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Impact of accounting for correlation between COVID-19 and influenza vaccination in a COVID-19 vaccine effectiveness evaluation using a test-negative design

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Abstract

Test-negative-design COVID-19 vaccine effectiveness (VE) studies use symptomatic SARS-CoV-2-positive individuals as cases and symptomatic SARS-CoV-2-negative individuals as

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Disclaimer: This study was conducted consistent with applicable federal law and CDC policy (45 C.F.R. part 46.102(1)(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.). The findings and conclusions of this report are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2023.11.025>.

controls to evaluate COVID-19 VE. To evaluate the potential bias introduced by the correlation of COVID-19 and influenza vaccination behaviors, we assessed changes in estimates of VE of bivalent vaccines against COVID-19-associated hospitalizations and emergency department/urgent care (ED/UC) encounters when considering influenza vaccination status or including or excluding influenza-positive controls using data from the multi-state VISION vaccine effectiveness network. Analyses included encounters during October 2022 – February 2023, a period of SARS-CoV-2 and influenza cocirculation. When considering influenza vaccination status or including or excluding influenza-positive controls, COVID-19 VE estimates were robust, with most VE estimates against COVID-19-associated hospitalization and ED/UC encounters changing less than 5 percentage points. Higher proportions of influenza-positive patients among controls, influenza vaccination coverage, or VE could impact these findings; the potential bias should continue to be assessed.

Keywords

COVID-19; SARS-CoV-2; Influenza; Negative; Test; Vaccine effectiveness

1. Introduction

COVID-19 vaccine effectiveness (VE) estimates have implications for policy decisions and for communicating the importance of vaccination to healthcare providers and the public. To mitigate potential biases due to testing practices and health seeking behavior, the test-negative design (TND) uses symptomatic test-positive individuals as cases and symptomatic test-negative individuals as controls [1]. COVID-19 TND VE studies, where symptomatic SARS-CoV-2-positive individuals are cases and symptomatic SARS-CoV-2-negative individuals are controls, may have the potential for bias when influenza-positive controls are included due to correlated COVID-19 and influenza vaccine behaviors [2]. In simulation studies, it has been shown that COVID-19 VE can be underestimated in the setting of positive correlation between COVID-19 and influenza vaccination status, especially when a substantial proportion of controls are influenza-positive [2], but this is has not been evaluated in real-world data. Due to limited co-circulation of influenza and SARS-CoV-2, the potential bias introduced by inclusion of influenza-positive controls in COVID-19 VE studies was assumed to be minimal during the 2020/2021 and 2021/2022 respiratory virus seasons; however, there was substantial co-circulation during the 2022/2023 season [3,4]. We explored differences in COVID-19 VE estimates when considering influenza vaccination status or including or excluding influenza-positive controls in studies estimating bivalent VE against COVID-19-associated emergency department/urgent care (ED/UC) encounters and hospitalizations during October 2022 – February 2023, a period when SARS-CoV-2 and influenza co-circulated.

2. Materials and methods

We included hospitalizations and ED/UC encounters during October 15, 2022 – February 4, 2023, among immunocompetent adults aged 18 years with COVID-19-like illness captured in electronic health record data from 4 sites participating in the VISION Network.

Most encounters occurred during the BA.4/BA.5 SARS-CoV-2 variant predominance period. All patients received molecular testing (e.g., reverse transcription polymerase chain reaction) for SARS-CoV-2 and information on influenza molecular testing was also collected. Encounters were excluded if a patient had an immunocompromising condition based on International Classification of Diseases, Tenth Revision (ICD-10) discharge codes [5].

COVID-19 and influenza vaccination status were determined on the index date of the encounter. The index date was defined as the earlier of the molecular SARS-CoV-2 test or ED/UC encounter date or hospital admission date. For COVID-19 vaccination, patients were classified as unvaccinated (no COVID-19 vaccine doses received), vaccinated with monovalent doses only, or vaccinated with one mRNA bivalent booster dose (regardless of number of previous monovalent doses received). Patients who received an mRNA bivalent COVID-19 vaccine dose 7 days before the index date were included in the bivalent vaccination group. Patients who received only monovalent COVID-19 vaccine doses were included if they received any combination of 1–4 doses of monovalent mRNA (Moderna or Pfizer-BioNTech), Janssen (Johnson & Johnson), or Novavax vaccine doses 7 days before the index date. Patients were excluded when they received vaccine schedules that were not recommended, including: recipients of a single monovalent mRNA dose or a single Novavax dose, any vaccine dose received < 7 days before the index date, a bivalent dose received 150 days before the index date, >1 bivalent dose received, >3 monovalent doses received for patients < 50 years, or a bivalent dose received prior to September 2, 2022.

For influenza vaccination, patients were classified on the index date as vaccinated based on electronic health records, local immunization information systems, or claims record documentation of 1 2022–2023 influenza vaccine dose 14 days prior, or unvaccinated if there was no record of receiving any 2022–2023 influenza vaccine dose. Date of influenza vaccination was determined as the date of first influenza vaccination. Patients were excluded from models that included adjustment with influenza vaccination status if influenza vaccination occurred < 14 days prior to the index date.

Demographic and clinical characteristics of SARS-CoV-2-positive and SARS-CoV-2-negative encounters were compared using the standardized mean difference (SMD), with an absolute SMD > 0.20 indicates a nonnegligible difference in variable distributions between patients with a positive SARS-Cov-2 test result versus patients with a negative SARS-CoV-2 test result. Similarly demographic and clinical characteristics of unvaccinated and vaccinated patients were compared using the SMD.

Absolute (comparing vaccinated with unvaccinated) and relative (comparing bivalent with 1, 2, 3, or 4 doses monovalent vaccinated) VE were estimated, as previously performed in the VISION network [6,7]. VE was estimated comparing the odds of vaccination among SARS-CoV-2 PCR-positive case-patients and SARS-CoV-2-negative control-patients, regardless of influenza infection and vaccination status. In addition to an overall influenza-unrestricted model (Model A), changes in COVID-19 VE estimates were assessed by adjustments at both the analysis phase and the study design phase (Table 1). Model B included influenza vaccination status in the analytic model. Model C excluded encounters with missing or indeterminate influenza test results within the window of 10 days prior through 72 h after

the ED/UC encounter or hospital admission date. Model D excluded influenza-positive controls but retained presumptive influenza-negative controls from influenza tests within the window of 10 days prior through 72 h after the ED/UC encounter or hospital admission date (i.e., controls with missing or indeterminate influenza test results were included). Model E excluded influenza-positive controls and controls with missing or indeterminate influenza test results but retained confirmed influenza-negative controls from influenza tests within the window of 10 days prior through 72 h after the ED/UC encounter or hospital admission date. All models were adjusted for age, sex, race and ethnicity, geographic region, and calendar time (days since January 1, 2021). Age and calendar day were modeled as natural cubic splines.

Analyses were conducted using R (version 4.2.2; The R Foundation). This study was conducted consistent with applicable federal law and Centers for Disease Control and Prevention policy and was reviewed and approved by Institutional Review Boards at participating sites or under a reliance agreement with the Institutional Review Board of Westat, Inc.

3. Results

A total of 23,612 hospitalizations (11.5 % SARS-CoV-2 positive and 88.5 % SARS-CoV-2 negative) and 131,620 ED/UC encounters (11.6 % SARS-CoV-2 positive and 88.4 % SARS-CoV-2 negative) were included in this analysis (Table 2). Among hospitalized patients, 20.3 % of case-patients and 15.3 % of control-patients were unvaccinated with any COVID-19 vaccine doses (Supplementary Table 1). A bivalent dose was received by 19.1 % of hospitalized case-patients and 27.1 % of hospitalized control-patients. Among ED/UC encounters, 24.3 % of case-patients and 20.0 % of control-patients were unvaccinated against COVID-19. A bivalent dose was received by 14.8 % and 21.4 % of case- and control-patients with ED/UC encounters, respectively. Among hospitalized encounters the prevalence of having received a bivalent dose among patients who had received an influenza vaccine was 8.5 (95 % confidence interval [CI]: 7.9 – 9.1) times that of patients who had not received an influenza vaccine; among ED/UC encounters the prevalence of having received a bivalent dose among patients who received an influenza vaccine was 11.5 (95 % CI: 11.1 – 11.9) times that of patients who had not received an influenza vaccine. A 2022–2023 influenza vaccine was received by 46.8 % of hospitalization patients and 36.3 % of ED/UC patients at the time of their encounter; 7.4 % of hospitalization patients and 12.6 % of ED/UC patients had a positive influenza test at the time of their encounter, most (>95 %) of whom tested negative for SARS-CoV-2.

For models in which there was relatively good precision around VE estimates, only slight differences (less than 2 percentage points for most estimates) were seen between Model A and all other models (Figs. 1 and 2). VE estimates were robust across encounter types and age groups (Supplementary Figures 1 and 2). Among adults aged 18–64 years the median difference between Model A and other models for VE against COVID-19 hospitalization was 1 percentage point (interquartile range: –0.25 – 3.25 percentage points), and the median difference between Model A and other models for VE against COVID-19 ED/UC encounters was 0.5 percentage points (interquartile range: –5 – 2.25 percentage points).

Among adults aged ≥ 65 years the median difference between Model A and other models for VE against COVID-19 hospitalization was 1 percentage point (interquartile range: 0 – 1.25 percentage points), and the median difference between Model A and other models for VE against COVID-19 ED/UC encounters was 1 percentage point (interquartile range: -0.25 – 2 percentage points).

4. Discussion

During a period with co-circulation of SARS-CoV-2 and influenza, bivalent COVID-19 VE estimates were robust, generally varying less than 5 percentage points when influenza-positive cases were or were not included or after adjusting for influenza vaccination status. Although receipt of influenza vaccine could confound estimation of COVID-19 VE, we demonstrated that VE estimates were remarkably similar, regardless of whether influenza vaccination status was included in the model used to estimate VE or influenza-positive controls were included or excluded in analyses. This was true for estimates of VE against COVID-19-related hospitalizations and ED/UC encounters and across age groups.

Simulation studies have demonstrated that including influenza-positive patients among SARS-CoV-2 negative controls may introduce confounding bias when COVID-19 and influenza vaccine receipt are strongly correlated [2]. If influenza VE is sufficiently high, controls with influenza are less likely to be vaccinated against influenza compared with the source population. If COVID-19 and influenza vaccination rates are strongly correlated, including patients with influenza as controls in COVID-19 VE studies will enrich the control population with participants who are unvaccinated against COVID-19 compared with the source population from which the cases were generated, and thus bias the COVID-19 VE towards the null hypothesis of 0 % VE. COVID-19 and influenza vaccination correlation can also bias influenza VE studies; this has been demonstrated in influenza VE studies [8,9]. The robustness of COVID-19 VE estimates reported in this study may be explained by the relatively low proportion of influenza-positive, SARS-CoV-2-negative controls in the study population as well as the moderate effectiveness of influenza vaccines during the 2022/2023 season [10]. Simulation studies found that bias was low when patients with influenza represented 20 % or less of controls and when influenza VE was less than 40 % [2]. In this study less than 10 % of patients were confirmed influenza-positive among hospitalized SARS-CoV-2-negative controls, and less than 15 % of patients were confirmed influenza-positive among SARS-CoV-2-negative ED/UC encounters. Influenza VE during the study period was estimated to range from 29 % to 51 %, depending on population and outcome [10].

The limitations of estimating COVID-19 VE in the VISION Network have been described elsewhere [6]. Specific to this assessment of changes in COVID-19 VE estimates when considering influenza vaccination status or including or excluding influenza-positive controls in the analysis, SARS-CoV-2 and influenza testing were clinician-directed, and not all patients in this analysis received influenza testing. However, COVID-19 VE estimates were similar when assuming SARS-CoV-2-negative controls that were not tested for influenza were all influenza-negative (Model D) or influenza-positive (Model E). Additionally, influenza positivity was relatively low among SARS-CoV-2-negative controls

in this study, compared with influenza positivity estimates shown in simulation studies to cause biased VE estimates [2]. Thus, the findings of this study may not be generalizable to time periods with significantly higher influenza activity. However, influenza positivity was higher among CLI ED/UC encounters compared with CLI hospitalizations in this study, yet VE against COVID-19-related ED/UC encounters were similarly robust. Finally, influenza VE was moderate during the study period [10]. COVID-19 VE estimates are expected to be impacted by bias when influenza VE is high [2], and the findings of this study may not be generalizable to time periods when influenza VE is high.

5. Conclusions

These analyses indicate that inclusion of influenza-positive controls did not meaningfully impact estimated bivalent VE for COVID-19 vaccines for hospitalizations or ED/UC encounters. However, this study cannot rule out confounding in COVID-19 VE studies due to correlation between influenza and COVID-19 vaccination behaviors; changes in influenza circulation (and influenza test-positivity in included SARS-CoV-2-negative controls), influenza vaccine coverage, or VE may impact future estimates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

Allison L. Naleway reports institutional support from Pfizer for an unrelated study of meningococcal B vaccine safety during pregnancy and from Vir Biotechnology for an unrelated influenza study. Nicola P. Klein reports institutional support from Pfizer, Merck, GSK, Sanofi Pasteur, and Seqirus. Manjusha Gaglani reports institutional funding from CDC for the Ambulatory US Flu/COVID VE Network and the HAIVEN Adult Inpatient Flu/COVID VE study and institutional subcontracts for the IVY-3 PHS project and RECOVER study. All other authors have no conflicts of interest to report.

Data availability

The authors do not have permission to share data.

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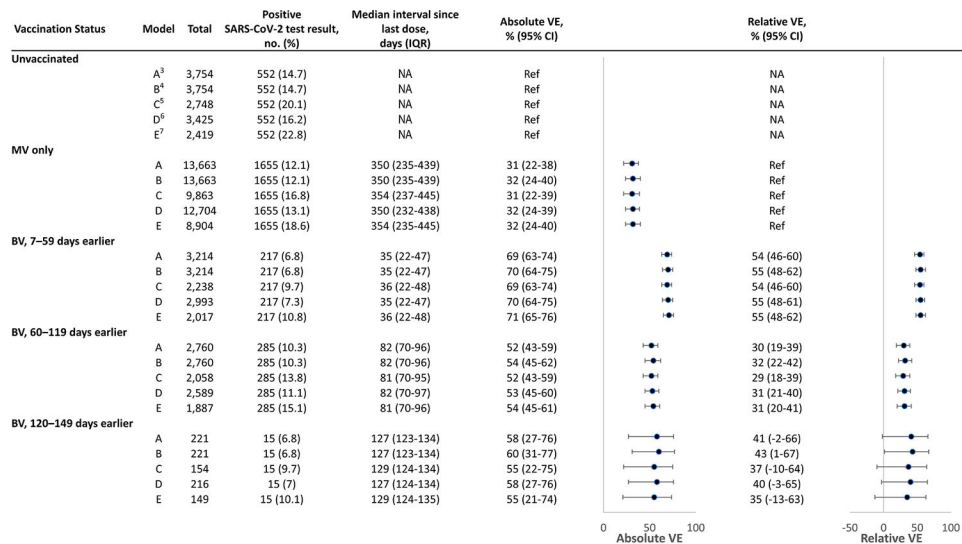


Fig. 1.

Estimates of absolute and relative COVID-19 vaccine effectiveness¹ against laboratory-confirmed COVID-19–associated hospitalizations among adults aged ≥ 18 years, by adjustment method for influenza-positive controls — six states², October 2022–January 2023. Abbreviations: IQR: interquartile range; CI: confidence interval; VE: vaccine effectiveness; MV: monovalent; BV: bivalent. ¹ VE was calculated as $(1 - \text{odds ratio}) \times 100\%$, estimated using a test-negative case-control design, adjusting for age, sex, race and ethnicity, geographic region, and calendar time (days since January 1, 2021). Unvaccinated was the reference group for absolute VE; receipt of monovalent doses only was the reference group for relative VE. ² California, Minnesota and Wisconsin, Oregon and Washington, and Utah. ³ Model A: included all controls (influenza-negative, influenza-positive, influenza-indeterminate, influenza-unknown) and did not adjust for influenza vaccination status. ⁴ Model B: included all controls (influenza-negative, influenza-positive, influenza-indeterminate, influenza-unknown) and adjusted influenza vaccination status. ⁵ Model C: included all controls tested for influenza (influenza-negative and influenza-positive) and did not adjust for influenza vaccination status. ⁶ Model D: included all presumptive influenza-negative controls (influenza-negative, influenza-indeterminate, and influenza-unknown) and did not adjust for influenza vaccination status. ⁷ Model E: included confirmed influenza-negative controls and did not adjust for influenza vaccination status.

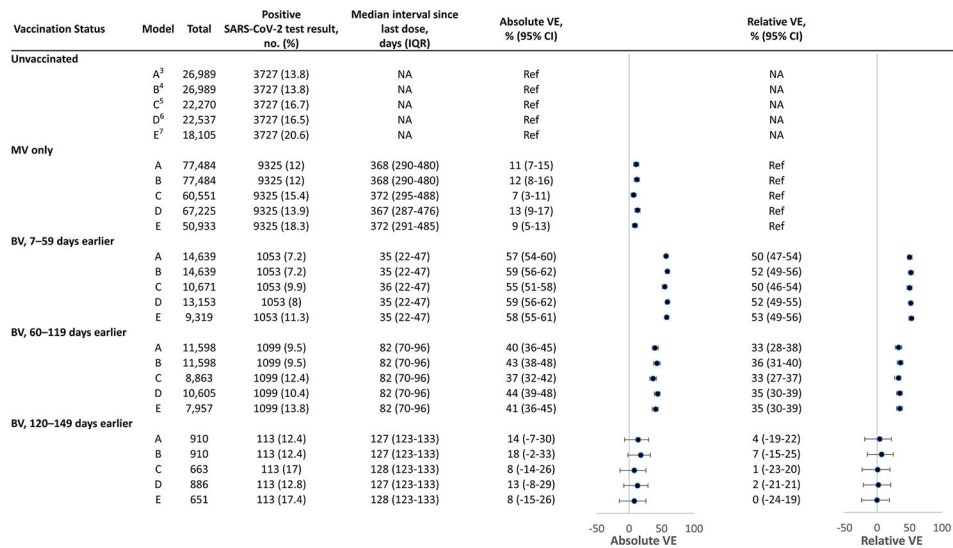


Fig. 2.

Estimates of absolute and relative COVID-19 vaccine effectiveness¹ against laboratory-confirmed COVID-19–associated emergency department or urgent care (ED/UC) encounters among adults aged 18 years, by adjustment method for influenza-positive controls — six states², October 2022–January 2023. Abbreviations: IQR: interquartile range; CI: confidence interval; VE: vaccine effectiveness; MV: monovalent; BV: bivalent. ¹ VE was calculated as $(1 - \text{odds ratio}) \times 100\%$, estimated using a test-negative case-control design, adjusting for age, sex, race and ethnicity, geographic region, and calendar time (days since January 1, 2021). Unvaccinated was the reference group for absolute VE; receipt of monovalent doses only was the reference group for relative VE. ² California, Minnesota and Wisconsin, Oregon and Washington, and Utah. ³ Model A: included all controls (influenza-negative, influenza-positive, influenza-indeterminate, influenza-unknown) and did not adjust for influenza vaccination status. ⁴ Model B: included all controls (influenza-negative, influenza-positive, influenza-indeterminate, influenza-unknown) and adjusted influenza vaccination status. ⁵ Model C: included all controls tested for influenza (influenza-negative and influenza-positive) and did not adjust for influenza vaccination status. ⁶ Model D: included all presumptive influenza-negative controls (influenza-negative, influenza-indeterminate, and influenza-unknown) and did not adjust for influenza vaccination status. ⁷ Model E: included confirmed influenza-negative controls and did not adjust for influenza vaccination status.

Table 1

Model definitions.

Model Name	Control Definition	Covariates^I	Exposures
A	All Controls (influenza-negative, influenza-positive, influenza-indeterminate, influenza-unknown)	age, race and ethnicity, sex, calendar day (days since Jan 1, 2021), and geographic region	Absolute VE: unvaccinated, monovalent, and bivalent Relative VE: monovalent and bivalent
B	All Controls (influenza negative, influenza-positive, influenza-indeterminate, influenza-unknown)	age, race and ethnicity, sex, calendar day (days since Jan 1, 2021), geographic region, influenza vaccination	Absolute VE: unvaccinated, monovalent, and bivalent Relative VE: monovalent and bivalent
C	All Tested Controls (influenza-negative, influenza-positive)	age, race and ethnicity, sex, calendar day (days since Jan 1, 2021), and geographic region	Absolute VE: unvaccinated, monovalent, and bivalent Relative VE: monovalent and bivalent
D	Influenza Presumed Negative (influenza-negative, influenza-indeterminate, influenza-unknown)	age, race and ethnicity, sex, calendar day (days since Jan 1, 2021), and geographic region	Absolute VE: unvaccinated, monovalent, and bivalent Relative VE: monovalent and bivalent
E	Influenza Confirmed Negative (influenza negative)	age, race and ethnicity, sex, calendar day (days since Jan 1, 2021), and geographic region	Absolute VE: unvaccinated, monovalent, and bivalent Relative VE: monovalent and bivalent

^I Age and calendar days were modeled as natural cubic splines

Table 2

Characteristics of hospitalizations and ED/UC encounters among immunocompetent adults aged 18 years with COVID-19-like illness,¹ by SARS-CoV-2 test result — six states,² October 2022–January 2023.

Characteristic	Overall, no. (col. %)	SARS-CoV-2 test result status, no. (column %)		SMD ³
		Case-patients (positive)	Control patients (negative)	
All hospitalizations (row %)	23,612 (100.0)	2,724 (11.5)	20,888 (88.5)	—
Age group, years				
18–49	3,573 (15.1)	246 (9)	3,327 (15.9)	0.31
50–64	4,224 (17.9)	376 (13.8)	3,848 (18.4)	
65–74	4,987 (21.1)	521 (19.1)	4,466 (21.4)	
75–84	6,189 (26.2)	843 (30.9)	5,346 (25.6)	
85	4,639 (19.6)	738 (27.1)	3,901 (18.7)	
Influenza vaccination status				
Unvaccinated	12,567 (53.2)	1,494 (54.8)	11,073 (53)	0.01
Vaccinated	11,045 (46.8)	1,230 (45.2)	9,815 (47)	
Influenza infection status				
Positive	1,741 (7.4)	56 (2.1)	1,685 (8.1)	0.01
Negative	14,736 (62.4)	2,084 (76.5)	12,652 (60.6)	
No influenza result within testing window	7,135 (30.2)	584 (21.4)	6,551 (31.4)	
All ED/UC encounters (row %)	131,620 (100.0)	15,317 (11.6)	116,303 (88.4)	—
Age group, years				
18–49	59,481 (45.2)	6,264 (40.9)	53,217 (45.8)	0.13
50–64	25,909 (19.7)	2,981 (19.5)	22,928 (19.7)	
65–74	19,361 (14.7)	2,239 (14.6)	17,122 (14.7)	
75–84	17,204 (13.1)	2,403 (15.7)	14,801 (12.7)	
85	9,665 (7.3)	1,430 (9.3)	8,235 (7.1)	
Influenza vaccination status				
Unvaccinated	83,778 (63.7)	10,086 (65.8)	73,692 (63.4)	0.03
Vaccinated	47,842 (36.3)	5,231 (34.2)	42,611 (36.6)	
Influenza infection status				
Positive	16,545 (12.6)	411 (2.7)	16,134 (13.9)	0.03
Negative	83,294 (63.3)	11,211 (73.2)	72,083 (62)	
No influenza results in testing window	31,781 (23.6)	3,695 (24.1)	28,086 (24.1)	

Abbreviations: SMD = standardized mean or proportion difference; ED = emergency department; UC = urgent care.

¹ Hospitalizations or ED/UC encounters with a discharge code consistent with COVID-19-like illness were included. COVID-19-like illness diagnoses included acute respiratory illness, respiratory signs or symptoms or febrile signs or symptoms using diagnosis codes from the *International Classification of Diseases, Tenth Revision*. Clinician-ordered molecular assays (e.g., real-time reverse transcription–polymerase chain reaction) for SARS-CoV-2 occurring 14 days before to < 72 h after the date of admission were included.

² California, Minnesota and Wisconsin, Oregon and Washington, and Utah.

³ An absolute SMD > 0.20 indicates a nonnegligible difference in variable distributions between patients with a positive SARS-Cov-2 test result versus patients with a negative SARS-CoV-2 test result.