HHS Public Access

Author manuscript

Epidemiology. Author manuscript; available in PMC 2023 April 13.

Published in final edited form as:

Epidemiology. 2022 September 01; 33(5): 660–668. doi:10.1097/EDE.0000000000001501.

Understanding Variation in Rotavirus Vaccine Effectiveness Estimates in the United States:

The Role of Rotavirus Activity and Diagnostic Misclassification

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Disclosure: J.A.E. has research support from Merck, Pfizer, and GlaxoSmithKline and consults for Sanofi Pasteur and Meissa Vaccines. G.A.W. received an honorarium from Merck for authorship of chapters in the Merck Manual. M.M.M. has laboratory agreements with Merck Sharp & Dohme and Sanofi. C.J.H. has research support from Merck, GlaxoSmithKline, Pfizer, and Astra-Zeneca and has received honoraria from Frontline Medical Communications for contributions to Pediatric News. J.E.S. has research support from Merck. T.L.L. is a member of the Amgen Methods Advisory Council, for which he receives consulting fees and travel support. B.A.L. reports grants and personal fees from Takeda Pharmaceuticals and personal fees from World Health Organization, outside the subject of the submitted work. The other authors report no 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 Centers for Disease Control and Prevention.

Replication code will be made available on a GitHub repository. Data are not publicly available as New Vaccine Surveillance Network data are not part of CDC public-use datasets.

Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

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Abstract

Background: Estimates of rotavirus vaccine effectiveness (VE) in the United States appear higher in years with more rotavirus activity. We hypothesized rotavirus VE is constant over time but appears to vary as a function of temporal variation in local rotavirus cases and/or misclassified diagnoses.

Methods: We analyzed 6 years of data from eight US surveillance sites on 8- to 59-month olds with acute gastroenteritis symptoms. Children's stool samples were tested via enzyme immunoassay (EIA); rotavirus-positive results were confirmed with molecular testing at the US Centers for Disease Control and Prevention. We defined rotavirus gastroenteritis cases by either positive on-site EIA results alone or positive EIA with Centers for Disease Control and Prevention confirmation. For each case definition, we estimated VE against any rotavirus gastroenteritis, moderate-to-severe disease, and hospitalization using two mixed-effect regression models: the first including year plus a year–vaccination interaction, and the second including the annual percent of rotavirus-positive tests plus a percent positive–vaccination interaction. We used multiple overimputation to bias-adjust for misclassification of cases defined by positive EIA alone.

Results: Estimates of annual rotavirus VE against all outcomes fluctuated temporally, particularly when we defined cases by on-site EIA alone and used a year–vaccination interaction. Use of confirmatory testing to define cases reduced, but did not eliminate, fluctuations. Temporal fluctuations in VE estimates further attenuated when we used a percent positive–vaccination interaction. Fluctuations persisted until bias-adjustment for diagnostic misclassification.

Conclusions: Both controlling for time-varying rotavirus activity and bias-adjusting for diagnostic misclassification are critical for estimating the most valid annual rotavirus VE.

Keywords

New Vaccine Surveillance Network; Rotavirus; Test-negative design; Vaccination; Vaccine effectiveness

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Before the United States introduced rotavirus vaccines, rotavirus was the leading cause of severe acute gastroenteritis (AGE) in children less than 5 years old and was estimated to cause 58,000 to 70,000 hospitalizations annually in this age group.[1] Two rotavirus vaccine products, one approved in 2006 and the other in 2008 in the United States,[2,3] resulted in a median 80% reduction in rotavirus-associated hospitalizations.[4] Before vaccine introduction, rotavirus gastroenteritis (RVGE) displayed annual seasonality, with peak activity occurring in winter months.[5,6] In the years after vaccine introduction, rotavirus activity appeared to shift to biennial seasonality.[7,8] Seasonal winter spikes still occurred in odd-numbered years,

though activity was much lower than prevaccine levels.[6–8] Even-numbered years appeared to have attenuated seasonality and often did not have enough activity to meet seasonal start and end thresholds based on national surveillance data.[6,8]

In high resource countries, including the United States, rotavirus vaccines are highly effective. A recent meta-analysis of 13 US-based case–control studies reported 84% [95% confidence interval (CI) = 80%, 87%] and 83% (95% CI = 72%, 89%) vaccine effectiveness (VE) for the two rotavirus vaccine products.[4] These estimates are similar to those reported for the same vaccine products in other high resource countries, although VE is lower in lower resource countries.[9–11] Many studies report only a single estimate of rotavirus VE, regardless of the length of the observation period. The few studies examining annual VE in the United States report fluctuating estimates. Specifically, these estimates of rotavirus VE appear to vary in a biennial pattern, with higher estimates of rotavirus VE in odd-numbered, high-activity years and lower estimates of rotavirus VE in even-numbered, low-activity years.[7,12] Rotavirus VE may vary between high and low resource countries for several reasons; however, in the same population, the biologic protection offered by a vaccine should be constant over place and time (in the absence of factors such as potential waning immunity).[13] Nevertheless, estimates of VE may appear to vary relative to the rotavirus force of infection.

The force of infection, defined as the rate at which susceptible individuals in a population become infected (e.g., infection incidence rate), influences an uninfected individual's probability of coming into contact with an infectious individual or otherwise receiving an infectious exposure. When estimated conditionally on an individual's known exposure to the infectious agent, VE reflects an individual's vaccine-conferred biologic protection.[14] Because this estimate requires knowledge of an individual's infectious contacts, VE is more often estimated unconditionally and exposure to infection is assumed to be equivalent between vaccinated and unvaccinated groups.[14] However, because the probability of an infectious contact depends on the force of infection, unconditional estimates of VE obtained from studies with different forces of infection may not be directly comparable and may differ even when the underlying biologic protection is the same.[15] This distinction is relevant when estimating annual VE using data from multiple years when the burden of circulating rotavirus has been demonstrated to vary annually, as is true for the United States.[6,8]

The force of infection also influences misclassification bias. Because the positive and negative predictive values of a diagnostic test depend on a population's disease prevalence,[16] a time-varying prevalence (driven by a time-varying force of infection) would result in temporally changing diagnostic misclassification bias of VE estimates. While diagnostic misclassification may affect all study designs, it is a crucial point for the test-negative case–control design. This study design relies on high predictive values to accurately classify individuals with similar symptoms as cases (positive test result for the pathogen under study) or controls (negative test result).[17] We hypothesized that true rotavirus VE is constant over time in the United States and aimed to (1) estimate crude annual observed VE; (2) estimate VE adjusted for the force of infection; and (3) model the impact of diagnostic misclassification using multiyear US surveillance data.

METHODS

The New Vaccine Surveillance Network (NVSN) has conducted active, prospective surveillance in the United States since early 2006 (methodology previously published).[8,18] Eight surveillance sites have participated in NVSN for at least 1 year: Monroe Carrell Jr. Children's Hospital at Vanderbilt (Nashville, Tennessee), Golisano Children's Hospital at University of Rochester School of Medicine and Dentistry (Rochester, New York), Cincinnati Children's Hospital Medical Center, (Cincinnati, Ohio), Seattle Children's Hospital (Seattle, Washington), Texas Children's Hospital (Houston, Texas), Children's Mercy -Kansas City (Kansas City, Missouri), University of California San Francisco Benioff Children's Hospital (Oakland, California), and University of Pittsburgh Medical Center Children's Hospital of Pittsburgh (Pittsburgh, Pennsylvania). Institutional review boards at the Centers for Disease Control and Prevention (CDC) and study sites provided protocol approvals. Most sites participated in recruitment and enrollment for the years covered in this analysis. The Oakland site participated during all but the last year, and the Pittsburgh site participated during the last year only. Surveillance and laboratory protocols were consistent across sites for all years.

Study Population

Children less than 5 years old were eligible for enrollment if they were hospitalized for, or presented to, outpatient clinics and emergency departments with AGE (defined as ≥3 diarrheal episodes within 24 hours and/or at least one episode of vomiting). Parents or guardians of eligible children provided written informed consent for participant enrollment. Enrollment occurred December 1, 2011, through June 30, 2016, and December 1, 2016, through November 30, 2017, with the gap due to changes in grant support. In this analysis, surveillance years are defined as occurring July to June and are referred to by the year ending a particular winter season (e.g., study year 2014 refers to AGE cases enrolled between July 1, 2013, and June 30, 2014). Study years 2013–2016 encompass a full year of surveillance, while study years 2012 and 2017 only cover December to June.

Rotavirus Testing

Stool specimens were obtained within 10 days of AGE symptom onset.[12] Specimens were first tested for rotavirus at surveillance sites by enzyme immunoassay (EIA) (Premier Rotaclone; Meridian Bioscience, Inc.). Samples testing positive for rotavirus were shipped to the CDC for genotyping by reverse transcription-polymerase chain reaction (RT-PCR) and nucleotide sequencing. Samples that could not be genotyped were retested by EIA and qRT-PCR at the CDC.[19,20] Seven samples with site-indeterminate or site-positive EIA results but no CDC testing were excluded from the analytic dataset.

Verification of Vaccination

Children who did not have any rotavirus vaccine doses recorded were considered unvaccinated. Vaccine receipt was verified using records from healthcare professionals and/or regional immunization information systems. Children were considered fully vaccinated if they received at least two valid doses of Rotarix (RV1) or three valid doses of RotaTeq (RV5). Doses were considered valid if given at least 14 days before symptom

onset. Children who did not complete a full vaccine series or who received doses of both vaccine formulations, doses where the formulation was unknown, doses before 1 month or after 7 months of age, doses less than 28 days apart, or invalid doses were excluded from the analytic dataset.

Statistical Analysis

We limited this analysis to children at least 8 months old and no older than 59 months to reduce confounding by age specific to the rotavirus vaccination schedule, as the maximum recommended age for a rotavirus vaccine dose is 8 months and 0 days.[2] For fully vaccinated children, at least 14 days were required between the last vaccine dose and enrollment. To examine differences in VE estimates, we used two definitions for RVGE cases and controls. In the first set of analyses, cases were children in the analytic dataset with a stool specimen positive for rotavirus by site EIA, and controls were children with a stool specimen negative for rotavirus by site EIA. In the second set of analyses, cases were children with a stool specimen positive for rotavirus by site EIA and by confirmatory CDC testing, and controls were children with a stool specimen either negative by site EIA or positive by site EIA but negative by CDC testing (referred to as "confirmatory testing" onward). A test-negative case–control design was used to estimate VE against three outcomes: RVGE of any severity, moderate-to-severe RVGE (defined as a Vesikari score ≥11),[21] and RVGE-related hospitalizations. For estimation of VE against each rotavirus outcome of interest, AGE cases of any-severity, moderate-to-severe AGE cases, and AGE hospitalizations were included in each respective test-negative analytic dataset. Children initially enrolled in outpatient clinics or emergency departments but later hospitalized for AGE were considered an AGE hospitalization.

We used two sets of mixed-effect logistic regression models to estimate annual VE against each of the three outcomes of interest using the two definitions for cases and controls. The first set of models (hereafter referred to as the *standard approach*, illustrated in Equation 1) included vaccination status (fully vaccinated or unvaccinated), year (with 2015 as the referent due to largest sample size), and an interaction term between vaccination status and year. To examine the effect of varying rotavirus force of infection, the second set of models (hereafter referred to as the *force-of-infection approach*, illustrated in Equation 2) included vaccination status, annual percent of rotavirus-positive tests (obtained from the National Respiratory and Enteric Virus Surveillance System),[6] and an interaction term between vaccination status and percent-positive. The percent-positive metric serves as a relative measure of rotavirus force of infection and therefore disease prevalence. All models included a random intercept for NVSN surveillance site to account for clustering by site. VE was estimated as (1 − odds ratio) × 100%. Year and percent-positive were perfectly correlated, which meant we were unable to include both variables and their respective interaction terms with vaccination status in a single model.

Sensitivity Analysis

We also stratified data by year and used mixed-effect models with vaccination status and a random intercept for site, comparing the VE estimates from these stratified models to those from the standard approach. Comparing these estimates allowed us to assess if the standard

approach's regression model was compensating for sparse data in some years, which may occur even with large datasets.[22] We also checked for possible residual confounding by age by including a dichotomous age variable (under-24 months or 24+ months of age) in the previously described regression models. We additionally hoped to restrict analysis to months with peak rotavirus activity, but were unable to do so due because exact dates were not available for the surveillance data. The percent-positive metric was reported only by study year or season (which spans different weeks each year).

Bias Analysis

To evaluate the role of possible time-varying diagnostic misclassification, we used the multiple overimputation approach described by Endo et al.[23] to adjust for misclassification in test-negative designs. Briefly, the sensitivity and specificity of the test used to determine case status were used with a multiple overimputation approach to generate 100 imputed datasets of rotavirus test results adjusted for misclassification. As there is no established sensitivity and specificity for use of an EIA in conjunction with confirmatory testing, we were only able to use this approach for the analyses using site EIA results alone to assign case status. However, using only the site EIA result to assign case status replicates the conduct of most rotavirus VE studies. We varied sensitivity in increments of 0.05 from 0.75 to 0.95 and specificity in increments of 0.01 from 0.97 to 1.0. Although we were interested in assessing specificities less than 0.97, a large percentage of the imputed datasets resulted in regression models with convergence issues when specificity was <0.97. We assumed sensitivity and specificity did not vary by vaccination status.

RESULTS

Across the 6 years studied, we included a total of 8208 children in this analysis. The number of incident cases among all children exhibited annual winter seasonality. For children with RVGE defined by site EIA only, the number of incident cases exhibited biennial winter seasonality (eFigure 1; http://links.lww.com/EDE/B928). 83% (n = 6,776) were fully vaccinated and 57% (n = 4,711) were between 8 and 23 months old on the date of stool specimen collection. When cases were defined by the site EIA case definition, 62% of 1036 cases and 85% of 7172 controls were fully vaccinated (Table). When cases were defined by the combined site EIA and confirmatory testing case definition, 59% of 905 cases and 85% of 7303 controls were fully vaccinated (Table). Further description of the distribution of cases and controls for each definition by age, study year, vaccination status, and gastroenteritis severity can be found in the Table.

Vaccine Effectiveness from the Standard Approach

Using only site EIA results to define cases, annual estimates of VE against any-severity RVGE ranged between 58% [95% confidence interval (CI) = 35%, 72%) in 2014 and 80% (95% CI = 60%, 90%) in 2012 (Figure 1, eTable 1; http://links.lww.com/EDE/B928). Annual estimates of VE against moderate-to-severe RVGE ranged between 70% (95% CI = 45%, 84%) in 2014 and 81% (95% CI = 72%, 87%) in 2013, and annual estimates of VE against RVGE hospitalization ranged between 72% (95% CI = 37%, 87%) in 2014 and 92% (95% CI = 69%, 98%) in 2012. Biennial fluctuations in estimated VE were observed in

years 2013 to 2017 against any-severity RVGE and in years 2012 to 2015 against moderate-to-severe RVGE (eTable 1; http://links.lww.com/EDE/B928).

Using the confirmatory testing case definition, annual estimates of VE against any-severity RVGE ranged between 69% (95% CI = 55%, 79%) in 2017 and 79% (95% CI = 58%, 90%) in 2012 (Figure 1, eTable 1; http://links.lww.com/EDE/B928). Annual estimates of VE against moderate-to-severe RVGE ranged between 75% (95% CI = 54%, 87%) in 2014 and 86% (95% CI = 64%, 95%) in 2016, and annual estimates of VE against RVGE hospitalization ranged between 73% (95% CI = 51%, 85%) in 2017 and 94% (95% CI = 73%, 99%) in 2012. Biennial fluctuations in VE estimates were observed in years 2013 to 2017 against any-severity RVGE (eTable 1; http://links.lww.com/EDE/B928). The two case definitions yielded similar high-activity-year estimates but diverged more in low-activity years. For both case definitions, annual VE estimates fluctuated substantially, though estimates were more precise (i.e., narrower CIs) in high-activity years than in low-activity years (where overall rotavirus case numbers were smaller). Estimates of VE did not substantially change when we included a dichotomous age variable in the models (eTable 2; http://links.lww.com/EDE/B928) or when we used stratified models instead of a season-vaccination interaction term (eTable 3; http://links.lww.com/EDE/B928).

Vaccine Effectiveness from the Force-of-Infection Approach

When we adjusted for the force of infection and used only site EIA results to define cases, annual estimates of VE against any-severity RVGE ranged between 65% (95% CI = 51%, 75%) in 2016 and 73% (95% CI = 67%, 77%) in 2013 and 2015 (Figure 1, eTable 1; http://links.lww.com/EDE/B928). Annual estimates of VE against moderate-to-severe RVGE ranged between 75% (95% CI = 61%, 85%) in 2016 and 77% (95% CI = 70%, 82%) in 2013 and 2015. Annual estimates of VE against RVGE hospitalization ranged between 78% and 79%, with similar 95% CIs for all estimates. For all outcomes, annual VE estimates from the force-of-infection approach fluctuated less than the annual estimates from the standard approach when only site EIA defined cases. Fluctuations diminished as outcome severity increased.

Using the confirmatory testing case definition, annual estimates of VE against any-severity RVGE ranged between 74% and 75%, and annual estimates of VE against moderate-to-severe RVGE ranged between 78% and 79%. Estimated VE against RVGE hospitalization was 80% for all years (Figure 1, eTable 1; http://links.lww.com/EDE/B928). Estimates of VE against any-severity RVGE only modestly fluctuated over all study years relative to estimates from the standard approach using the confirmatory case definition.

Slight fluctuations in estimates for VE against moderate-to-severe RVGE occurred, and even less fluctuation in estimates of VE against RVGE hospitalization occurred. Overall, estimates from the force-of-infection approach fluctuated less and were more precise than estimates from the standard approach regardless of RVGE case definition used. VE estimates using confirmatory testing to define cases were slightly higher than those when site EIA only defined cases for all study years. Estimates of VE did not substantially change when the dichotomous age variable was included in the models (eTable 2; http://links.lww.com/EDE/B928).

Misclassification-Adjusted Estimates

Estimates of VE against any-severity RVGE, moderate-to-severe RVGE, and RVGE hospitalization were higher overall once adjusted for misclassification. As the assumed EIA specificity increased while the assumed EIA sensitivity was fixed at 85%, the modeled bias diminished between the observed and misclassification-adjusted VE (Figure 2). Because of lower prevalence, bias-adjusting for imperfect specificity more noticeably increased VE estimates during low-prevalence years. However, estimates generated from the standard approach still fluctuated after misclassification adjustment. Estimates from the force-of-infection approach were nearly constant after misclassification adjustment, even for outcomes when the original estimates fluctuated (e.g., VE against any-severity RVGE).

EIA sensitivity had little impact on the magnitude of modeled bias for any specificity assumption (eFigure 2 and eTables 4–6; http://links.lww.com/EDE/B928). VE estimates obtained using the same specificity assumption but different sensitivity assumptions varied slightly more during odd years, when the RVGE force of infection was higher. When EIA specificity and sensitivity were assumed to be 0.97 and 0.85, respectively, and the force-of-infection approach was used, annual estimates of VE against any-severity RVGE, moderate-to-severe RVGE, and RVGE hospitalization were approximately 79% to 80%, 83%, and 83% to 86%, respectively, for all years (Figure 2, eTables 4–6; http://links.lww.com/EDE/B928).

DISCUSSION

Based on the presumption that VE should be stable over time, we tested the hypothesis that adjusting for a time-varying force of infection and/or diagnostic misclassification would increase stability in VE estimates over time. Failure to account for the force of infection may bias rotavirus VE estimates and explain the biennial patterns in previously reported annual rotavirus VE. We confirmed that annual estimates of rotavirus VE against any-severity RVGE, moderate-to-severe RVGE, and RVGE hospitalization fluctuated substantially when the standard approach was used for estimation and only site EIA results defined case status. Adding confirmatory testing to define case status improved but did not eliminate fluctuations in VE estimates. When we used the force-of-infection approach, fluctuations were attenuated for annual estimates of VE against any-severity RVGE and negligible for estimates of VE against moderate-to-severe RVGE and RVGE hospitalization. This attenuation is consistent with the previously outlined rationale for VE estimates not being comparable when the baseline force of infection is not explicitly considered. However, even after we used the force-of-infection approach, biennial patterns in annual VE estimates persisted until we also adjusted for diagnostic misclassification.

Diagnostic misclassification generally biased annual VE estimates towards the null regardless of whether the standard or force-of-infection approach was used. Bias towards the null is generally expected when nondifferential sensitivity and specificity is assumed but is less predictable under different conditions. EIA specificity appeared more influential on the overall magnitude of modeled bias than EIA sensitivity. This variation in the magnitude of bias driven by specificity is consistent with the hypothesized time-varying diagnostic misclassification. The relatively low prevalence of rotavirus in the United States suggests

that false positives from slightly imperfect specificity generate larger modeled biases. Use of the force-of-infection approach in conjunction with adjustment for time-varying diagnostic misclassification was critical for generating the most stable VE estimates.

Researchers should consider both force of infection and diagnostic misclassification when estimating VE using a test-negative design. Sensitivity seemed more influential on VE in high-prevalence years, although its overall magnitude of impact was minor relative to specificity. More importantly, both adjusting for diagnostic misclassification and accounting for the relative annual force of infection virtually eliminated annual changes in rotavirus VE estimates, yielding a near-constant VE estimate over time as would be expected when the biologic protection conferred by vaccination is constant in a population.

Our annual rotavirus VE estimates against RVGE hospitalization were consistent with estimates reported in the literature using both the standard and force-of-infection approach,[4] although the estimates from the force-of-infection approach were more consistent and on the greater effectiveness end of the established VE range. Rotavirus VE against hospitalizations has been reported to range from 70% to >90% in the United States.[10] However, considering these smaller studies only occurred over the course of 1 or 2 years, it is possible that some of the variation in VE could be attributable to not controlling for differing baseline forces of infection between the studies.

Our findings suggest that rotavirus vaccines may be similarly effective against all RVGE outcomes once the biases due to the force of infection and diagnostic misclassification are addressed. Our annual VE estimates moved further from the null overall as the RVGE outcome severity increased, again consistent with the established trend of greater estimated rotavirus VE against more severe outcomes.[10,18] Annual estimates from the standard approach after adjustment for misclassification similarly strengthened with outcome severity. However, the VE estimates obtained from the force-of-infection approach after adjustment for misclassification were strikingly similar regardless of outcome severity.

This analysis is subject to limitations. First, the proxy measure used to account for the force of infection is a relative measure (i.e., a percentage) rather than absolute incidence. Therefore, the relationships between the force of infection and VE estimation cannot be absolutely quantified and the qualitatively described relationships may not apply to settings outside of the United States. Second, use of the percent of tests positive as a proxy for prevalence requires assumptions of consistent testing patterns over time, which may vary from year to year in practice and may be related to background incidence. However, other studies have shown that the estimates from the National Respiratory and Enteric Virus Surveillance System are consistent with those from hospital discharge data and active rotavirus surveillance data.[24] We also did not assess genotype-specific VE as a possible source of variation, but reports suggest the same genotype (G12P[8]) was dominant during all study years (including the 2017 study year's as-yet unpublished report).[25,26] The consistency of the dominant genotype reduces concerns that some of the annual variation in VE estimates could derive from differential protection against certain genotypes. While EIA sensitivity and specificity are characterized, they are not definitively known and may have changed from the values established before vaccine introduction,[25] so we cannot define

the exact magnitude of diagnostic misclassification. We assumed that EIA sensitivity and specificity were nondifferential by vaccination status, which is reasonable for rotavirus vaccine[27] but may not be true for other vaccines. Finally, while the test-negative design does mitigate bias from differences in healthcare seeking behavior that might affect other case–control designs, the percent of children vaccinated in the control group (85.5%) may be an overestimate of the actual vaccination coverage nationally among children under 5 years of age (consistently reported as <80%),[28] thus underestimating rotavirus VE. We also did not report age-stratified VE estimates to account for waning immunity, although we would not expect waning immunity to contribute to fluctuations in observed VE once all age cohorts were vaccinated, as in the years of data analyzed.

We demonstrate that the force of infection plays an important role in the estimation of VE. Future analyses should control for the force of infection when comparing estimates of VE over time or between locations. While explicitly including the force of infection in analysis mitigates a large portion of its influence on VE estimates, it may still residually affect VE estimates through diagnostic misclassification. This point is especially important for the increasingly popular test-negative design for vaccine evaluation, but diagnostic misclassification affects all study designs to some degree. Although ideal VE studies would only include those exposed to the pathogen of interest to estimate biologic protection conditional on exposure to infection,[13] exposure is generally not possible to observe. Therefore, well-designed analyses incorporating the force of infection may offset some of the effect of variation in individual-level exposures, with such considerations ideally included in the study design. Restricting analysis to periods of high disease activity may mitigate the impact of the force of infection on VE estimates. However, this approach does not account for temporal differences in the force of infection and therefore limits the comparability of VE estimates over time. Although this work focuses on rotavirus vaccines, evaluation of other vaccines may be subject to similar issues around the force of infection. Ongoing evaluation of COVID-19 vaccines may be complicated by the pandemic's distinct changes in force of infection over time. Without consideration of methodologic nuances of VE estimation, studies of COVID-19 vaccines may report variable VE estimates over time, and result in conflicting messages about vaccine protection. Explicitly accounting for the force of infection warrants routine consideration in VE studies to differentiate true changes in VE from apparent variation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We would like to thank the following individuals (presented in lastname alphabetical order) for their assistance and support: Christina Albertin, Sahle Amsalu, Jayme Alexander, Rokaia Allan, Nancy Back, Brittney Cassell, Kyle Connolly, Jacqueline DellaTorre, Krista Doerflein, Vanessa Florian, Wende Fregoe, Noreen Jeffrey, Monika Johnson, Katharine King, Amy Kinzler, Kirsten Lacombe, Rendie McHenry, Nicole Meyer, Samar Musa, Jenelle Putzig, Marilyn Rice, Anthony Rohlfs, Chelsea Rohlfs, Michelle Roth, Elizabeth Schlaudecker, Jessica Schloemer, Kevin Schmidt, Lynne Shelley, Joseph Sorter, Bonnie Strelitz, Austin Voelker, Kathryn Weiskircher, Michael Whalen.

Data collection was supported by cooperative agreements with the Centers for Disease Control and Prevention (support award numbers 1UO1IP000458-01, 1UO1IP000459-01, 1UO1IP000464-01, 1UO1IP000460-01, 1UO1IP000457-01, 1UO1IP000461-01, 1UO1IP000463-01, 3UO1IP001059-01S1, 3UO1IP001049-01S1, 3UO1IP001063-01S1, 3UO1IP001057-01S1, 3UO1IP001050-01S1, 3UO1IP001054-01S1, 3UO1IP001051-01S1).

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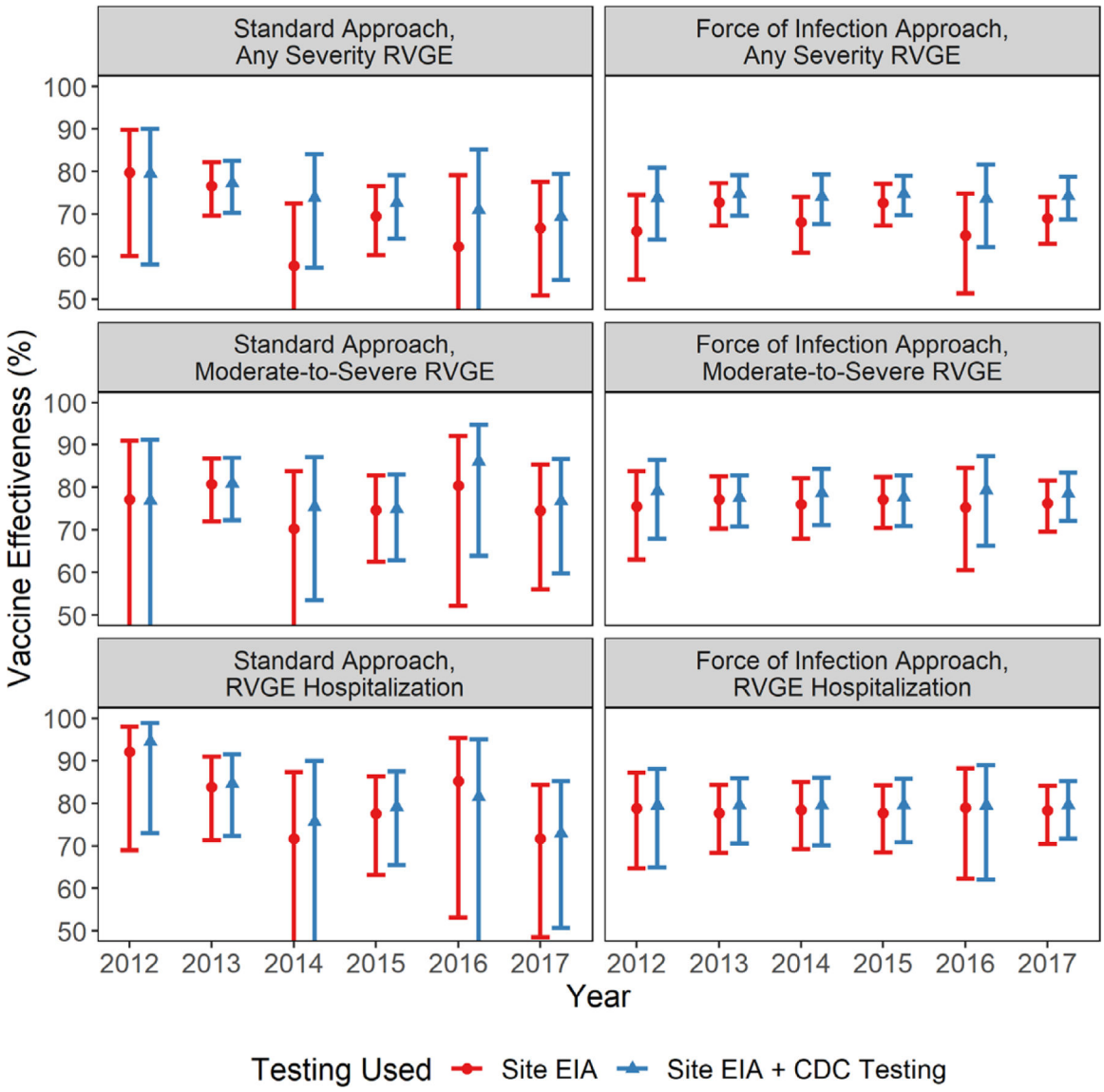

FIGURE 1.

Rotavirus vaccine effectiveness estimates against any-severity rotavirus gastroenteritis (RVGE), moderate-to-severe RVGE, and RVGE hospitalization using site enzyme immunoassay (EIA) only or site EIA and CDC testing to define cases and controls. The left column of panels presents estimates from the standard approach (mixed-effect regression models including vaccination status, year, and a vaccination-year interaction term). The right column of panels presents estimates from the force of infection approach (mixed-effect regression models including vaccination status, annual percent of rotavirus-positive tests, and a vaccination-percent positive interaction term).

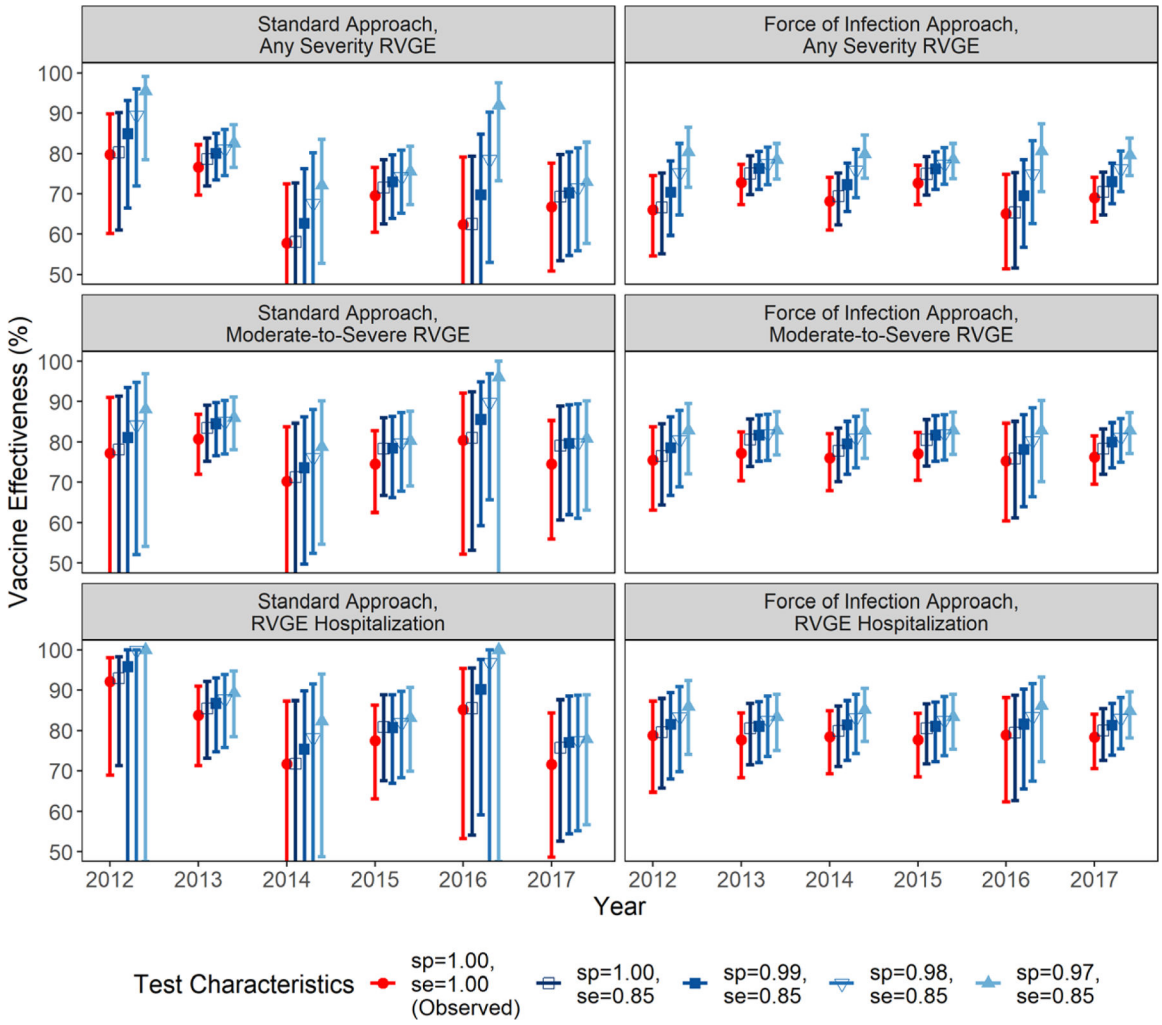

FIGURE 2.

Misclassification-adjusted vaccine effectiveness (VE) estimates and 95% confidence intervals against any-severity rotavirus gastroenteritis (RVGE), moderate-to-severe RVGE, and RVGE hospitalization. The left-most estimate for each year represents the VE obtained using original enzyme immunoassay (EIA) test results to define cases and controls. The remaining estimates represent the VE estimated under different EIA specificity (sp) assumptions and 85% sensitivity (se), with lower specificity for a year's estimates viewed left to right.

TABLE.

Descriptive Statistics by Case or Control Status for Children with Acute Gastroenteritis, Presented by Whether EIA Only or Site EIA and CDC Testing Defined Cases and Controls

	Defined by Site EIA Only				Defined by Site EIA and Confirmatory Testing			
	Controls (n = 7172)		Cases (n = 1036)		Controls (n = 7303)		Cases (n = 905)	
	N	(%)	n	(%)	N	(%)	n	(%)
Vaccination status								
Unvaccinated	1,042	(15)	390	(38)	1,060	(15)	372	(41)
Fully vaccinated	6,130	(85)	646	(62)	6,243	(85)	533	(59)
Gastroenteritis severity								
Moderate-to-severe	2,134	(30)	540	(52)	2,160	(30)	514	(57)
Hospitalized	1,287	(18)	299	(29)	1,306	(18)	280	(31)
Study year								
2012	585	(8)	37	(4)	589	(8)	33	(4)
2013	1,445	(20)	312	(30)	1,459	(20)	298	(33)
2014	1,478	(21)	121	(12)	1,525	(21)	74	(8)
2015	1,653	(23)	345	(33)	1,691	(23)	307	(34)
2016	1,425	(20)	63	(6)	1,446	(20)	42	(5)
2017	586	(8)	158	(15)	593	(8)	151	(17)
Age (months)								
8–23	4,216	(59)	495	(48)	4,279	(59)	432	(48)
24–59	2,956	(41)	541	(52)	3,024	(41)	473	(52)

EIA, enzyme immunoassay.