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SUPPLEMENT ARTICLE

A Preliminary Assessment of Rotavirus Vaccine Effectiveness in Zambia

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Background. Diarrhea is the third leading cause of child death in Zambia. Up to one-third of diarrhea cases resulting in hospitalization and/or death are caused by vaccine-preventable rotavirus. In January 2012, Zambia initiated a pilot introduction of the Rotarix live, oral rotavirus vaccine in all public health facilities in Lusaka Province.

Methods. Between July 2012 and October 2013, we conducted a case-control study at 6 public sector sites to estimate rotavirus vaccine effectiveness (VE) in age-eligible children presenting with diarrhea. We computed the odds of having received at least 1 dose of Rotarix among children whose stool was positive for rotavirus antigen (cases) and children whose stool was negative (controls). We adjusted the resulting odds ratio (OR) for patient age, calendar month of presentation, and clinical site, and expressed VE as (1 – adjusted OR) × 100.

Results. A total of 91 rotavirus-positive cases and 298 rotavirus-negative controls who had under-5 card-confirmed vaccination status and were ≥6 months of age were included in the case-control analysis. Among rotavirus-positive children who were age-eligible to be vaccinated, 20% were hospitalized. Against rotavirus diarrhea of all severity, the adjusted 2-dose VE was 26% (95% confidence interval [CI], −30% to 58%) among children ≥6 months of age. VE against hospitalized children ≥6 months of age was 56% (95% CI, −34% to 86%).

Conclusions. We observed a higher point estimate for VE against increased severity of illness compared with milder disease, but were not powered to detect a low level of VE against milder disease.

Keywords. rotavirus vaccine; vaccine effectiveness; Zambia; immunization; rotavirus.

Globally, an estimated 751 000 deaths in children <5 years of age were caused by diarrhea in 2010, making it the second leading cause of death in children <5 years of age [1]. Africa accounts for 46% of the world's child diarrheal deaths but only 13% of its population [2]. Rotavirus infection caused approximately 37% of diarrhea-attributable deaths worldwide in 2008 [3]. Diarrhea is the third leading cause of child death in Zambia. In 2009, Zambia reported an annual diarrheal burden of 10 million episodes among its 2.4 million children <5 years of age, reflecting an average of >2 episodes per child per year [4]. Up to one-third of diarrhea cases resulting in hospitalization and/or death are caused by vaccine-preventable rotavirus [5–7].

Research from other countries, particularly in Latin America and several African countries including South Africa and Malawi, has shown the promise of the rotavirus vaccine in reducing child deaths attributable to rotavirus, incident severe gastroenteritis, and related hospital admission [8–11].

In January 2012 the Zambian government, in partnership with the Centre for Infectious Disease Research in Zambia (CIDRZ) and Ark, initiated a 2-year, pilot introduction of the Rotarix live, oral rotavirus vaccine in all public health facilities in Lusaka Province. Details of this program rollout are available elsewhere [12]. In November 2013, following this sucessful pilot, Zambia became the 17th Gavi-eligible country to introduce the vaccine nationally. The recommended schedule for Rotarix in Zambia aligned with the standard Expanded Programme on Immunization (EPI) visits with 2 doses recommended at 6 and 10 weeks of age, but allowing the first dose to be administered between 6 and 20 weeks of age. The pentavalent diphtheria-tetanus-pertussis (DTP), *Haemophilus influenzae* type b (Hib), and hepatitis B (HepB) vaccine has been a part of Zambia's EPI since 2005, with the first 2 doses recommended at 6 and 10 weeks of age, making it a good comparator for vaccine uptake.

As part of a larger evaluation of diarrhea-related child illness in Lusaka and Ndola, Zambia, we conducted a case-control study to evaluate the effectiveness of the rotavirus vaccine in this population. Here we present vaccine effectiveness (VE) findings from the regional pilot vaccine introduction in Lusaka Province, Zambia.

METHODS

Study Sites

This study was conducted between July 2012 and October 2013 at 6 sentinel, public health facilities in Lusaka Province, which were included in the pilot vaccine rollout. Three facilities were in

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Lusaka District, the most densely populated, urban district in Zambia, and 1 additional facility was in each of the 3 remaining districts—Kafue, Chongwe, and Luangwa—which contain a lower-density, more rural population. Facilities were purposively selected. We selected facilities with inpatient departments, sufficient under-5 patient volume, space to support study activities, and geographical consistency with the pilot vaccine rollout.

Screening, Enrollment, and Study Procedures

The study team conducted active surveillance for children presenting with diarrhea at each of the study sites. A child was considered eligible if they met the following criteria: age 0–59 months; admitted to the inpatient department or under care in the outpatient department at the time of screening; and caregiver verbal confirmation of child presenting with diarrhea (defined as the passing of ≥3 abnormally loose stools in the past 24 hours). Additionally, children were determined to be eligible if there was an indication of potentially severe diarrhea by confirmation of at least 1 of the following symptoms assessed through physical examination by the study nurse or verbal confirmation by the caregiver: sunken eyes, loss of normal skin turgor, intravenous rehydration prescribed/administered, blood in stool, and hospitalization for diarrhea or dysentery. Study nurses targeted enrollment of younger children, attempting to enroll approximately two-thirds of the sample from children <24 months of age.

As part of the larger evaluation of diarrheal disease, caregivers who voluntarily consented to participate completed a 3-part assessment: part 1 immediately upon enrollment, targeted to occur as soon as possible after the child entered care; part 2 at the child's discharge from health services (same day if an outpatient); and part 3 thirty days after enrollment. Part 1 data utilized for the VE evaluation included individual and household demographics (eg, age, sex, caregiver education level, family size), maternal health status, the child's symptoms, history and treatment of the current illness, and child health background. The child's vaccination history and growth trajectory were recorded from the under-5 card (child health record). If the under-5 card was unavailable, verbal confirmation of vaccination status was requested from the caregiver. The child's health status during the study assessment was documented based on a combination of health facility record review for the current visit and a clinical examination of the child by the study nurse. A stool sample was collected for laboratory assessment. Part 2 included a review of the child's health status and treatment received while in care. Part 3 determined child vital status at 30 days after enrollment.

A combination of parts 1 and 2 provided the 7 components required for assessment of the child's disease severity using a Vesikari score (diarrheal stool and vomiting frequency and duration based on caregiver report, treatment based on admission status, temperature, and dehydration based on clinical assessment) [13].

Stool specimens were refrigerated and transported from the study sites to the CIDRZ laboratory. They were tested for rotavirus antigen by enzyme immunoassay (EIA) using a monoclonal antibody solid phase sandwich. The Meridian Rotaclone EIA kit for the detection of rotavirus antigen in fecal samples (catalog number 696004) was used for the analysis.

The study was approved by research ethics authorities at the Zambian Ministry of Health, the University of Zambia, the University of Alabama at Birmingham, and the University of North Carolina at Chapel Hill.

Vaccine Effectiveness Analysis

Children who presented with moderate to severe diarrhea and who were age-eligible to have received rotavirus vaccine and had under-5 card-confirmed vaccination records were included in the VE analysis. Children whose stool specimen tested positive for rotavirus by EIA were classified as cases, whereas those with EIA-negative results were controls. A child was considered age-eligible for the vaccine if the rotavirus vaccine was available in the child's health facility when the child was 6 weeks of age. A child was considered vaccinated if she or he received a minimum of 1 dose of vaccine at least 14 days before presentation to the study site.

Data Processing and Analysis

Study data were collected on paper forms by trained research nurses stationed at the study clinic sites, who conducted quality control on the data they collected. Centrally, the data were again checked for quality by the study Quality Control Nurse and investigators before they were entered onto a database constructed in SQL 2008 and Access 2010. Severity of rotavirus diarrhea was classified using the 20-point Vesikari scoring system. EIA results were entered by a laboratory technician into a separate database that was merged with other study data using the participant's study-assigned unique identification number.

Statistical Analysis

Sociodemographic and clinical characteristics of cases and controls were compared using χ^2 analyses for categorical variables. For continuous variables, medians were compared using the Wilcoxon rank-sum test. We reviewed age at vaccination, rotavirus vaccine coverage by rotavirus result, and rotavirus vaccine uptake compared to pentavalent vaccine (DTP-Hib-HepB) uptake.

We used unconditional logistic regression, controlling for month and year of birth, month and year of admission, and clinical site to calculate the adjusted odds ratio (aOR) for rotavirus vaccination compared to no vaccination. To account for residual confounding related to age given the small sample size, we restricted our results to children aged ≥6 months. VE was expressed as $(1 - \text{aOR}) \times 100$.

RESULTS

Presentation of Rotavirus Diarrhea

Among all 1506 children <5 years of age enrolled in the study in Lusaka, rotavirus detection between July 2012 and October 2013 showed 2 peaks, 1 around October (a hot, dry month

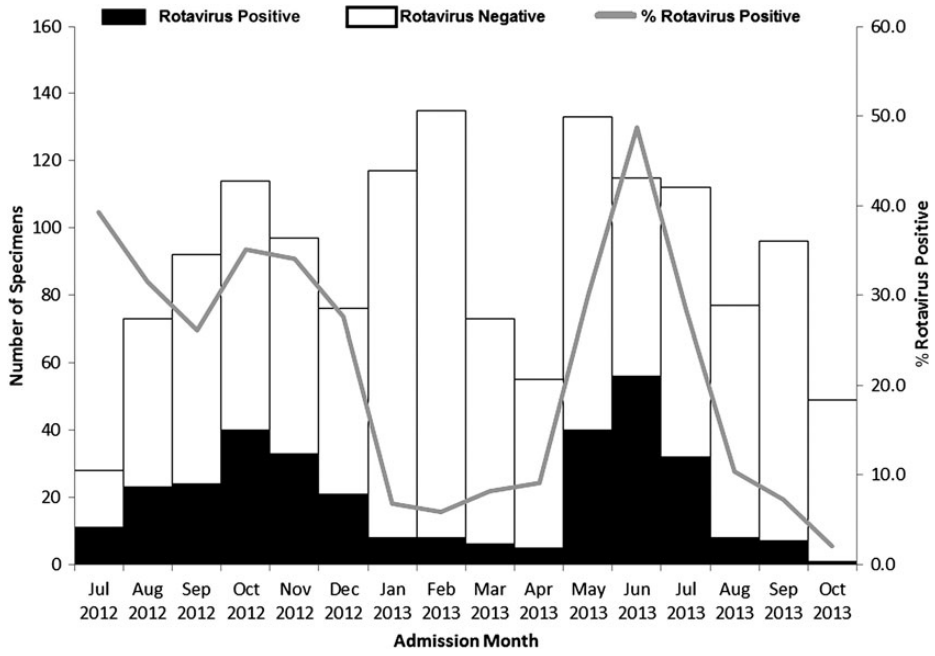

Figure 1. Rotavirus detection among children <5 years of age, July 2012–October 2013.

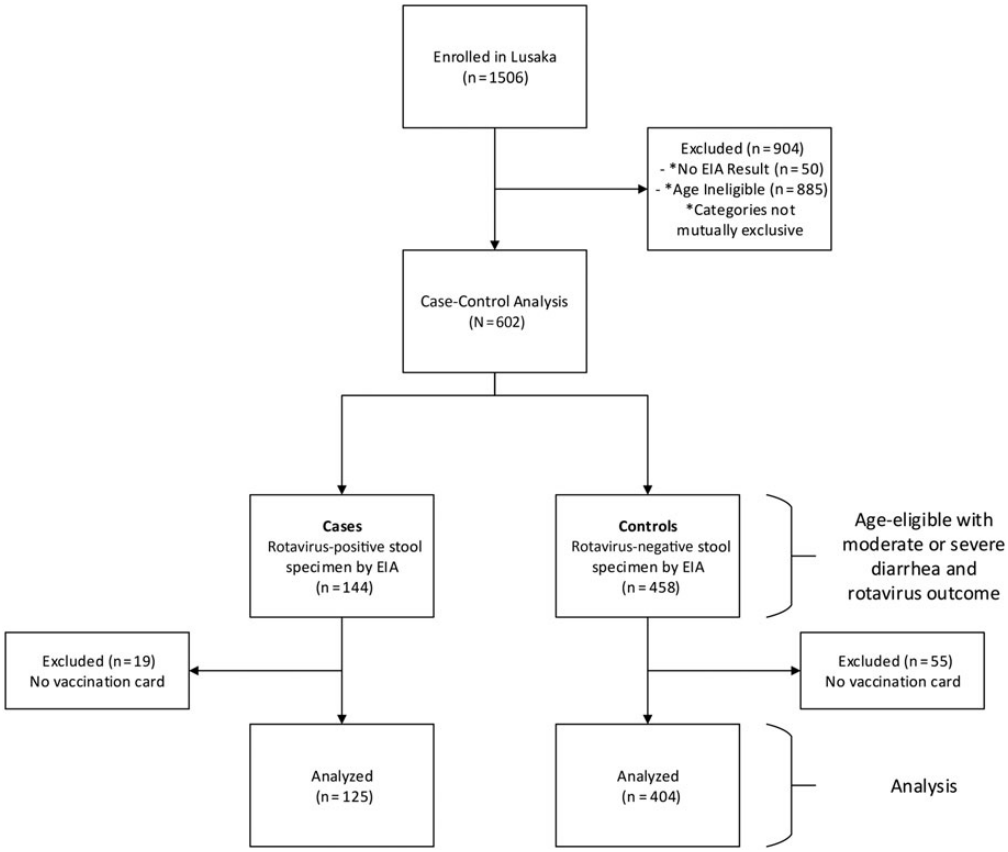

Figure 2. Inclusion flow chart. Abbreviation: EIA, enzyme immunoassay.

Table 1. Comparison of Cases and Controls Age-Eligible for Rotavirus Vaccine (≤6 Weeks of Age at Time of Vaccine Introduction)

Characteristic	Rotavirus-Positive Cases (n = 144), No. (%)	Rotavirus-Negative Controls (n = 458), No. (%)	*P* Value
Age, mo, median (range)	8 (0–18)	8 (0–21)	.54
Male sex	68/140 (49)	217/438 (50)	.84
Any chronic disease	4/143 (3)	25/442 (6)	.17
Heart disease	0/139 (0)	1/421 (0.2)	.80
Diabetes	0/138 (0)	2/429 (0.5)	.66
Asthma	0/141 (0)	2/438 (0.5)	.22
Epilepsy	1/141 (1)	3/438 (1)	.98
Malnutrition	2/141 (1)	19/434 (4)	.22
Human immunodeficiency virus	1/137 (1)	3/424 (1)	.95
Tuberculosis	1/138 (1)	0/423 (0)	.21
Premature birth	6/139 (4)	17/426 (4)	.71
Respondent's relationship to child			.04[a]
Mother	135/143 (94)	444/451 (98)	
Father	5/143 (4)	3/451 (1)	
Grandmother	1/143 (1)	2/451 (0.4)	
Aunt	2/143 (1)	1/451 (0.2)	
Other relative guardian	0/143 (0)	1/451 (0.2)	
Respondent's education level			.69
Primary	62/137 (45)	195/380 (51)	
Secondary	69/137 (50)	165/380 (43)	
Tertiary	1/137 (1)	5/380 (1)	
Other/unknown/refused	5/137 (4)	16/380 (4)	
Mother's current health			.69
Alive, well	136/139 (98)	411/424 (97)	
Alive, ill	2/139 (1)	11/424 (3)	
Dead	1/139 (1)	2/424 (4)	
No. of siblings			.22
0	38/138 (29)	130/425 (31)	
1	35/138 (25)	117/425 (28)	
2	31/138 (22)	90/425 (21)	
3	13/138 (9)	52/425 (12)	
4–6	21/138 (15)	33/425 (8)	
≥7	0/138 (0)	1/425 (0.2)	
No. of rooms in child's home			.92
<2	79/139 (57)	228/402 (67)	
2–4	38/139 (27)	105/402 (26)	
≥5	22/139 (16)	69/402 (17)	
Toilet facility in child's home			.96
Flush/pour to sewer or septic tank	39/139 (28)	110/403 (27)	
Flush/pour to pit latrine or ventilated improved pit latrine	16/139 (12)	50/403 (12)	
Pit latrine with slab or without slab (open pit)	84/139 (60)	243/403 (60)	
Hanging toilet/hanging latrine or no facility (bush/field)	0/139 (0)	0/403 (0)	
Median expenditure made by child's household on food in past 30 d (range)[b]	600 (50–1 000 000)	400 (20–1 500 000)	.002[a]
Median expenditure made by child's household on nonfood items in past 30 d (range)[b]	450 (12–1 000 000)	300 (10–1 500 000)	.02[a]

[a] Statistically significant at the .05 level.

[b] No. of children with nonmissing data on household food expenditure: 93 for rotavirus positive and 258 for rotavirus negative; No. of children with nonmissing data on household nonfood expenditure: 82 for rotavirus positive and 227 for rotavirus negative.

before the rainy season) and 1 in June (a cool, dry month after the rainy season) (Figure 1).

Vaccine Effectiveness Analysis Sample

We excluded 904 children enrolled in diarrhea surveillance from the VE analysis, of whom 885 (98%) were excluded because they were age-ineligible to receive vaccine either because they were enrolled in the study prior to vaccine rollout at their district or were too old to receive the vaccine. A total of 125 rotavirus-positive cases and 404 rotavirus-negative controls that had under-5 card-confirmed vaccination status were included in the case-control analysis (Figure 2).

Table 2. Clinical Characteristics of Children Age-Eligible for Rotavirus Vaccine (≤6 Weeks of Age at Time of Vaccine Introduction)

Characteristic	Rotavirus Positive (n = 144), No. (%)	Rotavirus Negative (n = 458), No. (%)	*P* Value
Duration of diarrhea			.006[a]
1–4 d	91/140 (65)	309/441 (70)	
5 d	24/140 (17)	35/441 (8)	
≥6 d	25/140 (18)	97/441 (22)	
Maximum No. of diarrhea episodes in 24 h			.008[a]
1–3	59/141 (42)	245/446 (55)	
4–5	67/141 (48)	177/446 (40)	
≥6	15/141 (11)	24/446 (5)	
Vomiting (% yes)	80/143 (56)	155/451 (34)	<.001[a]
If yes, duration of vomiting			.008[a]
1 d	6/80 (8)	22/151 (15)	
2 d	27/80 (34)	72/151 (48)	
≥3 d	47/80 (59)	57/151 (38)	
If yes, maximum No. of vomiting episodes in 24 h			.08
1	2/78 (3)	14/151 (9)	
2–4	68/78 (87)	129/151 (85)	
≥5	8/8078 (10)	8/151 (5)	
Highest recorded temperature			.13
<37°C	75/143 (52)	278/458 (61)	
37°C–<38.5°C	53/143 (37)	125/458 (27)	
38.5°C–<38.9°C	3/143 (2)	17/458 (4)	
≥39°C	12/143 (8)	36/458 (8)	
Capillary refill time			.11
Normal (<2 sec)	119/142 (84)	407/453 (90)	
Sluggish (2–3 sec)	22/142 (15)	42/453 (9)	
Delayed (>3 sec)	1/142 (1)	4/453 (1)	
Child's skin turgor at admission			.53
Goes back quickly (immediately)	60/139 (43)	214/451 (47)	
Goes back slowly (1–2 sec)	75/139 (54)	229/451 (51)	
Goes back very slowly (>2 sec)	4/139 (3)	8/451 (2)	
Buccal mucosa/lips			.80
Moist	22/143 (15)	80/454 (18)	
Dry	119/143 (83)	369/454 (81)	
Parched/cracked	2/143 (1)	5/454 (1)	
Eyes			.81
Normal	52/143 (36)	152/455 (33)	
Deep set	13/143 (9)	43/455 (9)	
Sunken	78/143 (55)	260/455 (57)	
Condition on arrival			.02[a]
Normal/appropriate	45/143 (31)	180/453 (39)	
Fussy/restless but consolable	75/143 (52)	236/453 (52)	
Severely irritable/inconsolable	18/143 (13)	36/453 (8)	
Lethargic/somnolent	5/143 (4)	4/453 (1)	
Obtunded/comatose	0/143 (0)	0/453 (0)	
Child's thirst status at admission			.75
Drank normally, not thirsty	121/136 (89)	371/426 (86)	
Thirsty, drank eagerly	12/136 (9)	45/426 (10)	
Drank poorly, not able to drink	1/136 (1)	2/426 (0.4)	
Unknown	2/136 (1)	46/426 (3)	
Hospitalized (% yes)	29/144 (20)	93/458 (20)	.97
Vesikari score			<.001[a]
≤10 (mild)	80/137 (58)	349/433 (81)	
11–14 (moderate)	47/137 (34)	71/433 (16)	
≥15 (severe)	10/137 (7)	13/433 (3)	

[a] Statistically significant at the .05 level.

Table 3. Vaccine Coverage of Children Age-Eligible for Rotavirus Vaccine by Rotavirus Test Result

Vaccination Status	Rotavirus Positive (n = 144), No. (%)	Rotavirus Negative (n = 458), No. (%)	*P* Value
Verified vaccination status			.65
Card seen	125 (87)	404 (88)	
Card not seen	19 (13)	54 (12)	
Coverage among children with card-verified vaccination status			
Rotavirus vaccine	n = 125	n = 404	.79
0 doses	39 (31)	122 (30)	
1 dose	16 (13)	44 (11)	
2 doses	70 (56)	238 (59)	
Pentavalent vaccine	n = 125	n = 404	.02[a]
0 doses	8 (6)	12 (3)	
1 dose	6 (5)	21 (5)	
2 doses	24 (19)	44 (11)	
3 doses	87 (70)	327 (81)	

[a] Statistically significant at the .05 level.

Characteristics of Cases and Controls

Cases and controls were similar in age, sex, chronic disease prevalence, and household demographics. The rotavirus cases were more often brought in by a caregiver other than their mother and reported higher median expenditure on food and nonfood items in the child's household 30 days prior to the child's presentation at the health facility (Table 1).

Compared to antigen-negative children, those who were rotavirus positive had more severe diarrhea (including a greater duration and maximum number of diarrhea episodes), were more likely to have vomiting and for a longer duration, were in worse clinical condition on arrival at the facility, and had a higher Vesikari score compared to controls (Table 2). Only 20% of cases and controls were hospitalized.

Vaccine Coverage and Age Appropriateness

Vaccine coverage among cases and controls was high, at 70% for at least 1 dose and 58% for 2 doses of rotavirus vaccine. Although cases had lower pentavalent vaccine coverage, there were no significant differences between cases and controls for rotavirus vaccine coverage (Table 3).

Rotavirus vaccination timing was consistent with recommended schedules, compared to pentavalent vaccine administration (Figure 3). The median age at rotavirus and pentavalent vaccine administration was 6 weeks for dose 1 and 11 weeks for dose 2. Among children vaccinated against rotavirus, 79% received their first dose within 2 weeks of the recommended age for vaccination and 64% received their second dose within 2 weeks of the recommended age. Among children receiving pentavalent vaccine, 84% and 71% received their first and second doses, respectively, within 2 weeks of the recommended age.

Vaccine Effectiveness, Children Aged ≥6 Months

Against rotavirus diarrhea of all severity, the adjusted 2-dose VE among children ≥6 months of age was 26% (95% confidence interval [CI], −30% to 58%). Against rotavirus diarrhea that required hospitalization, it was 56% (95% CI, −34% to 86%).

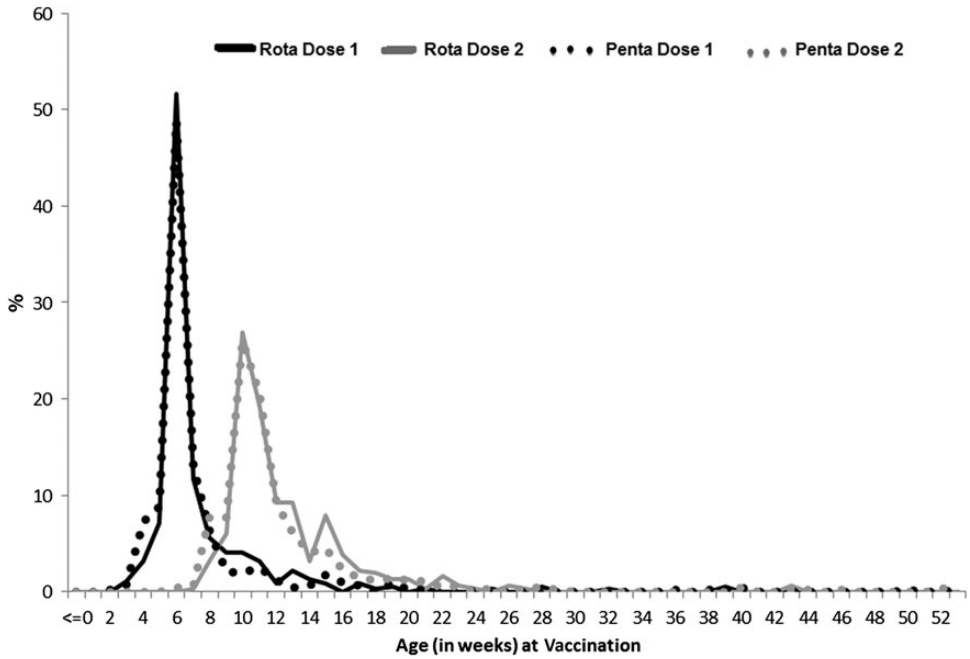

Figure 3. Age at rotavirus (Rota) and pentavalent (Penta) vaccination among children age-eligible to receive rotavirus vaccine.

VE against very severe rotavirus (Vesikari ≥15) for children with 2 doses was 48% (95% CI, −163% to 90%) (Table 4).

DISCUSSION

Our study is the first report on rotavirus VE in Zambia, in the context of a regional pilot project. We observed a higher point estimate for VE among children with more severe illness compared with children with milder illness, consistent with what has been reported elsewhere [14–16]. For children ≥6 months of age who were hospitalized, we observed 57% effectiveness with at least 1 dose of vaccine.

Among age-eligible children, more children received the pentavalent vaccine, to which the rotavirus vaccine timing was synchronized, than the rotavirus vaccine. This likely represents the challenges that the health system experienced in supply and training of staff to support new vaccine rollout, even with the dedicated support accompanying the pilot [12]. This suggests that additional research on ways to limit missed opportunities for rotavirus vaccine administration would be useful as rotavirus becomes part of the routine immunization program of additional countries. It is unclear, however, why cases have lower pentavalent coverage than controls.

Interestingly, although the study was conducted in a period just over 1 calendar year, our results confirm the typical trend on the seasonality of rotavirus disease as has been reported elsewhere; 1 peak in the cool dry seasons (May–July) and a second, but smaller peak in the hot dry season (September–October) [6, 17]. Future research characterizing trends in under-5 diarrhea seasonality may demonstrate shifts based on vaccination effects and the impact of other etiologic agents of diarrhea.

The overall trend of VE, with an aOR ranging from 17% to 60% for at least 1 dose, is consistent with other studies from developing countries [14, 15, 18]. These findings support prior reports of the relatively lower VE of live oral vaccines in low- to middle-income countries such as Zambia, compared with more developed countries [14, 19]. Effective public health efforts to reduce diarrhea must continue to emphasize the importance of other preventive practices alongside vaccination to minimize cases.

The study is limited by its small sample size of severe rotavirus cases and its high vaccination coverage. Only 20% of the children enrolled through the outpatient surveillance required hospitalized care in our study. Rotavirus is the most common cause of severe gastroenteritis in young children and accounts for a higher proportion of cases among children hospitalized for acute gastroenteritis than among children requiring outpatient care. Furthermore, rotavirus vaccines are more effective in preventing severe disease than mild disease. Whereas 23% of all diarrhea cases in the study were severe and 4% very severe, the study also included mild diarrhea. Thus, given the high proportion of children receiving outpatient care enrolled in our study, we were not powered to detect a low-level VE against

Table 4. Vaccine Effectiveness by Dose of Rotavirus Vaccine Among Children Aged ≥6 Months

Doses of Rotavirus Vaccine[a]	Rotavirus Positive	Rotavirus Negative	Unadjusted VE, % (95% CI)	Adjusted VE[b], % (95% CI)
Cases, all severity	n = 91	n = 298		
0 doses	32 (35)	88 (30)	ref	ref
1 dose	7 (8)	28 (9)	31 (–73, 73)	29 (–82, 73)
2 doses	52 (57)	182 (61)	21 (–31, 53)	26 (–30, 58)
At least 1 dose	59 (65)	210 (70)	23 (–27, 53)	27 (–27, 58)
Hospitalized cases[c]	n = 18	n = 298		
0 doses	9 (50)	88 (30)	ref	ref
1 dose	1 (6)	28 (9)	65 (–188, 96)	62 (–261, 96)
2 doses	8 (44)	182 (61)	57 (–15, 84)	56 (–34, 86)
At least 1 dose	9 (50)	210 (70)	58 (–9, 84)	57 (–27, 85)
Cases with Vesikari score ≥11[c]	n = 35	n = 298		
0 doses	11 (31)	88 (30)	ref	ref
1 dose	1 (3)	28 (9)	71 (–131, 96)	77 (–99, 97)
2 doses	23 (66)	182 (61)	–1 (–117, 53)	5 (–125, 59)
At least 1 dose	24 (69)	210 (70)	9 (–95, 57)	17 (–91, 64)
Cases with Vesikari score ≥ 15[c]	n = 8	n = 298		
0 doses	4 (50)	88 (30)	ref	ref
1 dose	0 (0)	28 (9)	. . .	. . .
2 doses	4 (50)	182 (61)	52 (–98, 88)	48 (–163, 90)
At least 1 dose	4 (50)	210 (70)	58 (–71, 90)	60 (–103, 92)

Data are presented as No. (%) unless otherwise specified.

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

[a] Protection conferred 14 days after vaccine receipt.

[b] Adjusted for month and year of admission, month and year of birth, and clinic.

[c] All controls included in analysis.

mild disease. All children in the study were aged ≤21 months, with a median age of 8 months, so we were also not able to assess waning immunity in this population.

In conclusion, we found that rotavirus vaccine may provide better protection against severe disease compared with milder disease, which is consistent with other research conducted in the region, but there is need for a more robust evaluation to ascertain a definitive estimate of rotavirus VE in Zambia.

Notes

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