of the number of children in the home were based on 808 included children and 817 excluded children, and comparisons of the number of persons in the home were based on 808 included children and 815 excluded children.

^cDifferences in continuous variables were assessed with the Wilcoxon rank-sum test; differences in categorical variables were assessed with Mantel-Haenszel χ^2 tests.

^dBased on anthropometry done during admission or enrollment; being moderately or severely underweight was defined as a weight-for-age z score < -2 based on WHO growth standards. Comparison includes patients aged <2 years only, and excludes extreme values thought to be biologically implausible (z scores below -6 or above +6).

Table 2

Comparison of Characteristics of Rotavirus-Positive Cases and Rotavirus-Negative Diarrhea Controls, Uganda, October 2018–December 2022.

Characteristic ^a	Rotavirus-Positive Cases ^b (N = 187)	Rotavirus-Negative Controls ^b (N = 622)	P-value ^c
Location			
Lubaga hospital	84 (45)	313 (50)	0.11
Mulago hospital	66 (35)	213 (34)	
Naguru hospital	37 (20)	96 (15)	
Age, months	11 (8–14)	9 (7–13)	<0.001
Age categories			
4–5 months	8 (4)	84 (14)	0.002
6–11 months	98 (52)	321 (52)	
12–23 months	69 (37)	186 (30)	
≥24 months	12 (6)	31 (5)	
Male sex	110 (60)	371/621 (60)	0.82
Chronic medical condition	8/182 (4)	17/606 (3)	0.28
Moderately or severely underweight^d	45/174 (26)	125/574 (22)	0.26
Maternal education			
None	4/187 (2)	14/620 (2)	0.20
Primary school	45/187 (24)	137/620 (22)	
Secondary school	98/187 (52)	300/620 (48)	
Post-secondary	28/187 (15)	116/620 (19)	
University or above	12/187 (6)	53/620 (9)	
No. of children (<5 years) in home	2 (1–2)	2 (1–2)	0.49
No. of persons in home	4 (3–5)	4 (3–6)	0.06
Socioeconomic parameters			
Electricity in home	167 (89)	585/621 (94)	0.02
Ownership of a car	22/185 (12)	123/621 (20)	0.01
Mobile in home	179/186 (96)	600 (96)	0.88
Computer in home	36/186 (19)	129/619 (21)	0.66

^aData are median (IQR), n (%), or n/N (%).

^bMissing values were excluded in bivariate analyses and new denominators are provided for each categorical variable with missing values; comparisons of the number of children in the home and of the number of persons in the home were based on 187 cases and 621 controls.

^cDifferences in continuous variables were assessed with the Wilcoxon rank-sum test; differences in categorical variables were assessed with Mantel-Haenszel χ^2 tests.

^dBased on anthropometry done during admission or enrollment; being moderately or severely underweight was defined as a weight-for-age z score < -2 based on WHO growth standards. Comparison includes patients aged <2 years only, and excludes extreme values thought to be biologically implausible (z scores below -6 or above +6).

Table 3

Effectiveness of Rotavirus Vaccine Against Emergency Department Visits and Hospitalizations for Rotavirus-Related Diarrhea, Stratified by Age Group, Undernutrition, Clinical Severity, and Strains, Uganda, October 2018–December 2022.

No. of doses of rotavirus vaccine ^a	Rotavirus-Positive Cases ^b	Rotavirus-Negative Controls ^b	Crude VE, % (95 % CI)	Adjusted VE, % (95 % CI) ^c
Age 4–59 Months	n = 187	n = 622		
0 doses	14 (7)	43 (7)	ref	ref
1 dose	32 (17)	81 (13)	–21 (–152, 42)	–8 (–128, 49)
2 doses	141 (75)	498 (80)	13 (–64, 54)	29 (–37, 63)
Age 4–11 Months	n = 106	n = 405		
0 doses	9 (8)	24 (6)	ref	ref
1 dose	24 (23)	59 (15)	–9 (–167, 56)	11 (–129, 66)
2 doses	73 (69)	322 (80)	40 (–36, 73)	62 (9, 84)
Age 12–23 Months	n = 69	n = 186		
0 doses	5 (7)	17 (9)	ref	ref
1 dose	7 (10)	20 (11)	–19 (–344, 68)	–13 (–340, 71)
2 doses	57 (83)	149 (80)	–30 (–269, 54)	–61 (–392, 47)
Age 12–59 Months	n = 81	n = 217		
0 doses	5 (6)	19 (9)	ref	ref
1 dose	8 (10)	22 (10)	–38 (–394, 61)	–32 (–389, 64)
2 doses	68 (84)	176 (81)	–47 (–309, 47)	–69 (–401, 43)
Normal weight-for-age^d	n = 129	n = 449		
0 doses	11 (9)	30 (7)	ref	ref
1 dose	18 (14)	51 (11)	4 (–131, 60)	12 (–118, 64)
2 doses	100 (78)	368 (82)	26 (–53, 64)	45 (–20, 74)
Moderately or severely underweight^d	n = 45	n = 125		
0 doses	3 (7)	8 (6)	ref	ref
1 dose	13 (29)	23 (18)	–51 (–570, 66)	–53 (–596, 66)
2 doses	29 (64)	94 (75)	18 (–231, 80)	16 (–250, 80)
Severe rotavirus^e	n = 139	n = 622		
0 doses	10 (7)	43 (7)	ref	ref
1 dose	21 (15)	81 (13)	–12 (–158, 52)	–1 (–138, 57)
2 doses	108 (78)	498 (80)	7 (–91, 55)	28 (–52, 66)
Very severe rotavirus^e	n = 56	n = 622		
0 doses	3 (5)	43 (7)	ref	ref
1 dose	7 (13)	81 (13)	–24 (–403, 70)	–13 (–368, 73)
2 doses	46 (82)	498 (80)	–32 (–343, 61)	–3 (–256, 70)
G3P[8]	n = 2	n = 622		
0 doses	7 (25)	43 (7)	ref	ref
1 dose	5 (18)	81 (13)	62 (–27, 89)	56 (–49, 87)
2 doses	16 (57)	498 (80)	80 (49, 92)	72 (24, 90)

No. of doses of rotavirus vaccine ^a	Rotavirus-Positive Cases ^b	Rotavirus-Negative Controls ^b	Crude VE, % (95 % CI)	Adjusted VE, % (95 % CI) ^c
Partially-heterotypic genotypes^f	n = 43	n = 622		
0 doses	9 (21)	43 (7)	ref	ref
1 dose	8 (19)	81 (13)	53 (-31, 83)	42 (-64, 80)
2 doses	26 (60)	498 (80)	75 (43, 89)	59 (1, 83)
Fully-heterotypic genotypes^g	n = 28	n = 622		
0 doses	2 (7)	43 (7)	ref	ref
1 dose	4 (14)	81 (13)	-6 (-503, 81)	-33 (-672, 77)
2 doses	22 (79)	498 (80)	5 (-318, 78)	-53 (-605, 67)

Abbreviations: No., number; VE, vaccine effectiveness; CI; confidence interval.

^aProtection conferred 14 days after vaccine receipt.

^bData are n (%).

^cAdjusted for age at admission, month-year of birth, and hospital.

^dBased on anthropometry done during admission or enrollment; normal weight-for-age was defined as a weight-for-age z score ≥ -2 and being moderately or severely underweight was defined as a weight-for-age z score < -2 , based on WHO growth standards. These analyses include patients aged <2 years only, and excludes extreme values thought to be biologically implausible (z scores below -6 or above $+6$).

^eBased on the 20-point clinical Vesikari scale, with a score of ≥ 11 classified as severe, and a score of ≥ 15 as very severe.

^fPartially-heterotypic strains included the following: G3P[8], G12P[8], G1P [6], G9P[8], and mixed genotypes G2G3P[4]P[8], G3G12P[8], G3G8P[8], G9G12P[8]; 2-dose VE against partially-heterotypic strains excluding mixed strains was estimated as 67 % (95 % CI: 15 %–87 %).

^gFully-heterotypic strains included the following: G2P[4], G3P[4], G3P[6], G8P[4], G9P[4], G9P[6], and mixed genotype G3G12P[6]; 2-dose VE against fully-heterotypic strains excluding mixed strains was estimated as -59 % (95 % CI: -632 %–66 %).