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Monovalent Rotavirus Vaccine Effectiveness Against Rotavirus Hospitalizations Among Children in Zimbabwe

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Abstract

Background.—Rotavirus is a leading cause of mortality among children <5 years old. We evaluated monovalent rotavirus vaccine effectiveness (VE) under conditions of routine use at 2 surveillance sites in Harare, Zimbabwe, after vaccine introduction in May 2014.

Methods.—Children aged <5 years hospitalized or treated in the accident and emergency department (A&E) for acute watery diarrhea were enrolled for routine surveillance. Copies of vaccination cards were collected to document vaccination status. Among children age-eligible to receive rotavirus vaccine, we estimated VE, calculated as 1 – odds ratio, using a test-negative case-control design

Results.—We included 903 rotavirus-positive cases and 2685 rotavirus-negative controls in the analysis; 99% had verified vaccination status. Rotavirus-positive children had more severe

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diarrhea than rotavirus-negative children; 61% of cases and 46% of controls had a Vesikari score ≥11 ($P < .01$). Among cases and controls, 31% and 37%, respectively, were stunted for their age ($P < .01$). Among children 6–11 months old, adjusted 2-dose VE against hospitalization or treatment in A&E due to rotavirus of any severity was 61% (95% confidence interval [CI], 21%–81%) and 68% (95% CI, 13%–88%) against severe rotavirus disease. Stratified by nutritional status, adjusted VE was 45% (95% CI, –148% to 88%) among stunted infants and 71% (95% CI, 29%–88%) among infants with a normal height for age

Conclusions.—Monovalent rotavirus vaccine is effective in preventing hospitalizations due to severe rotavirus diarrhea among infants in Zimbabwe, providing additional evidence for countries considering rotavirus vaccine introduction that live, oral rotavirus vaccines are effective in high-child-mortality settings.

Keywords

rotavirus; rotavirus vaccine; Zimbabwe

Diarrhea is a leading cause of mortality among children <5 years of age, accounting for about 480 000 deaths worldwide in 2016 [1]. Some of the recent progress in reducing the burden of diarrhea morbidity and mortality can be attributed to simple interventions including use of oral rehydration solution, use of zinc, breastfeeding and adequate complementary feeds, and improvement in water and sanitation [1]. In addition to these interventions, rotavirus vaccines have been an important strategy in controlling diarrhea worldwide since their licensure in 2006. In sub-Saharan Africa, nearly 40% of diarrhea hospitalizations among children <5 years of age were due to rotavirus in 2013 and continent-wide adoption of rotavirus vaccine would result in an estimated 48 000 (interquartile range, 42 822 52 462) fewer deaths annually [2, 3].

Since 2009, the World Health Organization (WHO) has recommended that all countries introduce rotavirus vaccine into their national immunization programs to further reduce the burden of diarrheal disease [4]. Zimbabwe introduced a 2-dose live, oral, monovalent rotavirus vaccine (Rotarix) nationally in May 2014 as part of the routine infant immunization program and recommended the vaccine be administered at 6 and 10 weeks of age with oral polio vaccine, pentavalent vaccine (diphtheria-tetanus-pertussis, hepatitis B, and Haemophilus influenza), and pneumococcal conjugate vaccine. High vaccination coverage was achieved shortly after introduction; in 2016, rotavirus vaccination coverage was estimated to be 91% among children <12 months old [5]. In the second year after rotavirus vaccine introduction, there was a 43% reduction in rotavirus hospitalizations among children 0–11 months of age and a 33% reduction among children 12–23 months of age [6]. Deaths due to rotavirus diarrhea were estimated to decrease by nearly 500, or 37%, per year in Zimbabwe with the introduction of rotavirus vaccine [2]. Other African countries that introduced monovalent rotavirus vaccine in their routine immunization programs have also reported significant reductions in rotavirus-related diarrhea, though the vaccine efficacy in clinical trials and effectiveness in postlicensure evaluations has been lower in developing than in developed countries [2, 7, 8]. In postlicensure vaccine effectiveness (VE) evaluations in other southern African countries, the full-series VE of Rotarix against hospitalizations was estimated to be 64% in Malawi, 54% in Botswana, and 56% in Zambia [9–11].

To evaluate the performance of monovalent rotavirus vaccine under conditions of routine use in Zimbabwe, we conducted a case-control evaluation of rotavirus VE in children with acute diarrhea at 2 surveillance sites in Harare, Zimbabwe.

METHODS

Surveillance Methods

The active surveillance methods for acute watery diarrhea in Zimbabwe have previously been described in detail [6]. In brief, children <5 years of age hospitalized or treated in the accident and emergency department (A&E) for acute watery diarrhea were enrolled for routine surveillance at 3 sentinel hospitals (Harare Central Hospital, Parirenyatwa Group Hospital, and Chitungwiza Central Hospital) during 2012–2017. Acute watery diarrhea was defined as ≥3 loose stools within 24 hours lasting no more than 7 days. Stool specimens were collected from eligible children within 48 hours of admission and tested by enzyme immunoassay at the Zimbabwe National Virology Laboratory. Through a structured interview, caregivers of enrolled children verbally provided illness history and sociodemographic characteristics. Following rotavirus vaccine introduction in May 2014, copies of vaccination cards were collected and reviewed to document the vaccination status of enrolled children.

Analytic Methods

We estimated rotavirus VE using a test-negative case-control design with rotavirus-positive cases and rotavirus-negative controls identified through the surveillance platform. Children born on or after 1 March 2014 and who were at least 6 months of age at the time of the hospitalization were included in the analysis. If a dose of rotavirus vaccine was administered at least 2 weeks before the onset of any symptoms, the child was considered vaccinated. We excluded children who were reported vaccinated against rotavirus but for whom documented vaccination dates were not available. Cases and controls enrolled at Harare Central and Parirenyatwa Hospitals only were included in the VE analysis. Children from Chitungwiza Hospital were excluded due to irregularities in vaccination histories.

We used an unconditional logistic regression model to estimate VE and 95% confidence interval (CI) of 2 doses of rotavirus vaccine against hospitalization or A&E admission due to rotavirus diarrhea among children 6–11 months of age and ≥12 months of age, controlling for age in months and the hospital where the child was enrolled. We calculated VE as (1 – odds ratio for rotavirus vaccine receipt among cases and controls) × 100% by classifying children who tested positive for rotavirus as cases and children who tested negative for rotavirus as controls. Sample size was calculated to achieve 80% power at the 5% significance level with a VE of at least 40% and 80% rotavirus vaccination coverage. We estimated that 242 rotavirus-positive cases <12 months of age with 2:1 ratio of controls to cases would be needed for this case-control VE evaluation. Due to the small number of incompletely vaccinated children, we were unable to accurately estimate the VE of a single dose of rotavirus vaccine in this population. However, we calculated VE for receipt of at least 1 dose of rotavirus vaccine. As a secondary analysis, we estimated 2-dose and any-dose VE against hospitalization or A&E admission for severe diarrhea, defined as

a modified Vesikari score ≥11 [12]. We also estimated 2-dose and any-dose VE against hospitalization or A&E admission among stunted children and nonstunted children. For the adjusted models, a forward selection strategy was implemented to determine potential confounders; any variable that changed the primary analysis VE by >10% was considered to be a confounder. Nutritional status was calculated using the WHO Anthro macro for SAS. Stunting, an indicator of chronic malnutrition, was defined as >2 standard deviations below the median height for age [13]. We created an indicator variable for month of birth; children born in May through October, months with historically high rotavirus disease in Zimbabwe, were considered born during the rotavirus season and those born in November through April were considered born outside the rotavirus season. We performed all analyses using SAS version 9.4 software and created the cumulative vaccination coverage curves using R version 3.4.3 software.

This evaluation was reviewed and approved by the by the Ministry of Health and Child Care of Zimbabwe and exempted by the Medical Research Council of Zimbabwe. It was determined to be public health nonresearch by the US Centers for Disease Control and Prevention and granted exception by the WHO ethical review committee.

RESULTS

Of the 4338 children who were age eligible to receive rotavirus vaccine (ie, born between 1 March 2014 and 31 December 2017), 3643 met the inclusion criteria for this analysis (Figure 1). Of the eligible children, 99% had verified vaccination status; there was no difference in the percentage of children with and without verified vaccination status by age group or rotavirus positivity. We included 903 rotavirus-positive cases and 2685 rotavirus-negative controls in this analysis.

Characteristics of the children included in the cohort are shown in Table 1. Among children >6 months old included in the analysis, the median age for cases and controls was 12 months. The percentage of cases enrolled by year was 1% in 2014, 27% in 2015, 39% in 2016, and 33% in 2017; the percentage of controls admitted by year was 1% in 2014, 18% in 2015, 39% in 2016, and 41% in 2017 ($P < .01$). Rotavirus-positive children had more severe diarrhea than rotavirus-negative children; 61% of cases vs 46% of controls had a modified Vesikari score ≥11 ($P < .01$). However, the mortality rate was similar in both groups, with 0% and 1% cases and controls, respectively, who died during the hospitalization ($P = .37$). Among cases, 31% were stunted for their age; 37% of controls were stunted ($P < .01$).

In terms of socioeconomic factors, a higher proportion of cases had electricity (71% rotavirus positive; 64% rotavirus negative; $P < .01$) and a refrigerator (59% rotavirus positive; 53% rotavirus negative; $P < .01$) in their household compared to controls. Both groups of children were similar in terms of mother's age, maternal education, the number of people living in the home, owning a car in the household, and at least 1 member of the household owning a mobile phone.

Rotavirus vaccination coverage was very high and adherent to the recommended ages of administration for both doses (Figure 2). By 1 year of age, 96% of enrolled children had

received the first dose of rotavirus vaccine and 94% had received the second dose. The majority of children received the first and second doses within 1 month of the recommended ages of 6 and 10 weeks, respectively. There was no difference in full series vaccination coverage between cases and controls; 94% had completed the rotavirus vaccine series prior to their hospitalization.

Among children 6–11 months of age, VE against hospitalization or treatment in A&E due to rotavirus diarrhea of any severity was 61% (95% CI, 21%–81%) with 2 doses, adjusted for age in months, season of birth, year of admission, and if the child's household had electricity (Table 2). The adjusted VE against hospitalization or treatment in A&E due to severe rotavirus diarrhea was 68% (95% CI, 13%–88%) in this age group. Stratified by nutritional status, the adjusted VE was 45% (95% CI, –148% to 88%) among stunted infants and 71% (95% CI, 29%–88%) among infants with a normal height for age.

Among children ≥12 months of age, VE against hospitalization or treatment in A&E due to rotavirus diarrhea of any severity was –48% (95% CI, –148% to 11%) with 2 doses, adjusted for age in months, season of birth, year of admission, and if the child's household had electricity. The adjusted VE against hospitalization or treatment in A&E due to severe rotavirus diarrhea was –38% (95% CI, –164% to 28%) in this age group. Stratified by nutritional status, the adjusted VE was –67% (95% CI, –313% to 32%) among stunted children ≥12 months old and –35% (95% CI, –178% to 35%) among children ≥12 months old with a normal height for age.

VE with any dose was comparable to 2-dose VE in all analyses.

DISCUSSION

In this evaluation of real-world monovalent oral rotavirus vaccine performance in Zimbabwe, we found VE against severe rotavirus disease among infants to be 68%, with high adherence to the recommended ages of vaccination. This estimate is slightly higher than rotavirus VE findings from neighboring countries using a similar protocol and other countries with high child mortality [7, 9–11]. In both age groups, the VE against hospitalizations due to severe rotavirus diarrhea disease was higher than VE against hospitalizations for rotavirus diarrhea of any severity. This is consistent with previously published findings [7]. There were very few partially vaccinated children in this population; therefore, the VE point estimates for 2 doses and any number of doses were very similar in all analyses. However, the estimated 2-dose rotavirus vaccination coverage in this study population is comparable to administrative estimates of national rotavirus vaccination coverage in Zimbabwe [5]. The VE point estimates for stunted and nonstunted children suggest malnutrition may play a role in vaccine performance, but our sample size was inadequate to detect statistically significant differences.

The infant VE estimate corroborates previous findings showing significant reductions in rotavirus hospitalizations in Zimbabwe; however, the much lower and nonsignificant VE among older children is not in agreement with observed reductions in rotavirus hospitalizations among children 12–23 months old of 21%–33% and among children 24–

59 months old of 5%–22% [6]. However, because the VE estimates for children ≥12 months old lack precision, they are difficult to interpret. Previous studies have found that immunity from rotavirus vaccination may wane in the second year of life [7] and, given the differences between the VE point estimate and CIs between infants and children ≥12 months old, our findings suggest this may be a factor in Zimbabwe. A recent study found that naturally acquired immunity to rotavirus may somewhat reduce the calculated rotavirus VE in populations with high incidence of disease, especially in older age groups [14]. In this population, we do not know how many children may have naturally acquired immunity; however, because of the high vaccination coverage and small number of unvaccinated children ≥12 months old (n = 86 rotavirus negative; n = 19 rotavirus positive), our estimated VE is susceptible to even minor changes in the distribution of unvaccinated children. While our findings suggest rotavirus vaccine may be less effective in preventing hospitalizations after the first year of life in Zimbabwe, we are unable to draw conclusions about the exact magnitude of, or reasons for, any difference between the 2 age groups.

Nutritional status and interference by maternal antibodies have been proposed as factors contributing to lower rotavirus VE in high-child-mortality settings compared with low-child-mortality countries [7, 15]. In developing our adjusted model, we found season of birth, a proxy for maternal antibodies against rotavirus at birth, to be an important confounder of rotavirus VE in this population. In models stratified by nutritional status, rotavirus vaccine provided no protection against hospitalization for malnourished infants compared to nonmalnourished infants. Evaluations of VE in Botswana and Malawi have also shown that rotavirus vaccination did not protect against hospitalizations in undernourished children and stunted children, respectively [11, 16]. Further research is needed to determine the magnitude of the impact of nutrition and rotavirus maternal antibodies in Zimbabwe.

This analysis has limitations. Both sites in this analysis are located in Harare, an urban setting, and primarily serve children living in Harare. Our findings may not be representative of rural or diverse socioeconomic settings in Zimbabwe. Second, vaccinated children without vaccination cards were excluded and may be different in other ways when compared to children with documentation of vaccination. However, the number of children excluded due to lack of verified vaccination history was very small and did not differ by rotavirus testing status. Finally, this evaluation was not powered to detect a difference in VE between the stunted and nonstunted groups and we are limited in interpreting these findings.

The results from this analysis in Zimbabwe show that monovalent rotavirus vaccine is effective in preventing hospitalizations due to severe rotavirus diarrhea among infants. While our VE is slightly higher than other estimates from neighboring countries, the findings of this analysis are consistent with a large ecological reduction in all-cause and rotavirus hospitalizations that have been previously reported [6]. This evaluation provides additional evidence for countries considering rotavirus vaccine introduction that live, oral rotavirus vaccines are effective in settings of high child mortality.

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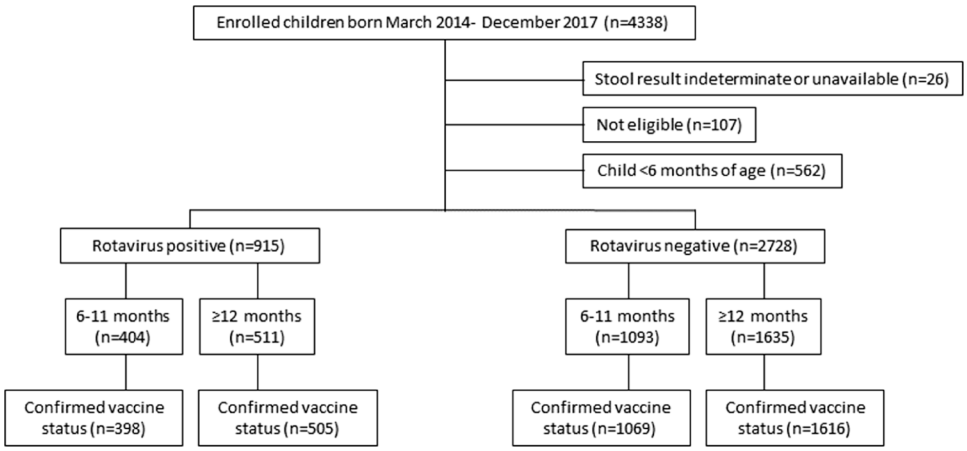

Figure 1.

Flowchart of enrolled children included in rotavirus vaccine effectiveness analysis, Zimbabwe, 2014–2017.

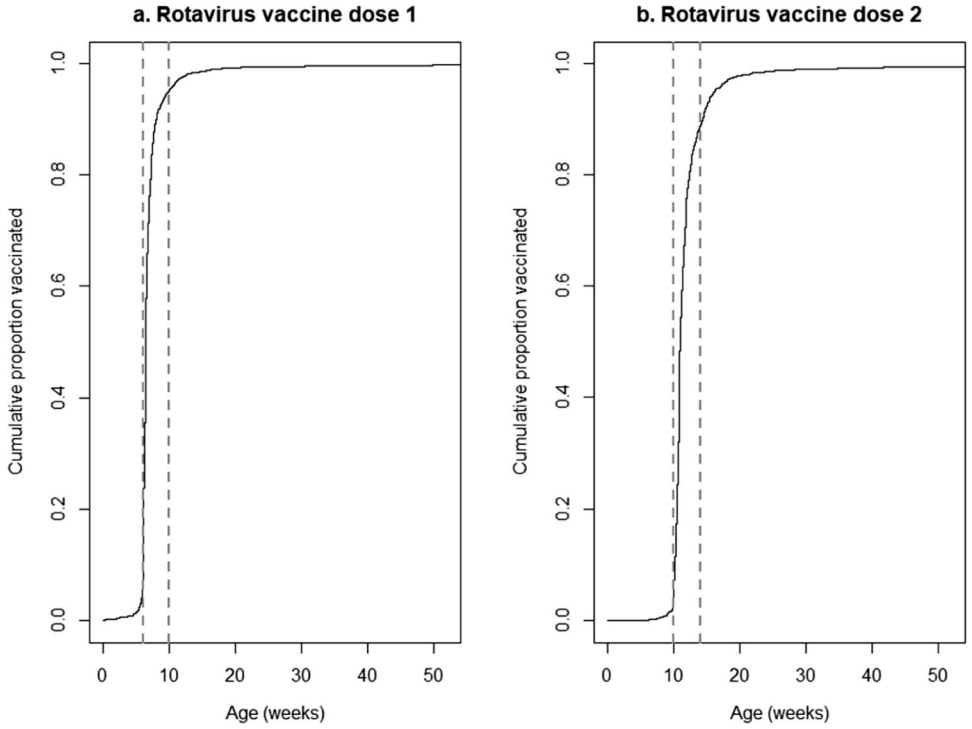

Figure 2.

Cumulative percentage of rotavirus vaccination by age, with the recommended ages for vaccination, Zimbabwe, 2014–2017.

Table 1.

Characteristics of Children Included in Analysis, Zimbabwe, 2014–2017

Characteristic	Rotavirus Positive (n = 903)		Rotavirus Negative (n = 2685)		*P* Value[a]
Age, mo, median (range)	12	(6–40)	13	(6–44)	...
Male sex	511	57	1566	(58)	.36
Enrollment hospital					
Harare Central	784	87	2428	(90)	...
Parirenyatwa	119	13	257	(10)	<.01
Admission year					
2014	9	1	30	(1)	...
2015	243	27	492	(18)	...
2016	357	39	1058	(39)	...
2017	294	33	1104	(41)	<.01
Rotavirus vaccination status					
2 doses	853	94	2527	(94)	...
1 dose	15	2	45	(2)	...
0 doses	35	4	113	(4)	.91
Nutritional status[b]					
Stunted[c]	261	31	908	(37)	<.01
Outcome[d]					
Died	2	0	15	(1)	.37
Vesikari score ≥11	548	61	1247	(46)	<.01
Maternal age, y, median (range)	27	(16–41)	27	(14–41)	...
Maternal education[e]					
None	9	1	14	(1)	...
Primary school	63	7	220	(8)	...
Secondary school	742	82	2179	(81)	...
Postsecondary school	61	7	183	(7)	...
University or above	27	3	84	(3)	.44

Characteristic	Rotavirus Positive (n = 903)		Rotavirus Negative (n = 2685)		*P* Value[a]
No. of persons in home, median (range)	4	(2–30)	4	(2–36)	
Socioeconomic parameters					
Electricity in home	643	71	1718	(64)	<.01
Refrigerator in home	533	59	1425	(53)	<.01
Car in home	233	26	616	(23)	.08
Mobile phone in home	878	97	2582	(96)	.10

Data are presented as no. (%) unless otherwise indicated.

[a] χ^2 test.

[b] Nutritional status was not available for 61 rotavirus-positive children and 229 rotavirus-negative children.

[c] Stunted was defined as >2 standard deviations below the median height for age.

[d] Outcome was missing for 48 rotavirus-positive children and 206 rotavirus-negative children.

[e] Outcome was missing for 1 rotavirus-positive child and 5 rotavirus-negative children.

Table 2.

Models of Vaccine Effectiveness Against Hospitalizations and Accident and Emergency Department Admissions due to All Diarrhea and Severe Diarrhea by Age Group, Zimbabwe 2014–2017

Model	Cases		Crude[a]		Adjusted[b]	
	Vaccinated/Total	%	VE, %	(95% CI)	VE, %	(95% CI)
Any severity						
6–11 mo						
2 doses vs 0 doses	371/398	93	42	(−10 to 69)	61	(21–81)
Any dose vs 0 doses	382/398	96	41	(−12 to 69)	60	(20–80)
≥12 mo						
2 doses vs 0 doses	482/505	95	−43	(−139 to 14)	−48	(−148 to 11)
Any dose vs 0 doses	486/505	96	−42	(−136 to 15)	−47	(−145 to 12)
Severe diarrhea[c]						
6–11 mo						
2 doses vs 0 doses	233/249	94	53	(−14 to 80)	68	(13–88)
Any dose vs 0 doses	239/249	96	52	(−15 to 80)	68	(13–88)
≥12 mo						
2 doses vs 0 doses	284/299	95	−31	(−149 to 31)	−38	(−164 to 28)
Any dose vs 0 doses	286/299	96	−30	(−147 to 32)	−37	(−162 to 29)
Stunted[d]						
6–11 mo						
2 doses vs 0 doses	95/103	92	3	(−267 to 75)	45	(−148 to 88)
Any dose vs 0 doses	100/103	97	0	(−279 to 74)	37	(−184 to 86)
≥12 mo						
2 doses vs 0 doses	152/158	96	−70	(−312 to 30)	−67	(−313 to 32)
Any dose vs 0 doses	152/158	96	−65	(−301 to 32)	−62	(−298 to 34)
Normal height for age						
6–11 mo						
2 doses vs 0 doses	253/270	94	64	(18–84)	71	(29–88)
Any dose vs 0 doses	258/270	96	64	(17–84)	71	(29–88)

Clin Infect Dis. Author manuscript; available in PMC 2022 February 17.

Model	Cases		Crude[a]		Adjusted[b]	
	Vaccinated/Total	%	VE, %	(95% CI)	VE, %	(95% CI)
≥12 mo						
2 doses vs 0 doses	297/311	95	−28	(−163 to 38)	−35	(−178 to 35)
Any dose vs 0 doses	301/311	97	−27	(−162 to 38)	−34	(−177 to 35)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness.

[a] Adjusted for site and age in months.

[b] Adjusted for site, age in months, season of birth, year of admission, and electricity in the household.

[c] Vesikari score ≥11.

[d] >2 standard deviations below median height for age.