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Sustained Effectiveness of Rotavirus Vaccine Against Very Severe Rotavirus Disease Through the Second Year of Life, Bolivia 2013–2014

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Abstract

Background.—In Bolivia, monovalent rotavirus vaccine was introduced in 2008 and a previous evaluation reported a vaccine effectiveness (VE) of 77% with 2 doses of vaccine in children aged <3 years. This evaluation sought to determine if rotavirus vaccine provided protection through the second year of life against circulating genotypes.

Methods.—A case-control study was performed in 5 hospitals from April 2013 to March 2014. Among enrolled participants who met study criteria and had rotavirus stool testing performed and

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vaccine status confirmed, we calculated VE using a logistic regression model. Subgroup analyses were performed among children aged <1 year and those aged ≥1 year, among children with severe diarrhea (Vesikari score ≥11) and very severe diarrhea (Vesikari score ≥15), and among G and P strains with at least 40 specimens.

Results.—A total of 776 children were enrolled. For children <1 year and ≥1 year of age with severe diarrhea, VE for 2 doses was 75% (95% confidence interval [CI], 46%–88%) and 53% (95% CI, 9%–76%), respectively. For children <1 year and ≥1 year of age with very severe diarrhea, VE for 2 doses was 80% (95% CI, 44%–93%) and 74% (95% CI, 35%–90%), respectively. Genotype-specific analysis demonstrated similar VE for the 4 most common G and P types (G3, G9, P[6] and P[8]).

Conclusions.—A monovalent rotavirus vaccine remains effective against a broad range of circulating strains as part of a routine immunization program >5 years after its introduction in Bolivia. Although VE appears to wane in children aged ≥1 year, it still provides significant protection, and does not wane against severe disease.

Keywords

rotavirus; gastroenteritis; childhood mortality; middle-income country; diarrhea

Acute gastroenteritis (AGE) remains one of the top causes of childhood mortality worldwide, and rotavirus is the leading cause of severe childhood AGE [1]. In 2009, the World Health Organization recommended use of rotavirus vaccine in all countries and especially in those countries with high child mortality due to AGE. Currently, 2 live attenuated oral rotavirus vaccines, a human monovalent strain (RV1) (Rotarix, Glaxo SmithKline Biologics) and a pentavalent bovine-human reassortant vaccine (RV5) (RotaTeq, Merck Vaccines) are available for use in routine childhood immunization programs [2].

In high-income countries such as the United States, rotavirus vaccines have demonstrated effectiveness of 70%–92% [3, 4] in preventing hospital admission for AGE in routine use. However, in low- and middle-income countries, where the vaccine is likely to have the most benefit due to the high disease burden, vaccine effectiveness (VE) is modest, ranging from 49% in Nicaragua, to 76% in El Salvador, to 66% in Guatemala in children <5 years old [5-7]. Several Latin American countries, such as Mexico, Honduras, Bolivia, El Salvador, and Venezuela, have documented substantial reductions in all-cause AGE hospital admissions of 20%–64% and reductions in AGE-associated mortality of 5%–46% in children <5 years of age after the introduction of rotavirus vaccination [8, 9].

While the VE and impact of rotavirus vaccine has been well documented, especially in children <1 year old, the duration of protection of rotavirus vaccines in older ages has not been as thoroughly investigated. Bolivia, a low- to middle-income country in South America, introduced RV1 into the routine childhood immunization schedule in August 2008 with doses given at 2 and 4 months of age [10]. In Bolivia, a previous evaluation reported a VE of 77% with 2 doses of the vaccine. A subanalysis of VE in children ≥1 year of age showed a VE of 72%, but this estimate was based on a relatively small number of cases in this age group [11]. With accumulation of additional years of postvaccine data, the objective

of this evaluation was to determine if the effectiveness of the monovalent rotavirus vaccine is sustained through the second year of life against a range of circulating genotypes.

METHODS

From April 2013 to March 2014 we conducted a case-control evaluation at 5 hospitals in 4 of the largest cities in Bolivia (La Paz, El Alto, Cochabamba, and Santa Cruz) to assess the effectiveness of rotavirus vaccine under conditions of routine use. These hospitals were selected in accordance with World Health Organization guidelines [12].

This was a case-control study where cases were children who had at least 3 episodes of loose stools in a 24-hour period and who were admitted to the hospital overnight for treatment of AGE. Inclusion criteria were onset of diarrhea <14 days before the hospital visit; stool sample collected during the first 48 hours of admission that tested positive for rotavirus by enzyme immunoassay (EIA); born after 1 June 2008 and at least 8 weeks of age, making them eligible to receive the rotavirus vaccine as part of their routine childhood immunizations. We excluded cases when we were unable to contact a parent or caretaker to obtain consent or verify vaccination status with parental card or vaccination registry. Controls met the exact same criteria as cases except their stool tested negative for rotavirus by EIA (test-negative AGE controls).

To identify cases and controls, we utilized the World Health Organization hospital-based AGE surveillance and enrolled participants from the emergency department and inpatient wards at sentinel hospitals 24 hours a day [12]. Stool specimens were collected within 48 hours of hospital admission and stored at 2°C–8°C before transfer to the national laboratory for EIA testing or to Instituto de Biología Molecular y Biotecnología, Universidad Mayor de San Andrés laboratory for genotyping. Rotavirus testing was done with a commercially available EIA (ProSpecT enzyme-linked immunosorbent assay, Oxoid). Genotyping was performed on all rotavirus-positive stools with sufficient sample as described by Hull et al [13].

After providing written informed consent, caregivers underwent a face-to-face interview during which we collected vaccination history, demographics, socioeconomic factors, breastfeeding history and medical history, and history of present illness. Vaccination history was considered confirmed if the interviewer saw a copy of the vaccination card or a vaccination clinic record. A vaccine dose was considered valid if the child received it ≥14 days prior to admission.

Statistical Analysis

We performed bivariate analyses to assess for differences in demographic and socioeconomic factors comparing rotavirus-positive cases and test-negative controls using Wilcoxon rank-sum or χ^2 tests for significance. To estimate adjusted odds ratios, we used an unconditional logistic regression model that included hospital, age in months, and month/year of birth because test-negative controls were unmatched with regard to age and hospital. Socioeconomic factors that reached statistical significance on bivariate analysis ($P \leq .05$) were included in the initial model. We used a backward elimination strategy and

retained those factors whose removal resulted in a ≥10% change in our primary outcome. We calculated VE as (1 – adjusted odds ratio) × 100%. We did subgroup analyses to assess protection from partial dose vaccination (1 dose of RV1), strain-specific protection, and protection among children aged <1 year and those aged ≥1 year. Strain-specific VE estimates were restricted to those strains for which at least 40 specimens with the stain of interest were collected. Statistical significance was designated as $P < .05$. We used SAS statistical software (version 9.3) for analyses.

Ethics

This case-control study was approved by the Centers for Disease Control and Prevention, the Pan American Health Organization, and the Bolivian National Bioethics Committee. Surveillance coordinators obtained informed consent from the parents or legal guardian of the child.

RESULTS

Enrollment and Demographics

Nine-hundred fifty-seven children aged <5 years were screened to participate in the study. Ninety-one percent (n = 870) met study eligibility. Of the 401 potential cases and 469 test-negative controls, 49% (n = 197) and 48% (n = 224) were <1 year old, respectively; 51% (n = 204) and 52% (n = 245) were ≥1 year old. Ultimately, 88% (n = 173) and 92% (n = 206) of eligible <1-year-old cases and controls were included in the analyses, respectively. For children ≥1 year old, 90% (n = 183) of eligible cases and 87% (n = 214) of eligible test-negative controls were included in the analyses (Figure 1).

Demographic and socioeconomic factors between cases and test-negative controls were similar, except a lower proportion of cases had Internet in the household ($P = .02$) and a refrigerator ($P = .04$), compared with test-negative controls, and a larger proportion of cases had motorcycles compared with controls ($P = .01$) (Table 1).

Diarrhea Severity

Overall, rotavirus-positive cases had a median Vesikari score of 15 (interquartile range [IQR], 13–16) and controls 14 (IQR, 13–16) ($P = .12$; Table 2). Of children enrolled in the study aged ≥1 year, 94% (162/172) of cases and 89% (n = 171/193) of controls had a Vesikari score ≥11 ($P = .06$). For enrolled children <1 year of age, significantly more cases 97% (n = 158/163) than controls 91% (n = 174/192) had diarrhea with a Vesikari score ≥11 ($P = .02$). The same trends held true for Vesikari scores ≥15, with no significant difference between cases and controls in children ≥1 year old ($P = .26$); however, in children <1 year old, cases were more likely than controls to have a Vesikari score ≥15 (62% vs 51%, respectively; $P = .04$).

Among children ≥1 year old, controls had a longer duration of diarrhea compared with cases ($P = .001$), but cases had a higher maximum number of diarrhea episodes in a 24-hour period ($P = .01$) and higher maximum number of vomiting episodes in a 24-hour period with this illness ($P = .0001$) compared with controls.

Vaccine Coverage

A significantly lower proportion of rotavirus cases were vaccinated with either 1 or 2 doses of the rotavirus vaccine compared with controls in children <1 year old ($P = .001$) and those ≥1 year old ($P = .01$).

Vaccine Effectiveness

For all children with AGE, the adjusted VE of a full series of 2 doses of RV1 against hospital admission for rotavirus was 59% (95% confidence interval [CI], 37%–73%). Rotavirus VE improved with increasing number of doses and increasing severity for all children including children <1 year old and those ≥1 year old (Table 3). Vaccine effectiveness for 2 doses was 76% (95% CI, 50%–89%) for children <1 year old, and 45% (95% CI, 0%–70%) for those ≥1 year old, which were not significantly different ($P = .26$). Vaccine effectiveness was maintained for children aged <1 year with all disease severity categories and improved with increasing disease severity. In children ≥1 year old, high VE was maintained among children with the most severe disease (Vesikari score ≥15) but waned among children with less severe disease.

Genotypes

Of the 356 children enrolled in the study, 305 (86%) and 272 (76%) had sufficient sample to identify G and P genotypes, respectively. Single as opposed to mixed genotypes were found for 291 (95%) of G types and 238 (88%) of P types. A total of 4 G types and 4 P types were identified. The most common G types were G9 (n = 186 [64%]), G3 (n = 88 [30%]), and G2 (n = 9 [3%]). P[4] (n = 20 [8%]), P[6] (n = 63 [26%]), and P[8] (n = 154 [65%]) were the most common P types (Table 4). The most common combinations of G and P genotypes were G9P[8] (n = 109) and G3P[8] (n = 53). For genotypes with ≥40 samples, VE for 2 doses of RV1 was G3 (58%; 95% CI, 18%–78%), G9 (60%; 95% CI, 34%–76%), P[6] (57%; 95% CI, 18%–77%), and P[8] (67%; 95% CI, 44%–80%). For the 2 most common G and P combination strains, 2-dose rotavirus VE was 48% (95% CI, −26% to 78%) for G3P[8] and 77% (95% CI, 55%–88%) for G9P[8]. VE increased with increasing Vesikari score for each G and P strain and G and P combination strains. For example, P[6] VE improved to 66% (95% CI, 13%–87%) when calculating VE only for those children with a Vesikari score ≥15.

DISCUSSION

Studies in Latin America have demonstrated VE and reductions in AGE hospital admissions in several countries following rotavirus vaccine introduction into the national immunization program. Rotavirus VE in El Salvador, Nicaragua, and Guatemala in children ≥1 year of age ranges from 33% to 68% [5-7]. In our current study we found that VE waned with age, with lower effectiveness of 45% observed among children ≥1 year of age vs 76% among children <1 year of age, although this difference in effectiveness was not statistically significant. A similar pattern in waning of immunity was observed in El Salvador, where VE also declined when comparing children 6–11 months of age (VE, 83%; 95% CI, 68%–91%) with children 12–24 months (VE, 59%; 95% CI, 27%–77%) ($P = .046$) [6]. This general trend of RV

protectiveness waning in children >12 months was recently shown in a systematic review and meta-analysis from 5 different Latin American countries [14].

Our previous study in Bolivia, conducted approximately 1.5 years after vaccine introduction, demonstrated an overall VE of 69% (95% CI, 54%–79%) for children of all ages and 72% (95% CI, 52%–86%) for children ≥ 1 year old [11]. In the current evaluation, which occurred 5 years after vaccine introduction, more children aged 1–5 years were eligible for the vaccine, providing more time for the vaccine to wane. In contrast, in high-income settings such as the United States, high VE has been maintained into the third and fourth years of life [3, 4]. This difference in duration of immunity between high- and low-income settings may reflect a difference in immune response to the vaccine. In lower-income settings, the short-lived intestinal immune response to the vaccine may predominate and the systemic response may be less robust [15].

Of note, among children with the most severe AGE (Vesikari score ≥15), the effectiveness of the vaccine persisted into the second year of life in Bolivia for both children <1 year of age (75%) and children ≥1 year of age (74%). Similar results were found in a subanalysis of subjects in Nicaragua, where VE for very severe AGE in children aged 8–11 months (39%; 95% CI, 8%–190%) did not differ statistically from the VE found in children aged 12–19 months (13%; 95% CI, 3%–59%) [15]. Thus, although protection may wane against rotavirus AGE of all severity, protection against very severe AGE, for which children are most at risk for dying, may be longer-lasting. This finding is further supported by studies in Mexico and Brazil, which demonstrated significant declines in AGE mortality in all children following the introduction of rotavirus into the national immunization program [9, 16]. Sustained protection in demonstrated declines in AGE mortality provide important information for decision makers in low- and middle-income countries to consider the introduction and continued support of rotavirus vaccination.

In Bolivia, we found that the rotavirus vaccine protected against a range of circulating strains, including heterotypic strains G3P[8] and G9P[8]. Additionally, for strains with sufficient sample size, we found that VE increased with worsening Vesikari score. However, we did not have sufficient power to assess duration of protection, or protection against all strains encountered in genotyping analysis. However, studies in Bolivia, Mexico, and Brazil have also demonstrated heterotypic protection. Our previous study in Bolivia demonstrated VE of 59%–93% in the most commonly detected strains—G2P[4], G3P[8], G9P[6], and G9P[8]—with no significant difference between strains [11]. Furthermore, in Mexico the monovalent rotavirus vaccine was found to have a VE of 94% (95% CI, 16%–100%) against the emergent heterotypic strain G9P[4] in 2010, and in Brazil the rotavirus vaccine demonstrated protection against the fully heterotypic G2P[4] strain in children 6–11 months of age (VE, 77%; 95% CI, 42%–91%) [17, 18]. A large systematic review that analyzed VE in high- and middle-income countries did not demonstrate a significant difference in VE among homotypic and heterotypic strains within each country group [19]. However, a study in Australia enrolling low-income aboriginal infants found a lower VE [20]. Few data are available for low-income countries, and surveillance should expand to those countries and continue to include VE and genotype analysis.

This prospective observational evaluation depends on differences of exposure to vaccination. Vaccination verification occurred for similar proportions of cases and controls. However, if controls with unverified vaccination status were more likely to be vaccinated than cases with unverified vaccine history, we may have overestimated our VE. We attempted to minimize this and other healthcare-seeking behavior biases by enrolling both cases and controls at the same hospital sites, and interviewers were blinded to the case or control status of an individual when following up on the vaccination status so that equal effort was made to verify the vaccination status for all children.

In summary, this study shows good VE of RV1 incorporated into a routine child immunization program in Bolivia, a low- to middle-income country. Although rotavirus infection occurs mostly in young children, this evaluation demonstrates sustained protection in children aged ≥1 year, particularly in children with the most severe AGE symptoms. These data provide compelling evidence favoring broader use of the rotavirus vaccine in low-income settings to reduce the burden of severe and fatal rotavirus AGE in children.

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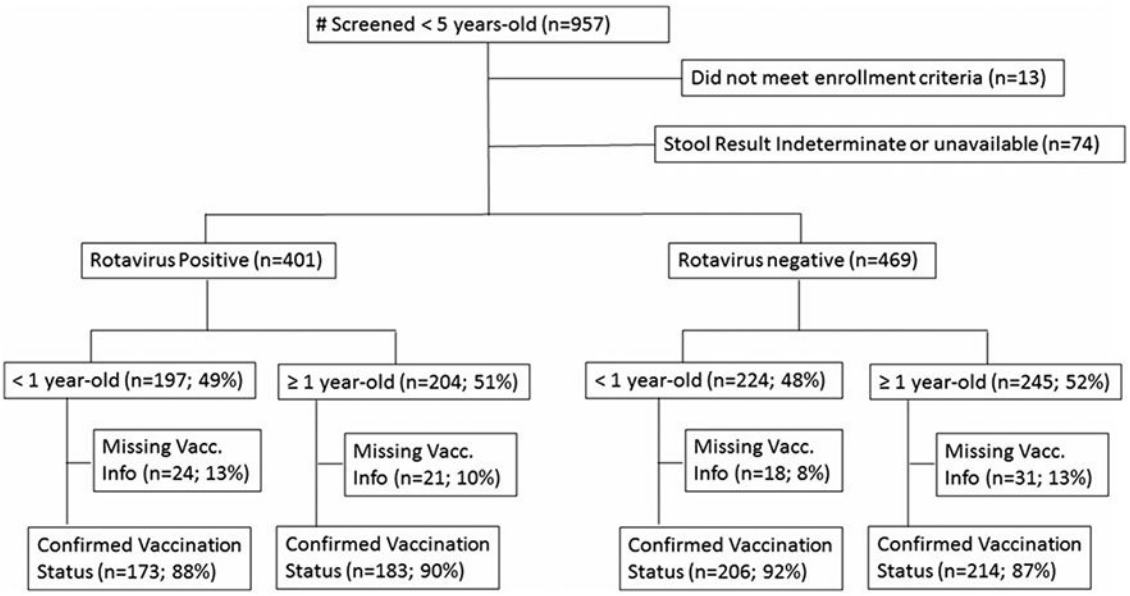

Figure 1.
Flow chart depicting enrollment of rotavirus case patients and test-negative controls.

Table 1.

Demographic and Socioeconomic Factors of Cases and Test-Negative Controls

Characteristic	Cases (n = 356)	Controls (n = 420)	*P* Value
Age, mo, median (IQR)	13 (8–18)	14 (8–17)	.73
Male sex	227 (64)	256 (61)	.42
Chronic medical condition	5 (19)	5 (22)	.94
Ever breastfed	343 (97)	402 (96)	.48
Daycare within 2 wk	109 (31)	129 (31)	.92
No. of children in the home, median (IQR)	2 (1–3)	2 (1–3)	.48
Socioeconomic indicators			
Electricity in the home	353 (99)	413 (98)	.31
Trash collection	276 (78)	349 (83)	.06
Automobile	103 (29)	133 (32)	.78
Internet in the household	47 (13)	81 (19)	.02[a]
Refrigerator	213 (60)	281 (67)	.04[a]
Portable water in the household	329 (92)	386 (92)	.79
Sewage at household	241 (68)	286 (68)	.54
Radio	316 (89)	365 (87)	.43
Television	348 (98)	405 (96)	.28
Bicycle	117 (33)	142 (34)	.76
Motorcycle	37 (10)	69 (16)	.01[a]
Telephone	82 (23)	110 (26)	.96
Computer	87 (24)	135 (32)	.30
Cell phone	342 (96)	408 (97)	.41
Home ownership	116 (33)	131 (31)	.68

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

Abbreviation: IQR, interquartile range.

[a]Significant to $P < .05$.

Table 2.

Vesikari Score and Clinical Characteristics Stratified by Cases, Controls, and Children Aged <1 Year and ≥1 Year

	Age <1 Year				Age ≥1 Year			
Characteristic	**No.**	**Cases**	**Controls**	***P* Value**	**No.**	**Cases**	**Controls**	***P* Value**
Vesikari score, median (IQR)	355	15 (14–16)	14 (13–16)	.12	365	15 (13–16)	15 (13–16)	.50
No. of days with diarrhea, median (IQR)	379	3 (1 −4)	3 (1 −4)	.49	397	2 (2–3)	2 (2–4)	.001[a]
Maximum No. of diarrhea episodes, median (IQR)	379	8 (6–10)	7 (5–10)	.03[a]	397	7 (5–10)	6 (4–8)	.01[a]
No. of days of vomiting, median (IQR)	338	2 (1–3)	2 (1–3)	.08	354	2 (1–3)	2 (1–3)	.85
Maximum No. of vomiting episodes, median (IQR)	338	5 (3–7)	5 (3–6)	.86	354	5 (4–10)	4 (3–7)	.0001[a]
Vomiting	378	163 (94)	174 (85)	.004[a]	397	172 (84)	182 (85)	.004[a]
Oral rehydration at home	378	79 (46)	86 (42)	.47	396	85 (46)	102 (48)	.78
IV fluids at the hospital	375	169 (98)	198 (98)	.82	396	178 (97)	208 (98)	.67
General condition								
Alert	377	1 (1)	5 (2)	.24	397	5 (3)	9 (4)	.24
Agitated, irritable		110 (64)	136 (66)			119 (65)	146 (68)	
Lethargic		61 (35)	64 (31)			59 (32)	214 (54)	
Sunken eyes	377	170 (98)	198 (97)	.45	384	181 (99)	203 (95)	.01[a]
Thirst status								
Drinking normally	377	4 (2)	10 (5)	.04[a]	393	1 (1)	12 (6)	.09
Thirsty, drinking		86 (50)	117 (57)			114 (63)	131 (62)	
Thirsty, too weak to drink		82 (48)	78 (38)			66 (36)	212 (54)	
Skin pinch								
Returns immediately	377	12 (7)	27 (14)	.17	384	15 (9)	44 (21)	.01[a]
Returns 1–2 sec		104 (63)	116 (59)			122 (70)	128 (61)	

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

Abbreviations: IQR, interquartile range; IV, intravenous.

[a]Significant to $P < .05$.

Table 3.

Vaccine Effectiveness Stratified by Age, Number of Rotavirus Doses, and Vesikari Score and Adjusted for Age in Months, Month and Year of Birth, and Hospital

	All Severity			Vesikari Score ≥11			Vesikari Score ≥15		
Age and No. of Doses	**Cases**	**Controls**	**Adjusted VE, % (95% CI)**	**Cases**	**Controls**	**Adjusted VE, % (95% CI)**	**Cases**	**Controls**	**Adjusted VE, % (95% CI)**
>2 mo–59 mo									
0 doses	91	64	ref	82	53	Ref	49	26	ref
1 dose	60	57	26 (25–58)	55	41	16 (−52 to 53)	40	20	8 (−100 to 58)
2 doses	203	298	59 (37–73)	181	250	54 (11–76)	104	145	72 (49–85)
2 mo–<1 y of age									
0 doses	54	36	ref	48	31	ref	26	16	ref
1 dose	36	38	45 (−49 to 73)	32	26	45 (−30 to 76)[a]	27	12	40 (−100 to 82)[a]
2 doses	82	131	76 (50–89)	77	116	75 (46–88)	48	70	80 (44–93)
≥1 y of age									
0 doses	37	28	ref	34	22	ref	23	10	ref
1 dose	24	19	−2 (−140 to 58)	23	15	−5 (−187 to 62)	13	8	56 (−83 to 89)
2 doses	182	214	45 (0–70)	104	134	53 (9–76)	56	75	74 (35–90)

Data are presented as No. unless otherwise specified. For children <1 year old and Vesikari score ≥11 and ≥15, VE estimates were adjusted for additional variables.

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

[a]Adjusted for additional socioeconomic variables trash pick-up, refrigerator, Internet, and motorcycle at the home.

Table 4.

Genotype Results for Sampled Sequences

	All Vesikari Scores			Vesikari Score ≥15		
Gentoype	**2 Doses RV Vaccine**	**0 Doses RV Vaccine**	**VE, % (95% CI)**	**2 Doses RV Vaccine**	**0 Doses RV Vaccine**	**VE, % (95% CI)**
G3[a]						
Cases	51	30	58 (18–78)	23	13	61 (19–81)
Controls	298	121	…	145	46	
G9[b]						
Cases	116	47	60 (34–76)	59	29	75 (48–88)
Controls	298	121		145	46	
P[6][c]						
Cases	46	25	57 (18–77)	25	15	66 (13–87)
Controls	298	121		145	46	
P[8][d]						
Cases	88	46	67 (44–80)	42	24	88 (53–90)
Controls	298	121		145	46	
G3P[8]						
Cases	24	14	48 (−26 to 78)	8	6	NA
Controls	298	121		145	46	
G9P[8]						
Cases	46	25	77 (55–88)	27	15	80 (52–92)
Controls	298	121		145	46	

Data are presented as No. unless otherwise specified. Mixed samples include 2 genotypes.

Abbreviations: CI, confidence interval; NA, not available; RV, rotavirus; VE, vaccine effectiveness.

[a]Includes 7 cases with mixed infection, including 1 G2/G3 and 6 G3/G9.

[b]Includes 14 cases with mixed infection, including 1 G12/G9, 7 G2/G9, and 6 G3/G9.

[c]Includes 20 cases with mixed infection, including 5 P[4]/P[6] and 15 P[6]/P[8].

[d]Includes 17 cases with mixed infection, including 2 P[4]/P[8] and 15 P[6]/P[8].