EPIDEMIOLOGY

Impact of dosing schedules on performance of rotavirus vaccines in Ghana

Ernest O. Asare[1,2]*, Mohammad A. Al-Mamun[3], George E. Armah[4], Benjamin A. Lopman[5], Virginia E. Pitzer[1,2]

There is currently limited evidence regarding how the rotavirus vaccine dosing schedule might be adjusted to improve vaccine performance. We quantified the impact of the previously implemented 6/10-week Rotarix vaccine (RV1) in Ghana to the model-predicted impact for other vaccine dosing schedules across three hospitals and the entire country. Compared to no vaccination, the model-estimated median percentage reductions in rotavirus ranged from 28 to 85% and 12 to 71% among children <1 and <5 years old, respectively. The median predicted reductions in rotavirus for the whole country ranged from 57 to 66% among infants <1 year and 35 to 45% among children <5 years old. The 1/6/10- and 6/10/14-week schedules provided the best and comparable reductions in rotavirus compared to the original 6/10-week schedule. A third dose could prevent an additional 9 to 14% of deaths. An additional dose of RV1 might be an effective strategy to improve rotavirus vaccine impact, particularly in settings with low vaccine effectiveness.

INTRODUCTION

Routine rotavirus vaccination has been recommended by the World Health Organization (WHO) as the most effective way to protect infants from rotavirus-associated gastroenteritis (RVGE) morbidity and mortality (*1*). Since the introduction of the rotavirus vaccine, there has been a substantial reduction in severe rotavirus diarrhea, rotavirus hospitalizations, and rotavirus mortality among children <5 years old (*2*, *3*). However, there is a clear differential in vaccine performance between low- and middle-income countries (LMICs) and high-income countries (HICs), with low to moderate vaccine performance in LMICs (*4*). In addition to this setting-specific variation, there is evidence of within-country variability in the impact of rotavirus vaccine, attributed to disparities in vaccine response, duration of vaccine-induced immunity, and rotavirus epidemiology (*5*). Therefore, it is imperative to understand the factors driving this disparity in vaccine impact in order to identify more effective strategies for improving rotavirus vaccine performance across LMICs (*6*).

The monovalent Rotarix vaccine was introduced in the Ghana routine Expanded Program on Immunization in April 2012, with two doses recommended at 6 and 10 weeks of age (*7*). Ghana subsequently switched to the ROTAVAC vaccine in 2020 with a three-dose schedule given at 6, 10, and 14 weeks. Despite high vaccination coverage (from 42% in 2012 to 94% in 2022) (*8*, *9*), there has been a varied and modest vaccine impact against RVGE in Ghana compared to HICs (*5*, *10*, *11*). Several factors such as co-infections and time of first infection (*12*–*14*), malnutrition (*15*), infant gut microbiome composition (*16*), and maternal antibodies (*17*) have been identified as factors explaining the differential rotavirus vaccine performance between HICs and LMICs, including Ghana. Another important factor that could influence vaccine performance is the dosing schedule; however, this has received relatively little attention to date.

Although the WHO recommended the removal of age restrictions for rotavirus vaccines due to the low risk of intussusception associated with the vaccine (*1*), most countries are still using the manufacturer-recommended vaccine dosing schedules (*18*). The reason for this may be partly due to the lack of evidence demonstrating the benefits of changing the dosing schedules for vaccine effectiveness and impact. The current flexibility in the dosing schedule provides an opportunity for countries to identify the optimal dosing schedule based on pre- and postvaccination rotavirus epidemiology. This dosing schedule flexibility is equally important for countries considering the introduction of rotavirus vaccine as it is for countries that want to switch vaccines or maintain their current vaccine program. However, there has been limited effort to assess the impact of different dosing schedules on the performance of rotavirus vaccines. One study from Ghana showed higher rates of seroconversion following three doses compared to the originally recommended 6- and 10-week schedule, but it is unclear how this might correspond to increased vaccine effectiveness and impact (*7*).

As a complement to clinical trials, mathematical models can be used to investigate the potential impact of dosing schedules on the performance of rotavirus vaccines. However, before these models can be used, it is important to first validate their performance. Several dynamical models have been developed to examine the impact of rotavirus vaccination on morbidity and mortality due to rotavirus (*19*). One widely used model for examining the transmission dynamics of rotavirus and the impact of vaccination was developed by Pitzer *et al.* (*20*). Previous validation of the model showed that it can predict both pre- and postvaccination rotavirus seasonal patterns and age distributions across different settings, including Ghana (*5*, *19*, *21*, *22*).

We used our previously validated mathematical model of rotavirus transmission dynamics to quantify the potential impact of changes to dosing schedules on the performance of rotavirus vaccines in Ghana. We sampled from model parameters estimated from fitting to data from three hospitals in different regions of Ghana separately to project the overall impact of different rotavirus vaccine dosing schedules over a 10-year period from April 2012 to March 2022. Our goal was to provide evidence supporting the potential benefits of different dosing schedules for rotavirus vaccine implementation.

[1]Department of Epidemiology of Microbial Diseases, Yale School of Public Health, Yale University, New Haven, CT, USA. [2]Public Health Modeling Unit, Yale School of Public Health, Yale University, New Haven, CT, USA. [3]Department of Pharmaceutical Systems and Policy, School of Pharmacy, West Virginia University, Morgantown, WV, USA. [4]Noguchi Memorial Institute for Medical Research, University of Ghana, Accra, Ghana. [5]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA.
*Corresponding author. Email: ernest.asare@yale.edu, eoheneasare@gmail.com

RESULTS

In the absence of rotavirus vaccination, the model estimated that the average annual incidence of moderate-to-severe RVGE would range between 2457 and 3497 cases per 100,000 person-years among children <5 years old over the 10-year period for the three settings (Table 1). The model-projected average annual incidence postvaccination varied substantially depending on both the estimated vaccine response rate (proportion of infants who responded to the first dose, S_{C1}; and proportion of infants who responded to the second dose, S_{C2}) and duration of vaccine-induced immunity ($1/\omega_{vh}$). For Accra, where we estimated a high vaccine response rate and longer duration of vaccine-induced immunity (see Table 2), the projected average annual incidence of RVGE was lowest, ranging from 854 to 1221 per 100,000 (Table 1). On the other hand, in Navrongo, with a lower vaccine response rate and shorter duration of immunity (see Table 2), the projected incidence was highest, ranging from 2743 to 3003 per 100,000. For Kumasi, the projected incidence was intermediate (ranging from 933 to 1348 per 100,000) (Table 1). The time series and age distribution of model-projected rotavirus infections across the three sites are provided in the Supplementary Materials (see section S2 for details). The results were similar assuming a homogeneous vaccine response (see section S3).

Compared to no vaccination (baseline), the estimated median percentage reduction in moderate-to-severe RVGE among children <5 years varied between dosing schedules and across settings, ranging from 55 to 71% for Accra, 36 to 55% for Kumasi, and 12 to 20% for Navrongo over the 10-year period following vaccine implementation (Fig. 1A). Among children <1 year, substantially greater median percent reductions in RVGE were predicted, ranging from 73 to 85% for Accra, 57 to 74% for Kumasi, and 28 to 36% for Navrongo (Fig. 1B). The difference in the predicted median percent reduction across settings is lower among children under the age of 1 year (threefold) than among children under the age of 5 years (sixfold). The estimated reduction differed across schedules, with higher reductions predicted for the three-dose compared to the two-dose schedules. The 6/10/14 and 1/6/10 weeks schedules provided the best and comparable vaccine

Table 1. The average and range of model-projected moderate-to-severe RVGE incidence over a 10-year period across the three sites and the whole country (cases per 100,000 person-years among children <5 years old).

Schedule	Accra	Kumasi	Navrongo	Ghana
Novacc	2731 (2653–2857)	2457 (2386–2568)	3497 (3421–3867)	3312 (3287–3332)
6/10	1151 (920–1694)	1303 (974–1573)	3002 (2765–3160)	2124 (1825–2632)
10/14	1221 (1002–1713)	1348 (1041–1539)	3003 (2774–3167)	2123 (1813–2555)
6/10/14	874 (519–1679)	946 (693–1509)	2743 (2463–2938)	1797 (1528–2597)
6/10/40	930 (589–1693)	1130 (834–1569)	2888 (2580–3075)	1869 (1628–2626)
1/6/10	854 (493–1740)	933 (670–1621)	2749 (2475–3011)	1814 (1537–2704)
1/10/14	896 (549–1753)	1100 (818–1684)	2810 (2515–3027)	1834 (1565–2709)

Table 2. Previously estimated model parameters obtained from mathematical models fitted to pre- and post-vaccination rotavirus surveillance data from three different hospitals (Accra, Kumasi, and Navrongo). The values in parentheses are 95% CIs. See Asare *et al.* (*5*) for more details on how the model parameters were estimated. Detailed definitions of the model parameters are provided in table S1. The S_{C1}, S_{C2}, and ω_{vh} were estimated assuming heterogeneity in the vaccine response rate (see the Supplementary Materials for details).

Parameter	Definition	Accra	Kumasi	Navrongo
R_0	Basic reproductive number	37.861 (36.22–39.54)	33.661 (29.50–36.20)	31.529 (30.36–32.78)
$1/\omega_m$	Average duration of maternal immunity (months)	4.838 (4.46–5.23)	4.714 (3.46–5.75)	1.890 (0.39–3.18)
b_1	Amplitude of annual seasonal forcing	0.077	0.167	0.999
ϕ_1	Annual seasonal offset (months)	7.203	4.127	1.05
b_2	Amplitude of biannual seasonal forcing	0.132	0.498	6.63E−08
ϕ_2	Biannual seasonal offset (months)	1.037	1.055	5.125
h	Proportion of moderate-to-severe diarrhea cases reported	0.107	0.017	0.012
d_3	Proportion of subsequent infections that are severe	9.54E−06	3.09E−07	2.54E−05
S_C	Vaccine response rate (homogeneous response)	0.989 (0.71–1.00)	0.649 (0.42–0.88)	0.203 (0.08–0.32)
$1/\omega_v$	Duration of vaccine-induced immunity assuming homogeneous response (months)	24.102 (11.11–48.38)	5.33 (1.23–14.29)	5.26 (2.46–8.40)
S_{C1}	Proportion who responded to the first dose	0.988 (0.64–1.00)	0.989 (0.68–1.00)	0.612 (0.36–0.87)
S_{C2}	Proportion who responded to the second dose	0.878 (0.75–1.00)	0.892 (0.46–1.00)	0.19 (0.11–0.48)
$1/\omega_{vh}$	Duration of vaccine-induced immunity assuming heterogeneous vaccine response (months)	46.451 (12.20–83.33)	8.194 (2.90–15.36)	5.465 (3.16–8.33)

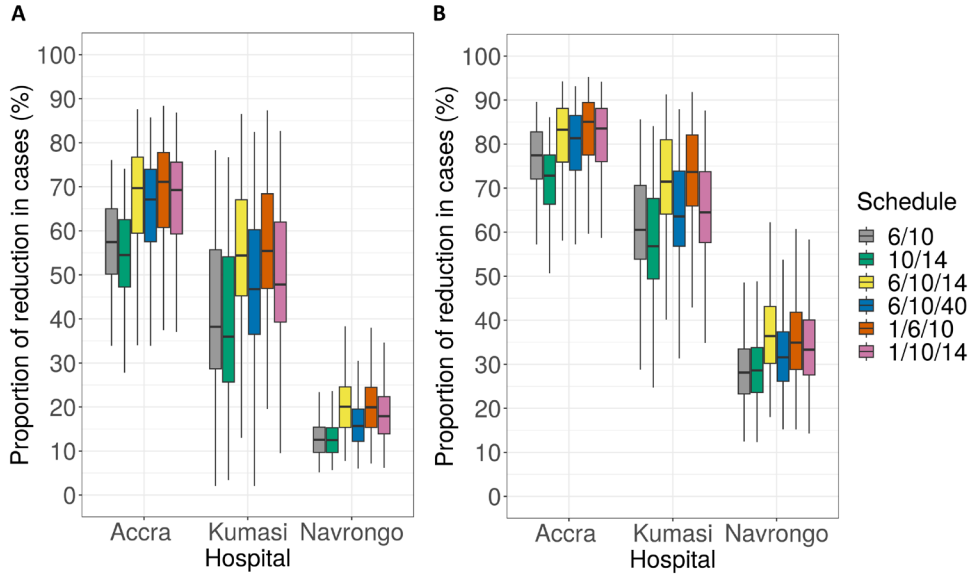

Fig. 1. Boxplots of the distribution of the model-projected percentage reductions in rotavirus over the three settings in Ghana between April 2012 and March 2022 using setting-specific estimated model parameters. (**A**) Children <5 years of age and (**B**) children <1 year of age. The colors indicate the various dosing schedules.

impact, while the lowest and comparable vaccine was predicted for 6/10 and 10/14 weeks schedules. Among the three-dose schedules, the 6/10/40 schedule had a slightly lower predicted vaccine impact. Results were similar, assuming homogeneity in vaccine response, with greater reductions in RVGE incidence for the three-dose schedules, particularly in Accra (see section S3).

The results from the overall Ghana scenario (i.e., when we sampled from the full range of estimated model parameters from the three different sites) are shown in Fig. 2. In the absence of vaccination, the highest model-projected number of RVGE cases per month was 928 (<5 years old) and 602 (<1 year old) (Fig. 2, A and B). In the absence of vaccination, we estimated that the average annual mean rotavirus incidence over Ghana would have been 3312 (range 3287 to 3332) per 100,000 over the 10-year period (Table 1). With vaccination, average annual mean rotavirus incidence would range from 1797 (6/10/14 weeks) to 2124 (6/10 weeks) per 100,000. The estimated median reduction was highest (45%) and lowest (35%) with the 6/10/14 and 10/14 weeks schedule, respectively (Fig. 2C). Among children <1 year of age, the median percent reductions tended to be higher, ranging between 57% (10/14 weeks) and 66% (6/10/14 weeks) (Fig. 2D).

Without vaccination, the model estimated 384 [95% confidence interval (CI), 344 to 424] and 50 (95% CI, 45 to 55) deaths per 100,000 person-years among individuals aged <1 and 1 to 4 years, respectively (Table 3). With vaccination, the predicted number of rotavirus deaths ranged between 145 (95% CI, 130 to 160) and 173 (95% CI, 154 to 191) for those aged <1 year and 50 (95% CI, 45 to 56) and 58 (95% CI, 52 to 64) for those aged 1 to 4 years. Slightly more deaths were predicted to occur among 1- to 4-year-old under the two-dose schedules compared to no vaccination, but adding a third dose partially alleviated this shift in the burden and could prevent an additional 9 to 14% of deaths compared to the current 6/10 schedule. Using no vaccination as the baseline, the estimated number needed to vaccinate (NNV) ranged from 712 to 835 to avert a single moderate-to-severe RVGE case and from 101,000 to 133,000 to prevent a single death (Table 4).

DISCUSSION

Currently, there is a lack of substantial evidence on the effect of dosing schedules on the potential impact of rotavirus vaccines, resulting in countries still using the manufacturers' recommended schedules. Our results demonstrate substantial differences in model-projected vaccine impact across different dosing schedules in Ghana, in particular between three-dose and two-dose schedules. A three-dose schedule could provide considerable improvements in vaccine impact compared to the commonly used two-dose schedule (6/10 and 10/14 weeks) across LMICs. Thus, implementing optimal dosing schedules may substantially improve rotavirus vaccine performance in LMICs.

Despite the modest performance of the vaccine in Navrongo, our projected vaccine impact over Ghana is substantial, ranging from 35 to 45% (for those under 5 years old) and 57 to 66% (for those under 1 year old) median reductions in moderate-to-severe RVGE compared to no vaccination. The disparities in vaccine performance across the sites further reveal that studies aimed at evaluating the country-level effectiveness of rotavirus vaccines should consider multiple sites instead of just one in order to provide a more accurate estimate of the vaccine's impact. Overall, we have shown that the rotavirus vaccine provides substantial health benefits and should be sustained in Ghana.

In the absence of vaccination, the model predicts rotavirus incidence patterns similar to general diarrhea patterns in Ghana (i.e., lower and comparable incidence in Accra and Kumasi and higher incidence in Navrongo) (*23*). The reasons underlying this may be due to a combination of important factors affecting rotavirus infections, which tend to be favorable in the northern part of the country. Compared to the southern part of the country, the northern part is associated with a high prevalence of childhood malnutrition (*24*), low coverage of water, sanitation, and hygiene infrastructure (*25*), and early exposure to rotavirus infection (*26*, *27*).

Our results reveal substantial differences in the model-projected percentage reduction in RVGE cases across dosing schedules. Compared to no vaccination, three-dose schedules resulted in a higher

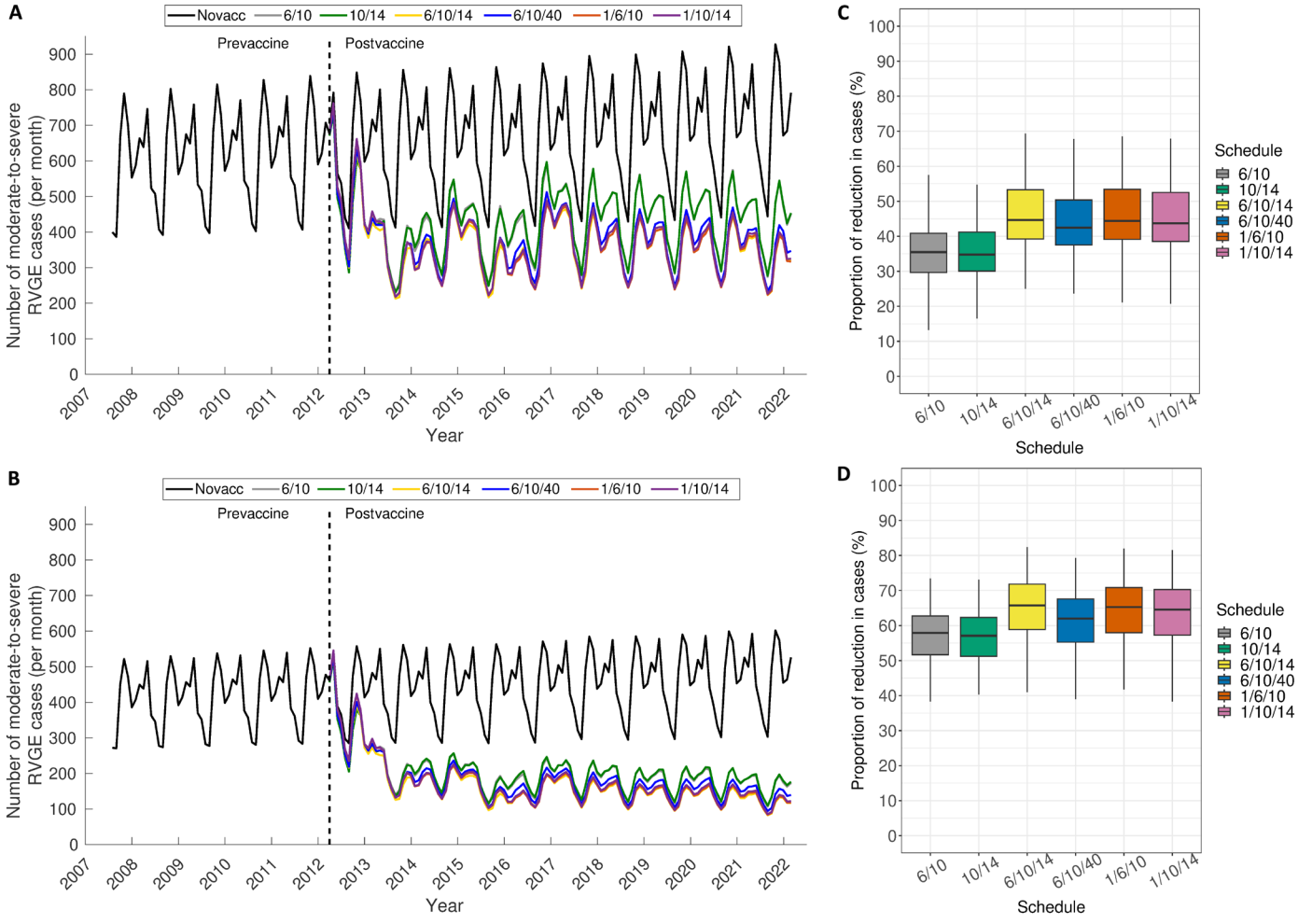

Fig. 2. The model projection of rotavirus vaccination over Ghana between April 2012 and March 2022. Time series of average model projected monthly rotavirus cases among children <5 years of age (**A**) and <1 year of age (**B**). The lines represent the average from 100 simulations sampled from the range of model-estimated parameters for Accra and Navrongo representing the extremes of rotavirus epidemiology in Ghana. Boxplots of the distribution of the model-projected percentage reductions in RVGE over Ghana for children <5 years of age (**C**) and <1 year of age (**D**).

Table 3. Rotavirus-caused deaths among individuals aged 1 year and 1 to 4 years per 100,000 person-years over a 10-year period in Ghana.

Schedule	<1 year	1–4 years
Novacc	384 (344–424)	50 (45–55)
6/10	173 (154–191)	58 (52–64)
10/14	173 (155–191)	58 (52–64)
6/10/14	145 (130–160)	51 (45–56)
6/10/40	157 (133–164)	51 (45–56)
1/6/10	149 (133–164)	50 (45–56)
1/10/14	151 (135–166)	51 (46–56)

percentage reduction in rotavirus cases compared to the two-dose schedules. This is consistent with data from a randomized clinical trial in Navrongo, Ghana that found a higher seroconversion rate in infants who received three doses compared to those who received two doses of the Rotarix vaccine (*7*). However, this higher vaccine response in three-dose compared with two-dose recipients is not consistent across LMICs, with some trials showing a higher response rate in two-dose recipients (*28*, *29*). We also found moderate to substantial variations in the predicted percentage reduction in RVGE among different dosing schedules with the same number of doses, in particular when the duration of vaccine-induced immunity was assumed to be shorter. Thus, both the number and timing

Table 4. The NNV to prevent one case and one death of moderate-to-severe RVGE among children 5 years old in Ghana over the 10-year period (April 2012 and March 2022).

Schedule	Cases	Deaths (×1000)
6/10	720 (529–784)	102 (69–113)
10/14	712 (530–773)	101 (69–112)
6/10/14	794 (603–858)	129 (87–143)
6/10/40	835 (620–908)	133 (91–148)
1/6/10	817 (617–885)	133 (90–147)
1/10/14	828 (619–899)	133 (90–147)

of doses administered is important when considering the optimal dosing schedule, which should be carefully selected based on country-specific rotavirus epidemiology.

The highest reductions in RVGE were predicted using parameters estimated from models fitted to the observed vaccine impact in Accra (associated with a higher R_0, higher vaccine response rate, and longer duration of vaccine-induced immunity), while the lowest were predicted with estimates from Navrongo (associated with a lower R_0, lower vaccine response rate, and shorter duration of vaccine-induced immunity). These findings suggest that alternative or next-generation vaccines with superior effectiveness relative to the current infant rotavirus vaccines are likely to reduce the rotavirus burden across LMICs. However, even with a comparable vaccine response rate between LMICs and HICs, the higher rotavirus transmission rate typically estimated for LMICs compared to HICs (*21*, *22*, *30*) could still result in a lower vaccine impact in LMICs, but these differences are likely to be minimal compared to what is currently observed. While improvements in sanitation and hygiene practices are likely to reduce the transmission rate of rotavirus, strategies aimed at improving the vaccine response rate in LMICs might have a greater effect in reducing RVGE incidence in these settings.

The timing of vaccination in relation to the age of first rotavirus infection may also play an important role in explaining differences in the predicted reduction in RVGE across the dosing schedules. Several studies have shown that infants who have been infected before vaccination are less likely to seroconvert (*12*, *13*, *27*). Thus, the first dose of the vaccine needs to be administered early in LMICs before infants are exposed to their first infection to maximize vaccine protection. For instance, a two-dose schedule of reassortant rotavirus tetravalent vaccine with the first dose administered within 1 month of age provided an efficacy of 63% in Navrongo (*27*), which is greater than what has been reported for another trial with an infant schedule in Ghana (*31*). Our results provide some evidence to support this hypothesis, with neonatal schedules (1/6/10 and 1/10/14 weeks) predicted to provide a comparable reduction in RVGE to a 6/10/14 weeks schedule in Navrongo, where we observed earlier infections associated with a shorter estimated duration of maternal immunity (*5*). While neonatal rotavirus vaccines have yet to be licensed, our results demonstrate that they could offer improved vaccine performance, as higher vaccine efficacies have been reported for neonatal compared to infant dosing schedules (*32*, *33*). In addition, there is also the potential for an increase in vaccination coverage when the first dose is administered at birth (*34*).

While there are financial and logistical challenges to adding a dose to the rotavirus vaccine schedule (*35*), these three-dose schedules could easily be included in existing infant immunization programs. For example, the cost of Ghana switching to the three-dose ROTAVAC vaccine in 2020 was estimated to be over $800,000 (*35*), but the implementation challenges were limited. For the three-dose 6/10/40-week schedule, the timing of the third dose coincides with the first dose of measles-containing vaccine, whereas the initial dose of the neonatal schedule (1/6/10 and 1/10/14 weeks) would be administered at birth along with the Bacille Calmette-Guérin vaccine.

The interplay between the duration of vaccine-induced immunity and the interval between doses can also influence the performance of different dosing schedules. The interval between doses should ideally be shorter than the duration of vaccine-induced immunity. For instance, when the vaccine-induced immunity was assumed to be shorter (5 to 6 months for Kumasi and Navrongo), the median predicted reduction in RVGE from the booster dose schedule (6/10/40) is substantially lower than the other three-dose schedules. This could be due to the long interval (~6 months) between the second and third doses for the 6/10/40 schedule. Using the same model fitted to data from Malawi, a third dose administered at 9 months of age was predicted to provide only a modest improvement in vaccine impact compared to the current 6/10 schedule (*21*). While a booster or additional doses have been suggested as a strategy for increasing vaccine performance in LMICs, optimal timing for additional doses and the interdose period need to be determined based on the duration of vaccine-induced immunity and rotavirus epidemiology of the country.

An important limitation of this study is that we used the same estimated vaccine response rate and duration of vaccine-induced immunity values obtained when the model was previously fitted to rotavirus surveillance following introduction of a two-dose monovalent Rotarix vaccine given at 6 and 10 weeks of age in Ghana to evaluate all of the different dosing schedules. Also, the fixed parameters of the model were derived from cohort studies conducted elsewhere. For instance, the relative risk of second and third infections came from cohort studies conducted in Mexico and India (*36*, *37*). While the relative risk of infection was remarkably consistent between the Mexico and India cohorts, these parameters may vary across settings and are likely to have an impact on the results. Last, our results cannot be generalized to other three-dose rotavirus vaccines due to variations in effectiveness as quantified by the vaccine response rate and duration of vaccine-induced immunity across rotavirus vaccine products. Nevertheless, our model could be used to evaluate the potential impact of other rotavirus vaccine products given such information. The current ongoing neonatal rotavirus vaccine trial in Ghana provides an opportunity to re-evaluate the

performance of neonatal dosing schedules against previously (Rotarix) and currently (ROTAVAC) used vaccines in Ghana.

Currently, there is insufficient evidence from randomized clinical trials demonstrating the importance of dosing schedules on rotavirus vaccine performance. Using a mathematical model, we have provided quantitative insights about the potential effect of different dosing schedules on rotavirus vaccine impact. Overall, in Ghana, the three-dose schedules consistently resulted in greater reductions in both rotavirus cases and deaths in comparison with the two-dose schedules despite the differences in rotavirus epidemiology and vaccine performance across the three sites, with the 1/6/10-weeks schedule providing a modestly better impact than the other three-dose schedules. The relative impact of a third dose of Rotarix vaccine in reducing morbidity and mortality is more substantial among <1-year-olds compared with older age groups. Since Rotarix is the most commonly used vaccine in LMICs, evaluating the impact of a third dose across settings remains relevant to rotavirus vaccine policy. Future research should aim to determine whether it would be cost-effective to include additional vaccine doses, considering the increased costs indicated by the schedule-specific NNV, to avert a single moderate-to-severe RVGE case and death. Furthermore, there is a need to evaluate the impact and cost-effectiveness of four-dose schedules compared to three-dose schedules. Given that the WHO has recommended removal of the age restrictions for rotavirus vaccines, it is essential that countries consider alternative dosing schedules and identify the optimal dosing schedule to improve vaccine performance in LMICs. Our model can be a useful tool to identify the optimal country-specific vaccine schedule for countries considering the introduction of a rotavirus vaccine or switching to a different vaccine.

MATERIALS AND METHODS

Model description

We used a previously developed age-structured compartmental model of rotavirus transmission dynamics introduced by Pitzer *et al.* (*20*), which has been used widely and validated extensively for both pre- and post-vaccination rotavirus transmission dynamics across different settings (*5*, *19*, *21*, *22*). A detailed description of the model is provided in the section S1. In this study, we use previously estimated parameters (Table 2) obtained when the models were fitted separately to prevaccination rotavirus inpatient surveillance data from three different hospitals in Ghana (Korle-Bu Teaching Hospital in Accra, Komfo Anokye Teaching Hospital in Kumasi and War Memorial Hospital in Navrongo) (*5*) to simulate overall rotavirus patterns in Ghana between April 2012 and March 2022. Note that the estimated values of R_0 are dependent on the model structure and should not be overinterpreted (*19*). Model vaccine effectiveness estimates (as quantified by the vaccine response rate and duration of vaccine-induced immunity) were based on the observed impact of the Rotarix vaccine introduced in Ghana in April 2012. We previously estimated a substantially higher vaccine response rate and duration of vaccine-induced immunity in Accra compared to Navrongo, with intermediate values estimated for Kumasi (Table 2).

We assumed homogeneous mixing (i.e., equal probabilities of contact, transmission, and infection across all age groups). This assumption is widely used in rotavirus modeling and tends to provide realistic estimates of rotavirus age patterns (*22*, *30*, *38*). We assumed that the severity of infections decreases with an increasing number of previous infections. Since the first infection is usually the most severe and occurs at an early age, the severity of the infection is indirectly age specific. The model was divided into 42 age groups, comprising monthly intervals for infants less than 2 years, yearly intervals from 2 to 4 years, 5-year intervals from 5 to 70 years, and those above 70 years.

Vaccine coverage was assumed to be fixed and ranged from 42% in 2012 to 94% in 2022 based on data from the Ghana Health Service (for details, see https://doi.org/doi:10.5061/dryad.4mw6m90kv) (*8*, *9*). We assumed equal vaccination coverage for all doses across schedules. This assumption is based on the fact that the previous Rotarix vaccine coverage data for dose 1 (6 weeks) and dose 2 (10 weeks) in Ghana is comparable (*39*). Furthermore, the coverage of DPT1 and DPT3 vaccination is similar in Ghana (*9*). The aim was to estimate the impact of these schedules while keeping other variables fixed.

We explored two different scenarios for the vaccine response. For our main analysis, we assumed heterogeneity in vaccine response, in which the probability of "responding" to subsequent vaccine doses (and moving to an immunized compartment in the model) is lower for those who failed to respond to the first dose. Since the model was fitted to surveillance data under the current two-dose schedule, we assumed that the proportion of infants who would respond to the third dose (for the three-dose schedules) was the same as the proportion estimated to respond to the second dose. As a sensitivity analysis, we assumed homogeneity in vaccine response, in which the probability of responding to each vaccine dose is equal and independent. See the Supplementary Materials for details.

Rotavirus vaccine dosing schedules

We explored various vaccine dosing schedules (Table 5) including current two- and three-dose infant dosing schedules (6/10, 10/14, and 6/10/14 weeks), neonatal dosing schedules (1/6/10 and 1/10/14 weeks) and a booster dosing schedule (6/10/40 weeks). The number of doses

Table 5. List of considered dosing schedules, the number of doses, and age of infants for vaccine administration in the model.

Schedule (weeks)	Number of doses	Age at vaccination (months)
1/6/10	3	0, 2, 3
1/10/14	3	0, 3, 4
6/10/14	3	2, 3, 4
6/10/40	3	2, 3, 9
6/10	2	2, 3
10/14	2	3, 4

and age at which infants receive different doses of the vaccine for each schedule are provided in Table 5. Since the model assumes monthly age classes up to age 2, and to reflect the observed timeliness of vaccine administration (*40*), the age of vaccination is approximated to the nearest month. For example, we assume that, on average, infants receive the 6-week dose when they age into the 2-month age group and the 10-week dose when they age into the 3-month age group.

The rationale behind these three infant schedules (6/10, 10/14, and 6/10/14 weeks) is that they have been used in clinical trials of the Rotarix vaccine (*41*). We also considered a neonatal schedule, which has been used in clinical trials for the RV3-BB vaccine in development (*33*). Last, the booster dose was evaluated to determine whether a delayed third dose of the Rotarix vaccine at 9 months will reduce the shift in rotavirus burden to older infants following vaccine introduction (*42*).

Simulations of the different dosing schedules

We used a beta distribution (*43*) to sample from the 95% CIs of four key model parameters (transmission rate, duration of maternal immunity, vaccine response rate, and duration of vaccine-induced immunity) while using the mean estimates of the other parameters (Table 2). For each setting, 100 parameter sets were generated to predict rotavirus vaccine impact. To simulate rotavirus vaccine impact for the entire country, we sampled from beta distributions of the key model parameters, with the upper and lower bounds defined by the point estimates from Accra and Navrongo, respectively (Table 2).

The overall effect of vaccination for each of the dosing schedules over the 10-year period (April 2012 to March 2022) was calculated as a percentage change using no vaccination as a baseline. The percentage reduction for each of the dosing schedules is given by

$$\text{percentage reduction}\,(\%) = \left(\frac{\text{no vaccination} - \text{vaccination}}{\text{no vaccination}}\right) * 100$$

where "vaccination" and "no vaccination" indicate model-estimated moderate-to-severe RVGE cases with and without vaccination, respectively.

Furthermore, we estimated the rotavirus-caused mortality by multiplying the model-estimated incidence of moderate-to-severe RVGE under each schedule by the rotavirus case fatality risk (CFR). The rotavirus-specific CFR data were extracted from across the WHO Africa region from a previously published systematic review (*44*). The pooled age-stratified CFR and associated 95% CI were estimated using a random-effects model. The estimated age-stratified CFR was 1.2% (95% CI, 0.2 to 6.9%) and 0.9% (95% CI, 0.3 to 2.7%) among those aged <1 year and 1 to 4 years, respectively. Within these CIs, we sampled uniformly and multiplied the model-predicted incidence of moderate-to-severe RVGE by the CFR to estimate the mortality attributed to rotavirus in Ghana.

Last, we calculated the NNV to avert one case and one death due to moderate-to-severe RVGE among children <5 years of age for the vaccine schedules. The estimated NNV for each schedule over the 10-year period was calculated by dividing the cumulative model-estimated number of vaccination doses by the averted moderate-to-severe RVGE cases or deaths (using no vaccination as the reference).

Supplementary Materials

This PDF file includes:

Supplementary Text
Figs. S1 to S6
Table S1
References

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Acknowledgments

Funding: This work was supported by the National Institutes of Health/National Institute of Allergy and Infectious Diseases grant R01AI112970 (V.E.P.). **Author contributions:** Conceptualization: E.O.A., V.E.P., B.A.L., and G.E.A. Methodology: E.O.A., V.E.P., G.E.A., B.A.L., and M.A.A.-M. Investigation: E.O.A., V.E.P., G.E.A., M.A.A.-M. Visualization: E.O.A., V.E.P., B.A.L., M.A.A.-M. Supervision: G.E.A., B.A.L., and V.E.P. Writing–original draft: E.O.A. Writing–review and editing: E.O.A., M.A.A.-M., G.E.A., B.A.L., and V.E.P. **Competing interests:** V.E.P. is a member of the WHO Immunization and Vaccine–related Implementation Research Advisory Committee (IVIR-AC). The other authors declare that they have no other competing interests. **Data and materials availability:** All data and code needed to evaluate the conclusions in the paper are available in the paper and/or the Supplementary Materials and are available at Dryad (https://datadryad.org/stash/dataset/doi:10.5061/dryad.4mw6m90kv).

Submitted 8 December 2023
Accepted 11 November 2024
Published 11 December 2024
10.1126/sciadv.adn4176