Title

Absolute and Relative Vaccine Effectiveness of Primary and Booster Series of COVID-19 Vaccines (mRNA and Adenovirus Vector) Against COVID-19 Hospitalizations in the United States, December 2021–April 2022

Journal

Open Forum Infectious Diseases, 10(1)

ISSN

2328-8957

Authors

Lewis, Nathaniel M
Murray, Nancy
Adams, Katherine
et al.

Publication Date

2023-01-04

DOI

10.1093/ofid/ofac698

Peer reviewed

Open Forum Infectious Diseases

MAJOR ARTICLE

Absolute and Relative Vaccine Effectiveness of Primary and Booster Series of COVID-19 Vaccines (mRNA and Adenovirus Vector) Against COVID-19 Hospitalizations in the United States, December 2021–April 2022

Nathaniel M. Lewis,[1] Nancy Murray,[1] Katherine Adams,[1] Diya Surie,[1] Manjusha Gaglani,[2] Adit A. Ginde,[3] Tresa McNeal,[2] Shekhar Ghamande,[2] David J. Douin,[4] H. Keipp Talbot,[5] Jonathan D. Casey,[6] Nicholas M. Mohr,[7] Anne Zepeski,[7] Nathan I. Shapiro,[8] Kevin W. Gibbs,[9] D. Clark Files,[9] David N. Hager,[10] Harith Ali,[10] Matthew E. Prekker,[11] Anne E. Frosch,[12] Matthew C. Exline,[13] Michelle N. Gong,[14] Amira Mohamed,[15] Nicholas J. Johnson,[16] Vasisht Srinivasan,[17] Jay S. Steingrub,[18] Ithan D. Peltan,[19] Samuel M. Brown,[19] Emily T. Martin,[20] Arnold S. Monto,[20] Adam S. Lauring,[21] Akram Khan,[22] Catherine L. Hough,[22] Laurence W. Busse,[23] William Bender,[23] Abhijit Duggal,[24] Jennifer G. Wilson,[25] Alexandra June Gordon,[25] Nida Qadir,[26] Steven Y. Chang,[26] Christopher Mallow,[27] Carolina Rivas,[27] Hilary M. Babcock,[28] Jennie H. Kwon,[28] James D. Chappell,[29] Natasha Halasa,[29] Carlos G. Grijalva,[30] Todd W. Rice,[6] William B. Stubblefield,[31] Adrienne Baughman,[31] Christopher J. Lindsell,[32] Kimberly W. Hart,[32] Jillian P. Rhoads,[33] Meredith L. McMorrow,[1] Mark W. Tenforde,[1] Wesley H. Self,[34] Manish M. Patel,[1] for the Influenza and Other Viruses in the Acutely Ill (IVY) Network

[1]CDC COVID-19 Response Team, Atlanta, Georgia, USA, [2]Baylor Scott and White Health, Texas A&M University College of Medicine, Temple, Texas, USA, [3]Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA, [4]Department of Anesthesiology, University of Colorado School of Medicine, Aurora, Colorado, USA, [5]Departments of Medicine and Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee, USA, [6]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA, [7]Department of Emergency Medicine, University of Iowa, Iowa City, Iowa, USA, [8]Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA, [9]Department of Medicine, Wake Forest School of Medicine, Winston-Salem, North Carolina, USA, [10]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [11]Department of Emergency Medicine and Medicine, Hennepin County Medical Center, Minneapolis, Minnesota, USA, [12]Department of Medicine, Hennepin County Medical Center, Minneapolis, Minnesota, USA, [13]Department of Medicine, The Ohio State University, Columbus, Ohio, USA, [14]Department of Medicine, Montefiore Health System, Albert Einstein College of Medicine, Bronx, New York, USA, [15]Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York, USA, [16]Department of Emergency Medicine and Division of Pulmonary, Critical Care and Sleep Medicine, University of Washington, Seattle, Washington, USA, [17]Department of Emergency Medicine, University of Washington, Seattle, Washington, USA, [18]Department of Medicine, Baystate Medical Center, Springfield, Massachusetts, USA, [19]Department of Medicine, Intermountain Medical Center, Murray, Utah and University of Utah, Salt Lake City, Utah, USA, [20]School of Public Health, University of Michigan, Ann Arbor, Michigan, USA, [21]Departments of Internal Medicine and Microbiology and Immunology, University of Michigan, Ann Arbor, Michigan, USA, [22]Department of Medicine, Oregon Health and Sciences University, Portland, Oregon, USA, [23]Department of Medicine, Emory University, Atlanta, Georgia, USA, [24]Department of Medicine, Cleveland Clinic, Cleveland, Ohio, USA, [25]Department of Emergency Medicine, Stanford University School of Medicine, Stanford, California, USA, [26]Department of Medicine, University of California-Los Angeles, Los Angeles, California, USA, [27]Department of Medicine, University of Miami, Miami, Florida, USA, [28]Department of Medicine, Washington University, St. Louis, Missouri, USA, [29]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee, USA, [30]Department of Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee, USA, [31]Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA, [32]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA, [33]Vanderbilt Institute for Clinical and Translational Research, Vanderbilt University Medical Center, Nashville, Tennessee, USA, and [34]Department of Emergency Medicine and Vanderbilt Institute for Clinical and Translational Research, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Background. Coronavirus disease 2019 (COVID-19) vaccine effectiveness (VE) studies are increasingly reporting relative VE (rVE) comparing a primary series plus booster doses with a primary series only. Interpretation of rVE differs from traditional studies measuring absolute VE (aVE) of a vaccine regimen against an unvaccinated referent group. We estimated aVE and rVE against COVID-19 hospitalization in primary-series plus first-booster recipients of COVID-19 vaccines.

Methods. Booster-eligible immunocompetent adults hospitalized at 21 medical centers in the United States during December 25, 2021–April 4, 2022 were included. In a test-negative design, logistic regression with case status as the outcome and completion of primary vaccine series or primary series plus 1 booster dose as the predictors, adjusted for potential confounders, were used to estimate aVE and rVE.

Results. A total of 2060 patients were analyzed, including 1104 COVID-19 cases and 956 controls. Relative VE against COVID-19 hospitalization in boosted mRNA vaccine recipients versus primary series only was 66% (95% confidence interval [CI], 55%–74%); aVE was 81% (95% CI, 75%–86%) for boosted versus 46% (95% CI, 30%–58%) for primary. For boosted Janssen vaccine recipients versus primary series, rVE was 49% (95% CI, −9% to 76%); aVE was 62% (95% CI, 33%–79%) for boosted versus 36% (95% CI, −4% to 60%) for primary.

Received 05 October 2022; editorial decision 23 December 2022; accepted 29 December 2022; published online 31 December 2022

Correspondence: Jillian P. Rhoads, PhD, 2525 West End Ave., 620th Floor, Nashville, TN, 37203 (jillian.p.rhoads.1@vumc.org). Wesley H. Self, MD, 149 2525 West End Ave., 6th Floor, Nashville, TN 37203 (wesley.self@vumc.org).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofac698

Conclusions. Vaccine booster doses increased protection against COVID-19 hospitalization compared with a primary series. Comparing rVE measures across studies can lead to flawed interpretations of the added value of a new vaccination regimen, whereas difference in aVE, when available, may be a more useful metric.

Keywords. absolute vaccine effectiveness; booster vaccine series; COVID-19; primary vaccine series; relative vaccine effectiveness.

Observational coronavirus disease 2019 (COVID-19) vaccine effectiveness (VE) studies have generally assessed absolute VE (aVE) of a vaccine regimen by comparing the frequency of the outcome (eg, infection, hospitalization, death) in vaccinated (primary series [1, 2] or first booster [3, 4]) versus unvaccinated groups to estimate risk reduction for disease based on vaccination [1–4]. Relative VE (rVE), in contrast, has often been used to compare the risk reduction benefits of different influenza vaccine products (eg, adjuvanted vs high-dose vaccines) based on their effectiveness versus an unvaccinated group [5, 6]. As booster doses were added to COVID-19 vaccination schedules, rVE was also increasingly used to assess the VE of booster regimens by comparing disease incidence between those receiving a booster dose and those receiving the primary series alone [7, 8].

Observations of waning effectiveness for first booster doses during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron-predominant period [9, 10] have prompted ongoing evaluation of the additional benefit of (1) a first booster compared with a primary series and, increasingly, (2) a second booster dose compared with a first. However, both widespread primary series and first booster vaccination in some settings and population groups (eg, older adults) have led to some COVID-19 VE reporting solely rVE to characterize their added value, without the context of an unvaccinated comparator group [11, 12]. Assessing rVE results in terms of absolute improvement in protection for a population can be challenging.

Relative VE for recipients of a vaccine primary series plus booster dose versus the primary series alone can be expressed as follows:

$$rVE = 1 - \frac{(Risk\ among\ vaccinated_{boosted})}{(Risk\ among\ vaccinated_{primary})}$$

Relative VE can also be expressed in relation to aVE estimation:

$$rVE = 100\% \times \frac{aVE_{boosted} - aVE_{primary}}{1 - aVE_{primary}}$$

Therefore, rVE is the proportion of residual disease remaining after the first vaccine regimen that is prevented by the second, new vaccine regimen. The increased reporting of rVE estimates poses several interpretive challenges. Estimates of rVE might not be comparable across outcomes or studies when the absolute VE varies for the comparator vaccine. That is, for the same rVE reported in 2 different studies, the absolute reduction in disease burden provided by the newer regimen (eg, the primary series plus first booster dose) compared with the older one (eg, the primary series) can be quite different depending on the aVE of the older regimen [6]. We sought to better contextualize the rVE of COVID-19 boosters against COVID-19 hospitalization and to develop the interpretation of rVE as an increasingly common metric in COVID-19 booster studies. To achieve these goals, we estimated rVE for boosted versus primary-series-only COVID-19 vaccine recipients as well as aVE for each of the 2 regimens, among booster-eligible patients during the Omicron-predominant period.

METHODS

Setting

During December 25, 2021–April 4, 2022, a period in which the B.1.1.529 (Omicron) variant of SARS-CoV-2 was close to 100% predominant (including an estimated >90% BA.1 or BA.2 lineages) [13], adults admitted to 21 hospitals in 18 US states within the Influenza or Other Viruses in the Acutely Ill (IVY) Network [2, 4, 14, 15] who received testing for SARS-CoV-2 were included in a VE analysis. The analysis start date of December 25, 2021 was approximately 1 month after the emergency use authorization of a first booster dose (following a primary series of 2 mRNA doses or 1 Janssen dose) was expanded to include all adults aged ≥18 years [16] and coincided with the start of the period when the SARS-CoV-2 Omicron variant dominated in the United States. This activity was determined to be public health surveillance by each participating site and the Centers for Disease Control and Prevention (CDC) and was conducted consistent with applicable federal law and CDC policy (see 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq).

Participants

Patients were eligible for analysis if they were immunocompetent adults (≥18 years old) hospitalized with COVID-19-like illness (CLI), defined as having 1 or more of the following: fever, cough, shortness of breath, loss of taste, loss of smell, use of respiratory support for the acute illness, or new pulmonary findings on chest imaging consistent with pneumonia. Test-positive case patients had CLI and tested positive for SARS-CoV-2 by a molecular or antigen test within 14 days of illness onset. Test-negative control patients had CLI and received negative SARS-CoV-2 test results by molecular test [16]. Control patients were time matched to cases within 2 weeks and could

not have been previously enrolled during the prior 30 days; no cases appeared more than once during the study period.

Data Collection

Patients or their proxies were interviewed regarding demographic and clinical characteristics, and medical record searches were completed to collect information about chronic medical conditions. Information about receipt of prior COVID-19 vaccination doses, including dates and vaccine product received, was obtained through self-report and review of source documentation (including state vaccination registries, medical records, and vaccination cards). The COVID-19 vaccination was considered verified with information such as dates of vaccination, vaccine products, and lot numbers using a systematic search of hospital electronic medical records, state vaccination registries, or vaccination cards (when available).

Patient Consent Statement

The IVY Network surveillance program is approved as a public health surveillance activity. This study is conducted with a waiver of informed consent granted by the Institutional Review Boards at the US Centers for Disease Control and Prevention, the IVY Network coordinating center at Vanderbilt University, and at each participating institution.

Vaccination Groups

For immunocompetent adults, a mRNA primary series refers to a 2-dose series of an mRNA vaccine (BNT162b2 [Pfizer] or mRNA-1273 [Moderna]) with the second dose ≥14 days before illness onset, and a Janssen primary series refers to 1 dose of Ad26.COV2 (Janssen [Johnson & Johnson]) ≥14 days before illness onset. Three vaccination groups were considered: (1) unvaccinated patients: received no COVID-19 vaccine doses before illness onset; (2) primary series only recipients - mRNA primary series recipients or Janssen primary series recipients who were eligible for but had not received a booster vaccine dose (≥150 days since mRNA primary series or ≥60 days since Janssen primary series) or had received the booster dose <7 days before illness onset; and (3) primary series plus booster recipients - boosted mRNA vaccine recipients or boosted Janssen recipients who received any single booster dose ≥7 days before illness onset. All other vaccine recipients outside of these 3 groups were excluded from the analysis, including recipients who received the single-dose mRNA vaccine, recipients who received 2 booster doses, and recipients who were not ineligible for booster in the primary series.

Statistical Analysis

We reported differences in sociodemographic characteristics and baseline clinical conditions by vaccination status. We summarized continuous variables as medians and interquartile ranges, and categorical variables were reported as counts and percentages. Differences in distribution and association, respectively, were tested using the Wilcoxon rank-sum test for continuous variables and χ^2 tests with continuity correction for categorical variables. A test-negative design was used to evaluate aVE and rVE. Estimates of rVE against COVID-19 hospitalization were calculated among 2 subgroups: (1) booster-eligible mRNA primary series recipients versus booster recipients and (2) booster-eligible Janssen primary series recipients versus booster recipients.

We estimated aVE and rVE using multivariable logistic regression, where the odds ratio (OR) is modeled with case-status as the outcome and vaccination group (vaccinated without booster, vaccinated with booster, or unvaccinated, depending on analysis) as the exposure of interest while adjusting for sex, race/ethnicity, US Census region of the admitting hospital, age, number of pre-existing conditions, and admission date (biweekly intervals). Covariates were selected a priori based on clinical knowledge and past IVY analyses [2, 4, 13, 14]. The VE was calculated as (1-OR) × 100% [17]. Profile likelihood confidence intervals (CIs) not containing 0 (zero) were considered statistically significant. Analyses were conducted using R software (Vienna, Austria) [18].

Scenario Analysis

We demonstrated, through hypothetical numerical examples, how a fixed rVE could have different practical meanings under differing estimates of aVE. We assumed (1) 2 different vaccines each with a different aVE estimate for the primary series, (2) a constant rVE estimate for a booster dose of either vaccine relative to the primary series alone, and (3) completion of both primary series and booster within a hypothetical population of 2000 people. Using these inputs, we calculated outputs as the number of events averted by (1) implementation of the primary series alone and (2) implementation of the primary series plus booster dose. To isolate the effects of rVE on events averted and for purposes of illustration, we assumed that all input parameters were true unbiased estimates not requiring adjustment for confounding variables. To contextualize the results of the current study and the scenario analysis, we used the International Vaccine Access Center database [19] to identify extant studies using rVE to compare COVID-19 vaccine regimens.

RESULTS

Current Study

During December 25, 2021–April 4, 2022, a period during which the Omicron variant of SARS-CoV-2 predominated, the IVY Network enrolled 2105 patients, 45 of whom were excluded due to missing one of the covariates of age, sex, race,

ethnicity, region, number of conditions, or admission date, leaving 2060 hospitalized patients included in the analytic dataset for this study (1104 case-patients and 956 non-COVID-19 controls). Among all participants, median age was 63 years, 48% of patients were female, and 61% were non-Hispanic White. Among 1104 case patients with laboratory-confirmed COVID-19, 309 (28%) were vaccinated with 2-dose mRNA primary series only, 148 (13%) with 3 doses of mRNA vaccine (primary series plus 1 booster); 58 (5%) with 1-dose Janssen primary series only, 25 (2%) with 1-dose Janssen plus any booster (primary series plus 1 booster); and 564 (51%) were unvaccinated. Among 956 controls without COVID-19, 245 (26%) were vaccinated with mRNA primary series, 372 (39%) with mRNA primary series plus mRNA booster; 38 (4%) with Janssen primary series, 40 (4%) with Janssen primary series plus any booster; and 261 (27%) were unvaccinated.

Patients who received 2 doses of COVID-19 mRNA vaccine (compared with those unvaccinated) were older ($P < .001$), had more chronic medical conditions ($P < .001$), and were less likely to test positive for SARS-CoV-2 ($P < .001$); recipients of a booster dose (compared to those who received the primary series only) were older ($P < .001$), and booster status was not independent of race/ethnicity ($P = .002$) (Table 1). Adults hospitalized with COVID-19 after 1 dose of Janssen (compared with being unvaccinated) had more chronic medical conditions ($P < .001$); those who received a Janssen primary series plus any booster (compared to those who received the primary series only) had more chronic medical conditions ($P < .001$), were older ($P = .049$), and were less likely to test positive for SARS-CoV-2 ($P = .007$). For mRNA vaccine recipients, median days since the last full dose of vaccine ($P < .001$) were greater among primary series recipients (274 days [interquartile range

Table 1. Characteristics of Unvaccinated Patients, mRNA Vaccine Recipients, and Janssen Vaccine Recipients ($n = 2060$), IVY Network, December 2021–April 2022

	Group (*n*)				
Characteristic, *n* (%)	Unvaccinated ($n = 825$)	mRNA Primary Series ($n = 554$)	mRNA Primary Series Plus Booster ($n = 520$)[a]	Janssen Primary Series ($n = 96$)	Janssen Primary Series Plus Booster ($n = 65$)[b]
Clinical Group					
COVID-19 Case	564 (68.4)	309 (55.8)	148 (28.5)	58 (60.4)	25 (38.5)
Age in Years					
Median (IQR)	58 (44–70)	65 (53–74)	68 (58–78)	61 (51–69)	62 (52–70)
18–49 years	265 (32.1)	106 (19.1)	58 (11.2)	22 (22.9)	12 (18.5)
50–64 years	269 (32.6)	158 (28.5)	153 (29.4)	38 (39.6)	29 (44.6)
≥65 years	291 (35.3)	290 (52.3)	309 (59.4)	36 (37.5)	24 (36.9)
Sex					
Female	370 (44.8)	277 (50.0)	263 (50.6)	41 (42.7)	30 (46.2)
Race/ethnicity					
Non-Hispanic White	465 (57.9)	316 (58.3)	351 (68.3)	52 (54.2)	35 (56.5)
Non-Hispanic Black	173 (21.5)	112 (20.7)	91 (17.7)	21 (21.9)	13 (21.0)
Hispanic, Any Race	120 (14.9)	85 (15.7)	52 (10.1)	19 (19.8)	9 (14.5)
Non-Hispanic, all other races	45 (5.6)	29 (5.4)	20 (3.9)	4 (4.2)	5 (8.1)
Unknown	22 (2.6)	12 (2.1)	6 (1.1)	0 (0.0)	3 (4.4)
US Census Region					
Northeast	182 (22.1)	151 (27.3)	120 (23.1)	24 (25.0)	16 (24.6)
South	307 (37.2)	206 (37.2)	162 (31.2)	40 (41.7)	16 (24.6)
Midwest	165 (20.0)	81 (14.6)	95 (18.3)	7 (7.3)	14 (21.5)
West	171 (20.7)	116 (20.9)	143 (27.5)	25 (26.0)	19 (29.2)
Number of chronic medical conditions[c], median (IQR)	1 (1–2)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Days from vaccine dose 1 to illness onset, median (IQR)	–	303 (266–338)	346 (316–372)	255 (203–293)	292 (257–329)
Days from last full dose to illness onset, median (IQR)	–	274 (238–310)	77 (52–107)	255 (203–293)	56 (33–87)

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; mRNA, messenger ribonucleic acid.

[a]Among the 520 who received an mRNA primary series plus mRNA booster, 191 received a Moderna primary series and booster, 295 received a Pfizer primary series and booster, 16 received a Moderna primary series with Pfizer booster, and 18 received a Pfizer primary series with Moderna Booster.

[b]Among the 65 who received the Janssen primary series plus any booster, 21 received a Moderna booster, 27 received a Pfizer booster, and 17 received a Janssen Booster.

[c]Chronic medical conditions are defined as chronic cardiovascular disease (heart failure, peripheral vascular disease that limits mobility, prior myocardial infarction, cardiac arrhythmias including atrial fibrillation and ventricular arrhythmias, vascular heart disease, or hypertension), chronic lung disease (asthma, chronic obstructive pulmonary disease cystic fibrosis, pulmonary fibrosis, pulmonary hypertension, home oxygen use [except at night for sleep disorder], tracheostomy, home noninvasive ventilation use [except at night for sleep disorder], home invasive mechanical ventilation), diabetes mellitus (diabetes mellitus without end organ damage, diabetes mellitus with end organ damage).

{IQR}, 238–310 days]) than for boosted recipients (77 days [IQR, 52–107 days]; the trend was similar for Janssen recipients (255 days [IQR, 203–293 days] vs 56 days [IQR, 33–87 days], $P < .001$). Case patients (compared with control patients) also differed by race/ethnicity distribution ($P = .018$) (see Supplemental Table 1). Time since last full vaccine dose was longer for vaccinated case patients compared with vaccinated control patients (median 237 days [IQR, 102–289 days] vs 124 days [IQR, 64–259 days]).

Relative VE against COVID-19 hospitalization in mRNA primary series plus booster recipients (vs primary series recipients) was 66% (95% CI, 55%–74%); aVE (vs unvaccinated patients) was 81% (95% CI, 75%–86%) for mRNA primary series plus booster recipients vs 46% (95% CI, 30%–58%) for primary series recipients (difference, 35); rVE for patients aged ≥65 years was 71% (rVE = 71% [95% CI, 59% vs 80%], aVE = 85% [95% CI, 78%–90%] vs 48% [95% CI, 24%–65%]; difference, 37), whereas those aged 18–64 years had an rVE of 60% (rVE = 60% [95% CI, 38%–74%]), aVE = 76% [64%–84%] vs 44% [95% CI, 22%–60%]; difference, 32) (Figure 1). In comparison, for Janssen primary series plus booster recipients (vs primary series recipients), rVE was 49% (95% CI, −9% to 76%); aVE (vs unvaccinated patients) was 62% (33%–79%) for primary series plus booster recipients versus 36% (95% CI, −4% to 60%) for primary series recipients (difference, 26) (Figure 2).

Scenario Analysis

The actual reduction in disease associated with a given rVE depends on difference between the aVE of the primary series plus booster dose and the aVE of the primary series alone. As an illustration, we assumed that the primary series of vaccine A (aVE, 75%) and the primary series of vaccine B (aVE, 25%) are each delivered in a population of 2000 people (Figure 3), resulting in effectiveness against an event/outcome for 1500 in the population receiving vaccine A and for 500 in the population receiving vaccine B. When we assume an rVE of 50% for the corresponding booster dose for each vaccine primary series, an additional 250 events are averted by a booster dose of vaccine A while an additional 750 are averted by a booster dose of vaccine B.

Current studies using rVE to assess the effectiveness of primary series plus 2 booster doses versus a primary series plus 1 booster dose report rVE of 11%–85% against infection and 54%–87% against hospitalization (Table 2). However, many studies assessing both infection and

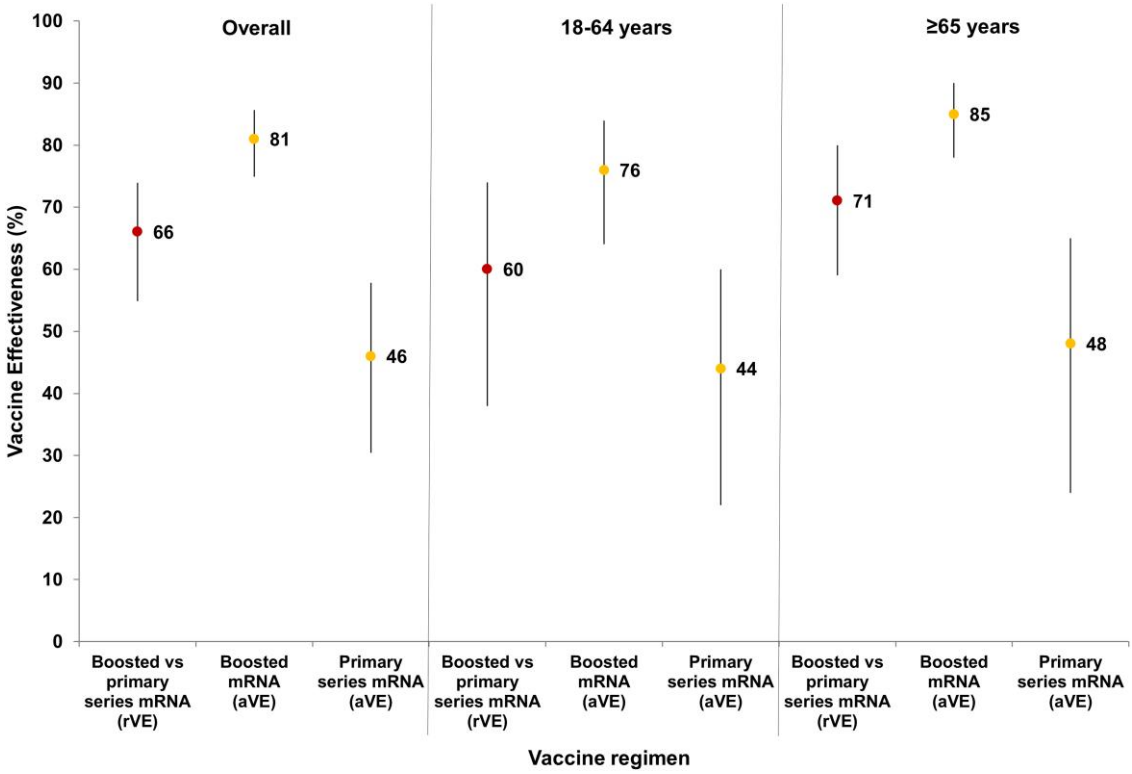

Figure 1. Absolute and relative vaccine effectiveness (rVE) against hospitalization (point estimates [95% confidence intervals]) for primary series plus first mRNA booster dose and mRNA vaccine primary series alone (overall, 18–64 years and ≥65 years), December 2021–April 2022. The rVE point estimates at the left of each age category are denoted by red dots, absolute vaccine effectiveness (aVE) point estimates in the middle and at the right of each age category are denoted by yellow dots, and 95% confidence intervals are delineated by black vertical lines going through the corresponding dots for each point estimate.

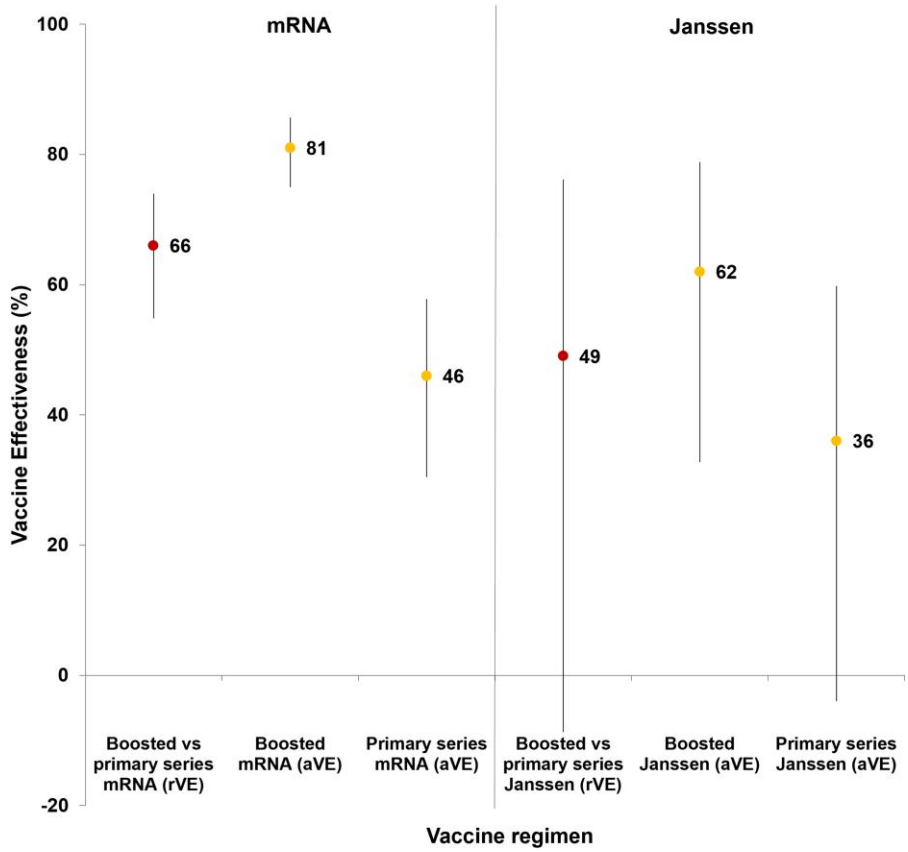

Figure 2. Absolute and relative vaccine effectiveness (rVE) against hospitalization (point estimates [95% confidence intervals]) for mRNA and Janssen vaccine primary series plus first booster dose and primary series alone, December 2021–April 2022. The rVE point estimates are denoted by red dots at the left of each vaccine type category, absolute vaccine effectiveness (aVE) point estimates are denoted by yellow dots in the middle and at the right of each vaccine type, and 95% confidence intervals are delineated by black vertical lines going through the corresponding dots for each point estimate.

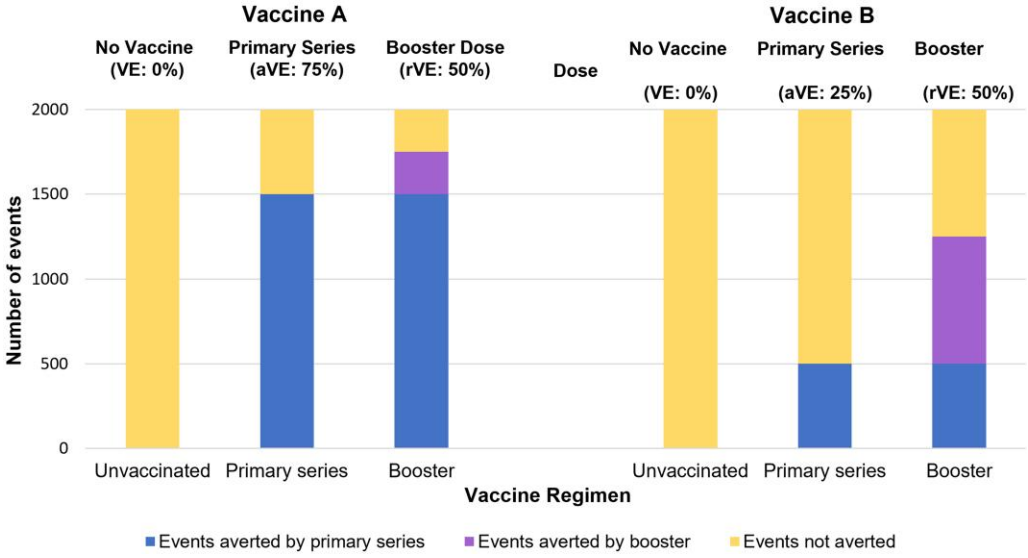

Figure 3. Scenario exercise comparing events averted by primary series alone and primary series plus first booster vaccine dose ($n = 2000$). Clustered bars show the additional number of events averted by adding a vaccine booster (purple/middle section of each bar) to a primary series alone (blue/bottom section of each bar). Unvaccinated persons are represented by the yellow/top section of each bar. Abbreviations: aVE, absolute vaccine effectiveness; rVE, relative vaccine effectiveness; VE, vaccine effectiveness.

Table 2. Studies Using Relative Effectiveness to Evaluate the Effectiveness of a COVID-19 Vaccine Booster Dose ($n = 16$)[a], 2021–2022

Study (Country), Study Type	Dates (Predominant Variants)	Study Design	Population (%Fully Vaccinated)	Primary Series or 1st Booster Evaluated (No. of Recipients)	Follow-up Time Point, Primary Series or 1st Booster	1st or 2nd Booster Evaluated (No. of Recipients)	Follow-up Time Point, 1st or 2nd Booster	Outcomes Evaluated	Estimand (Formula), Estimator	rVE Reported (95% CI)	aVE Reported (95% CI), Primary or 1st Booster vs 1st or 2nd Booster
Studies Reporting rVE and aVE (primary series vs 1st booster)											
1. Lewis et al [30] (USA), primary series vs 1st booster (current study)	December 25, 2021–April 4, 2022 (Omicron)	Test-negative	1357 immunocompetent, booster-eligible adults aged ≥18 y (62% fully vaccinated)	BNT162b2 or mRNA-1273 primary series only ($n = 669$)	≥150 d	BNT162b2 or mRNA-12 731st booster ($n = 520$)	≥7 d	Hospitalization	OR (1-OR), multivariable logistic regression	66% (55%–74%)	81% (75%–86%) vs 46% (31%–58%)
				Adenovirus vector vaccine primary series only ($n = 103$)	≥150 d	BNT162b2 or mRNA-1273 1st booster ($n = 65$)	≥7 d	Hospitalization		49% (–9% to 76%)	62% (33%–79%) vs 36% (–4%–60%)
2. Andrews et al [7] (UK), primary series vs 1st booster	September 13, 2021 (Delta)	Test-negative case control	374 795 adults aged ≥50 y (96% fully vaccinated)	ChAdOx1-S primary series ($n = 266 505$)	≥140 d	BNT162b2 1st booster ($n = 25 672$)	≥14 d	Symptomatic disease	OR (1-OR), multivariable logistic regression	89% (88%–90%)	94% (93%–94%) vs 50% (48%–53%)
								Hospitalization		89% (75%–95%)	99% (97%–100%) vs 90% (88%–91%)
				BNT162b2 primary series only ($n = 108 290$)	≥140 d	BNT162b2 1st booster ($n = 42 013$)	≥14 d	Symptomatic disease	OR (1-OR), multivariable logistic regression	85% (84%–85%)	94% (94%–95%) vs 63% (62%–65%)
								Hospitalization		83% (73%–90%)	99% (98%-99%) vs 93% (92%-94%)
3. Tartof et al [8] (USA), primary series vs 1st booster	December 14, 2020–December 5, 2021 (Alpha, Delta)	Retrospective cohort	3 133 075 adults aged ≥18 y (35% fully vaccinated)	BNT162b2 primary series only ($n = 829 100$)	≥6 mo	BNT162b2 1st booster ($n = 276 037$)	≥14 d	Infection	RR (1-RR), Kaplan-Meier	75% (71%–78%)	88% (86%–89%) vs 49% (46%–51%)
							…	Hospitalization		70% (48%–83%)	97% (95%–98%) vs 88% (85%–90%)

Table 2. Continued

Study (Country), Study Type	Dates (Predominant Variants)	Study Design	Population (%Fully Vaccinated)	Primary Series or 1st Booster Evaluated (No. of Recipients)	Follow-up Time Point, Primary Series or 1st Booster	1st or 2nd Booster Evaluated (No. of Recipients)	Follow-up Time Point, 1st or 2nd Booster	Outcomes Evaluated	Estimand (Formula), Estimator	rVE Reported (95% CI)	aVE Reported (95% CI), Primary or 1st Booster vs 1st or 2nd Booster
4. Plumb et al [20] (USA), primary series vs 1st booster	June 20, 2021–February 4, 2022 (Delta, Omicron)	Test-negative	10 754 adults aged ≥18 y with previous SARS-CoV-2 infection (45% fully vaccinated)	BNT162b2 or mRNA-1273 primary series only (n = 3534)	≥150 d	BNT162b2 or mRNA-1273 1st booster (n = 1301)	≥14 d	Hospitalization	OR (1-OR), conditional logistic regression	56% (44%–66%)	67% (61%–72%) vs 39% (33%–45%)
Studies Reporting rVE and aVE (1st booster vs 2nd booster)											
5. Grewal et al [21] (Canada), 1st booster vs 2nd booster	December 30, 2021–March 2, 2022 (Omicron)	Test-negative	56 806 LTCF residents aged ≥60 y old (93% fully vaccinated)	BNT162b2 or mRNA-1273 primary series plus 1st booster (BNT162b2 or mRNA-1273) (n = 30 222)	≥84 d	BNT162b2 or mRNA-1273 2nd booster (n = 7548)	≥7 d	Infection	OR (1-OR), multivariable logistic regression	40% (34%–45%)	65% (60%–70%) vs 42% (35%–48%)
								Symptomatic infection	…	63% (51%–71%)	87% (81%–91%) vs 66% (54%–75%)
								Severe outcomes	…	54% (31%–70%)	92% (87%–95%) vs 82% (75%–88%)
Studies Reporting rVE only (primary series vs 1st booster)											
6. Abu-Raddad et al [24] (Qatar), primary series vs 1st booster	January 5, 2021–January 9, 2022 (Alpha, Delta)	Retrospective cohort	511 348 persons, all age groups (100% fully vaccinated)	BNT162b2 primary series only (n = 189 483)	49 d	BNT162b2 1st booster (n = 66 191)	49 d	Symptomatic disease	HR (1-HR) Cox proportional hazards	50% (47%–53%)	…
				mRNA-1273 primary series only (n = 189 483)	35 d	mRNA-1273 1st booster (n = 66 191)	35 d	Symptomatic disease		51% (43%–57%)	…
7. Sharma et al [11] (USA), primary series vs 1st booster	January 1–November 25, 2021 (Alpha, Delta)	Observational cohort	258 260 adult veterans aged ≥18 y (100% fully vaccinated)	BNT162b2 primary series only (n = 74 032)	≥14 d	BNT162b2 1st booster (n = 74 032)	≥14 d	Infection	RR (1-RR), Kaplan-Meier	46% (38%–53%)	…
								Hospitalization		47% (36%–55%)	…

Table 2. Continued

Study (Country), Study Type	Dates (Predominant Variants)	Study Design	Population (%Fully Vaccinated)	Primary Series or 1st Booster Evaluated (No. of Recipients)	Follow-up Time Point, Primary Series or 1st Booster	1st or 2nd Booster Evaluated (No. of Recipients)	Follow-up Time Point, 1st or 2nd Booster	Outcomes Evaluated	Estimand (Formula), Estimator	rVE Reported (95% CI)	aVE Reported (95% CI), Primary or 1st Booster vs 1st or 2nd Booster
				mRNA-1273 primary series only ($n = 55\,098$)	≥8 d	mRNA-1273 1st booster ($n = 55\,098$)	≥8 d	Infection		45% (27%–58%)	…
								Hospitalization		50% (26%–66%)	…
8. Barda et al [12] (Israel), primary series vs 1st booster	July 30, 2020–September 23, 2021 (Delta)	Observational cohort	1 456 642 immunocompetent persons aged ≥12 y (100% fully vaccinated)	BNT162b2 primary series only ($n = 728\,231$)	≥5 mo	BNT162b2 1st booster ($n = 728\,231$)	≥7 d	Hospitalization	RR (1-RR), Kaplan-Meier	93% (88%–97%)	…
								Severe disease		92% (82%–97%)	…
								COVID-19-related death		81% (59%–97%)	…
9. Butt et al [22] (USA), primary series vs 1st booster	September 22–December 25, 2021 (Omicron)	Retrospective cohort	791 372 adult veterans aged 66–77 y (IQR) (100% fully vaccinated)	BNT162b2 primary series only ($n = 236\,693$)	≥4.5 mo	BNT162b2 1st booster ($n = 236\,693$)	≥14 d	Symptomatic infection	HR (1-HR), Cox proportional hazards	84% (78%–88%)	…
								Hospitalization		77% (65%–85%)	…
				mRNA-1273 primary series only ($n = 158\,993$)	≥4.5 mo	mRNA-1273 1st booster ($n = 158\,993$)	≥14 d	Symptomatic infection		87% (83%–90%)	…
								Hospitalization		94% (93%–95%)	…
10. Patalon et al [25] (Israel), primary series vs 1st booster	August 1–October 4, 2021 (Delta)	Retrospective case control	500 323 adults aged ≥40 y (100% fully vaccinated)	BNT162b2 primary series only ($n = 227\,380$)	≥150 d	BNT162b2 primary series only ($n = 272\,852$)	7–65 d	Infection	OR (1-OR), GEE logistic regression	12% (8%–17%)–85% (83%–86%)[b]	…
11. McConeghy et al [23] (USA), primary series vs 1st booster	September 22–December 18, 2021 (Delta, Omicron)	Observational cohort	14 210 nursing home residents aged 69–87 y (IQR) (100% fully vaccinated)	BNT162b2 or mRNA-1273 primary series only ($n = 8538$)	≥6 mo	BNT162b2 or mRNA-1273 booster ($n = 5672$)	10–66 d	Infection	RR (1-RR), Kaplan-Meier with IPTW	50% (29%–65%)–58% (32%–78%)[b]	…

Table 2. Continued

Study (Country), Study Type	Dates (Predominant Variants)	Study Design	Population (%Fully Vaccinated)	Primary Series or 1st Booster Evaluated (No. of Recipients)	Follow-up Time Point, Primary Series or 1st Booster	1st or 2nd Booster Evaluated (No. of Recipients)	Follow-up Time Point, 1st or 2nd Booster	Outcomes Evaluated	Estimand (Formula), Estimator	rVE Reported (95% CI)	aVE Reported (95% CI), Primary or 1st Booster vs 1st or 2nd Booster
								Hospitalization		97% (88%–100%)[b]	…
12. Patalon et al [9] (Israel), primary series vs 1st booster	January 1–21, 2021 (Omicron)	Observational cohort	389 265 persons aged ≥16 y (100% fully vaccinated)	BNT162b2 primary series only (*n* = 54 221)	≥5 mo	BNT162b2 1st booster (*n* = 335 044)	0–5 mo	Infection	OR (1-OR), conditional logistic regression	16% (12%–20%)–59% (55%–64%)[b]	…
13. Korves et al [29] (USA), primary series vs 1st booster	September 23, 2021–March 3, 2022 (Delta, Omicron)	Self-controlled case series	259 Veterans aged 60–71 y (med) in care for ≥2 y (100% fully vaccinated)	BNT162b2 or mRNA-1273 primary series only (*n* = 179)	247 d (average)	BNT162b2 or mRNA-1273 1st booster (*n* = 80)	4–6 d (control interval), 4–6 d (exposure interval)	Infection	OR (1-OR), conditional logistic regression	50% (20%–68%)–70% (42%–84%)[b]	…
Studies Reporting rVE only (1st booster vs 2nd booster)											
14. Magen et al [27] (Israel), 1st booster vs 2nd booster	January 3–February 18, 2022 (Omicron)	Retrospective case control	364 244 adults aged ≥60 y (100% fully vaccinated)	BNT162b2 primary series plus 1st booster (*n* = 182 122)	≥4 mo	BNT162b2 2nd booster (*n* = 182 122)	7–30 d	Symptomatic infection	RR (1-RR), Kaplan-Meier	55% (53%–58%)	…
								Hospitalization		68% (59%–74%)	…
								Severe COVID-19		62% (50%–74%)	…
15. Gazit et al [26] (Israel), 1st booster vs 2nd booster	January 10–March 13, 2022 (Omicron)	Retrospective case control	97 499 adults aged ≥60 y (100% fully vaccinated)	BNT162b2 primary series plus 1st booster (*n* = 69 623)	≥4 mo	BNT162b2 2nd booster (*n* = 27 876)	7–69 d	Infection	OR (1-OR), conditional logistic regression	27% (4%–45%)–64% (62%–67%)[b]	…
								Hospitalization		73% (37%–86%) –87% (0%–98%)[b]	…

Table 2. Continued

Study (Country), Study Type	Dates (Predominant Variants)	Study Design	Population (%Fully Vaccinated)	Primary Series or 1st Booster Evaluated (No. of Recipients)	Follow-up Time Point, Primary Series or 1st Booster	1st or 2nd Booster Evaluated (No. of Recipients)	Follow-up Time Point, 1st or 2nd Booster	Outcomes Evaluated	Estimand (Formula), Estimator	rVE Reported (95% CI)	aVE Reported (95% CI), Primary or 1st Booster vs 1st or 2nd Booster
16. Regev-Yochay et al [28] (Israel), 1st booster vs 2nd booster	December 27, 2021–January 30, 2022 (Omicron)	Open-label nonrandomized trial	725 healthcare workers aged ≥18 y (100% fully vaccinated)	BNT162b2 primary series plus 1st booster ($n = 307$)	≥5 mo	BNT162b2 2nd booster ($n = 153$)	≥8 d	Infection	RR (1-RR), Poisson regression	30% (−9% to 55%)	…
								Symptomatic infection		43%[b]	…
				mRNA-1273 primary series plus 1st booster ($n = 149$)	≥5 mo	mRNA 2nd booster ($n = 116$)	≥8 d	Infection		11% (−43% to 44%)	…
								Symptomatic infection		31%[c]	…

Abbreviations: aVE, absolute vaccine effectiveness; CI, confidence interval; COVID-19, coronavirus disease 2019; d, days; HR, hazard ratio; IPTW, inverse probability treatment weighting; IQR, interquartile range; LTCF, long-term care facility; mRNA, messenger ribonucleic acid; mo, months; OR, odds ratio; RR, rate ratio or risk ratio; rVE, relative effectiveness; y, years.

[a]Studies were selected during April–June 2022 through review of the International Vaccine Access Center database [18] in the category of COVID-19 Data—Effectiveness Studies. To be included, the studies had to (1) analyze effectiveness of a first booster dose compared with a primary series or a second booster dose compared with a first booster dose and (2) use rVE as a measure of vaccine effectiveness, either alone or in conjunction with aVE of each option.

[b]Range of rVE reported; rVE varies by follow-up time point.

[c]Confidence intervals not reported.

hospitalization as outcomes report rVE estimates for infection and hospitalization within 10 points of one another, whereas aVE estimates for these outcomes diverge considerably [7–10]. These metrics underline that rVE cannot be translated into a precise reduction in risk from a booster dose or taken as evidence of greater or lesser vaccine effectiveness in one study versus another.

DISCUSSION

This study adds to the body of evidence that a recent first booster dose of mRNA vaccine for recipients of an mRNA primary series results in lower risk of COVID-associated hospitalization (aVE, 81%) compared with the primary series alone (aVE, 46%). An increase in aVE was observed both for patients aged ≥65 years (85% vs 48%) and those aged 18–64 years (76% vs 44%). We also found that the J&J primary series followed by any booster resulted in lower risk of hospitalization (aVE, 62%) compared with the 1-dose J&J primary series alone (36%). These aVE estimates translated into rVE of 66% for boosted mRNA primary series recipients (71% among patients aged ≥65 years and 60% among those aged 18–64 years, respectively) and 49% for boosted Janssen primary series recipients. A positive rVE was observed for the booster in every category, although it spanned zero for boosted Janssen vaccine recipients. However, a positive rVE does not always result in a substantial reduction in disease burden, and there are several factors involved in evaluating the public health utility of a booster dose. For example, the relatively lower rVE reported for boosted Janssen primary series recipients (compared with mRNA primary series recipients) does not indicate poor effectiveness, rather it reflects a large improvement in effectiveness over the low effectiveness observed for the primary series alone.

Comparing the findings of the current study to other similarly designed studies highlights some interpretive challenges. Among 16 studies additional studies, only 4 (25%) reported aVE; 3 were studies of primary series versus first booster [7,8,20] and 1 was first versus second booster [21]. The mRNA rVE reported in the current study (66%) against hospitalization (compared with primary series alone) was lower than in 2 of the 3 studies (83% [7] and 70% [8], respectively) comparing the primary series and the first booster. However, the absolute increase in aVE observed for the first mRNA booster in the current study (difference: 36) is highest among the 3 studies. In the other 2 studies, the aVE of the primary series against hospitalization was already high and the point estimate change in aVE (differences 6 and 9, respectively) was small, which is typical of studies conducted before the Omicron-predominant period. In the third study [20], where rVE was lower than the current study, the aVE of the primary series was low and the resulting difference with aVE from the first booster dose was large (difference, 28). This result was similar to the current study and more typical of studies covering the Omicron-predominant period. Higher rVE reported in several studies [7, 8, 10, 22] could also be associated with larger reductions in risk that might be more common in older populations [7, 10, 22, 23] or could be associated with smaller reductions in risk typical of studies in locales with near-universal vaccination or during earlier variant-predominant periods (eg, Alpha, Delta) with generally higher aVE for the primary series alone [8, 24]. Two studies that demonstrate large changes in rVE observed based on time elapsed after a 1st booster dose (12%–85% during 7–65 days after a first booster dose in one study [11], 27%–64% during 7–69 days after a second booster dose in another study [25]) show that follow-up period can also substantially influence rVE metrics. As studies of second boosters of mRNA vaccines proliferate [20, 26–28] and novel study designs to estimate rVE are introduced [29], it will be important to consider these details and interpret rVE with caution.

We have also shown through a simple scenario analysis that with an equal rVE and baseline disease burden, the actual reduction in disease burden with the introduction of a new vaccination regimen can differ substantially. Because rVE is a measure of incremental effectiveness of the second vaccine option relative to the first option, its interpretation depends on the aVE of the first vaccine option (eg, primary series or first booster). With higher aVE, the residual disease burden will be lower than a vaccination regimen with a lower aVE. Consequently, the actual benefits in terms of events averted by a new vaccination regimen, such as a booster, will be greater in populations with lower aVE before the introduction of the booster. These issues create challenges in the interpretation of rVE across factors such as different vaccines, populations, and time periods. Without an unvaccinated control group against which the effectiveness of each option can be evaluated, the additional reduction in risk provided by one option over the other is often unclear. In instances in which aVE of a booster dose cannot be estimated, studies should ideally report the aVE of the primary series, which, in combination with rVE, can be used to estimate the aVE of the booster. However, this estimate may become less accurate when the primary series and booster have been evaluated during different strain-predominant periods. Alternatively, published studies can provide data from similarly designed studies to provide the risk reduction context for the series against which the newer regimen is being compared. Despite these difficulties in interpretation, studies may be compelled to use rVE as the sole measure of effectiveness when there is no unvaccinated comparison group with which to create an aVE estimate. However, rVE can also be useful (when

provided alongside aVE) as a snapshot of additional, incremental effectiveness offered by a new dosing regimen or product compared with the original option.

The results have some limitations given the complexities of estimating rVE and aVE. Although booster doses were associated with better protection against COVID-19 hospitalization than the primary series, understanding the durability of protection over time or against emerging SARS-CoV-2 variants will require ongoing surveillance. Second, although adjustments were made for calendar time, age, and race/ethnicity, among other potential confounders, unmeasured or residual confounding is possible. A complete case analysis was performed, and bias may be present based on strong missing data mechanism assumptions. Third, most hospitalized patients had multiple chronic medical conditions, and the overall VE observed in this analysis might underestimate protection in healthier populations. Although chronic conditions have been observed to reduce effectiveness [30], sample size was insufficient to differentiate VE by number of conditions. Fourth, the influence of prior infection on VE is not fully known due to a lack of definitive prior infection history among hospitalized patients (eg, inability or refusal to answer) and the likelihood of undercapture [31]; however, a previous sensitivity analysis showed that effectiveness did not change after removing patients with prior infection [13]. Fifth, it was not possible to estimate potential waning of VE due to the time-limited nature of the study, but previous analyses have shown waning for booster doses with increasing time since vaccination [6]. Finally, the broader parameters for ascertaining case status (ie, both molecular and antigen tests) and vaccination status (ie, including self-reported only, although these patients accounted for ≤5% of the total) could potentially overestimate totals of cases and vaccinated patients, respectively.

CONCLUSIONS

We found COVID vaccine primary series plus booster continues to provide substantial protection against COVID-19 hospitalization. However, we found that interpretation of the actual benefits of COVID-19 vaccine booster doses is difficult when considering rVE alone without the benefit of additional contextual data including aVE of the vaccine regimens being compared. As public health agencies evaluate rVE estimates across studies, understanding the rVE of booster doses for COVID-19 vaccines against COVID-19 hospitalization and its relationship to aVE will be important for assessing the potential for additional booster doses to further reduce risk of severe illness and hospitalization.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Financial support. This work was funded by the United States Centers Disease Control and Prevention (Grants 75D30120F00002 and 75D30122C12914; to W. H. S.).

Potential conflicts of interest. Funding for this work was provided to all participating sites by the US Centers for Disease Control and Prevention (CDC). M. G. reports grants from the CDC, CDC-Abt Associates, CDC-Westat, and Janssen, and a leadership role as co-chair of the Infectious Disease and Immunization Committee of the Texas Pediatric Society, Texas Chapter of American Academy of Pediatrics. A. A. G. reports grants from the National Institutes of Health (NIH), Department of Defense (DoD), AbbVie, and Faron Pharmaceuticals. T. M. reports payment/honoraria from the Society of Hospital Medicine. J.D.C. reports funding from NIH and DoD. K.W.G. reports funding from NIH/National Heart, Lung, and Blood Institute (NHLBI) for the ACTIV-4HT NECTAR trial. D. C. F. reports consulting fees from Cytovale and participation on a DSMB for Medpace. D. N. H. reports grants from NIH/NHLBI for the ACTIV-4HT NECTAR trial and Incyte Corporation and participation as a DSMB chair for the SAFE EVICT Trial of vitamin C in COVID-19. A. E. F. reports grants from NIH. M. C. E. reports payment/honoraria from Abbott Lab for sponsored talks. M. N. G. reports grants from NIH/NHLBI and Agency for Healthcare Research and Quality (AHRQ), consulting fees from Endpoint, a leadership role on the American Thoracic Society (ATS) executive committee and board as well as support from ATS for meeting travel expenses, and participation on a DSMB for Regeneron. N. J. J. reports grants from NIH/NHLBI/NINDS and the University of Washington Royalty Research Fund and payment for expert testimony for the Washington Department of Health. I. D. P. reports grants from NIH, Janssen, Regeneron, and Asahi Kasei Pharma. S. M. B. reports grants from NIH and DoD, participation as the DSMB chair for Hamilton Ventilators, and participation as a member of the DSMB for New York University COVID clinical trials. E. T. M. reports grants from Merck, CDC, and NIH and payment/honoraria from the Michigan Infectious Disease Society. A. S. M. reports grants from CDC and NIAID/NIH and participation on a DSMB for the US Food and Drug Administration (FDA). A. S. L. reports grants from CDC, NIH/NIAID, and Burroughs Wellcome Fund and consulting fees from Sanofi and Roche. A. K. reports grants from United Therapeutics, Gilead Sciences, and 4D Medical and a leadership role on the guidelines committee for Chest. C. L. H. reports grants from NIH and American Lung Association and participation as a DSMB member for iSPY COVID and Team (ANZICS). A. D. reports consulting fees from ALung technologies. S.Y.C. reports consulting fees from La Jolla Pharmaceuticals, PureTech Health, and Kiniska Pharmaceuticals, payment/honoraria from La Jolla Pharmaceuticals, and participation on a DSMB for an investigator-initiated study conducted at UCLA. J. H. K. reports grants from NIH/NIAID. J. D. C. reports grants and other support from NIH. N. H. reports grants from NIH, Quidel, and Sanofi and honoraria for speaking at the American Academy of Pediatrics (AAP) conference. C. G. G. reports grants from NIH, CDC, FDA, AHRQ, Sanofi, and Syneos Health and consulting fees from Pfizer, Merck, and Sanofi. T. W. R. reports grants from AbbVie Inc., consulting fees from Cumberland Pharmaceuticals, Inc. and Cytovale, Inc., membership on a DSMB for Sanofi, Inc., a leadership role as immediate past president of the American Society of Parenteral and Enteral Nutrition, and stock options in Cumberland Pharmaceuticals, Inc. W. B. S. reports grants from the NIH/NHLBI. C. J. L. reports grants from NIH, DoD, CDC, bioMerieux, Entegrion Inc., Endpoint Health, and AbbVie, patents for risk stratification in sepsis and septic shock, participation on DSMBs for clinical trials unrelated to the current work, a leadership role on the executive committee for the Board of Directors of the Association for Clinical and Translational Science, and stock options in Bioscape Digita. W. H. S. reports receiving the primary funding for this project from the US CDC and research funding from Merck and Gilead Sciences.

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.

References

1. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med **2021**; 384:403–16.
2. Tenforde MW, Patel MM, Ginde AA, et al. Effectiveness of severe acute respiratory syndrome coronavirus 2 messenger RNA vaccines for preventing coronavirus disease 2019 hospitalizations in the United States. Clin Infect Dis **2022**; 74:1515–24.
3. Accorsi EK, Britton A, Fleming-Dutra KE, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 Omicron and Delta variants. JAMA **2022**; 327:639–51.
4. Tenforde MW, Patel MM, Gaglani M, et al. Effectiveness of a third dose of Pfizer-Biontech and Moderna vaccines in preventing COVID-19 hospitalization among immunocompetent and immunocompromised adults United States, August–December 2021. MMWR Morb Mortal Wkly Rep **2022**; 71:118–24.
5. Izurieta HS, Lu M, Kelman J, et al. Comparative effectiveness of influenza vaccines among US Medicare beneficiaries ages 65 years and older during the 2019–2020 season. Clin Infect Dis **2021**; 73:e4251–9.
6. Lewis NM, Chung JR, Uyeki TM, et al. Interpretation of relative efficacy and effectiveness for influenza vaccines. Clin Infect Dis **2021**; 75:170–5.
7. Andrews N, Stowe J, Kirsebom F, et al. Effectiveness of COVID-19 booster vaccines against COVID-19-related symptoms, hospitalization and death in England. Nat Med **2022**; 28:831–7.
8. Tartof SY, Slezak JM, Puzniak L, et al. Effectiveness of a third dose of BNT162b2 mRNA COVID-19 vaccine in a large US health system: a retrospective cohort study. Lancet Reg Health Am **2022**; 9:100198.
9. Patalon R, Saciuk Y, Peretz A. Waning effectiveness of the third dose of the BNT162b2 mRNA COVID-19 vaccine. Nat Commun **2022**; 13.
10. Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-dose and 3-dose effectiveness of mRNA vaccines against COVID-19-associated emergency department and urgent care encounters and hospitalizations among adults during periods of Delta and Omicron variant predominance—VISION Network, 10 states, August 2021–January 2022. MMWR Morb Mortal Wkly Rep **2022**; 71:255–63.
11. Sharma A, Oda G, Holodniy M. Effectiveness of mRNA-based vaccines during the emergence of SARS-CoV-2 omicron variant. Clin Infect Dis **2022**; 75:2186–92.
12. Barda N, Dagan N, Cohen C, et al. Effectiveness of a third dose of the BNT162b2 mRNA COVID-19 vaccine for preventing severe outcomes in Israel: an observational study. Lancet **2021**; 398:2093–100.
13. Adams K, Rhoads JP, Surie D, et al. Vaccine effectiveness of primary series and booster doses against COVID-19 associated hospital admissions in the United States: living test negative design study. BMJ **2022**; 379:e072065.
14. Lauring AS, Tenforde MW, Chappell JD. Clinical severity of, and effectiveness of mRNA vaccines against, COVID-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ **2022**; 376:e069761.
15. Tenforde MW, Patel MM, Gaglani M, et al. Effectiveness of a third dose of Pfizer-BioNTech and Moderna vaccines in preventing COVID-19 hospitalization among immunocompetent and immunocompromised adults—United States, August–December 2021. MMWR Morb Mortal Wkly Rep **2022**; 71:118–24.
16. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. Vaccine **2013**; 2013:2165–8.
17. US Food and Drug Administration. Coronavirus (COVID-19) update: FDA expands eligibility for COVID-19 vaccine boosters. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-expands-eligibility-covid-19-vaccine-boosters. Accessed 19 November 2021.
18. R Core Team. R: a language and environment for statistical computing. Vienna, Austria. Available at: https://www.R-project.org/. Accessed 18 August 2022.
19. International Vaccine Access Center (IVAC). Johns Hopkins Bloomberg School of Public Health. VIEW-hub. Available at: www.view-hub.org. Accessed 18 August 2022.
20. Plumb ID, Feldstein LR, Barkley E, et al. Effectiveness of COVID-19 mRNA vaccination in preventing COVID-19-associated hospitalization among adults with previous SARS-CoV-2 infection—United States. MMWR Morb Mortal Wkly Rep **2022**; 71:549–55.
21. Grewal R, Kitchen SA, Nguyen L, et al. Effectiveness of a fourth dose of COVID-19 vaccine among long-term care residents in Ontario, Canada. BMJ **2022**; 378:e071502.
22. Butt AA, Talisa VB, Shaikh OS, et al. Relative vaccine effectiveness of a SARS-CoV-2 mRNA vaccine booster dose against the omicron variant. Clin Infect Dis **2022**; 75:2161–8.
23. McConeghy KW, Bardenheier B, Huang AW, et al. Infections, Hospitalizations, and Deaths Among US Nursing Home Residents With vs Without a SARS-CoV-2 Vaccine Booster. JAMA Netw Open **2022**; 5:e2245417.
24. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Effect of mRNA vaccine boosters against SARS-CoV-2 omicron infection in Qatar. N Engl J Med **2022**; 386: 1804–16.
25. Patalon T, Gazit S, Pitzer VE, Prunas O, Warren JL, Weinberger DM. Odds of testing positive for SARS-CoV-2 following receipt of 3 vs 2 doses of the BNT162b2 mRNA vaccine. JAMA Intern Med **2022**; 182:179–84..
26. Gazit S, Saciuk Y, Perez G, et al. Short term, relative effectiveness of four doses versus three doses of BNT162b2 vaccine in people aged 60 years and older in Israel: retrospective, test negative, case-control study. BMJ **2022**; 377:e071113.
27. Magen O, Waxman JG, Makov-Assif M, et al. Fourth dose of BNT162b2 mRNA COVID-19 vaccine in a nationwide setting. N Engl J Med **2022**; 386:1603–14.
28. Regev-Yochay G, Mandelboim M, Amit S, et al. Efficacy of a fourth dose of COVID-19 mRNA vaccine against omicron. N Engl J Med **2022**; 386:1377–80.
29. Korves C, Izurieta HS, Smith J et al. Relative effectiveness of booster vs. 2-dose mRNA Covid-19 vaccination in the Veterans Health Administration: Self-controlled risk interval analysis. Vaccine **2022**; 40:4742–7.
30. Lewis NM, Naioti EA, Self WH, et al. Effectiveness of mRNA vaccines against COVID-19 hospitalization by age and chronic medical conditions burden among immunocompetent US adults, March–August 2021. J Infect Dis **2022**; 225: 1694–700.
31. Clarke KE, Jones JM, Deng Y, et al. Seroprevalence of infection-induced SARS-CoV-2 antibodies—United States, September 2021–February 2022. MMWR Morb Mortal Wkly Rep **2022**; 71:606–8.