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Effect of Age at Vaccination on Rotavirus Vaccine Effectiveness in Bolivian Infants

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Abstract

Background—Rotavirus vaccines are less effective in developing countries versus developed countries. One hypothesis for this difference in performance is that higher levels of maternal antibodies in developing countries may interfere with vaccine response, suggesting that delayed dosing could be beneficial. The present analysis aims to assess whether rotavirus vaccine effectiveness (VE) varies by age at vaccination during routine use in Bolivia.

Methods—Data were merged from two post-licensure evaluations of monovalent rotavirus vaccine (RV1) in Bolivia, where two doses of RV1 are recommended at two and four months of age. For each dose, children were classified as receiving each dose "early," "on-time," or "late." Stratified unconditional logistic regression models were used to estimate VE, using unvaccinated children as the referent. VE was calculated as (1 – odds ratio) × 100%. Models were adjusted for hospital, age, and time since RV1 introduction (via including terms for month and year of birth).

Results—VE for two doses of RV1 tended to be higher in infants receiving the first dose early (VE 92%; 95% confidence interval [CI] [70%, 98%]), when compared to infants receiving their first dose on time (72% [62%, 81%]) or late (68% [51%, 79%]). Estimates of VE were not substantially different when comparing children by age at second dose (early: VE 76% [50%, 89%]; on time: VE 70% [50%, 89%]; late: VE 75% [60%, 84%]), including all children.

Conclusions—Our results indicate that early administration may improve VE and support the current WHO recommendations for the RV1 schedule.

Keywords

Rotavirus; Pediatric gastroenteritis; Rotavirus vaccine; Vaccine effectiveness; Global health

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DISCLOSURES AND CONFLICTS OF INTEREST:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention (CDC).

All authors declare that they have no conflict of interest.

INTRODUCTION

Worldwide, diarrheal illnesses caused an estimated 500,000 under-5 deaths in 2015, making them a leading cause of childhood mortality (1). Rotavirus (RV) is the most common cause of severe diarrheal disease in children, accounting for an estimated 36% of diarrheal hospitalizations (2). Although RV occurs worldwide, the brunt of the mortality burden is borne by developing countries, with an estimated 90% of RV-related deaths in 2013 occurring in low-income countries (3). Because RV occurs globally and affects children regardless of individual or community socioeconomic status, vaccination is the preferred strategy to reduce its burden (4).

Two live, oral, attenuated vaccines are currently available for use: Rotarix® (RV1, 2 doses; GlaxoSmithKline) and RotaTeq® (RV5, 3 doses; Merck) (4). The first dose for each vaccine is recommended between 6 and 12 weeks of age, with the subsequent dose(s) to be given with at least a 4-week interval. Both vaccines have demonstrated direct and indirect impact on diarrhea-related morbidity and mortality (5, 6). However, efficacy and effectiveness vary widely by region, with the highest efficacy seen in developed regions including the US and Europe (91% against severe RV diarrhea), and the lowest efficacy seen in developing countries of South Asia and sub-Saharan Africa (46 – 59%) (7). In Latin America, rotavirus vaccination is moderately effective (80%) against severe RV diarrhea (7), but RV-attributable deaths have declined substantially since vaccine introduction (3).

Among other factors, higher levels of maternal antibodies to rotavirus in developing countries are hypothesized to be one of the factors that might interfere with vaccine response and explain the regional disparity in rotavirus vaccine performance. Supporting this hypothesis are data from randomized clinical trials (RCTs) of RV1 in South Africa, the Philippines, and Vietnam showing that a delayed 2-dose schedule of RV1 had a superior immune response to an early 2-dose schedule (8, 9). Similar trends were seen in recent RCTs evaluating RV1 at 6/10 versus 10/14 versus 6/10/14 weeks in Ghana (seroconversion of 29% vs. 37% vs. 43%, respectively) (10) but not in Pakistan (seroconversion of 36% vs. 39% vs. 37%, respectively) (11); however, neither study showed a statistically significant difference between the 6/10 and 10/14 schedules. While immunogenicity of rotavirus vaccines does not necessarily correlate with efficacy, a post hoc analysis of data from a previously conducted RCT of RV5, pooled across three African countries (Ghana, Kenya, Mali) (12), also found a lower efficacy in children receiving the first dose of rotavirus vaccine at < 8 weeks (23.7%; 95% CI: -8.2 – 46.3%) compared to those immunized at ≥ 8 weeks (59.1%; 95% CI: 34.0 – 74.6%).

Given that all of the above studies were RCTs, and that the results are neither definitive or in complete agreement, gathering more data on this question is useful. Existing case-control studies of vaccine effectiveness (VE) provide a means of evaluating the effectiveness of RV vaccine in infants receiving the first dose earlier as compared to later. These evaluations typically leverage existing hospital-based RV surveillance systems and compare RV vaccination completeness in children hospitalized for RV diarrhea versus children hospitalized for non-RV diarrhea. Using data from two post-licensure evaluations in Bolivia (13, 14), we conducted a post-hoc analysis to describe the effectiveness of rotavirus

vaccination 1) in infants who received their first dose early (≤ 56 days) versus on time (57 – 70 days) or late (> 70 days); and 2) in infants who received their second dose early (< 110 days) versus on time (110 – 150 days) or late (> 150 days). In each group, the unvaccinated children act as the reference.

MATERIALS AND METHODS

Study Design and Population

We conducted a post-hoc analysis of data from two case-control VE evaluations conducted in four cities in Bolivia, a lower-middle income country in South America that introduced RV1 in August 2008 (15, 16). The design, methods, and results of these evaluations have previously been reported in detail (13, 14). Briefly, the first evaluation was conducted between March 2010 and June 2011 in six hospitals in four major cities in Bolivia (13), while the second evaluation was conducted between April 2013 and March 2014 in the same four cities in five of the six same hospitals (14). In both studies, children admitted to the hospital for at least one night for the treatment of acute gastroenteritis (AGE; defined as at least 3 loose stools in a 24hr. period prior to hospitalization, with diarrhea lasting < 14 days before hospitalization) were enrolled. Cases were those AGE patients who tested positive for RV by enzyme immunoassay (EIA) testing of a fecal specimen, and controls were AGE patients who tested negative for RV. Cases and controls also had to be age-eligible for RV vaccination (born after June 1, 2008 [6 weeks prior to rotavirus vaccine introduction in Bolivia] and were at least 8 weeks of age upon admission). Although the first evaluation also recruited non-diarrhea hospital controls, these are not used in the present analysis to ensure consistency in controls for the two studies. Vaccine information for participants was confirmed by visual inspection of the vaccination card or clinic record of the child.

Definitions and Statistical Methods

Data from the two evaluations were merged. The immunization schedule in Bolivia recommends two doses of RV1 given at two and four months of age (16). Age at each RV1 dose was calculated from the date of birth and date of immunizations for each child. Improbable or outlying ages at each dose (< 28 days or > 112 days for dose 1; < 75 days or > 365 days for dose 2) were set to missing, and remaining vaccine doses were counted provided they had been administered at least 14 days prior to admission. Categories were based on distribution of age at vaccination, rather than strictly on adherence to the recommended schedule. For dose 1, children were categorized as “early receipt” if their calculated age at vaccination was 28 – 56 days, “on-time receipt” if their calculated age at vaccination was 57 – 70 days, “late receipt” if their calculated age at vaccination was 71 – 112 days, and “unvaccinated” if they did not report receipt of RV1. For dose 2, children were categorized as “early receipt” if their calculated age at vaccination was 75 – 109 days, “on-time receipt” if their calculated age at vaccination was 110 – 150 days, “late receipt” if their calculated age at vaccination was 151 – 365 days, and “unvaccinated” if they did not report receipt of RV1. Children with missing dates for the first dose of vaccine were excluded from all analyses, while children with missing dates for the second dose of vaccine were excluded from the dose-2 analyses. For analyses regarding the timing of dose 2, children who received

only one dose of RV1 were excluded. For all analyses, children less than six months of age at the time of admission were excluded to avoid residual confounding by age.

To assess vaccine effectiveness (VE) in each group, separate unconditional logistic regression models were constructed for "early," "late," and "on-time" receipt, using "unvaccinated" infants as the reference group in each model. We also calculated VE for the overall study population. VE was calculated as (1 – odds ratio) × 100%. Models were adjusted *a priori* for hospital, age, and time since RV1 introduction (via controlling for month and year of birth). Dose 2 models were also adjusted for "early" receipt of dose 1. Potential sociodemographic confounders, including nutritional status, were selected based on bivariate logistic regression on vaccination status and RV status. These were included in final models if their removal changed VE estimates by > 10%. Collinearity was assessed using condition indices and variance inflation factors and found not to be an issue. Statistical comparisons could not be made between vaccination categories given overlapping reference groups.

RESULTS

Participants and Age at RV1 Doses

From the first evaluation, 1116 children (399 cases, 717 controls) were available for analysis (i.e., had sufficient controls, RV test result, and vaccination information); from the second evaluation, 868 children (401 cases, 467 controls) were available for analysis. After excluding children with missing ages at vaccination, unverified vaccination records, and those younger than six months, the final sample size was 1439 (581 cases, 858 controls). Age at the first dose of RV1 was right skewed (Figure 1). The sample included 198 unvaccinated children, 22 children with an "early receipt" of dose 1, 840 children with an "on-time receipt" of dose 1, and 379 with a "late receipt" of dose 1 (Table 1). Unvaccinated children were slightly older at admission than those receiving their first dose of RV1 early, but this difference was not significantly different. Children who received their first dose of RV1 on time had slightly more educated mothers. Nutrition and most household assets were similar across most groups. Unvaccinated children were significantly more likely to have rotavirus-positive diarrhea as compared to children receiving at least one dose of RV1. Age at the second dose of RV1 was also right skewed (Figure 2). Sixty-five children were categorized as receiving dose 2 "early," 807 as receiving dose 2 "on time," and 219 as receiving dose 2 "late." Overall age at admission ranged from 6 months to 58 months (Interquartile range [IQR] 10 – 17 mo.). Among infants completing a full course of RV1, the time between completion of vaccination and admission for AGE ranged from 1 month to 48 months (IQR 5.5 – 13 mo.).

Vaccine Effectiveness

Vaccine effectiveness (VE) for two doses of RV1 tended to be higher in infants receiving the first dose of RV1 early (adjusted VE 92% with 95% confidence interval [CI]: 70 – 98%), when compared to infants receiving their first dose on time (adjusted VE 72% [60 – 81%]) or infants receiving their first dose late (adjusted VE 68% [51 – 79%]), though confidence

intervals were overlapping (Table 2). Estimates of VE for a single dose of RV1 had wide confidence intervals.

Estimates of VE for two doses of RV1 were not substantially different when comparing children by age at receipt of the second dose (adjusted VE 76% [50 – 89%] for early receipt; 70% [57 – 79%] for on-time receipt; 75% [60 – 84%] for late receipt). While the point estimate for early receipt was slightly higher than other groups, confidence intervals were wide and overlapping across all models (Table 3).

DISCUSSION

In this secondary analysis of vaccine effectiveness data from two evaluations in Bolivia, we found that VE tended to be higher in children receiving an earlier first dose of RV1 as compared to children receiving this dose later, although statistical significance could not be evaluated due to overlapping reference groups and small sample size when stratified by age at dose receipt. It may be that VEs are not significantly different when comparing among infants receiving dose 1 early, infants receiving dose 1 on-time, and infants receiving dose 1 later. No meaningful differences were noted based on timing of the receipt of the second dose.

Our results of higher effectiveness in infants receiving RV1 early were in contrast to several studies showing higher immune response in infants receiving RV1 late (8–12), or no differences (17). These differences could be attributable to different study populations: our analysis population was Bolivian, while the previously conducted studies featured African (10, 12, 17) or Asian (9, 11) populations. It is possible that maternal antibody levels in Bolivian mothers could be different from those in Asian or African mothers, thus resulting in different interference. Further, the previous studies primarily used an immunologic rather than a clinical endpoint in a controlled setting, while the present analysis was an observational effectiveness evaluation. It could be that younger infants have not yet experienced as many insults to their gut health, and thus have a healthier gut and gut flora as compared to older infants, and are thus more able to mount an immune response to the vaccine (18). Additionally, age at vaccination may simply be outweighed by other factors in more impoverished settings, as the previous study demonstrating no difference by age was in Pakistan (11).

This analysis is subject to the following limitations. Firstly, because it was a post-hoc analysis of data from two observational evaluations, the number of children in the “early” vaccine receipt strata are quite low, which can negatively impact power and the stability of the estimates. Additionally, statistical significance of differences in VE estimates could not be tested given the fact that each model used the same reference population. Further, it is possible that residual confounding could be present, for instance by the timing of dose 1 in dose 2 models. Nonetheless, the point estimates for the “early” as compared to the “late” dose-1 children are distinct, and this difference was larger in the adjusted model. Secondly, although vaccine records were verified for all participants, it is possible that some infants who are classified as unvaccinated did in fact receive one or more doses of rotavirus vaccine; this would tend to decrease the VE estimates across all groups. Lastly, this analysis only

included children from a single country, so results may not be generalizable to other countries or regions. Though this analysis did not specifically address VE by rotavirus genotype, previous research has demonstrated good effectiveness across strains (19); strain-specific VE estimates from the two evaluations included in the present analysis have been previously reported (13, 14). Strengths of this analysis include the ability to merge data across multiple years of study and the ability to control for age, hospital, and sociodemographics.

In summary, our analysis indicated that early administration of RV1 provides similar and potentially even better protection against severe rotavirus disease as compared to later administration. Though sample sizes were small, this evaluation provides support for keeping current RV-vaccine schedules consistent with standard Expanded Program on Immunization (EPI) immunizations (e.g., at 2 and 4 months of age, coinciding with the first dose of OPV and DTP), as opposed to changing the RV schedule to begin the series in older infants (e.g., giving first dose of rotavirus with the second dose of OPV or DTP). Early administration of RV vaccines could also have the benefit of reducing potential risk of intussusception (20), as well as providing earlier protection from RV. More research is needed in diverse populations to determine the potential impact of changing to an earlier or later dosing schedule for RV vaccines.

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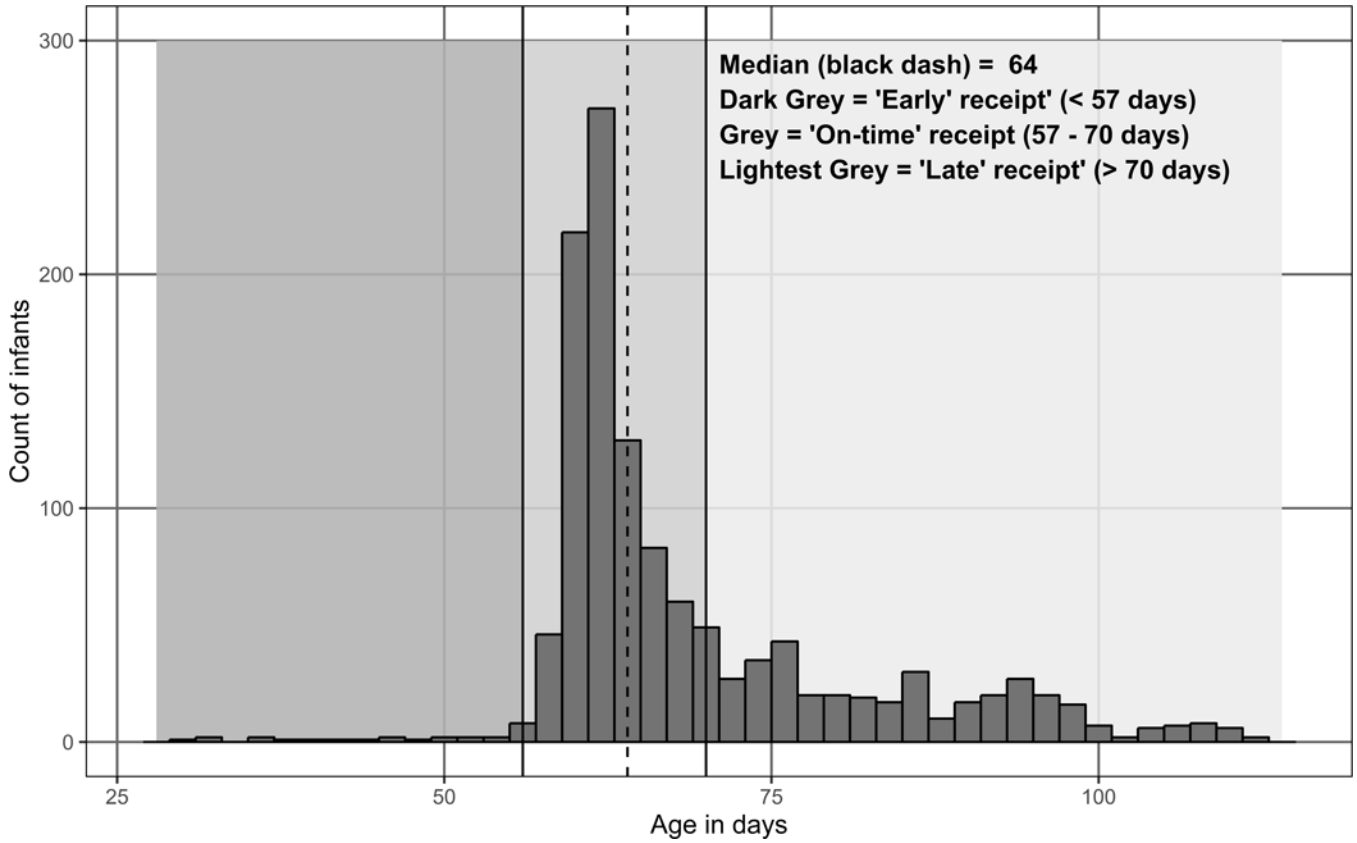

Figure 1. Histogram of age (days) at first dose of RV1 (N = 1241)

Age at first dose of RV1 was right skewed, with a median of 64 days. “Early” receipt is defined as infants < 57 days of age at receipt of first dose. “On-time” receipt is defined as infants 57 – 70 days of age at receipt of first dose. “Late” receipt is defined as infants > 70 days of age at receipt of first dose.

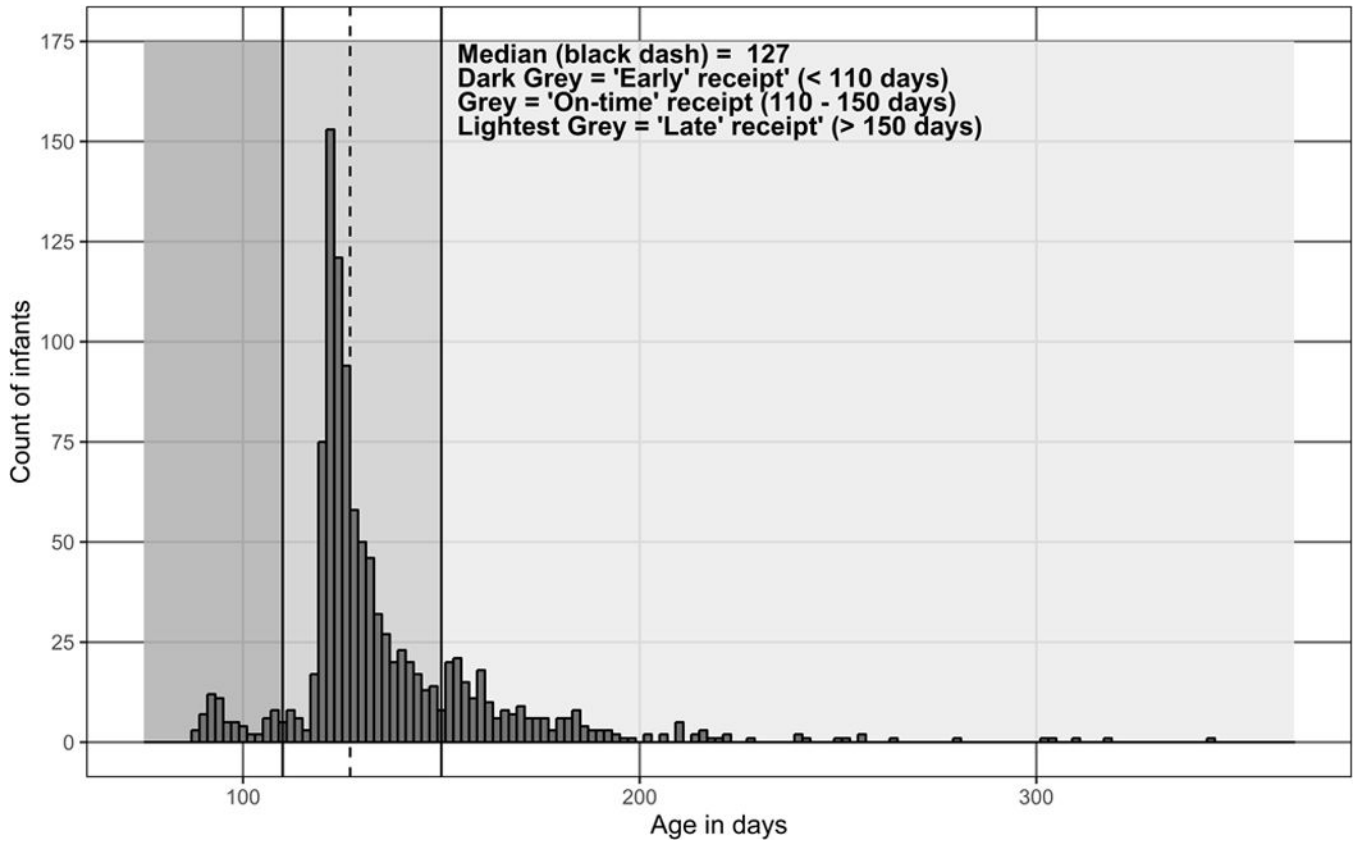

Figure 2. Histogram of age (days) at second dose of RV1 (N = 1091)

Age at second dose of RV1 was right skewed, with a median of 129 days. “Early” receipt is defined as infants 75 – 109 days of age at receipt of first dose. “On-time” receipt is defined as infants 110 – 150 days of age at receipt of first dose. “Late” receipt is defined as infants 151 – 365 days of age at receipt of first dose.

Table 1

Characteristics of the study population by vaccination status

	No vaccination		Early dose 1		On-time dose 1		Late dose 1	
	N or Mean ± SD	%	N or Mean ± SD	%	N or Mean ± SD	%	N or Mean ± SD	%
N								
	198	–	22	–	840	–	379	–
Rotavirus status *								
Rotavirus-positive (case)	128	64.6	6	27.3	293	34.9	154	40.6
Rotavirus-negative (control)	70	35.4	16	72.7	547	65.1	225	59.4
Demographics								
Age (mo) at admission	14.7 ± 7.9	–	14.0 ± 3.7	–	14.7 ± 6.5	–	14.5 ± 6.8	–
Male	102	51.5	11	50.0	408	48.6	205	54.1
Low birth weight (< 2500g) *	19	10.2	0	0.0	55	6.7	56	15.3
Nutrition								
Currently breastfed	117	60.3	13	59.1	534	64	226	60.9
Stunted (Length-for-Age Z score < - 2) *	46	23.8	4	19.0	104	12.9	71	19.3
Wasted (Weight-for-Length / Height Z score < - 2)	45	23.7	4	19.0	144	17.8	76	20.8
Sociodemographics								
Maternal Education *								
Less than secondary	74	38.9	8	38.1	231	28.6	125	34.8
Secondary	101	53.2	10	47.6	415	51.3	177	49.3
University or above	15	7.9	3	14.3	163	20.1	57	15.9
Assets and Utilities								
Electricity	192	97	21	95.5	825	98.2	369	97.4
Refrigerator *	87	43.9	10	45.5	479	57.0	197	52.0
Television	185	93.4	19	86.4	802	95.5	356	93.9
Cell phone	109	55.1	10	45.5	482	57.4	201	53.0

* Indicates significant difference ($p < 0.05$) among groups, using Fisher's Exact Test for categorical variables or ANOVA for continuous variables.

Table 2

Estimates of Vaccine Effectiveness, Stratified by Age at Dose 1*

	Overall				Early Dose 1 (< 57 days)				On-time Dose 1 (57 - 70 days)				Late Dose 1 (> 70 days)			
	N	**VE**	**95% CI**	**P value**	**N**	**VE**	**95% CI**	**P value**	**N**	**VE**	**95% CI**	**P value**	**N**	**VE**	**95% CI**	**P value**
Crude model																
No doses	198	ref	–	–	198	ref	–	–	198	ref	–	–	198	ref	–	–
1 dose	147	40	(7, 61)	0.022	4	45	(-364, 94)	0.55	69	29	(-25, 59)	0.23	74	48	(11, 70)	0.017
2 doses	1094	71	(61, 79)	< 0.0001	18	84	(55, 96)	0.002	771	73	(63, 81)	< 0.0001	304	65	(50, 76)	< 0.0001
Fully adjusted (hospital, mo / yr, maternal education, stunting)																
No doses	198	ref	–	–	198	ref	–	–	198	ref	–	–	198	ref	–	–
1 dose	147	23	(−24, 53)	0.28	4	56	(−351, 96)	0.47	69	17	(−59, 56)	0.58	74	28	(−32, 61)	0.28
2 doses	1094	70	(58, 79)	< 0.0001	18	92	(70, 98)	0.0006	771	72	(60, 81)	< 0.0001	305	68	(51, 79)	< 0.0001

*Overall estimates exclude those with missing date information for dose 1.

Table 3

Estimates of Vaccine Effectiveness, Stratified by Age at Dose 2

	Overall*				Early Dose 2 (< 110 days)				On-time Dose 2 (110 – 150 days)				Late Dose 2 (> 150 days)			
	N	**VE**	**95% CI**	**P value**	**N**	**VE**	**95% CI**	**P value**	**N**	**VE**	**95% CI**	**P value**	**N**	**VE**	**95% CI**	**P value**
Crude model																
No doses	198	ref	–	–	198	ref	–	–	198	ref	–	–	198	ref	–	–
2 doses	1091	71	(61, 79)	< 0.0001	65	77	(59, 88)	< 0.0001	807	71	(60, 79)	< 0.0001	219	70	(56, 80)	< 0.0001
Fully adjusted (hospital, mo / yr, maternal education, stunting, "early" receipt of dose 1)																
No doses	198	ref	–	–	198	ref	–	–	198	ref	–	–	198	ref	–	–
2 doses	1091	71	(58, 79)	< 0.0001	65	76	(50, 89)	0.0007	807	70	(57, 79)	< 0.0001	219	75	(60, 84)	< 0.0001

*Overall estimates exclude those with missing date information for either dose, and those with only 1 dose.