



Published in final edited form as:

Am J Epidemiol. 2025 November 04; 194(11): 3168–3174. doi:10.1093/aje/kwae467.

Accounting for local incidence when estimating rotavirus vaccine efficacy among countries: a pooled analysis of monovalent rotavirus vaccine trials

Avnika B. Amin,

Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, United States, Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, United States

Lance A. Waller,

Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, United States

Jacqueline E. Tate,

Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States

Timothy L. Lash,

Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, United States

Benjamin A. Lopman

Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, United States

Abstract

Rotavirus vaccine appears to perform sub-optimally in countries with higher rotavirus burden. We hypothesized that differences in the magnitude of rotavirus exposures may bias vaccine efficacy (VE) estimates, so true differences in country-specific rotavirus VE would be exaggerated without accommodating differences in exposure. We estimated VE against any-severity and severe rotavirus gastroenteritis (RVGE) using Poisson regression models fit to pooled individual-level data from Phase II and III monovalent rotavirus vaccine trials conducted between 2000 and 2012.

¹N/A indicates not applicable

Correspondence address: avnika.amin@alumni.emory.edu.

American Journal of Epidemiology Submitted Manuscript1

Special Collection: N/A

Joint authorship: N/A

Clinical trial registration number and website: N/A

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

Conflict of interest: L.A.W. reports honoraria from London School of Tropical Medicine and Hygiene as a member of the Independent Advisory Committee of the Global Burden of Disease Study. T.L.L. participates in the Amgen Inc. Methods Advisory Council, for which he receives consulting fees and travel support. B.A.L. reports personal fees from Epidemiological Research and Methods; Hillevar, Inc; and Merck Sharp & Dohme outside the submitted work.

The standard approach model included terms for vaccination, country, and a vaccination-country interaction. Other models used proxies for exposure magnitude like severe RVGE rate or age at severe RVGE instead of country. Country-specific proxies were calculated from placebo group data or extracted from an external meta-analysis. Analyses included 83,592 infants from 23 countries in the Americas, Europe, Africa, and Asia. Using the standard approach, VE against severe RVGE substantially varied (10–100%). Using the severe RVGE rate proxy brought VE from all but two countries between 80% and 86%. Heterogeneity for VE against any-severity RVGE was similarly attenuated. Adjusting for exposure proxies reduced heterogeneity in country-specific rotavirus VE estimates. This phenomenon may extend to other vaccines against partially immunizing pathogens with global disparities in burden.

Keywords

clinical trials; rotavirus; vaccine efficacy; infectious exposures; bias; force of infection

Introduction

Before rotavirus vaccine introduction, rotavirus was a substantial cause of morbidity and mortality among children less than five years old, resulting in approximately 2 million hospitalizations and 352,000 to 592,000 deaths each year globally.¹ Countries began introducing rotavirus vaccines into their national immunization programs in 2006.² Currently, four rotavirus vaccines are prequalified by the World Health Organization: GlaxoSmithKline's (GSK) Rotarix (RV1), Merck's RotaTeq (RV5), the Serum Institute of India's Rotasiil, and Bharat Biotech's Rotavac. By the end of 2023, over 120 countries had introduced at least one of these vaccines into their national immunization schedules.³ Rotavirus vaccination has reduced morbidity and mortality among children less than five years old, with approximately 14,600 to 46,700 deaths in 2016 avoided by vaccination.⁴

The two vaccine formulations in use the longest — RV5 and RV1 — are considered safe and effective. Pre-licensure clinical trials in the early 2000s for RV5 and RV1 reported 98.0% (95% CI: 88.3–100%) and 95.8% (95% CI: 89.6–98.7%) efficacy, respectively, against severe RVGE.⁵ However, these trials were conducted predominantly in high-income countries with low child mortality. Additional trials in lower-income countries with higher child mortality revealed heterogeneity in rotavirus vaccine performance, with efficacy against severe RVGE ranging from 18% to 98% for RV5 and from 49% to 96% for RV1.^{6–9} Moreover, rotavirus vaccine effects appeared consistently lower in countries with higher child mortality.^{10–12}

Individual-level factors that interfere with the immune response mounted after vaccination, like nutritional deficiencies, co-administered oral poliovirus vaccine, and transplacental antibody transfer,^{13–16} may affect rotavirus vaccine efficacy (VE). Generally, children in high child mortality settings are more subject to immune-interfering factors than children in low child mortality settings, which has been proposed as one explanation for the observed trend of lower VE in higher child mortality settings.¹⁷ Therefore reducing the impact of interfering factors should mean VE from high child mortality settings becomes similar to

VE observed in low child mortality settings.¹⁸ However, interventions like withholding breastfeeding or providing nutritional supplementation only modestly improve rotavirus vaccine immunogenicity,¹⁹ leaving a persistent heterogeneity in VE.

One explanation for the persistent heterogeneity may be differences in rotavirus exposure between infants in high and low child mortality settings. At a given point in time, the population-level infection prevalence affects an individual's probability of being exposed to infection. Given that high child mortality settings usually have greater rotavirus prevalence than low child mortality settings,⁴ infants in high child mortality settings likely have more exposures to rotavirus in a given time period than their counterparts in low child mortality settings. Crucially, because VE is conceptually a reduction in susceptibility *per infectious exposure* for partially immunizing pathogens,²⁰ standard VE estimates will be confounded by the number of infectious exposures *even in randomized controlled trials*.²¹ The magnitude of bias therefore varies as a function of the population-level prevalence and, by extension, incidence.

The ideal solution is to record each infectious exposure for use in analysis; however, collecting such data accurately is difficult, if not impossible. We hypothesized that rotavirus VE is more similar between countries than comparisons of published estimates would suggest and that heterogeneity in infectious exposures might underlie part of the observed differences in vaccine performance. Using multi-country data from RV1 clinical trials, we evaluated the utility of different proxies for the magnitude of infectious exposure by comparing VE estimates adjusted for each proxy to crude, country-specific VE.

Methods

We pooled individual-level data from infants enrolled in eleven of GSK's Phase II and III clinical trials of RV1 conducted between 2000 and 2012. We included randomized, double-blind, placebo-controlled trials that enrolled only healthy infants, had similar key inclusion/exclusion criteria, and used similar vaccine schedules, gastroenteritis (i.e., outcome) definitions, and stool sample collection timings (Supplemental Table 1). Five trials collected stool samples for all episodes of gastroenteritis (referred to as any-severity trials), one trial collected stool samples for episodes of gastroenteritis leading to medical intervention, and the remaining five trials collected stool samples for episodes of gastroenteritis resulting in oral rehydration therapy administration and/or hospitalization. One trial included multiple RV1 treatment arms with different 50% cell culture infectious dose (CCID₅₀) concentrations, but infants assigned to RV1 arms with CCID₅₀ <10^{6.0} were excluded from analysis. Finally, for multi-country trials, trial data for each country were included if at least one episode of severe gastroenteritis (defined as a Vesikari score ≥11 in trial protocols)²² occurred in the placebo group.

Protocol-specified follow-up ranged from approximately one to two years after infants received the last study dose, so we restricted analysis to data collected during infants' first year of life for consistency. We ultimately created two pooled datasets: one including data from all eleven trials and one including data only from the five any-severity trials. Data were deidentified and obfuscated by GSK before sharing. Emory University's Institutional

Review Board determined this study did not meet the definition of human subjects research requiring approval. Data management and analyses were conducted in R (version 4.0.3). Analysis code and dummy data are available at <https://github.com/AAmin23/dissertation>.

Proxy metrics for infectious exposures

Data from placebo-assigned infants who received at least one placebo dose were used to estimate three country-specific proxy metrics for the magnitude of infectious exposure: RVGE rate (only for countries in the any-severity trial dataset), severe RVGE rate, and median age (in weeks) at the first severe RVGE episode. Follow-up time for the rate calculations started on the day of first placebo dose and ended at one of three events: RVGE episode (defined as a rotavirus-positive ELISA), infant's first birthday (estimated from age at first dose), or last recorded study visit prior to the first birthday. As a fourth, external metric, we extracted the estimated median age (in weeks) of rotavirus-positive hospital admissions for each country before its rotavirus vaccine introduction (or the median age of the country's child mortality stratum if no country-specific age was estimated) from a recently published review.²³

Statistical analysis

We included infants in RV1 VE analyses if they received two study doses per their assigned treatment arm with 21 to 90 days between doses, did not have RVGE until 14 days after the second study dose, and attended at least one study visit after the second study dose. Two trials featured a three-dose regimen of one placebo dose followed by two RV1 doses. For these trials, we considered the RV1 doses as the first and second study doses. Follow-up time for VE analyses began 14 days after the second study dose and ended as described previously.

For our main analyses, we used Poisson regression models to estimate VE against severe RVGE (using all pooled data) and VE against any-severity RVGE (using any-severity trial data only). The *standard* model (which represents a crude VE calculation) included variables for RV1 vaccination (yes/no), country, and a vaccination-country interaction term. We compared VE estimates from the standard model against VE estimates from other models where we replaced instances of the country variable with a proxy metric for infectious exposures (see equations in Supplementary Material). For estimation of VE against severe RVGE, we examined three metrics: severe RVGE rate (the *severe rate* model), median age at the first episode of severe RVGE (the *severe age* model), and median age at rotavirus-positive hospital admission (the *hospitalization age* model). For estimation of VE against any-severity RVGE, we examined an additional fourth metric, the any-severity RVGE rate (the *any-severity rate* model). The metric for the hospitalization age model came from an external meta-analysis,²³ while the rest of the metrics were derived from placebo group data. We also assessed VE against severe RVGE using only the any-severity trial data and each of the five described models to assess the sensitivity of our results to differences in the stool collection protocols.

In the regression models, we specified country as a multinomial categorical variable and the exposure proxy metrics as continuous variables. We included countries with sparse

data in our model to capture as much variation as possible for the continuous variables. VE was calculated as $(1 - e^{\beta}) * 100\%$, where β represented the estimated model coefficients comparing vaccinated and unvaccinated infants in a particular country. We calculated confidence intervals for the relative risk and transformed these to reflect confidence bounds for VE (i.e., one minus each of the relative risk confidence bounds). Because metrics were treated as continuous variables in the main analysis, we assessed the possibility of an induced dose-response relationship in two ways for the severe RVGE rate, which was our most robust measure. We first assigned countries to quartiles based on their severe RVGE rate and included them as categorical variables in place of the country variables in the standard model to estimate quartile-specific VE. We then evaluated a natural-logarithm transformation of the severe RVGE rate and refit the severe RVGE rate model to all pooled data. Finally, we assessed the sensitivity of the hospitalization age metric for VE against severe RVGE using all pooled data and restricting to countries that had a country-specific median age at hospitalization.

To confirm that the standard model was equivalent to a crude VE calculation, we stratified data by country and compared each country's crude VE estimate to the country-specific VE estimates from the standard model. To then quantify the sensitivity of our VE estimates to sparse data, we averaged each β and a weakly-informative prior distribution for each β (weighted by the inverse of their respective variance) and recalculated VE.²⁴ We specified a prior yielding 50% VE (with 2.5th and 97.5th quantiles of 30% and 80%, respectively) when weighting any-severity VE estimates and a prior that yielded 60% VE (with 2.5th and 97.5th quantiles of 30% and 88%, respectively) for weighting severe VE estimates.

Results

We included 83,592 infants from 23 countries and 11 RV1 trials in our RV1 VE analyses. 774 RVGE episodes occurred, of which 373 were severe. A quarter ($n = 22,309$) of infants resided in either Mexico or Peru and half ($n = 40,955$) were female. The median age at first study dose was 8 weeks (interquartile range (IQR): 6–11) and median duration of follow-up was 29 weeks (IQR: 4.4–33). 53% ($n = 45,305$) of infants received two RV1 doses. Most characteristics did not substantially differ between treatment groups, although infants who received RV1 had longer median follow-up time (29 weeks; IQR: 4.6–33) than infants who received a placebo (25 weeks; IQR: 4.3–33), likely due to higher RVGE incidence and therefore earlier censoring in the unvaccinated (Table 1).

Approximately 14% ($n = 11,949$) of infants in the entire pooled dataset were enrolled in any-severity trials in eight countries. 640 RVGE episodes occurred, of which 258 were severe. Nearly 79% ($n = 9,399$) of infants in any-severity trials resided in China, Finland, or South Africa and half ($n = 5,808$) were female. The median age at first study dose administration was 10 weeks (IQR: 7.0–12) and median duration of follow-up was 34 weeks (IQR: 30–38). 63% ($n = 7,481$) received two RV1 doses. No characteristics substantially differed between treatment groups (Table 2).

Proxy metrics for infectious exposures

Our calculated proxies varied greatly between countries in both the overall and any-severity trial pooled datasets. In the overall pooled dataset, the severe RVGE rate ranged from 0.18 episodes to 12.23 episodes per 100 infant-years (Supplemental Table 2). Median age at first severe RVGE episode in the first year of life ranged from 16.9 to 46.0 weeks. In the any-severity trial data, the RVGE rate ranged from 1.48 episodes to 21.91 episodes per 100 infants-years and the severe RVGE rate from 1.48 episodes to 12.23 episodes per 100 infant-years. Median age at first severe RVGE episode ranged from 19.9 to 41.9 weeks. No clear relationship between median age at first episode of severe RVGE and either any-severity RVGE rate or severe RVGE rate was apparent (Supplemental Figure).

RV1 VE against severe RVGE

When fitting models to all pooled data, country-specific RV1 VE estimates were least heterogeneous from the severe rate model. Twenty-one of the 23 estimates were between 80% and 86% and accompanied by narrow, precise 95% CIs (Table 3). In contrast, VE estimates from the standard model substantially varied from 10% (95% CI: <0,94%) to 100% (95% CI: <0,100%) and were accompanied by wide, imprecise 95% CIs. Relative to the standard model's Bayesian Information Criterion (BIC) of 4,817, using the severe rate proxy strongly improved model fit (BIC: 4,466).²⁵ Using log-transformed severe RVGE rate did not substantially change VE estimates (Supplemental Table 3). RV1 VE estimates were higher for quartiles containing lower rates when we used quartiles of severe RVGE rate in lieu of a continuous rate variable (Supplemental Table 4).

Results from models using age-based proxies had less heterogeneity and more precision than the standard model but more heterogeneity and less precision than the severe rate model (Table 3). VE estimates using the severe age model ranged from 54% (95% CI: 18,74%) to 84% (95% CI: 73,90%), while those from the age at hospitalization model ranged from 26% (95% CI: <0,49%) to 99% (95% CI: 96,99%). When excluding data from countries with only a child mortality stratum-specific median age at hospitalization, VE estimates from the age at hospitalization model were less heterogeneous but less precise compared to when all pooled data were used (Supplemental Table 5).

Similar qualitative trends in VE estimate heterogeneity, 95% CI precision, and model fit were observed when using only the any-severity trial data and comparing the severe rate model and age-based proxy models to the standard model (Supplemental Table 6). One additional infectious exposure proxy, the any-severity rate, was evaluated with this dataset. Use of this metric strongly improved model fit (BIC: 2,717) compared to the standard model (BIC: 2,783) but somewhat reduced model fit compared to the severe rate model (BIC: 2,711). RV1 VE estimates from the any-severity rate model were still relatively heterogeneous, ranging from 59% (95% CI: 39,72%) to 97% (95% CI: 91,99%) compared to the narrow range of 70% (95% CI: 55,80%) to 87% (95% CI: 76,93%) VE in the severe rate model.

RV1 VE against any-severity RVGE

When fitting models to any-severity trial data, country-specific RV1 VE estimates were again least heterogeneous in results from the severe rate model. Five of the eight estimates were between 70% and 75% (Table 4). As observed with the models for VE against severe RVGE, the standard model had the most variation in VE estimates and the least precise 95% CIs. The models using the any-severity rate proxy and the age-based proxies resulted in less heterogeneous, more precise VE estimates than the standard model but more heterogeneous, less precise VE estimates than the severe rate model. When compared to the standard model's BIC, the severe rate model yielded the strongest improvement in model fit.

Estimate sensitivity to sparse data

RV1 VE estimates and 95% CIs from the standard model and stratified analysis were identical for VE against any-severity and severe RVGE (Tables 2 and 3, Supplemental Table 7). The imprecise estimates for many countries suggested sparse data issues with the standard model. When weighting estimates from the standard approach model, VE estimates against any-severity RVGE substantially shrunk (>10-point change) towards the 50% VE prior for four of eight countries in any-severity trials (Supplemental Table 8). Prior-weighted VE estimates against severe RVGE substantially shrunk towards the prior for 16 of 23 countries (Supplemental Table 9). However, weighting did not appreciably change estimates for VE against either RVGE outcome obtained from any proxy-adjusted models.

Discussion

When compared to the standard VE estimation approach, adjustment for rate-based proxy metrics of infectious exposure reduced heterogeneity in country-specific rotavirus VE estimates. Country-specific estimates of RV1 VE against any-severity and severe RVGE varied substantially when we used the standard model. Consistent with previous findings, RV1 VE estimates against severe RVGE were generally higher than VE estimates against any-severity RVGE. These model structures also resulted in more precise VE estimates than those from the standard model, since treating the metrics as continuous variables required fewer degrees of freedom. The observed reduction in VE estimate heterogeneity when using RVGE rates, which should be a function of the unobserved exposures to rotavirus, is consistent with our hypothesis as to why VE estimates in different countries are less comparable when infectious exposures are not explicitly considered. However, our VE estimates apply to the first year of life only; heterogeneity in reported VE for the second year of life onward may be a function of both unobserved exposures to rotavirus and differential rates of waning immunity.

However, not all metrics decreased heterogeneity in RV1 VE estimates similarly. Age-based metrics modestly decreased heterogeneity in country-specific VE estimates, even though the average age of infection theoretically increases as infants experience fewer rotavirus exposures. The lack of decreased heterogeneity, the modest correlation between RVGE rates and median age at RVGE outcomes, and the similar or higher BICs compared to the standard model all support the idea that age-based metrics may not reflect the desired information about underlying rotavirus exposures. Because we limited trial data to the first year of life,

the median age metric we calculated using trial data could not be higher than 52 weeks, which is likely not reflective of the true severe RVGE age distribution in a country. To examine a wider range of ages, we used external information for our median age at RVGE hospitalization metric. However, many countries in our dataset lacked a hospitalization age estimate in the review, so we assigned them the median age for their respective child mortality quintile.²³ Many countries therefore had the same median age of disease at RVGE hospitalization, which likely does not reflect the true variation in ages. Age of disease may still be a useful metric for rotavirus exposures given a sufficiently granular data source.

Incorporating valid proxies for infectious exposures may help address the underlying confounding due to differences in infectious exposures between countries,²¹ thus reducing apparent heterogeneity in vaccine effects. Adjusting for trial site or country may be intended to address known differences in disease burden; however, these variables are inherently categorical and do not address the underlying relationship between the magnitude of infectious exposure and subsequent bias of VE estimates. A better proxy for the relationship may be disease or infection rate, which is more directly tied to infectious exposures. Some of the increased precision in VE estimates when using rate-based proxies may be because they were continuous variables, which generally reduce loss of information and have better power compared to their categorical counterparts. Others have demonstrated improved estimate precision when using continuous variables instead of categorical variables.²⁶ We see a similar phenomenon when comparing the model using continuous severe RVGE rate to the model using quartiles of severe RVGE rate.

We assumed that our proxy metrics only reflected the unobserved magnitude of infectious exposures to rotavirus. However, these metrics may correlate with other country-level prevalence of factors that directly influence VE (e.g., higher RVGE rate in countries that still use oral poliovirus vaccine). Additionally, in higher-incidence settings, the rotavirus concentration may be higher per infectious exposure, which could also result in a lower true VE.^{4,27} Our proxy metrics may inadvertently control the higher prevalence of factors thereby directly influencing VE in higher-incidence settings. Finally, some countries had relatively few episodes of RVGE in the placebo group, which limits the robustness of their calculated infectious exposure metrics.

Our work was subject to other limitations aside from our proxy metrics for infectious exposures. The multi-country trials were not powered for country-specific analyses, though VE estimates from proxy-adjusted models did not appear overly sensitive to sparse data. However, the lack of power highlights a methodologic challenge when estimating VE and its associated confidence intervals, which is most noticeable in estimation from the standard model. Since most data originated from trials with more serious RVGE as the endpoint of interest, we could not robustly examine any-severity RVGE rate as a proxy metric or evaluate VE estimates against any-severity RVGE. We also could not adjust for concomitant oral poliovirus vaccine administration, which is known to influence RV1 immunogenicity, due to strong collinearity with the country and proxy metrics.¹⁵ This limitation could explain the persistently low estimates in Malawi and South Africa, as their trial protocols were the only ones that also had protocol-specified concomitant oral poliovirus vaccine administration. Finally, we did not examine the impact of RVGE misclassification, which

may also relate to observed heterogeneity in VE estimates.²⁸ Misclassification could explain why adjusting for the severe RVGE rate resulted in greater attenuation of VE heterogeneity than adjusting for the any-severity RVGE rate, as more infants with severe disease shed higher viral quantities, reducing the likelihood of diagnostic misclassification.²⁷

Overall, we demonstrate proof-of-concept for reducing the impact of unobserved infectious exposures when estimating VE from epidemiologically-different settings. Our country-specific estimates of RV1 VE against severe RVGE when controlling for the severe RVGE rate were generally within seven percentage points (78% to 85% VE) of each other. This range is substantially less than the heterogeneity of reported VE estimates in the literature but on the lower side of VE estimates from low child mortality countries.²⁹ Based on these findings, we argue that failure to account for infectious exposures to rotavirus may explain a substantial amount of the heterogeneity among country-specific estimates reported in the literature for RV1 VE. RV1 evaluations should try to address differences in the magnitude of infectious exposures, either with proxies of exposure or direct measurement of exposure when possible, to reduce artifacts from uncontrolled confounding. This principle may apply to RV5, imperfectly-immunizing vaccines for other pathogens, and observational studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements2:

We would like to thank GlaxoSmithKline for enabling access to the data and www.clinicalstudydatarequest.com for facilitating the initial proposal and data request submission. We also thank Dr. Andrew Clark and Dr. Mateusz Hasso-Agopsowicz for confirming our assignment of the median age at first rotavirus-associated hospitalization for each country was consistent with their work.

Funding:

This work was supported by the National Institute of Allergy and Infectious Diseases (grants R01 GR111026 and R01 AI148127 to B.A.L. and A.B.A.)

Data Availability Statement:

Deidentified individual-level data collected for the trials may be made available by GlaxoSmithKline after submission of a research proposal via clinicalstudydatarequest.com and their subsequent review.

References

1. Parashar UD, Hummelman EG, Bresee JS, Miller MA & Glass RI Global Illness and Deaths Caused by Rotavirus Disease in Children. *Emerg. Infect. Dis* 9, 565–572 (2003). [PubMed: 12737740]
2. Chavers T, Oliveira LHD, Parashar UD & Tate JE Post-licensure experience with rotavirus vaccination in Latin America and the Caribbean: a systematic review and meta-analysis. *Expert Rev. Vaccines* 17, 1037–1051 (2018). [PubMed: 30365904]
3. International Vaccine Access Center. Rotavirus-Vaccine Introduction-Current Vaccine Intro Status. View-hub <https://view-hub.org/map>.
4. Troeger C et al. Rotavirus Vaccination and the Global Burden of Rotavirus Diarrhea Among Children Younger Than 5 Years. *JAMA Pediatr.* 172, 958 (2018). [PubMed: 30105384]

5. Cortese MM, Parashar UD, & Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm. Rep. Morb. Mortal. Wkly. Rep. Recomm. Rep* 58, 1–25 (2009).
6. Armah GE et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. *The Lancet* 376, 606–614 (2010).
7. Vesikari T et al. Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine. *N. Engl. J. Med* 354, 23–33 (2006). [PubMed: 16394299]
8. Madhi SA et al. Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants. *N. Engl. J. Med* 362, 289–298 (2010). [PubMed: 20107214]
9. Phua KB et al. Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: Randomised, double-blind, controlled study. *Vaccine* 27, 5936–5941 (2009). [PubMed: 19679216]
10. Jonesteller CL, Burnett E, Yen C, Tate JE & Parashar UD Effectiveness of Rotavirus Vaccination: A Systematic Review of the First Decade of Global Postlicensure Data, 2006–2016. *Clin. Infect. Dis* 65, 840–850 (2017). [PubMed: 28444323]
11. Lamberti LM, Ashraf S, Walker CLF & Black RE A Systematic Review of the Effect of Rotavirus Vaccination on Diarrhea Outcomes Among Children Younger Than 5 Years. *Pediatr. Infect. Dis. J* 35, 992–998 (2016). [PubMed: 27254030]
12. Soares-Weiser K, Bergman H, Henschke N, Pitan F & Cunliffe N Vaccines for preventing rotavirus diarrhoea: vaccines in use. *Cochrane Database Syst. Rev* 2019, CD008521 (2019). [PubMed: 31684685]
13. Prendergast AJ Malnutrition and vaccination in developing countries. *Philos. Trans. R. Soc. B Biol. Sci* 370, 20140141 (2015).
14. Harris VC et al. Significant Correlation Between the Infant Gut Microbiome and Rotavirus Vaccine Response in Rural Ghana. *J. Infect. Dis* 215, 34–41 (2017). [PubMed: 27803175]
15. Baker JM, Tate JE, Leon J, Haber MJ & Lopman BA Antirotavirus IgA seroconversion rates in children who receive concomitant oral poliovirus vaccine: A secondary, pooled analysis of Phase II and III trial data from 33 countries. *PLoS Med* 16, e1003005 (2019). [PubMed: 31887139]
16. Becker-Dreps S et al. Rotavirus-Specific IgG Antibodies from Mothers' Serum may Inhibit Infant Immune Responses to the Pentavalent Rotavirus Vaccine. *Pediatr. Infect. Dis. J* 34, 115–116 (2015). [PubMed: 25741808]
17. Desselberger U Differences of Rotavirus Vaccine Effectiveness by Country: Likely Causes and Contributing Factors. *Pathogens* 6, 65 (2017). [PubMed: 29231855]
18. Halloran ME Overview of Vaccine Field Studies: Types of Effects and Designs. *J. Biopharm. Stat* 16, 415–427 (2006). [PubMed: 16892904]
19. Church JA, Parker EP, Kirkpatrick BD, Grassly NC & Prendergast AJ Interventions to improve oral vaccine performance: a systematic review and meta-analysis. *Lancet Infect. Dis* 19, 203–214 (2019). [PubMed: 30712836]
20. O'Hagan JJ, Lipsitch M & Hernán MA Estimating the per-exposure effect of infectious disease interventions. *Epidemiol. Camb. Mass* 25, 134–138 (2014).
21. Struchiner CJ & Halloran ME Randomization and baseline transmission in vaccine field trials. *Epidemiol. Infect* 135, 181–194 (2007). [PubMed: 17291359]
22. Ruuska T & Vesikari T Rotavirus Disease in Finnish Children: Use of Numerical Scores for Clinical Severity of Diarrhoeal Episodes. *Scand. J. Infect. Dis* 22, 259–267 (1990).
23. Hasso-Agopsowicz M et al. Global Review of the Age Distribution of Rotavirus Disease in Children Aged <5 Years Before the Introduction of Rotavirus Vaccination. *Clin. Infect. Dis* 69, 1071–1078 (2019). [PubMed: 30689799]
24. Hamra GB, MacLehose RF & Cole SR Sensitivity Analyses for Sparse-Data Problems—Using Weakly Informative Bayesian Priors. *Epidemiol. Camb. Mass* 24, 233–239 (2013).
25. Neath AA & Cavanaugh JE The Bayesian information criterion: background, derivation, and applications. *WIREs Comput. Stat.* 4, 199–203 (2012).

26. Morgan TM & Elashoff RM Effect of Categorizing a Continuous Covariate on the Comparison of Survival Time. *J. Am. Stat. Assoc* 81, 917–921 (1986).
27. Bennett A et al. Duration and Density of Fecal Rotavirus Shedding in Vaccinated Malawian Children With Rotavirus Gastroenteritis. *J. Infect. Dis* 222, 2035–2040 (2020). [PubMed: 31834930]
28. Amin AB et al. Understanding Variation in Rotavirus Vaccine Effectiveness Estimates in the United States: The Role of Rotavirus Activity and Diagnostic Misclassification. *Epidemiology* 33, 660–669. [PubMed: 35583516]
29. Burnett E, Parashar UD & Tate JE Real-world effectiveness of rotavirus vaccines, 2006–19: a literature review and meta-analysis. *Lancet Glob. Health* 8, e1195–e1202 (2020). [PubMed: 32827481]

Table 1.

Characteristics of infants included in analyses of vaccine efficacy against severe rotavirus gastroenteritis (Vesikari score ≥ 11).

Characteristic, n (%) ^a	Placebo (n = 39,064)		RV1 (n = 44,528)	
Sex				
Female	19,113	(49)	21,842	(49)
Male	19,951	(51)	22,686	(51)
Country				
Argentina	3,051	(7.8)	3,922	(8.8)
Brazil	1,584	(4.1)	1,731	(3.9)
Chile	1,546	(4.0)	1,571	(3.5)
China	1,592	(4.1)	1,592	(3.5)
Colombia	2,324	(5.9)	2,849	(6.4)
Czechia	100	(0.3)	198	(0.4)
Dominican Republic	1,881	(4.8)	1,905	(4.3)
Finland	957	(2.4)	1,883	(4.2)
France	50	(0.1)	93	(0.2)
Honduras	1,899	(4.9)	2,049	(4.6)
Hong Kong	1,471	(3.8)	1,467	(3.3)
Japan	250	(0.6)	497	(1.1)
Malawi	505	(1.3)	1,041	(2.3)
Mexico	5,609	(14)	5,715	(13)
Nicaragua	1,810	(4.6)	1,836	(4.1)
Panama	2,160	(5.5)	2,446	(5.5)
Peru	5,478	(14)	5,507	(12)
Singapore	3,226	(8.3)	3,241	(7.3)
South Africa	1,074	(2.7)	2,301	(5.2)
Spain	108	(0.3)	224	(0.5)
Taiwan	529	(1.4)	534	(1.2)
United States	82	(0.2)	149	(0.3)
Venezuela	1,778	(4.6)	1,777	(4.0)
Rotavirus gastroenteritis				
None	38,546	(99)	44,272	(99)
Mild or moderate (Vesikari score <11)	235	(0.6)	166	(0.4)
Severe (Vesikari score ≥11)	283	(0.7)	90	(0.2)
Characteristic, median (IQR)				
Age at first study dose (weeks)	8.0	(6.0–11)	8.0	(6.0–11)
Duration of follow-up from 14 days after second study dose to censoring (weeks)	25	(4.3–33)	29	(4.6–33)

^a Percentages may not sum to 100 due to rounding

Table 2.

Characteristics of infants included in analyses of vaccine efficacy against any-severity rotavirus gastroenteritis. These infants were enrolled in trials where stool samples were collected for all episodes of acute gastroenteritis.

Characteristic, n (%) ^a	Placebo (n = 4,468)		RV1 (n = 7,481)	
Sex				
Female	2,206	(49)	3,602	(48)
Male	2,262	(51)	3,879	(52)
Country				
China	1,592	(36)	1,592	(21)
Czechia	100	(2.2)	198	(2.7)
Finland	957	(21)	1,883	(25)
France	50	(1.1)	93	(1.2)
Malawi	505	(11)	1,041	(14)
South Africa	1,074	(24)	2,301	(31)
Spain	108	(2.4)	224	(3.0)
United States	82	(1.8)	149	(2.0)
Rotavirus gastroenteritis				
None	4,063	(91)	7,246	(97)
Mild or moderate (Vesikari score <11)	222	(5.0)	160	(2.1)
Severe (Vesikari score ≥11)	183	(4.1)	75	(1.0)
Characteristic, median (IQR)				
Age at first study dose (weeks)	8	(6–12)	10	(7–12)
Duration of follow-up from 14 days after second study dose to censoring (weeks)	35	(30–38)	34	(30–37)

Abbreviations: RV1, GlaxoSmithKline's Rotarix vaccine

^aPercentages may not sum to 100 due to rounding

Table 3.

VE estimates against severe (Vesikari score ≥ 11) RVGE and 95% confidence intervals (CIs) from models fit to all pooled data. Smaller BIC indicates better model fit.

Country	Models using proxies of infectious exposures							
	Standard model ^a		Severe rate model ^b		Severe age model ^c		Hospitalization age model ^d	
	VE (%)	95% CI	VE (%)	95% CI	VE (%)	95% CI	VE (%)	95% CI
Argentina	75	(36, 90)	85	(78,90)	75	(68,80)	83	(77,88)
Brazil	90	(21, 99)	85	(78,90)	72	(64,78)	83	(77,88)
Chile	10	(-1344,94) ^e	86	(79,91)	72	(64,78)	87	(81,91)
China	72	(41,87)	84	(78,89)	72	(64,78)	89	(84,93)
Colombia	93	(49,99)	85	(78,90)	81	(72,87)	83	(77,88)
Czechia	100	(-Inf,100) ^f	84	(77,88)	81	(72,87)	96	(93,98)
Dominican Republic	68	(-212,97) ^e	86	(79,91)	63	(46,75)	83	(77,88)
Finland	97	(91,99)	78	(72,83)	81	(72,86)	96	(93,98)
France	75	(-179,98) ^e	82	(76,86)	70	(60,77)	60	(48,70)
Honduras	100	(-Inf,100) ^f	86	(79,90)	61	(40,75)	79	(72,84)
Hong Kong	100	(-Inf,100) ^f	86	(79,90)	77	(70,82)	99	(96,99)
Japan	88	(-9,99) ^e	84	(78,89)	74	(67,80)	98	(95,99)
Malawi	55	(32,70)	73	(61,81)	75	(68,80)	46	(25,60)
Mexico	92	(37,99)	86	(79,90)	66	(52,76)	83	(77,88)
Nicaragua	100	(-Inf,100) ^f	86	(79,90)	72	(64,78)	83	(77,88)
Panama	81	(-73,98) ^e	86	(79,90)	71	(62,77)	83	(77,88)
Peru	93	(46,99)	86	(79,90)	84	(73,90)	79	(72,84)
Singapore	100	(-Inf,100) ^f	86	(79,91)	78	(71,83)	96	(93,98)
South Africa	77	(60,87)	82	(77,86)	69	(59,77)	26	(-9,49)
Spain	100	(-Inf,100) ^f	80	(75,84)	71	(62,77)	96	(93,98)
Taiwan	100	(-Inf,100) ^f	85	(78,90)	67	(54,76)	89	(84,93)
United States	100	(-Inf,100) ^f	85	(78,89)	58	(33,74)	96	(93,98)
Venezuela	67	(-218,97) ^e	85	(78,90)	54	(18,74)	77	(70,82)
BIC	4,817		4,466		4,941		4,819	

Abbreviations: BIC, Bayesian Information Criterion; RVGE, rotavirus gastroenteritis; VE, vaccine efficacy

^a Interaction between country and vaccination variables

^b Interaction between severe RVGE rate and vaccination variables

^c Interaction between median age at first episode of severe RVGE and vaccination variables

^d Interaction between median age at RVGE hospitalization and vaccination variables

^e Five or fewer events in both trial arms combined

^f Zero events in the vaccine arm

Table 4.

Vaccine efficacy (VE) estimates against any-severity rotavirus gastroenteritis (RVGE) and 95% confidence intervals (CIs) from models fit to the any-severity trial data. Smaller BIC indicates better model fit.

Country	Models using proxies of infectious exposures									
	Standard model ^a		Any-severity rate model ^b		Severe rate model ^c		Severe age model ^d		Hospitalization age model ^e	
	VE (%)	95% CI	VE (%)	95% CI	VE (%)	95% CI	VE (%)	95% CI	VE (%)	95% CI
China	70	(54,80)	83	(76,88)	74	(66,80)	62	(55,68)	77	(71,82)
Czechia	80	(-1,96)	84	(77,89)	74	(66,80)	78	(69,84)	84	(76,89)
Finland	89	(82,93)	76	(70,80)	66	(59,71)	77	(68,83)	84	(76,89)
France	80	(-4,96)	75	(69,79)	70	(64,75)	59	(49,66)	64	(57,69)
Malawi	42	(22,58)	51	(37,62)	59	(45,69)	68	(62,73)	60	(52,67)
South Africa	67	(57,75)	67	(61,72)	71	(65,76)	58	(49,66)	55	(45,64)
Spain	100	(-Inf,100) ^f	78	(72,83)	68	(63,73)	61	(53,67)	84	(76,89)
United States	100	(-Inf,100) ^f	89	(82,94)	75	(66,82)	38	(6,59)	84	(76,89)
BIC	5,972		5,892		5,984		6,067		5,953	

Abbreviations: Bayesian Information Criterion (BIC)

^a Interaction between country and vaccination variables

^b Interaction between any-severity RVGE rate and vaccination variables

^c Interaction between severe RVGE rate and vaccination variables

^d Interaction between median age at first episode of severe RVGE and vaccination variables

^e Interaction between median age at RVGE hospitalization and vaccination variables

^f Zero events in the vaccine arm