



Published in final edited form as:

Vaccine. 2025 January 01; 43(Pt 2): 126492. doi:10.1016/j.vaccine.2024.126492.

Assessment and Mitigation of Bias in Influenza and COVID-19 Vaccine Effectiveness Analyses — IVY Network, September 1, 2022–March 30, 2023

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Disclaimer: 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 (CDC).

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Abstract

Background: In test-negative studies of vaccine effectiveness (VE), including patients with co-circulating, vaccine-preventable, respiratory pathogens in the control group for the pathogen of interest can introduce a downward bias on VE estimates.

Methods: A multicenter sentinel surveillance network in the US prospectively enrolled adults hospitalized with acute respiratory illness from September 1, 2022–March 31, 2023. We evaluated bias in estimates of VE against influenza–associated and COVID-19–associated hospitalization based on: inclusion vs exclusion of patients with a co-circulating virus among VE controls; observance of VE against the co-circulating virus (rather than the virus of interest), unadjusted and adjusted for vaccination against the virus of interest; and observance of influenza or COVID-19 against a sham outcome of respiratory syncytial virus (RSV).

Results: Overall VE against influenza–associated hospitalizations was 6 percentage points lower when patients with COVID-19 were included in the control group, and overall VE against COVID-19–associated hospitalizations was 2 percentage points lower when patients with influenza were included in the control group. Analyses of VE against the co-circulating virus and against the sham outcome of RSV showed that downward bias was largely attributable the correlation of vaccination status across pathogens, but also potentially attributable to other sources of residual confounding in VE models.

Conclusion: Excluding cases of confounding respiratory pathogens from the control group in VE analysis for a pathogen of interest can reduce downward bias. This real-world analysis demonstrates that such exclusion is a helpful bias mitigation strategy, especially for measuring influenza VE, which included a high proportion of COVID-19 cases among controls.

Keywords

vaccine effectiveness; influenza; COVID-19; RSV; bias; estimation

Introduction

Test-negative design (TND) studies of influenza vaccine effectiveness (VE), in which symptomatic patients are enrolled as test-positive cases or test-negative controls at the point of care, were originally developed to reduce biases in case-control studies introduced by potential case status misclassification and differential health care-seeking between cases and non-cases.^{1,2} However, bias, while reduced overall, can still persist in TND studies due to incomplete capture of confounders such as exposure history, effects of vaccine policy, or propensity to seek vaccination among patients.^{1,2} Until recently, studies of influenza vaccine effectiveness (VE) in adults have not required extensive consideration of biases introduced by other vaccine-preventable respiratory pathogens. The emergence of SARS-CoV-2 and the development of COVID-19 vaccines introduced a scenario of co-circulating pathogens in which patients frequently receive vaccines for both influenza and SARS-CoV-2. In addition, an RSV vaccine was approved for adults aged ≥ 60 years in 2023. When the uptake of vaccines against two pathogens is correlated, VE may be underestimated if cases of a potentially confounding pathogen are included among the controls for estimates of VE against the pathogen of interest.^{3,4} As cases of one pathogen may be more likely to be unvaccinated for both pathogens or vaccinated for both pathogens, their inclusion among controls for the estimation of VE against the other pathogen may increase the proportion of unvaccinated controls, resulting in a lower VE estimate.

Correlation in vaccine uptake may occur, for example, due to concerns raised over one vaccine (e.g., safety, mistrust) that inhibit the uptake of the other,³ or patient recommendations from healthcare providers (i.e., to get vaccinated for multiple respiratory pathogens) that promote uptake of the other.⁵ Some recent influenza VE studies^{6,7} have observed moderate downward bias when COVID-19 cases were included among controls and have excluded COVID-19 cases from the control group to mitigate this bias. Further explorations of both influenza and COVID-19 VE have found that downward bias may increase with higher proportions of confounding pathogen cases in the control group, higher effectiveness of the vaccine of interest and of the vaccine against the confounding pathogen, or higher vaccination coverage.^{4,8}

However, recent studies of both influenza and COVID-19 VE have suggested that other causes of residual confounding beyond correlated vaccination behavior could still bias VE estimates upwards or downwards. Although recent influenza and COVID-19 VE analyses have typically adjusted for covariates such as age, sex, race, ethnicity, location, or comorbidities,^{6,7,9} these adjustments do not always account for complex biases. For

example, downward bias due to confounding by indication can occur when persons who are more likely to become cases are also more likely to be vaccinated due to health-seeking behavior or healthcare provider intervention (e.g., those who are frail or have underlying comorbidities). During previous influenza seasons, null or negative VE against influenza-associated hospitalization has often been attributed to selection biases in which influenza cases admitted to the hospital were more likely to be vaccinated against influenza.^{10,11} Similarly, recent assessments of COVID-19 VE bias have suggested differences in levels of exposure to the virus (e.g., greater risk-taking following vaccination) and propensity to seek care between vaccine recipients and non-recipients could push VE estimates downward.^{12,13} In contrast, upward bias theoretically could occur if other health-seeking or health-promoting behaviors (e.g., adoption of non-pharmaceutical interventions to prevent infection) are associated with vaccination for a respiratory pathogen.

To understand the nature and extent of bias introduced by co-circulating, vaccine-preventable, diseases existing in real-world observational data used for VE estimation, we used a sample of prospectively enrolled, hospitalized patients from a network of medical centers to examine the sources and magnitude of bias in VE estimates against influenza-associated and COVID-19-associated hospitalization, including correlation of vaccination status across pathogens and other potential causes. After summarizing the results, we provide recommendations for interpreting and mitigating bias in VE estimates for influenza, COVID-19, and now RSV as a vaccine-preventable respiratory infection.

Methods

Twenty-four hospitals from 19 US states within the Investigating Respiratory Viruses in the Acutely Ill (IVY) Network prospectively enrolled patients into this multi-pathogen acute respiratory illness (ARI) surveillance program from September 1, 2022–March 31, 2023. The IVY Network is funded by the Centers for Disease Control and Prevention (CDC) and coordinated from Vanderbilt University Medical Center. This program was given a waiver of informed consent by CDC and each participating site and was conducted in a manner consistent with applicable federal law and CDC policy.^a Personnel at all sites were trained to follow a standard protocol outlining eligibility criteria, data collection, and specimen collection procedures. Patient eligibility criteria included: (1) age ≥ 18 years; (2) hospital admission; (3) clinical presentation consistent with ARI, defined as having ≥ 1 of the following: fever, cough, shortness of breath, new hypoxemia, or new pulmonary findings on chest imaging consistent with pneumonia; and (4) a clinically obtained molecular or antigen test for influenza virus, SARS-CoV-2, or respiratory syncytial virus (RSV) within 10 days of symptom onset and within 3 days of hospital admission. Relevant exclusions were applied to both influenza and COVID-19 VE models (Supplementary Table 1). Methods of clinical and laboratory testing and vaccination ascertainment have been described elsewhere.^{6,7}

The analysis comprised five different models to evaluate bias in VE based on seasonal influenza vaccination (compared with patients who did not receive the current season's dose) or bivalent COVID-19 vaccination (compared with patients who have never received any

^a45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

COVID-19 vaccine [monovalent-only vaccine recipients excluded]) (see Table 1). During August 2022–March 2023, CDC recommended a bivalent COVID-19 mRNA vaccine dose for all persons aged ≥ 5 years who had received a monovalent primary vaccination series ≥ 2 months prior, and in December 2022–April 2023 recommended a bivalent vaccine dose for most persons aged ≥ 6 years regardless of previous monovalent vaccination, plus optional additional bivalent booster doses for moderately or severely immunocompromised persons aged ≥ 6 months and adults aged ≥ 65 years.¹⁴ During the same period, influenza vaccination was recommended for everyone aged ≥ 6 months (excepting those with allergies to influenza vaccines), with a preferential recommendation for the use of higher dose and adjuvanted flu vaccines in people aged ≥ 65 years, over standard dose, unadjuvanted flu vaccines.¹⁵

In Analysis 1, correlation was calculated as relative risk (RR) of influenza vaccination given bivalent COVID-19 vaccination, or vice versa, and defined as low (RR: 0 to <2), moderate (RR: 2 to <4), and high (RR: ≥ 4). Analyses 2–5 used logistic regression to compare the odds of vaccination among hospitalized case patients versus controls. All VE models, except where specified explicitly as “unadjusted,” were adjusted for categorical age in years (≤ 59 , 60–64, 65–74, ≥ 75); sex (male/female), race and ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, other, unknown), Census region (Northeast, Midwest, South, or West, to capture regional variation in transmission), and biweekly period of hospital admission. VE against influenza–associated hospitalization was then calculated as: $(1 - \text{adjusted odds ratio of vaccination}) \times 100\%$. Bias was estimated as the percentage point difference (i.e., absolute change) in VE from the referent outcome and categorized as low (0 to <5 points), moderate (5 to <10 points) and high (≥ 10 points). The five analyses were conducted as follows:

1. Correlation of vaccination status: The overall RR of vaccination for the confounding pathogen was calculated for influenza and COVID-19 vaccine recipients.
2. VE estimation excluding and including cases of the confounding pathogen as controls: Bias based on including cases of the confounding pathogen as controls for VE against the outcome of interest was estimated using percentage point change in VE. Status of vaccination for the confounding pathogen was added as a covariate for each outcome to assess any additional change in bias.
3. Negative control exposure (NCE) analysis measuring VE of vaccination for the confounding pathogen against hospitalization associated with the pathogen of interest: For each reversed pairing of exposure and outcome, significant VE above the null was interpreted as evidence of confounding bias.¹⁶ Status of vaccination for the pathogen of interest was added as a covariate in each model to determine the degree of bias attributable to correlated vaccination status.
4. Negative control outcome (NCO) analysis of COVID-19 VE and influenza VE against RSV–associated hospitalization: VE against RSV–associated hospitalization was selected as an expected null outcome unrelated to correlation of vaccination status as no vaccine was available for RSV before 2023. Significant positive or negative VE above or below the null was interpreted as evidence of confounding bias.¹⁶

5. **Simulation Analysis:** Simulations of influenza VE and bivalent COVID-19 VE were conducted using different proportions of cases of the confounding pathogen among controls to estimate bias that could occur under different conditions of co-circulation.⁴ Bias, or percentage point change (i.e., absolute change) in VE was calculated based on VE for the respective pathogen (influenza or COVID-19) and population category (overall, aged ≥ 60 years, and immunocompromised) reported in the IVY Network during 2022–2023. Confidence intervals on the bias estimates were calculated using iterations of the simulation including 1,000 iterations/repetitions, with a sample size of 200,000 in each. The deviation around the bias was then used to calculate the variability. For patients aged >60 years, the RR chosen for simulation modeling was the largest of the three age groups (60–64, 65–74, and ≥ 75 years) as more bias is generally found with higher correlation of vaccination status across pathogens. The risk of influenza-associated hospitalization or COVID-19-associated hospitalization among unvaccinated patients was set to a proportion of 0.05 for both outcomes.⁴ The following proportions of the confounding vaccine preventable pathogen in the control group were tested: 0, 0.1, 0.25, 0.5, 0.75, 0.9, and 1.0.

Results

A total of 759 influenza-positive patients were enrolled as cases, and 3262 influenza- and COVID-19-negative controls were enrolled as influenza VE controls; the number of controls increased to 5400 when 2138 COVID-19 cases, accounting for 40% of controls, were included (see Table 2). A total of 1126 COVID-19-positive patients were enrolled as cases and 1823 COVID-19- and influenza-negative controls were enrolled as bivalent COVID-19 VE controls; the number of controls increased to 2210 when 387 influenza cases, accounting for 18% of controls, were included. Finally, a total of 399 RSV patients were enrolled as cases and 4269 RSV-negative, influenza-negative, and COVID-19-negative (i.e., triple-negative) patients were used as controls for the RSV negative control outcome analysis. Most patients were aged ≥ 60 years and seasonal influenza vaccination was more common than bivalent COVID-19 vaccination.

1. Correlation of Vaccination Status

The overall RR of influenza vaccination was >2 among COVID-19 bivalent vaccine recipients, and the overall RR of COVID-19 bivalent vaccination was >5 among influenza vaccine recipients (Supplementary Table 2). This correlation was slightly higher among patients with cardiovascular disease or obesity and even higher among patients aged <60 years and who reported no categories of chronic medical conditions.

2. Estimation of Bias Based on Excluding or Including Confounding Pathogen Cases among VE Controls

Inclusion of patients with COVID-19 among controls for VE against influenza-associated hospitalization decreased VE estimates by 5–7 percentage points (moderate bias) for all subgroups except patients who were 18–59 years old or who had no high-risk conditions (2–4 percentage points [low bias]), while inclusion of influenza cases among controls for

VE against COVID-19–associated hospitalization decreased VE estimates by 2–4 percentage points (low bias) for all subgroups (Figure 1). For both influenza- and COVID-19-associated hospitalization, when cases of the confounding pathogen were included among controls, adjusting the model using status of vaccination against the confounding pathogen as a co-variate did not reduce bias; rather, both VE estimates further decreased by <1 percentage point.

3. Negative Control Exposure (NCE)

Influenza VE against COVID-19–associated hospitalization was 23% (95% CI: 14% to 30%) and bivalent COVID-19 VE against influenza–associated hospitalization was 37% (95% CI: 16% to 53%) (Figure 2). Estimates decreased to 21% (95% CI: –4% to 40%) and 18% (95% CI: 9% to 25%), respectively, when cases of the opposite pathogen were included among controls. In both NCE VE models, adding vaccination status for the confounding pathogen as a covariate reduced VE estimates to where confidence intervals crossed the null.

4. Negative Control Outcome (NCO)

In unadjusted models, neither influenza vaccination nor bivalent COVID-19 vaccination were effective against RSV–associated hospitalization (Influenza VE: –3%, 95% CI: –30% to 19%; bivalent COVID-19 VE: –9%, 95% CI: –52% to 21%), and these estimates were generally lower among older adults compared with younger adults (Figure 3). All VE point estimates decreased when models were adjusted for the same covariates used in the main VE models. Influenza vaccination was associated with negative VE (–37%, 95% CI: –78% to –6%) and bivalent COVID-19 vaccination VE was negative with a confidence interval that crossed the null (–47%, 95% CI: –122% to 3%).

5. Simulation Analysis

In an exploratory simulation analysis, bias in VE estimates increased with the proportion of cases of the confounding pathogen in the control group for VE against the pathogen of interest (Supplementary Table 3). For overall influenza VE, downward bias approached or exceeded 5 percentage points (moderate bias) when COVID-19 cases comprised ≥50% of the control group and 10 percentage points (high bias) at ≥75% of the control group. For COVID-19 VE, downward bias exceeded 5 points when influenza cases comprised ≥75% of the control group and did not reach 10 points.

Discussion

This analysis of patients hospitalized with acute respiratory illness during the 2022–2023 season reveals a significant correlation between seasonal influenza and bivalent COVID-19 vaccination, suggesting a strong association in vaccine acceptance for influenza and COVID-19. Although the cause of higher vaccination correlation observed in younger and healthier patients is unknown, explanations could include more self-selection for all available respiratory pathogen vaccinations among younger patients or vaccine mandates for working-age adults in some occupations. Notably, the correlation between vaccines was not evenly balanced. People who received COVID-19 vaccine were very likely to also receive the influenza vaccine, but this effect was not as strong for the likelihood of receiving the

bivalent COVID-19 vaccine if one had received influenza vaccine. Therefore, the presence and impact of bias needs to be evaluated specifically for each virus when estimating VE, to account for variation in co-vaccination and year-to-year differences in seasonality.

Estimates of VE against hospitalization associated with each pathogen decreased when cases of the opposite pathogen were included in the control group, albeit within a threshold (i.e., <10 percentage points) that has been categorized as low in previous studies.⁴ The downward bias was greater for influenza VE compared to bivalent COVID-19 VE in the adjusted models, which may reflect the relatively large number of COVID-19 cases compared with influenza, and the consequently higher proportion of COVID-19 cases among influenza controls. Adjusting for vaccination status for the confounding pathogen in models of VE against hospitalization associated with the pathogen of interest did not correct the downward bias observed when cases of the opposite pathogen were included as controls. This lack of mitigation may be because the bias introduced by correlated vaccination status is a proxy for the bias introduced by other factors (e.g., similarities between patients of certain age groups) that are addressed by other VE model covariates.

Real-world observational data from 2022–2023 showed that including influenza cases among controls for estimation of bivalent COVID-19 VE against COVID-19-associated hospitalizations and emergency department/urgent care (ED/UC) encounters shifted VE estimates downward by <5 percentage points,⁸ consistent with the bias observed here. Similarly, a study from the 2021–2022 influenza season estimated that the inclusion of COVID-19 cases among controls when estimating VE against influenza-associated hospitalization shifted estimates downward by 7–11 percentage points depending on the age group assessed,⁶ which was slightly greater decrease than observed in the current study. Our simulation analysis aligns with previous studies suggesting that bias will increase with higher proportions of cases of the confounding pathogen among controls, as well as higher VE for both the vaccine of interest and the confounding vaccine.^{4,8}

Negative control exposure (NCE) analyses showed significant influenza VE against COVID-19-associated hospitalization and significant but lower bivalent COVID-19 VE against influenza-associated hospitalization. Most estimates were slightly lower when confounding pathogen cases were included among controls (compared with excluded), suggesting that vaccination for influenza and COVID-19 are sufficiently correlated to exert some downward pressure on VE even when the vaccine exposure is biologically unrelated to the pathogen of interest. Adding vaccination status for the confounding pathogen as a covariate in the NCE models brought both VE estimates close to the null, suggesting that correlation of vaccination status accounted for much of the observed VE in the NCE analyses.

In the negative control outcome (NCO) analysis, null or negative bivalent COVID-19 VE and influenza VE were observed against RSV-associated hospitalization. While null VE against RSV would be interpreted as an absence of confounding bias,¹⁷ negative VE estimates were observed in some of the adjusted analyses. may suggest that patients in this sample who get vaccinated for COVID-19 or influenza have more risk factors (e.g., underlying conditions) that increase the likelihood of RSV-associated hospitalization.

These factors could exert some “hidden” residual downward bias on VE estimates in test-negative VE studies that are not necessarily related to correlated vaccination status.¹² In hospital-based networks, VE against influenza–associated hospitalization may be lower than anticipated due to high rates of vaccination among influenza cases in the inpatient population and comparatively poor health associated with reduced immune protection from the vaccine or more severe influenza–associated outcomes.^{10,11} Including patients with cases of other respiratory diseases in the control group for inpatient influenza VE has previously appeared to drive VE downward, even during the pre-COVID era when vaccine-preventable pathogens accounted for a much lower proportion of other circulating respiratory pathogens. A study of VE against influenza–associated hospitalization across the 2014–2015 and 2015–2016 influenza seasons found that, when compared with a control group presumed negative for influenza and all other respiratory pathogens, VE decreased by 2–5% when including patients testing positive for other respiratory pathogens and by 6–17% using only patients testing positive for other respiratory pathogens as controls.¹⁸

Correlated vaccination status thus likely accounts for some but not all of the low to moderate downward bias observed in our influenza and bivalent COVID-19 VE estimates. Where VE bias can be expected to be at least moderate, as in the case of influenza VE during a time of continued high COVID-19 incidence, excluding confounding pathogen cases from controls remains a method to reduce downward bias. However, this mitigation technique may not be sustainable during periods of multiple co-circulating, vaccine-preventable respiratory pathogens, which now include RSV.^{19–21} In this context, excluding cases of confounding pathogens from control groups may unacceptably reduce the size or comparability of control groups, and the precision of VE estimates. Researchers may therefore need to explain potential sources of bias more fully and identify more directly the factors (e.g., underlying health status, risk factors) that could influence both vaccine uptake and risk of infection across pathogens to support additional multivariable strategies.

This study has several limitations. First, the sample size limited VE estimation or precision for some subgroups, and the degree of bias could vary for subgroups that were not considered here. Second, our VE analyses focuses on hospitalization associated with influenza, COVID-19, or RSV as outcomes of interest and observed bias may differ for other clinical endpoints. Third, although the analysis controlled for several relevant potential confounders, residual confounding is possible. Fourth, while the results suggest that correlated vaccination status biases VE toward the null, it is not possible to estimate its precise contribution to the overall downward bias detected or to ascertain the other sources of residual confounding that exert downward bias.

Several strategies could be employed to properly communicate or further investigate the potential impact of biases on VE estimates. For example, future studies could report multiple VE estimates, with and without cases of other pathogens excluded from controls, and potentially with additional sensitivity analyses for VE against outcomes such as ICU admission and mortality. However, such strategies could lead to challenges in communication, reduce the generalizability of the findings to the overall population, and create uncertainty regarding which estimate should be considered the primary result. Researchers could also consider specifying a bias cutoff (e.g., >10 percentage points)

to determine when to exclude alternate viruses from controls, or to report the general level of downward bias in a pre-specified set of sub-analyses. If excluding cases of a relevant pathogen from a control group renders VE estimates too imprecise, the potential for downward bias should be acknowledged when reporting the estimate from the primary analysis inclusive of all enrolled controls.

In addition, future studies might collect additional data to disentangle the relationships between health status, health-seeking, vaccination, and VE when computing VE. For example, a joint estimation of vaccination for the pathogen of interest and effectiveness of the vaccine of interest, or more detailed adjustment for propensity for vaccination, seeking medical care, or being hospitalized for an acute respiratory illness, may help reduce these biases. Depending on the viral pathogen of interest, adjustment for propensity of different vaccination combinations could be explored. Finally, the Bayesian adaptive design framework could be modified to extend into examining within-season VE with priors (e.g., vaccination coverage and correlation between vaccinations) informed as data collection advances throughout a season.

Conclusions

Excluding cases of other vaccine-preventable respiratory pathogens from the controls in a VE analysis is an effective method to reduce downward bias. This approach may be particularly important during periods of high co-circulation resulting in large proportions of cases of these other pathogens among controls.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support for this work was supported by the US Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (contract numbers 75D30122C12914 and 75D30122C14944 to Wesley H. Self).

Conflict of Interests Statement

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Michelle Ng Gong reports grants from NHLBI as a HART co-investigator and APS steering committee co-chair, support for travel to the ATS meeting, participating on an advisory board from Novartis, Philips Healthcare, Regeneron, and Radiometer, and participating on the DSMB for Best clinical trials, outside the submitted work. Carlos G. Grijalva reports receiving compensation for participation in an advisory board for Merck, and receiving research support from CDC, NIH, FDA, AHRQ and SyneosHealth, outside the submitted work. Natasha Halasa receives current support from Merck (investigator-initiated grant), past support from Sanofi and Quidel, and served on an advisory board for Seqirus, outside the submitted work. Akram Khan reports receiving research funding from Dompe pharmaceuticals, 4D Medical, Eli Lilly, and Direct Biologics for patient enrollment in studies, outside the submitted work. Adam S. Luring reports consulting fees and research support from Roche, and research funding from NIAID, NSF, CDC, and Burroughs Wellcome Fund, outside the submitted work. Ithan Peltan reports funding from NIH (R35GM151147), funding from NHLBI and Janssen, and payments to his institution from Regeneron, Bluejay Diagnostics, and Novartis, outside the submitted work. Mayur Ramesh reports participating on an advisory board for AstraZeneca, Moderna, and Pfizer, outside the submitted work. Ivana A Vaughn reports funding from CDC via University of Michigan for US Flu VE Network, funding from eMaxHealth through her institution, and funding from Lilly USA through her institution, outside the submitted work. No other potential conflicts of interest were disclosed.

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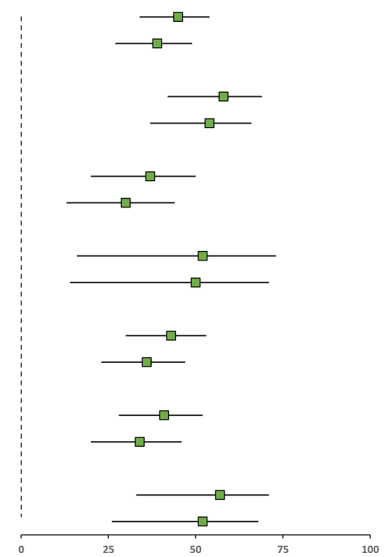
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(A) Influenza Vaccine Effectiveness

	Vaccinated Case Patients/Total Case Patients (%)	Vaccinated Control Patients/Total Control Patients (%)	Vaccine effectiveness (95% CI)
Overall			
Excluding COVID-19 cases as controls	249/759 (33%)	1657/3262 (51%)	45 (34 to 54)
Including COVID-19 cases as controls	249/759 (33%)	2645/5400 (49%)	39 (27 to 49)
Aged 18 to 59 years			
Excluding COVID-19 cases as controls	67/310 (22%)	486/1172 (41%)	58 (42 to 69)
Including COVID-19 cases as controls	67/310 (22%)	708/1828 (39%)	54 (37 to 66)
Aged ≥60 years			
Excluding COVID-19 cases as controls	182/449 (41%)	1171/2090 (56%)	37 (20 to 50)
Including COVID-19 cases as controls	182/449 (41%)	1937/3572 (54%)	30 (13 to 44)
No High Risk Conditions			
Excluding COVID-19 cases as controls	25/126 (20%)	139/373 (37%)	52 (16 to 73)
Including COVID-19 cases as controls	25/126 (20%)	206/572 (36%)	50 (14 to 71)
≥1 High Risk Conditions			
Excluding COVID-19 cases as controls	224/633 (35%)	1518/2889 (53%)	43 (30 to 53)
Including COVID-19 cases as controls	224/633 (35%)	2439/4828 (51%)	36 (23 to 47)
Immunocompetent			
Excluding COVID-19 cases as controls	198/622 (32%)	731/1389 (53%)	41 (28 to 52)
Including COVID-19 cases as controls	198/622 (32%)	1915/4122 (47%)	34 (20 to 46)
Immunocompromised			
Excluding COVID-19 cases as controls	51/137 (37%)	451/764 (59%)	57 (33 to 72)
Including COVID-19 cases as controls	51/137 (37%)	730/1288 (57%)	52 (26 to 68)

Vaccine effectiveness (95% CI)

**(B) Bivalent COVID-19 Vaccine Effectiveness**

	Vaccinated Case Patients/Total Case Patients (%)	Vaccinated Control Patients/Total Control Patients (%)	Vaccine Effectiveness (95% CI)
Overall			
Excluding Influenza cases as controls	503/1126 (45%)	1010/1823 (55%)	45 (35 to 54)
Including Influenza cases as controls	503/1126 (45%)	1169/2210 (53%)	43 (32 to 52)
Aged 18 to 59 years			
Excluding Influenza cases as controls	85/374 (23%)	223/674 (33%)	42 (20 to 58)
Including Influenza cases as controls	85/374 (23%)	708/1828 (39%)	40 (18 to 56)
Aged ≥60 years			
Excluding Influenza cases as controls	418/753 (56%)	787/1149 (68%)	45 (32 to 56)
Including Influenza cases as controls	418/753 (56%)	905/1366 (66%)	42 (28 to 53)
No High Risk Conditions			
Excluding Influenza cases as controls	31/135 (23%)	90/258 (35%)	60 (29 to 77)
Including Influenza cases as controls	31/135 (23%)	107/322 (33%)	56 (24 to 75)
≥1 High Risk Conditions			
Excluding Influenza cases as controls	472/991 (48%)	920/1565 (59%)	45 (33 to 54)
Including Influenza cases as controls	472/991 (48%)	1062/1888 (56%)	42 (30 to 51)
Immunocompetent			
Excluding Influenza cases as controls	386/896 (43%)	731/1389 (53%)	41 (28 to 52)
Including Influenza cases as controls	386/896 (43%)	862/1704 (51%)	39 (25 to 49)
Immunocompromised			
Excluding Influenza cases as controls	117/230 (51%)	279/434 (64%)	58 (37 to 72)
Including Influenza cases as controls	117/230 (51%)	307/506 (61%)	54 (32 to 69)

Vaccine Effectiveness (95% CI)

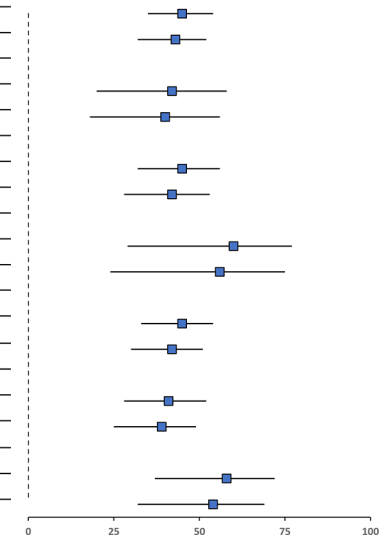


Figure 1. Vaccine effectiveness against influenza-associated hospitalization, excluding and including COVID-19 cases from controls (Panel A [Green]) and vaccine effectiveness against COVID-19-associated hospitalization, including and excluding influenza cases from controls (Panel B [Blue]).

Negative Control Exposure: Bivalent COVID-19 Vaccine Effectiveness Against Influenza / Influenza Vaccine Effectiveness Against COVID-19

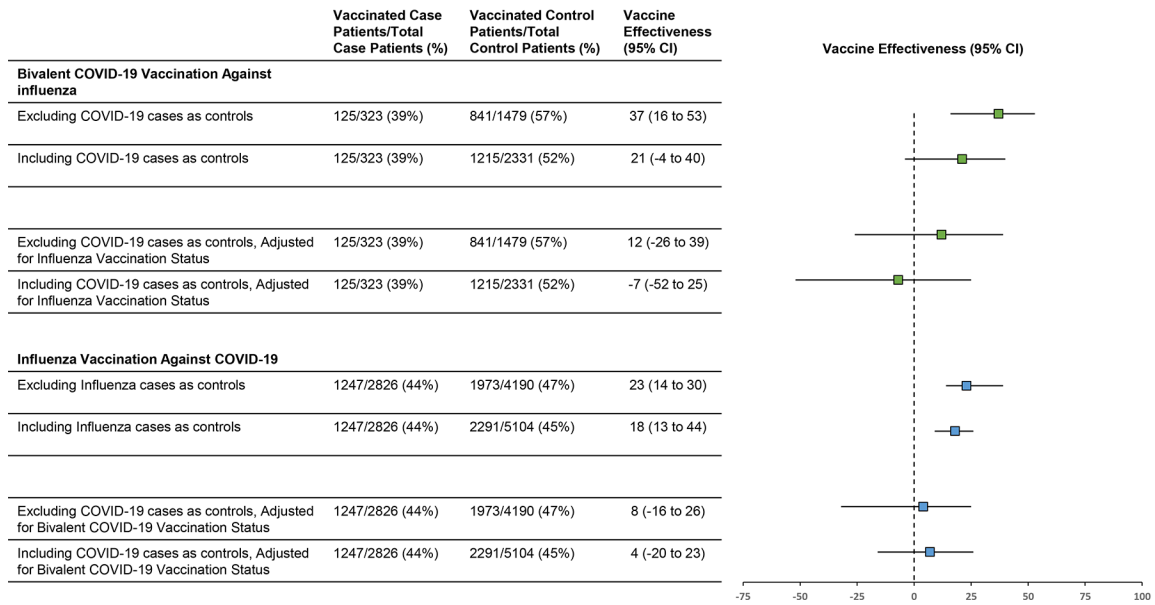
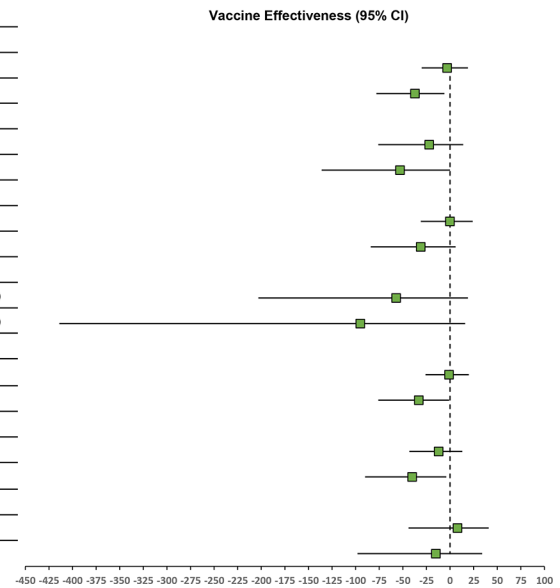


Figure 2.

Negative Control Exposure Assessment: Bivalent COVID-19 VE against influenza-associated hospitalization (Green), excluding and including COVID-19 cases among Controls, not adjusted for influenza vaccination status and adjusted for influenza vaccination status, and influenza vaccine effectiveness against COVID-19-associated hospitalization (Blue), excluding and including influenza cases from controls, not adjusted for bivalent COVID-19 vaccination status and adjusted for bivalent COVID-19 vaccination status.

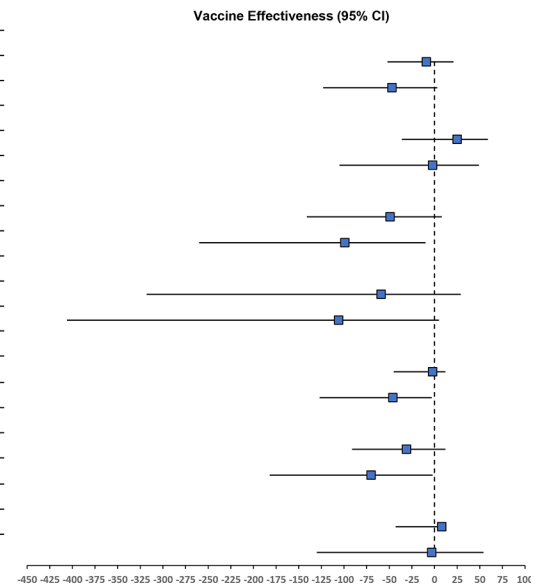
(A) Negative Control Outcome: Influenza Vaccine Effectiveness Against RSV

	Vaccinated Case Patients/Total Case Patients (%)	Vaccinated Control Patients/Total Control Patients (%)	Vaccine Effectiveness (95% CI)
Overall			
Unadjusted	173/358 (48%)	1810/3874 (47%)	-3 (-30 to 19)
Adjusted	173/358 (48%)	1810/3874 (47%)	-37 (-78 to -6)
Aged 18 to 59 years			
Unadjusted	55/135 (41%)	509/1417 (36%)	-22 (-76 to 14)
Adjusted	55/135 (41%)	509/1417 (36%)	-53 (-136 to 0)
Aged ≥60 years			
Unadjusted	118/223 (53%)	1301/2456 (53%)	0 (-31 to 24)
Adjusted	118/223 (53%)	1301/2456 (53%)	-31 (-84 to 6)
No High Risk Conditions			
Unadjusted	17/39 (44%)	161/488 (33%)	-57 (-203 to 19)
Adjusted	17/39 (44%)	161/488 (33%)	-95 (-414 to 26)
≥1 High Risk Conditions			
Unadjusted	156/319 (49%)	1649/3386 (49%)	-1 (-26 to 20)
Adjusted	156/319 (49%)	1649/3386 (49%)	-33 (-76 to -1)
Immunocompetent			
Unadjusted	129/273 (47%)	1308/2941 (44%)	-12 (-43 to 13)
Adjusted	129/273 (47%)	1308/2941 (44%)	-40 (-90 to -4)
Immunocompromised			
Unadjusted	44/85 (52%)	502/933 (54%)	8 (-44 to 41)
Adjusted	44/85 (52%)	502/933 (54%)	-15 (-98 to 34)



(B) Negative Control Outcome: Bivalent COVID-19 Vaccine Effectiveness Against RSV

	Vaccinated Case Patients/Total Case Patients (%)	Vaccinated Control Patients/Total Control Patients (%)	Vaccine Effectiveness (95% CI)
Overall			
Unadjusted	87/155 (56%)	950/1763 (54%)	-9 (-52 to 21)
Adjusted	87/155 (56%)	950/1763 (54%)	-47 (-123 to 3)
Aged 18 to 59 years			
Unadjusted	16/60 (27%)	214/656 (33%)	25 (-36 to 59)
Adjusted	16/60 (27%)	214/656 (33%)	-2 (-105 to 49)
Aged ≥60 years			
Unadjusted	71/95 (75%)	736/1107 (66%)	-49 (-141 to 8)
Adjusted	71/95 (75%)	736/1107 (66%)	-99 (-260 to -10)
No High Risk Conditions			
Unadjusted	8/18 (44%)	84/251 (33%)	-59 (29 to 77)
Adjusted ^a	8/18 (44%)	84/251 (33%)	-106 (-1044 to 7)
≥1 High Risk Conditions			
Unadjusted	79/137 (58%)	866/1512 (57%)	-2 (-45 to 12)
Adjusted	79/137 (58%)	866/1512 (57%)	-46 (-127 to -3)
Immunocompetent			
Unadjusted	64/111 (58%)	686/1345 (51%)	-31 (93 to 12)
Adjusted	64/111 (58%)	686/1345 (51%)	-70 (-182 to -2)
Immunocompromised			
Unadjusted	44/85 (52%)	502/933 (54%)	8 (-43 to 13)
Adjusted	44/85 (52%)	502/933 (54%)	-3 (-130 to 54)

**Figure 3.**

Influenza vaccine effectiveness against RSV–associated hospitalization, unadjusted and adjusted (Panel A [Green]); and bivalent COVID-19 vaccine effectiveness against RSV–associated hospitalization, unadjusted and adjusted (Panel B [Blue]). The lower confidence interval of the plot line marked as (a) on Panel B has a value (−1044) that extends beyond frame of the plot.

Table 1.

Analytical Models Used to Detect Bias

Pathogen of Interest	Outcome of Interest	Control Definitions	Model Parameters	Summary of Results
1. Correlation of Vaccination Status				
Influenza	Relative risk (RR) of current-year bivalent COVID-19 vaccination among recipients of seasonal influenza vaccination	N/A	N/A	High likelihood of bivalent COVID-19 vaccination among influenza vaccine recipients
COVID-19	RR of current-year influenza vaccination among recipients of COVID-19 bivalent booster vaccination	N/A	N/A	Moderate likelihood of bivalent COVID-19 vaccination among influenza vaccine recipients
2. Observed VE Bias				
Influenza	Influenza vaccine effectiveness (VE) against influenza-associated hospitalization	COVID-19 cases (1) included in and (2) excluded from controls	Model adjusted for covariates (age, sex, race/ethnicity, calendar time, HHS region), without and with bivalent COVID-19 vaccination status included as a covariate	- Moderate downward bias observed when COVID-19 cases are included among controls (compared with excluded) - Adjusting for bivalent COVID-19 vaccination status as a model covariate resulted in small increases in downward bias (compared with not adjusting for bivalent COVID-19 vaccination status) and loss of precision
COVID-19	Bivalent COVID-19 VE against COVID-19-associated hospitalization	Influenza cases (1) included in and (2) excluded from controls	Model adjusted for covariates (age, sex, race/ethnicity, calendar time, HHS region), without and with influenza vaccination status included as a covariate	- Low downward bias observed when cases of influenza are included among controls (compared with excluded) - Adjusting for COVID-19 vaccination status resulted in small increases in downward bias (compared with not adjusting for influenza vaccination status) and loss of precision
3. Negative Control Exposure (NCE)				
Influenza	Bivalent COVID-19 VE against influenza-associated hospitalization	COVID-19 cases (1) included in and (2) excluded from controls	Model adjusted for covariates (age, sex, race/ethnicity, calendar time, HHS region), without and with influenza vaccination status included as a covariate	- Significant VE above the null indicated residual confounding bias - Including cases of COVID-19 among controls reduced bias slightly toward the null - Adjusting for influenza vaccination status reduced bias substantially toward the null
COVID-19	Influenza vaccine effectiveness VE against COVID-19-associated hospitalization	Influenza cases (1) included in and (2) excluded from controls	Model adjusted for covariates (age, sex, race/ethnicity, calendar time, HHS region), without and with bivalent COVID-19 vaccination status included as a covariate	- Significant VE above the null indicated residual confounding bias - Including cases of influenza among controls reduced bias slightly

Pathogen of Interest	Outcome of Interest	Control Definitions	Model Parameters	Summary of Results
4. Negative Control Outcome (NCO)				
Influenza	Influenza vaccine effectiveness VE against RSV-associated hospitalization	Influenza and COVID-19 cases excluded from controls	Unadjusted model vs model adjusted for covariates (age, sex, race/ethnicity, calendar time, HHS region)	- Unadjusted model shows null VE overall and for all subgroups - Adjusted model shows negative VE against RSV-associated hospitalization observed overall and for some subgroups, null VE for remaining subgroups
COVID-19	Bivalent COVID-19 VE against RSV-associated hospitalization	Influenza and COVID-19 cases excluded from controls	Unadjusted model vs model adjusted for covariates (age, sex, race/ethnicity, calendar time, HHS region)	- Unadjusted model shows null VE overall and for all subgroups - Adjusted model shows null VE against RSV-associated hospitalization overall and for some subgroups, negative VE for remaining subgroups
5. Simulation Analysis				
Influenza	Influenza VE against influenza-associated hospitalization	COVID-19 cases included among controls	Simulation stratified by different proportions of cases of COVID-19 cases included among controls (0, 0.1., 0.25, 0.5, 0.75, 0.9, 1)	- Moderate bias first appears when COVID-19 cases account for 50% of controls; high bias at 75% of controls - Bias increases with higher VE or higher coverage
COVID-19	COVID-19 VE against COVID-19-associated hospitalization	Influenza cases included among controls	Simulation stratified by different proportions of cases of influenza cases included among controls (0, 0.1., 0.25, 0.5, 0.75, 0.9, 1)	- Moderate bias first appears when influenza cases account for 50% of controls; high bias at 90% of controls - Bias increases with higher VE or higher coverage

Table 2. Demographic and Clinical Characteristics of Influenza, COVID-19, and RSV Cases, and Corresponding Control Groups

	Influenza			COVID-19			RSV		
	Influenza-Positive Cases	Influenza- and COVID-19 Negative Controls (COVID-19 Cases Excluded)	Influenza-Negative Controls (COVID-19 Cases Included)	COVID-19 Cases	COVID-19- and Influenza- Negative Controls (Influenza Cases Excluded)	COVID-19 Negative Controls	RSV Cases	RSV-, Influenza-, and COVID-19- Negative Controls (Triple Negative)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Overall ^a	759	3262	5400	1126	1823	2210	399	4269	
Age Group									
<60 years	310 (40.8)	1172 (35.9)	1828 (33.8)	374 (33.2)	674 (37.0)	844 (38.2)	151 (37.8)	1553 (36.4)	
60–64 years	99 (13.0)	362 (11.1)	578 (10.7)	124 (11.0)	187 (10.3)	234 (10.6)	38 (9.5)	532 (12.5)	
65–74 years	173 (22.8)	847 (26.0)	1375 (25.5)	262 (23.3)	465 (25.5)	553 (25.0)	103 (25.8)	1108 (26.0)	
≥75 years	177 (23.3)	881 (27.0)	1619 (30.0)	366 (32.5)	497 (27.3)	579 (32.5)	107 (26.8)	1072 (25.1)	
≥60 years	449 (59.2)	2090 (64.1)	3572 (66.1)	752 (66.8)	1149 (63.0)	1366 (61.8)	248 (62.2)	2712 (63.5)	
Sex									
Female	414 (54.5)	1620 (49.7)	2690 (49.8)	547 (48.6)	877 (48.1)	1086 (49.1)	217 (54.4)	2074 (48.6)	
Male	345 (45.5)	1642 (50.3)	2710 (50.2)	579 (51.4)	946 (51.9)	1124 (50.9)	182 (45.6)	2191 (52.3)	
Race/Ethnicity									
White, Non-Hispanic	375 (49.4)	1893 (58.0)	3136 (58.1)	708 (62.9)	1122 (61.6)	1329 (60.1)	210 (52.6)	2569 (60.2)	
Black, Non-Hispanic	224 (29.5)	733 (22.5)	1209 (22.4)	223 (19.8)	391 (21.4)	488 (22.1)	94 (23.6)	944 (22.1)	
Hispanic	102 (13.4)	373 (11.4)	636 (11.8)	119 (10.6)	167 (9.2)	220 (10.0)	55 (13.8)	433 (10.1)	
Other	30 (3.9)	122 (3.7)	195 (3.6)	30 (2.7)	67 (3.7)	81 (3.7)	23 (5.8)	143 (3.3)	
Unknown	28 (3.7)	141 (4.3)	224 (4.1)	46 (4.1)	76 (4.2)	92 (4.2)	17 (4.3)	176 (4.1)	
Influenza Vaccine									
Yes	249 (32.8)	1657 (50.8)	2645 (49.0)	472 (41.9)	896 (49.1)	1029 (46.6)	173 (43.4)	1810 (42.4)	
No	510 (67.2)	1605 (49.2)	2755 (51.0)	609 (54.1)	871 (47.8)	1104 (50.0)	185 (46.4)	2064 (48.4)	
Bivalent COVID-19 Vaccine									
Yes	125 (16.5)	841 (25.8)	1215 (22.5)	503 (44.7)	1010 (55.4)	1169 (52.9)	87 (21.8)	950 (22.2)	
No	198 (26.1)	638 (19.6)	1116 (20.7)	623 (55.3)	813 (44.6)	1041 (47.1)	68 (17.0)	813 (19.0)	

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Numbers of cases differ when included as cases for the pathogen of interest or controls for the confounding pathogen due to differential exclusion criteria, i.e., influenza cases are fewer when included as COVID-19 controls because influenza cases with monovalent-only vaccination were excluded from COVID-19 analyses, but COVID-19 cases are greater when included as influenza controls because COVID-19 cases with monovalent-only vaccination could remain included as influenza controls.