Vaccine effectiveness of primary series and booster doses against covid-19 associated hospital admissions in the United States: living test negative design study

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ABSTRACT

OBJECTIVE

To compare the effectiveness of a primary covid-19 vaccine series plus booster doses with a primary series alone for the prevention of hospital admission with omicron related covid-19 in the United States.

DESIGN

Multicenter observational case-control study with a test negative design.

SETTING

Hospitals in 18 US states.

PARTICIPANTS

4760 adults admitted to one of 21 hospitals with acute respiratory symptoms between 26 December 2021 and 30 June 2022, a period when the omicron variant was dominant. Participants included 2385 (50.1%) patients with laboratory confirmed covid-19 (cases) and 2375 (49.9%) patients who tested negative for SARS-CoV-2 (controls).

MAIN OUTCOME MEASURES

The main outcome was vaccine effectiveness against hospital admission with covid-19 for a primary series plus booster doses and a primary series alone by comparing the odds of being vaccinated with each of these regimens versus being unvaccinated among cases versus controls. Vaccine effectiveness analyses were stratified by immunosuppression status (immunocompetent, immunocompromised). The primary analysis evaluated all covid-19 vaccine types combined, and secondary analyses evaluated specific vaccine products.

RESULTS

Overall, median age of participants was 64 years (interquartile range 52-75 years), 994 (20.8%) were immunocompromised, 85 (1.8%) were vaccinated with a primary series plus two boosters, 1367 (28.7%) with a primary series plus one booster, and 1875 (39.3%) with a primary series alone, and 1433 (30.1%) were unvaccinated. Among immunocompetent participants, vaccine effectiveness for prevention of hospital admission with omicron related covid-19 for a primary series plus two boosters was 63% (95% confidence interval 37% to 78%), a primary series plus one booster was 65% (58% to 71%), and for a primary series alone was 37% (25% to 47%) (P<0.001 for the pooled boosted regimens compared with a primary series alone). Vaccine effectiveness was higher for a boosted regimen than for a primary series alone for both mRNA vaccines (BNT162b2 (Pfizer-BioNTech): 73% (44% to 87%) for primary series plus two boosters, 64% (55% to 72%) for primary series plus one booster, and 36% (21% to 48%) for primary series alone (P<0.001); mRNA-1273 (Moderna): 68% (17% to 88%) for primary series plus two boosters, 65% (55% to 73%) for primary series plus one booster, and 41% (25% to 54%) for primary series alone (P=0.001)). Among immunocompromised patients, vaccine effectiveness for a primary series plus one booster was 69% (31% to 86%) and for a primary series alone was 49% (30% to 63%) (P=0.04).

CONCLUSION

During the first six months of 2022 in the US, booster doses of a covid-19 vaccine provided additional benefit beyond a primary vaccine series alone for

WHAT IS ALREADY KNOWN ON THIS TOPIC

Additional (booster) doses of covid-19 vaccines beyond the primary series are recommended for adults in the United States

As of 26 December 2021, omicron became the predominant SARS-CoV-2 variant

Additional data are needed to understand the effectiveness of booster doses to prevent severe omicron related covid-19

WHAT THIS STUDY ADDS

Among immunocompetent adults, vaccine effectiveness to prevent omicron related hospital admission for a primary covid-19 vaccine series plus two boosters was 63%, for a primary series plus one booster was 65%, and for a primary series alone was 37%

Among immunocompromised adults, vaccine effectiveness to prevent omicron related hospital admission for a primary series plus one booster dose was 69% and for a primary series alone was 49%

Booster doses of covid-19 vaccines provide additional benefit beyond a primary vaccine series alone for preventing omicron related hospital admissions

preventing hospital admissions with omicron related covid-19.

READERS' NOTE

This article is a living test negative design study that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication.

Introduction

The highly transmissible SARS-CoV-2 omicron variant, first identified in southern Africa in November 2021, became the dominant variant in the United States by late December 2021.[1 2] The surges in covid-19 infections driven by this variant and its emergent lineages (Pango BA.1, BA.2, BA.4, and BA.5) were the largest recognized in the US, with a peak of more than one million infections each day.[3] Emerging data on vaccine protection against disease caused by the omicron variant has been mixed. Early immunological studies showed evidence of immune evasion by omicron with decreased neutralization from either vaccine sera or monoclonal antibodies compared with previous variants.[4 5] Recent evidence suggests a rapid decline over time in antibody titers after booster doses.[6] Real world studies have shown decreased effectiveness of both primary series and booster doses of covid-19 vaccine regimens against symptomatic infection, with waning occurring as early as 5-9 weeks after a booster dose.[7-9] However, results from studies evaluating the protection provided by booster doses against severe covid-19 due to omicron have varied, with some studies suggesting robust protection similar to protection against earlier SARS-CoV-2 variants, and others suggesting reduced protection against omicron and further reductions over time as the time from booster dosing increases.[8 10-15] Additionally, questions remain about the effectiveness of booster vaccine doses and whether specific demographic and high risk groups benefit most from covid-19 booster doses.[16]

Understanding the effectiveness of covid-19 vaccines against severe disease caused by omicron and its lineages has been challenging, which likely plays a role in the variability of recent results that have emerged. Many patients admitted to hospital tested positive for SARS-CoV-2 in the first quarter of 2022; however, in part due to the high incidence of infections caused by omicron and universal testing on admission, some fraction of these detections were likely incidental in patients admitted for alternative reasons and might not have represented hospital admissions due to covid-19.[17 18] If vaccine effectiveness is lower against milder infections than severe infections, incidental detections of SARS-CoV-2 could artificially reduce vaccine effectiveness estimates against severe covid-19 when using any covid-19 detections among patients admitted to hospital as an outcome.[10] Increased time since vaccination with a primary series and widespread use of booster vaccine doses during the omicron period further complicate being able to distinguish the contribution of immune evasion of omicron from waning immunity.[8 10]

To overcome these challenges, we evaluated the effectiveness of covid-19 vaccines to prevent hospital admissions during the omicron predominant period in the US, using data from patients admitted to hospital primarily because of covid-19. We calculated vaccine effectiveness of a primary series plus one or two booster doses and a primary vaccine series alone by time since the last vaccine dose, thus providing data to help understand the effectiveness of booster doses and the interplay of immune evasion and waning immunity during the omicron surge. Lastly, as a complementary laboratory analysis to these clinical evaluations of vaccine effectiveness, we measured serum antibody concentrations in healthy adult volunteers to determine anti-SARS-CoV-2 responses before and after receiving booster doses.

Methods

Setting and design

This prospective, multicenter observational assessment was conducted by the Influenza and other Viruses in the AcutelY ill (IVY) Network in collaboration with the US Centers for Disease Control and Prevention. The IVY Network is a collaboration between 21 hospitals in the US and has published covid-19 vaccine effectiveness estimates iteratively throughout the pandemic (see supplemental table S1). The current analysis included adults admitted to hospital at IVY Network sites during the period of omicron predominance in the network: 26 December 2021 to 30 June 2022 (with a brief pause of enrollment from 25 January to 31 January 2022 for a protocol update). Using a test negative design, we calculated vaccine effectiveness for the prevention of omicron related hospital admissions with covid-19 for the covid-19 vaccines authorized for use in the US: BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Ad26.COV2 (Janssen/Johnson & Johnson)).[19-21] These activities were reviewed by CDC, were conducted consistent with applicable federal law and CDC policy (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), and were determined to be public health surveillance with waiver of informed consent by institutional review boards at CDC and each enrolling site.

Participants

Site staff prospectively identified and enrolled patients admitted to hospital with covid-19 (cases) and concurrent test negative patients (controls). Case patients were adults (≥18 years old) admitted to hospital with symptomatic covid-19 confirmed with a positive SARS-CoV-2 test result by reverse transcription polymerase chain reaction (RT-PCR) or antigen test within 14 days of symptom onset. Case patients had one or more of the following covid-19 associated signs or symptoms: fever, cough, shortness of breath, loss of taste, loss of smell, need for respiratory support (high flow oxygen by nasal cannula, non-invasive ventilation, or invasive mechanical ventilation) for the acute symptoms, or new pulmonary findings on chest imaging indicating pneumonia. Control patients

were adults admitted to hospital with at least one of the aforementioned covid-19 associated signs or symptoms who tested negative for SARS-CoV-2, influenza, and respiratory syncytial virus by RT-PCR within 14 days of symptom onset. Case-control status was determined by results of both clinical SARS-CoV-2 testing at the admitting hospital as well as standardized, central laboratory RT-PCR SARS-CoV-2 testing. Patients who tested positive for SARS-CoV-2 by either clinical testing or central laboratory testing were classified as cases, and patients who tested negative by both clinical and central laboratory testing were classified as controls. Sites sought to enroll case patients and control patients in a 1:1 ratio. Case patients and control patients were enrolled within two weeks of one another and not matched on other individual patient characteristics.

Data collection

Trained staff at enrolling sites collected patient data through patient or proxy interviews and medical record review on demographics, medical history, underlying health conditions (see supplemental table S2), covid-19 vaccination status, laboratory findings, and clinical outcomes. Patients were followed from admission until discharge, death, or hospital day 28 (whichever occurred first). Clinical outcomes included in-hospital death, invasive mechanical ventilation, supplemental oxygen therapy, vasopressor use, and admission to an intensive care unit. The composite outcome of death or invasive mechanical ventilation was used to identify patients with critical covid-19. Individual pre-existing health conditions were grouped into condition categories of cardiovascular, endocrine, gastrointestinal, hematologic, immunocompromising, neurologic, pulmonary, and renal. Verification of covid-19 vaccination was performed for information such as dates of vaccination, vaccine products, and lot numbers using a systematic search of hospital electronic medical records, state vaccine registries, and vaccination cards (when available).

Classification of vaccination status

We assessed effectiveness of a primary covid-19 vaccine series plus one and two booster doses and a primary series alone.[22] During the surveillance period, US recommendations for covid-19 vaccine dosing for primary series and booster doses varied depending on health status (notably, presence of immunocompromising conditions), age, vaccine product, and timing of previous vaccination. Although national US vaccine surveillance data do not distinguish vaccination status by medical conditions, the IVY Network collects detailed clinical data to facilitate descriptions of vaccine uptake by nuanced eligibility criteria.[3] Based on CDC recommendations, we classified patients into five mutually exclusive vaccination status groups: unvaccinated, partially vaccinated, primary series alone, primary series plus one booster dose, and primary series plus two booster doses (see supplemental table S3).

Among immunocompetent individuals (ie, those without an immunocompromising condition collected by the IVY Network; see supplemental table S2), we classified those as completing a primary series if they received either one dose of the adenovirus vector vaccine Ad26.COV2 (Janssen/Johnson & Johnson) or two doses (>3-8 weeks apart) of an mRNA vaccine (BNT162b2 or mRNA-1273), with the final dose ≥14 days before symptom onset.[22] Immunocompetent participants were classified as having received booster doses if they completed a primary series and received additional doses of any licensed covid-19 vaccine ≥7 days before symptom onset.

Among immunocompromised individuals, we classified participants as completing a primary series if they received either an initial Ad26.COV2 dose plus one additional covid-19 vaccine dose (AD26.COV2 or mRNA) or three doses of an mRNA vaccine ≥7 days before symptom onset. Immunocompromised participants were classified as receiving booster doses if they completed a primary series and received additional doses of any licensed covid-19 vaccine product ≥7 days before symptom onset.

Participants were classified as unvaccinated if they had never received a covid-19 vaccine. Those who received one mRNA covid-19 vaccine dose but did not complete a primary series were classified as partially vaccinated and excluded from this analysis. Among immunocompromised participants the sample size of patients who received two booster doses was not large enough to calculate vaccine effectiveness for a primary series plus two booster doses. We also excluded patients if they received booster doses before eligibility, based on US recommendations (see supplemental table S4).

Molecular diagnosis and sequencing

Upper respiratory tract specimens for SARS-CoV-2 testing were obtained from enrolled patients by nasal swab or saliva collection. The samples underwent standardized RT-PCR testing at a central laboratory at Vanderbilt University Medical Center (Nashville, TN) for detection of two SARS-CoV-2 nucleocapsid gene targets (N1 and N2). Samples with detection of either N1 or N2 with a cycle threshold ≤32 were shipped to the University of Michigan (Ann Arbor, MI) for viral whole genome sequencing using the ARTIC Network protocol (v4.1 primer set) and an Oxford Nanopore Technologies GridION instrument.[23] SARS CoV-2 variants and lineages are reported using the Pango nomenclature.[24] Case patients with a SARS-CoV-2 variant other than omicron identified through sequencing were excluded from this analysis.

Statistical analysis

To estimate vaccine effectiveness for the prevention of covid-19 associated hospital admission we compared the odds of antecedent covid-19 vaccination versus no vaccination between case patients and control patients.[21] Adjusted odds ratios were generated using multivariable logistic regression models with case status as the outcome, vaccination as the primary

independent variable, and prespecified covariables considered potential confounders: admission date (biweekly intervals), age (18-49, 50-64, and ≥65 years), sex, self-reported race and ethnicity, and US Health and Human Services region of the admitting hospital. Post hoc, we evaluated other potential covariables, including the number of categories of chronic medical conditions, residential status, highest level of education received, and hospital admissions within the past year; none of these other variables resulted in an absolute change in the adjusted odds ratio of vaccination by >5% when added to the prespecified model and were not included in the final model (see supplemental table S5).[25 26] Vaccine effectiveness was calculated as (1−adjusted odds ratio)×100. In a subgroup analysis, we assessed vaccine effectiveness for the prevention of hospital admission with covid-19 and hypoxemia (a more severely ill subset of patients admitted to hospital with covid-19), by limiting the vaccine effectiveness analysis to cases admitted with hypoxemia, defined as supplemental oxygen use or an oxygen saturation (SpO2) <92% within 24 hours of admission. Models were stratified by vaccination group (primary series plus one or two booster doses or primary series alone), immunosuppression status (immunocompetent or immunocompromised), age group (18-49 *v* ≥50 years), time from last vaccine dose to symptom onset, and vaccine product (Ad26.COV2, BNT162b2, or mRNA-1273). Time between last vaccine dose of a primary series and symptom onset was stratified into 14-150 days and >150 days to align with current US recommendations for the timing of a booster dose.[22] We dichotomized time between booster doses and symptom onset into 7-120 days and >120 days based on timing of eligibility for a second booster dose, as recommended in select populations.[22] Vaccine effectiveness by time period dominated by specific omicron lineages was calculated using cut-off dates determined by IVY Network sequencing data, with BA.1 being the predominant lineage from 26 December 2021 to 26 March 2022, BA.2 from 27 March to 18 June 2022, and BA.5 from 19 to 30 June 2022. All cases from each period were included unless sequencing confirmed a different lineage for the respective analyses.

Statistical differences among baseline characteristics, outcomes, and treatments were evaluated using Pearson's χ^2 test for binary or categorical variables and the Wilcoxon rank sum test for continuous variables. P values for vaccine effectiveness were calculated by fitting a multilevel regression model and performing a pairwise comparison across levels of categorical variables; we pooled boosted vaccine regimens with either one or two booster doses for comparison with the primary series vaccination group. Statistical analyses were performed using Stata 16 (College Station, TX) and GraphPad Prism version 9.3.1 for Windows (GraphPad Software, San Diego, CA).

Post-vaccination antibody responses

To complement the vaccine effectiveness analyses, we also evaluated anti-SARS-CoV-2 antibody responses after booster doses with BNT162b2, mRNA-1273, and Ad26.COV2. Healthy adult volunteers scheduled for their first booster dose were recruited at four IVY Network sites from 5 October 2021 to 28 January 2022. Enrolled participants reported never having symptoms of covid-19, either at the time of enrollment or in the past, and never testing positive for SARS-CoV-2.

Serum was collected before and 2-6 weeks after the booster dose. These serum samples were tested at CDC with the V-PLEX SARS-CoV-2 panel 2 kit (Meso Scale Diagnostics) for IgG against the spike protein, receptor binding domain, and nucleocapsid. Targets of the antibody responses were based on proteins from the USA-WA1/2020 strain. Participants with an increased anti-nucleocapsid antibody concentration (>11.8 binding antibody units (BAU) per millilitre) suggestive of a previous SARS-CoV-2 infection at either the pre-booster or the post-booster time point were excluded. An international reference standard (WHO NIBSC 20/136) consisting of pooled sera from patients infected during 2020 with ancestral strain viruses was used to establish the BAU/mL scale. Notably, as omicron variants have more than 30 mutations in the spike and 15 or more in the receptor binding domain, titers against omicron spikes will be lower.[27] We summarized the pre-booster and post-booster anti-spike and anti-receptor binding domain concentrations with spaghetti plots and geometric means. Some participants had previously contributed serum specimens for antibody measurements 2-6 weeks after a primary series (ie, after a second mRNA dose or after a first Ad26.COV2 dose) earlier in this programme.[28] When available, we displayed these post-primary series antibody measurements to facilitate evaluation of antibodies in the same individual after a primary series and both before and after a first booster dose.

Patient and public involvement

Patients were not involved in the original design of this study. Throughout the conduct of the study, patients were routinely engaged in the work via structured interviews with research staff, which included discussions about covid-19 and covid-19 vaccines.

Results

Participants in vaccine effectiveness analyses

From 26 December 2021 to 30 June 2022, 6553 patients who had been admitted to hospital were enrolled from 21 hospitals and 1793 (27.4%) were excluded from the analysis, with partial vaccination the most common reason (n=649) (see supplemental figures S1 and S3). In total, 4760 patients were included in the final analysis, comprising 2385 (50.1%) patients with covid-19 (cases) and 2375 (49.9%) test negative patients (controls), with a median overall age of 64 years (interquartile range 52-75 years). In total, 2308 (48.4%) participants were women, 926 (19.5%) were black participants, 658 (13.8%) were Hispanic, and 994 (20.8%) were immunocompromised (table 1).

Of the 2385 case patients, 876 (36.7%) were unvaccinated, 935 (39.2%) completed a primary

Table 1 | Baseline characteristics of participants by vaccination and covid-19 status admitted to one of 21 hospitals in 18 US states, during the omicron period (26 December 2021 to 30 June 2022). Values are numbers (percentages) unless stated otherwise

		Vaccination status				Covid-19 status	
Characteristics	Total (n=4760)	Unvaccinated (n=1433)	Completed primary series (n=1875)	Primary series+one booster dose (n=1367)	Primary series+two booster doses (n=85)	Cases (n=2385)	Controls (n=2375)
Median (IQR) age (years)	64 (52-75)	58 (44-69)	64 (53-74)	68 (59-78)	77 (69-84)	65 (53-76)	64 (51-74)
Women	2308/4760 (48.5)	685/1433 (47.8)	895/1875 (47.7)	686/1367 (50.2)	42/85 (49.4)	1146/2385 (48.1)	1162/2375 (48.9)
Race and ethnicity:							
Non-Hispanic white	2814/4760 (59.1)	787/1433 (54.9)	1059/1875 (56.5)	902/1367 (66.0)	66/85 (77.6)	1396/2385 (58.5)	1418/2375 (59.7)
Non-Hispanic black	926/4760 (19.5)	308/1433 (21.5)	380/1875 (20.3)	228/1367 (16.7)	10/85 (11.8)	441/2385 (18.5)	485/2375 (20.4)
Hispanic, any race	658/4760 (13.8)	228/1433 (15.9)	279/1875 (14.9)	147/1367 (10.8)	4/85 (4.7)	359/2385 (15.1)	299/2375 (12.6)
Non-Hispanic, all other	273/4760 (5.7)	77/1433 (5.4)	120/1875 (6.4)	72/1367 (5.3)	4/85 (4.7)	149/2385 (6.2)	124/2375 (5.2)
Other*	89/4760 (1.9)	33/1433 (2.3)	37/1875 (2.0)	18/1367 (1.3)	1/85 (1.2)	40/2385 (1.7)	49/2375 (2.1)
US census region†:							
Northeast	1143/4760 (24.0)	298/1433 (20.8)	434/1875 (23.1)	382/1367 (27.9)	29/85 (34.1)	600/2385 (25.2)	543/2375 (22.9)
South	1567/4760 (32.9)	543/1433 (37.9)	654/1875 (34.9)	358/1367 (26.2)	12/85 (14.1)	780/2385 (32.7)	787/2375 (33.1)
Midwest	938/4760 (19.7)	288/1433 (20.1)	359/1875 (19.1)	274/1367 (20.0)	17/85 (20.0)	463/2385 (19.4)	475/2375 (20.0)
West	1112/4760 (23.4)	304/1433 (21.2)	428/1875 (22.8)	353/1367 (25.8)	27/85 (31.8)	542/2385 (22.7)	570/2375 (24.0)
≥1 hospital admissions in past year	2412/4682 (51.5)	629/1400 (44.9)	1041/1847 (56.4)	698/1351 (51.7)	44/84 (52.4)	1097/2333 (47.0)	1315/2349 (56.0)
Self-reported past laboratory confirmed SARS-CoV-2 infection	663/4438 (14.9)	220/1343 (16.4)	261/1765 (14.8)	177/1255 (14.1)	5/75 (6.7)	222/2241 (9.9)	441/2197 (20.1)
Median No (IQR) of chronic conditions‡	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
Immunocompromising condition§	994/4760 (20.9)	267/1433 (18.6)	679/1875 (36.2)	48/1367 (3.5)	0/85 (0)	489/2385 (20.5)	505/2375 (21.3)
Obesity (BMI ≥30)	1871/4553 (41.1)	581/1382 (42.0)	712/1816 (39.2)	548/1278 (42.9)	30/77 (3.9)	931/2273 (41.0)	940/2280 (41.2)
Vaccine product received for primary series:							
BNT162b2 (Pfizer-BioNTech)	1847/3327 (55.5)	–	1058/1875 (56.4)	733/1367 (53.6)	56/85 (65.9)	866/1509 (57.4)	981/1818 (54.0)
mRNA-1273 (Moderna)	1186/3327 (35.6)	–	662/1875 (35.3)	499/1367 (36.5)	25/85 (29.4)	503/1509 (33.3)	683/1818 (37.6)
Mixed mRNA	21/3327 (0.6)	–	11/1875 (0.6)	10/1367 (0.7)	0/85 (0)	6/1509 (0)	15/1818 (0.8)
Ad26.COV2 (Janssen/Johnson & Johnson)	273/3327 (8.2)	–	144/1875 (7.7)	125/1367 (9.1)	4/85 (4.7)	134/1509 (8.9)	139/1818 (7.6)
Vaccine product received for last booster dose:							
BNT162b2	858/1452 (59.1)	–	–	807/1367 (59.0)	51/85 (60.0)	347/574 (60.5)	511/878 (58.2)
mRNA-1273	567/1452 (39.0)	–	–	534/1367 (39.1)	33/85 (38.8)	215/574 (37.5)	352/878 (40.1)
Ad26.COV2	27/1452 (1.9)	–	–	26/1367 (1.9)	1/85 (1.2)	12/574 (2.1)	15/878 (1.7)
Omicron lineage sequenced:							
BA.1	351/926 (37.9)	141/277 (50.9)	169/366 (46.2)	41/267 (15.4)	0/16 (0)	351/926 (37.9)	–
BA.2	497/926 (53.7)	117/277 (42.2)	170/366 (46.4)	195/267 (73.0)	15/16 (93.8)	497/926 (53.7)	–
BA.4	26/926 (2.8)	6/277 (2.2)	12/366 (3.2)	7/267 (2.6)	1/16 (6.3)	26/926 (2.8)	–
BA.5	52/926 (5.6)	13/277 (4.7)	15/366 (4.1)	24/267 (9.0)	0/16 (0)	52/926 (5.6)	–

BMI=Body mass index; IQR=interquartile range.
*Self-reported race and ethnicity as other or non-Hispanic, or patients for whom information on race and ethnicity was unavailable.
†Hospitals by region—north east: Baystate Medical Center (Springfield, MA), Beth Israel Deaconess Medical Center (Boston, MA), Montefiore Medical Center (Bronx, NY); south: Vanderbilt University Medical Center (Nashville, TN), University of Miami Medical Center (Miami, FL), Emory University Medical Center (Atlanta, GA), Johns Hopkins Hospital (Baltimore, MD), Wake Forest University Baptist Medical Center (Winston-Salem, NC), Baylor Scott and White Health (Temple, TX); midwest: University of Iowa Hospitals and Clinics (Iowa City, IA), University of Michigan Hospital (Ann Arbor, MI), Hennepin County Medical Center (Minneapolis, MN), Barnes-Jewish — St Louis, MO), Cleveland Clinic (Cleveland, OH), Ohio State University Wexner Medical Center (Columbus, OH); west: Stanford University Medical Center (Stanford, CA), UCLA Medical Center (Los Angeles, CA), UCHealth University of Colorado Hospital (Aurora, CO), Oregon Health and Science University Hospital (Portland, OR), Intermountain Medical Center (Murray, UT), University of Washington (Seattle, WA).
‡Included cardiovascular, neurologic, pulmonary, gastrointestinal, endocrine, kidney, and hematologic diseases; malignancy; immunosuppression not captured in other categories; autoimmune condition; or other condition (sarcoidosis, amyloidosis, or unintentional weight loss ≥4.5 kg (10 lb) in past 90 days).
§Included active solid organ cancer (active cancer defined as treatment for the cancer or newly diagnosed cancer in past six months), active hematologic cancer (eg, leukemia, lymphoma, or myeloma), HIV infection without AIDS, AIDS, congenital immunodeficiency syndrome, previous splenectomy, previous solid organ transplant, immunosuppressive drugs, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, scleroderma, or inflammatory bowel disease, including Crohn's disease or ulcerative colitis.

series alone, 541 (22.6%) completed a primary series plus one booster dose, and 33 (1.4%) completed a primary series plus two booster doses. Of the 2375 control patients, 557 (23.4%) were unvaccinated, 940 (39.6%) completed a primary series alone, 826 (34.8%) received a primary series plus one booster dose, and 52 (2.2%) received a primary series plus two booster doses. Unvaccinated patients were younger (median 58 (interquartile range 44-69) years) than those who completed a primary series alone (median 64 (53-74) years), a primary series plus one booster (median 68 (59-78) years), or primary series plus two boosters (median 77 (69-84) years) (P<0.001). Unvaccinated patients were less likely to have been admitted to hospital one or more times in the past year than those who were vaccinated with a primary series plus one or two booster doses or primary series alone (P<0.001) (table 1).

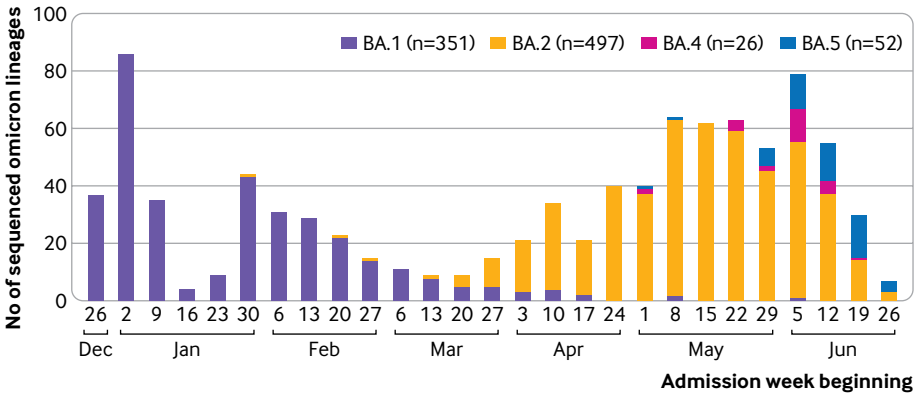

Fig 1 | SARS-CoV-2 sequenced omicron lineages by admission week among 2385 patients with covid-19 (cases), 26 December 2021 to 30 June 2022 (enrollment paused 25-31 January 2022). Case patients not infected with omicron (delta variant, B.1.1.519) confirmed through sequencing were excluded from analysis (n=55) and not displayed in this figure. Of 926 patients with a sequence confirmed omicron related infection, lineage was BA.1 in 351 (37.9%), BA.2 in 497 (53.7%), BA.4 in 26 (2.8%), and BA.5 in 52 (5.6%). Low sequencing totals in late January reflect a pause in IVY network enrollment during 25-31 January 2022 during a protocol update

Viral whole genome sequencing was performed for 1201 case patients, and a SARS-CoV-2 variant was successfully identified in 981 (81.7%). Among those with a variant identified, 926 (94.4%) were infected with omicron and 55 (5.6%) with delta. Patients with the delta variant were excluded from analyses. Of the 926 patients with omicron sequenced, 351 (37.9%) were infected with BA.1, 497 (53.7%) with BA.2, 26 (2.8%) with BA.4, and 52 (5.6%) with BA.5. Of the 497 patients with BA.2, 278 (55.9%) had the BA.2.12.1 lineage. BA.2 became the predominant lineage during the week starting 27 March 2022, whereas BA.5 became predominant from 19 June 2022 (fig 1).

Among vaccinated patients, most received a homologous mRNA primary series (91.2%), with lower proportions of patients receiving Ad26.COV2 (8.2%) or a heterologous mRNA (0.6%) primary series (fig 2). For booster dose products, 98.1% of patients received one or two mRNA vaccines, with only 1.8% receiving Ad26.COV2. Most mixing of vaccine products occurred after receipt of one dose of Ad26.COV2 or after two doses of the same mRNA product.

Vaccine effectiveness for prevention of hospital admission with covid-19

When considering all vaccine products (BNT162b2, mRNA-1273, and AD26.COV2), vaccine effectiveness for prevention of hospital admission with covid-19 among immunocompetent participants was higher for a primary series plus two boosters (63%, 95% confidence interval 37% to 78%) or one booster (65%, 58% to 71%) than a primary series alone (37%, 25% to 47%) (P<0.001) (fig 3). Among immunocompetent individuals vaccinated with either BNT162b2 or mRNA-1273, those who received one or two homologous booster doses (ie, a third or fourth dose of the same vaccine product) had significantly higher vaccine effectiveness against hospital admission with covid-19

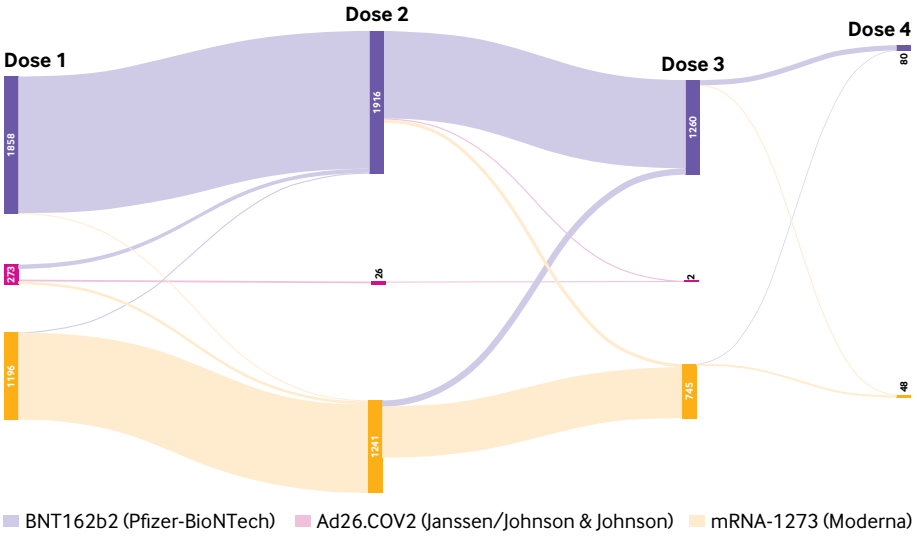

Fig 2 | Pattern of covid-19 vaccine products received across doses. The figure includes patients admitted to hospital with covid-19 (cases) and patients admitted to hospital with acute respiratory symptoms without covid-19 (controls), 26 December 2021 to 30 June 2022 (omicron period)

Group	Vaccine series	No of vaccinated covid-19 case patients/ total No (%)	No of vaccinated control patients/ total No (%)	Vaccine effectiveness (% (95% CI))	Vaccine effectiveness (% (95% CI))
Immunocompetent					
Overall	Primary	624/1339 (47)	572/1023 (56)		37 (25 to 47)
	Primary + one booster	524/1239 (42)	795/1246 (64)		65 (58 to 71)
	Primary + two boosters	33/748 (4)	52/503 (10)		63 (37 to 78)
Age group (years)					
18-49	Primary	137/345 (40)	136/318 (43)		13 (-23 to 38)
	Primary + one booster	57/265 (22)	109/291 (37)		49 (21 to 67)
	Primary + two boosters	-	-		-
≥50	Primary	487/994 (49)	436/705 (62)		44 (32 to 55)
	Primary + one booster	467/974 (48)	686/955 (72)		70 (62 to 75)
	Primary + two boosters	33/540 (6)	52/321 (16)		61 (33 to 78)
Number of chronic conditions					
0	Primary	85/242 (35)	53/133 (40)		9 (-49 to 45)
	Primary + one booster	46/203 (23)	49/129 (38)		45 (-3 to 71)
	Primary + two boosters	1/158 (1)	3/83 (4)		-
≥1	Primary	539/1097 (49)	519/890 (58)		39 (27 to 50)
	Primary + one booster	478/1036 (46)	746/1117 (67)		65 (58 to 72)
	Primary + two boosters	32/590 (5)	49/420 (12)		59 (28 to 76)
Vaccine product					
BNT162b2	Primary	334/1049 (32)	289/740 (39)		36 (21 to 48)
	Primary + one booster	272/987 (28)	394/845 (47)		64 (55 to 72)
	Primary + two boosters	14/729 (2)	30/481 (6)		73 (44 to 87)
mRNA-1273	Primary	209/924 (23)	214/665 (32)		41 (25 to 54)
	Primary + one booster	164/879 (19)	271/722 (38)		65 (55 to 73)
	Primary + two boosters	8/723 (1)	14/465 (3)		68 (17 to 88)
Mixed mRNA	Primary	2/717 (0)	4/455 (1)		-
	Primary + one booster	34/749 (5)	59/510 (12)		64 (42 to 78)
	Primary + two boosters	10/725 (1)	5/456 (1)		-
Ad26.COV2	Primary	79/794 (10)	65/516 (13)		32 (1 to 54)
	Primary + one booster	11/726 (2)	14/465 (3)		35 (-54 to 73)
	Primary + two boosters	0/715 (0)	1/452 (0)		-
Ad26.COV2 + mRNA	Primary	-	-		-
	Primary + one booster	42/757 (6)	57/508 (11)		52 (25 to 69)
	Primary + two boosters	1/716 (0)	2/453 (0)		-
Time between last dose and symptom onset (days)					
14-150	Primary	78/793 (10)	83/534 (16)		53 (33 to 67)
>150	Primary	546/1261 (43)	489/940 (52)		34 (21 to 45)
7-120	Primary + one booster	201/916 (22)	437/888 (49)		76 (69 to 81)
	Primary + two boosters	33/748 (4)	51/502 (10)		62 (35 to 78)
>120	Primary + one booster	323/1038 (31)	358/809 (44)		39 (22 to 53)
	Primary + two boosters	0/715 (0)	1/452 (0)		-
Hypoxemic subgroup					
Hypoxemic <24	Primary	337/787 (43)	572/1023 (56)		48 (36 to 57)
hours of admission	Primary + one booster	275/725 (38)	795/1246 (64)		74 (67 to 79)
	Primary + two boosters	19/469 (4)	52/503 (10)		63 (29 to 81)

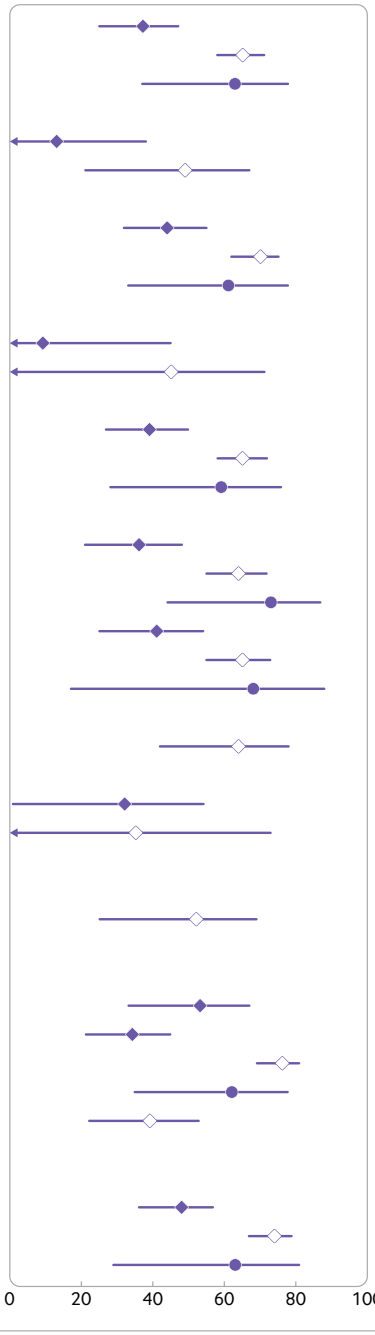

Fig 3 | Vaccine effectiveness among immunocompetent people for prevention of hospital admission with covid-19 in the United States during an omicron dominant period, 26 December 2021 to 30 June 2022. Multivariable logistic regression models were used to determine vaccine effectiveness, with vaccine status as the primary independent variable, case status as the dependent variable, and covariates: admission date (biweekly intervals), age (18-49, 50-64, and ≥65 years), sex, self-reported race and ethnicity, and US Health and Human Services region of the admitting hospital. Models stratified by age group were adjusted using age in years as a continuous variable. Vaccine effectiveness was not calculated for certain subgroups owing to limited sample size. Chronic conditions included cardiovascular, neurologic, pulmonary, gastrointestinal, endocrine, kidney, and hematologic disease; malignancy; immunosuppression not captured in other categories; autoimmune condition; or other condition (sarcoidosis, amyloidosis, or unintentional weight loss ≥4.5 kg (10 lb) in past 90 days). Vaccinated cases and controls counted under BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Ad26.COV2 (Janssen/Johnson & Johnson) received homologous product series for all doses. Mixed mRNA category included those receiving any heterologous combination of BNT162b2 and mRNA-1273. Ad26.COV2+mRNA received Ad26.COV2 for their first dose, followed by one dose of any mRNA product. Time between last vaccine dose and symptom onset was stratified into intervals to align with current US recommendations.[22] Hypoxemia within 24 hours of admission was defined as supplemental oxygen use or peripheral oxygen saturation (SpO2) <92%. Analysis by age group was restricted for those completing a primary series plus two boosters to 50 years and older owing to eligibility recommendations. CI=confidence interval

Group	Vaccine series	No of vaccinated covid-19 case patients/ total No (%)	No of vaccinated control patients/ total No (%)	Vaccine effectiveness (% (95% CI))	Vaccine effectiveness (% (95% CI))
Immunocompromised					
Overall	Primary	311/472 (66)	368/474 (78)		49 (30 to 63)
	Primary + one booster	17/178 (10)	31/137 (23)		69 (31 to 86)
Age group (years)					
18-49	Primary	38/84 (45)	56/89 (63)		75 (42 to 90)
	Primary + one booster	3/49 (6)	7/40 (18)		-
≥50	Primary	273/388 (70)	312/385 (81)		45 (21 to 62)
	Primary + one booster	14/129 (11)	24/97 (25)		74 (32 to 90)
Time between last dose and symptom onset (days)					
14-150	Primary	167/328 (51)	230/336 (68)		59 (41 to 72)
>150	Primary	144/305 (47)	138/244 (57)		33 (-2 to 56)
7-120	Primary + one booster	16/177 (9)	31/137 (23)		72 (35 to 88)
>120	Primary + one booster	1/162 (1)	0/106 (0)		-

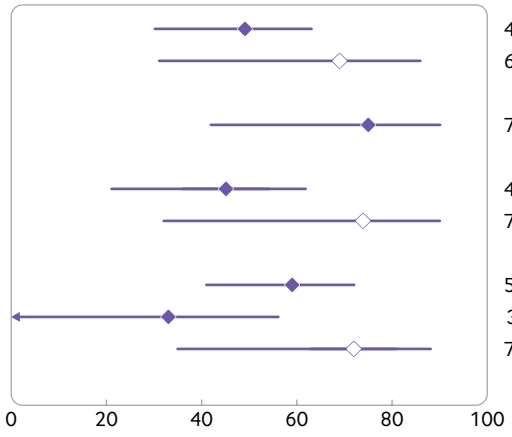

Fig 4 | Vaccine effectiveness among immunocompromised patients for prevention of hospital admission with covid-19 in the United States during an omicron dominant period, 26 December 2021 to 30 June 2022. Multivariable logistic regression models were used to determine vaccine effectiveness, with vaccine status as the primary independent variable, case status as the dependent variable, and the following covariates: admission date (biweekly intervals), age (18-49, 50-64, and ≥65 years), sex, self-reported race and ethnicity, and US Health and Human Services region of the admitting hospital. Models stratified by age group were adjusted using age in years as a continuous variable. Vaccine effectiveness was not calculated for certain subgroups owing to limited sample size. Immunocompromising conditions included: active solid organ cancer (active cancer defined as treatment for the cancer or newly diagnosed cancer in past six months), active hematologic cancer (eg, leukemia, lymphoma, or myeloma), HIV infection without AIDS, AIDS, congenital immunodeficiency syndrome, previous splenectomy, previous solid organ transplant, immunosuppressive drugs, systemic lupus erythematosus, rheumatoid arthritis, psoriasis, scleroderma, or inflammatory bowel disease, including Crohn's disease or ulcerative colitis. Time between last vaccine dose and symptom onset was stratified into intervals to align with current US recommendations.[22] CI=confidence interval

than those who received only a primary series. For BNT162b2, vaccine effectiveness for a primary series plus two boosters was 73% (44% to 87%), for a primary series plus one booster was 64% (55% to 72%), and for a primary series alone was 36% (21% to 48%) (P<0.001). For mRNA-1273, vaccine effectiveness for a primary series plus two boosters was 68% (17% to 88%), for one booster was 65% (55% to 73%), and for a primary series alone was 41% (25% to 54%) (P=0.001). Although the sample size of patients who received homologous booster doses with Ad26.COV2 was small (n=25 receiving one booster, n=1 receiving two boosters), the addition of a booster dose did not appear to increase vaccine effectiveness compared with an AD26.COV2 single dose primary series. Vaccine effectiveness against hospital admission with covid-19 for two doses of Ad26.COV2 (ie, one booster dose after a primary Ad26.COV2 dose) was 35% (−54% to 73%) and for a primary series alone was 32% (1% to 54%) (P=0.79). Among recipients of heterologous booster products (those who received a different product for the primary series and booster dose), vaccine

Group	Vaccine series	Median days since last dose (IQR)	No of vaccinated covid-19 case patients/ total No (%)	No of vaccinated control patients/ total No (%)	Vaccine effectiveness (% (95% CI))	Vaccine effectiveness (% (95% CI))
Omicron lineage						
BA.1 (26 Dec 2021-	Primary	197 (111 to 280)	561/1176 (48)	556/851 (65)		57 (47 to 64)
26 Mar 2022)	Primary + one booster	73 (48 to 102)	162/777 (21)	399/694 (57)		82 (77 to 86)
	Primary + two boosters	-	0/0 (0)	0/0 (0)		-
BA.2 (27 Mar-	Primary	241 (167 to 367)	304/501 (61)	337/574 (59)		0 (-29 to 23)
18 Jun 2022)	Primary + one booster	158 (116 to 188)	301/498 (60)	378/615 (61)		24 (0 to 42)
	Primary + two boosters	28 (15 to 42)	25/222 (11)	43/280 (15)		59 (23 to 78)

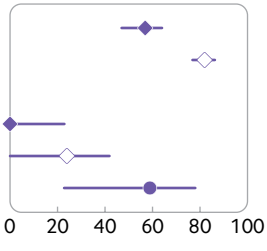

Fig 5 | Vaccine effectiveness by predominant omicron lineage (BA.1 or BA.2) for prevention of hospital admissions with covid-19 in the United States during an omicron dominant period, 26 December 2021 to 30 June 2022. Multivariable logistic regression models were used to determine vaccine effectiveness, with vaccine status as the primary independent variable, case status as the dependent variable, and the following covariates: admission date (biweekly intervals), age (18-49, 50-64, and ≥65 years), sex, self-reported race and ethnicity, and US Health and Human Services region of the admitting hospital. CI=confidence interval; IQR=interquartile range

Table 2 | In-hospital clinical outcomes and treatments for adults admitted to hospital with covid-19 during the omicron period (26 December 2021 to 15 June 2022), by vaccination status. Values are numbers (percentages) of total

Outcome	Total	Unvaccinated	Completed primary series	Primary series+one booster dose	Primary series+two booster doses
Status at 28 days after admission:					
Remained in hospital	152/2153 (7.1)	71/807 (8.8)	64/862 (7.4)	16/459 (3.5)	1/25 (4.0)
Discharged	1848/2153 (85.8)	661/807 (81.9)	745/862 (86.4)	419/459 (91.3)	23/25 (92.0)
Died	153/2153 (7.1)	75/807 (9.3)	53/862 (6.1)	24/459 (5.2)	1/25 (4.0)
Admitted to intensive care unit	547/2150 (25.4)	250/806 (31.0)	202/860 (23.5)	91/459 (19.8)	4/25 (16.0)
Any oxygen support:	1509/2153 (70.1)	600/807 (74.3)	586/862 (68.0)	305/459 (66.4)	18/25 (72.0)
HFNC	385/2153 (17.9)	196/807 (24.3)	145/862 (16.8)	43/459 (9.4)	1/25 (4.0)
NIPPV	232/2153 (10.8)	108/807 (13.4)	89/862 (10.3)	32/459 (7.0)	3/25 (12.0)
IMV	268/2153 (12.4)	142/807 (17.6)	87/862 (10.1)	36/459 (7.8)	3/25 (12.0)
ECMO	18/2153 (0.8)	15/807 (1.9)	3/862 (0.3)	0/459 (0)	0/25 (0)
Vasopressors	276/2153 (12.8)	137/807 (17.0)	97/862 (11.3)	40/459 (8.7)	2/25 (8.0)
New renal replacement therapy	61/2153 (2.8)	32/807 (4.0)	24/862 (2.8)	5/459 (1.1)	0/25 (0)
Venous thromboembolic event*	130/2153 (6.0)	71/807 (8.8)	44/862 (5.1)	15/459 (3.3)	0/25 (0)
Stroke	26/2153 (1.2)	14/807 (1.7)	8/862 (0.9)	4/459 (0.9)	0/25 (0)
Myocardial infarction	42/2153 (2.0)	18/807 (2.2)	14/862 (1.6)	10/459 (2.2)	0/25 (0)
Composite of death or IMV	338/2153 (15.7)	164/807 (20.3)	121/862 (14.0)	50/459 (10.9)	3/25 (12.0)
Treatment for severe covid-19:	1203/2012 (59.8)	496/733 (67.7)	474/807 (58.7)	223/447 (49.9)	10/25 (40.0)
Corticosteroids	1199/2012 (59.6)	495/733 (67.5)	472/807 (58.5)	222/447 (49.7)	10/25 (40.0)
Tocilizumab	53/2012 (2.6)	29/733 (4.0)	19/807 (2.4)	5/447 (1.1)	0/25 (0)
Baricitinib	96/2012 (4.8)	67/733 (9.1)	28/807 (3.5)	1/447 (0)	0/25 (0)
Anti-SARS-CoV-2 monoclonal antibodies	68/2012 (3.4)	19/733 (2.6)	36/807 (4.5)	12/447 (2.7)	1/25 (4.0)

ECMO=extracorporeal membrane oxygenation; HFNC=high flow nasal cannula; IMV=invasive mechanical ventilation; NIPPV=nasal intermittent positive pressure ventilation.
*Deep vein thrombosis or pulmonary embolism, or both.

effectiveness for mixed mRNA vaccine doses (ie, any combination of BNT162b2 and mRNA-1273) was 64% (42% to 78%), whereas vaccine effectiveness for a primary series Ad26.COV2 plus one mRNA booster was 52% (25% to 69%). A subgroup analysis of vaccine effectiveness among immunocompetent patients with covid-19 admitted with hypoxemia showed similar trends across vaccination status, with a higher vaccine effectiveness for a primary series plus one booster dose (74%, 67% to 79%) or primary series plus two booster doses (63%, 29% to 81%) than a primary series alone (48%, 36% to 57%).

Vaccine effectiveness for immunocompromised patients completing a primary series plus one booster (all but one patient received four doses of an mRNA vaccine) was 69% (31% to 86%) and primary series alone (all three doses of an mRNA vaccine) was 49% (30% to 63%) (fig 4). Vaccine effectiveness could not be estimated for a primary series plus two boosters in this patient group owing to no eligible participants receiving a second booster dose (ie, a fifth mRNA vaccine dose).

In analyses of vaccine effectiveness for the prevention of hospital admission with covid-19 stratified by time since the last vaccine dose, point estimates consistently showed a waning of protection at longer time points for both a primary series plus one booster dose and a primary series alone. Vaccine effectiveness after a primary series for immunocompetent participants at 14-150 days (median 108 days) since the last vaccine dose was 53% (33% to 67%) and at >150 days (median 291 days) was 34% (21% to 45%) (fig 3). Vaccine effectiveness after a booster dose for immunocompetent participants at 7-120 days (median 71 days) after the booster dose was 76% (69% to 81%) and at >120 days (median 173 days) was 39% (22% to 53%). All but one immunocompetent patient with a primary series plus two booster doses received these within 7-120 days before symptom onset (median 32 days), with vaccine effectiveness of 62% (35% to 78%). For immunocompromised patients, vaccine effectiveness for a primary series at 14-150 days (median 97 days) was 59% (41% to 72%) and at >150 days (median 192 days) was 33% (−2% to 56%) (fig 4). All but one immunocompromised patient with a primary series plus one booster dose received these within 7-120 days before symptom onset (median 34 days), with vaccine effectiveness of 72% (35% to 88%).

In stratified analyses by omicron lineage predominant period, vaccine effectiveness against hospital admissions with covid-19 was substantially higher during the period when BA.1 (26 December 2021 to 26 March 2022) than BA.2 (27 March to 18 June 2022) predominated (fig 5). Vaccine effectiveness after a primary series alone during the BA.1 period was 57% (47% to 64%) (median 197 (interquartile range 111–280) days), whereas during the BA.2 period was 0% (−29% to 23%) (median 241 (167–367) days). For a primary series plus one booster, vaccine effectiveness during the BA.1 period was 82% (77% to 86%) (median 73 (48-102) days) and during the BA.2 period was 24% (0% to 42%) (median 158 (116-188) days). As eligibility for second boosters began on 29 March 2022, vaccine effectiveness for a primary series plus two booster doses during the BA.1 period could not be estimated, but during the BA.2 period vaccine effectiveness was 59% (23% to 78%) (median 28 (interquartile range 15-42) days).

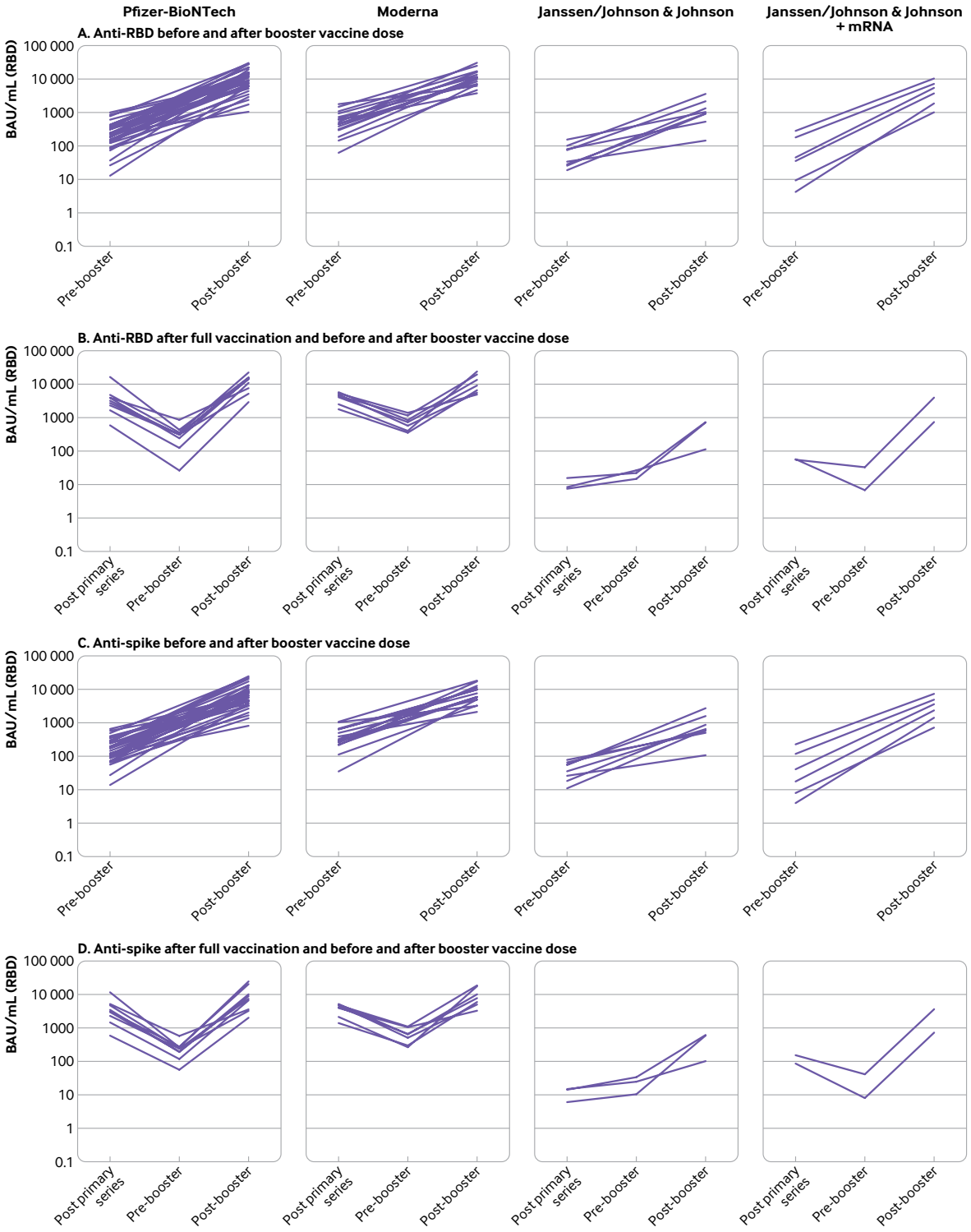

Fig 6 | Spaghetti plots of serum antibody concentrations to the SARS-CoV-2 receptor binding domain (anti-RBD) (panel A) and spike protein (anti-spike) (panel C) among healthy adult volunteers before and 2-6 weeks after covid-19 booster doses, 5 October 2021 to 28 January 2022. Targets of the antibody responses were based on proteins from the USA-WA1/2020 strain. Antibody concentrations 2-6 weeks after a primary series are also displayed for the subset of participants with anti-RBD (panel B) and anti-spike (panel D) measurements available from earlier participation in the programme. Each participant is represented with a single line connecting the antibody concentration at each time point. The Pfizer-BioNTech group included 33 participants who received three doses of BNT162b2, including nine who had antibody measurements after full vaccination. The Moderna group included 16 participants who received three mRNA-1273 doses, including seven who had antibody measurements after full vaccination. The Janssen/Johnson & Johnson group included eight participants who received two doses of Ad26.COV2, including three who had antibody measurements after full vaccination. The Janssen/Johnson & Johnson+mRNA group included six participants who received an mRNA vaccine (BNT162b2 or mRNA-1273) booster dose after a single Ad26.COV2 primary series dose, including two who had antibody measurements after the initial Ad26.COV2 dose. The data accompanying this figure are shown in supplemental table S6. BAU=binding antibody units

Clinical outcomes among unvaccinated and vaccinated patients admitted to hospital with covid-19

Clinical outcomes by day 28 of hospital stay were available for 2153 case patients admitted to hospital between 26 December 2021 and 15 June 2022; 1848 (86%) of these patients were discharged from the hospital before day 28, 152 (7%) remained in hospital at day 28, and 153 (7%) died in hospital before day 28 (table 2). Admission to an intensive care unit was more common among unvaccinated patients (31%) than vaccinated patients (22%, including 23% among those who completed a primary series alone, 20% among those who completed a primary series plus one booster, and 16% among those who completed a primary series plus two boosters) (P=0.001). The composite critical covid-19 outcome of death or invasive mechanical ventilation was more common among unvaccinated patients (20%) than vaccinated patients (13% among those with any vaccination regimen, including 14% among those who completed a primary series alone, 11% who completed a primary series plus one booster dose, and 12% who completed a primary series plus two boosters) (P<0.001). Among 2012 case patients with data available on in-hospital treatments, use of one treatment or more indicated for severe covid-19 (corticosteroids, tocilizumab, or baricitinib) was more common among unvaccinated patients (68%) than vaccinated patients (55% among those with any vaccination regimen, including 59% who completed a primary series alone, 50% who completed a primary series plus booster, and 40% who completed a primary series plus two boosters) (P<0.001).

Pre-booster and post-booster serum antibody results

Paired serum samples were collected before and after a covid-19 booster dose in 63 healthy volunteers, including 33 who had received a BNT162b2 booster dose after a BNT162b2 primary series, 16 with an mRNA-1273 booster dose after an mRNA-1273 primary series, eight with an Ad26.COV2 booster dose after an Ad26.COV2 primary series dose, and six with one mRNA booster dose after an Ad26.COV2 primary series dose (see supplemental table S6). Anti-receptor binding domain and anti-S antibody concentrations were higher after the booster dose compared with before the booster dose for all vaccines (fig 6; supplemental table S7). Post-booster anti-receptor binding domain and anti-S antibody concentrations were higher for participants who received three BNT162b2 doses and three mRNA-1273 doses compared with two Ad26.COV2 doses.

Discussion

Principal findings

In this analysis of adults admitted to one of 21 hospitals in the US during an omicron predominant period from 26 December 2021 to 30 June 2022, receipt of a covid-19 primary vaccine series plus one or two booster doses provided greater protection against admission to hospital with covid-19 than receipt of a primary series alone. This added protection of booster doses was seen across all age groups and for both immunocompetent and immunocompromised people. mRNA vaccines (BNT162b2 and mRNA-1273) provided greater protection than the Ad26.COV2 vaccine, when considering both a primary series alone and a boosted vaccine regimen. These clinical vaccine effectiveness findings were supported by serology results showing substantially higher anti-SARS-CoV-2 antibody titers after booster vaccine doses. These antibody and vaccine effectiveness data support US recommendations that all eligible people receive booster doses to protect against severe disease from the omicron variant.

Comparison with other studies and policy implications

Vaccines against covid-19 have been authorized for use in the US for more than a year, and as of June 2022 an estimated 77% of the adult population had received a primary series, of whom nearly half of those eligible to receive a first booster dose had not yet received it.[3] Modest waning in protection of a primary covid-19 vaccine series was initially shown during the delta variant period.[29-31] Our findings support the concept of waning protection for primary vaccine series against the omicron variant as well, with a decline in protection for both a primary series and a boosted vaccine regimen against hospital admission with covid-19 during the omicron period of more than 3-5 months after the last vaccine dose. These data add to the growing evidence of waning effectiveness of covid-19 vaccines over time.[32 33] Despite known immune evasion features of the omicron variant for vaccines currently available, our results show that vaccine effectiveness substantially increased after booster doses, consistent with results from other studies.[78] Data from immunological studies suggest that a broadening of the immune response occurs after a booster dose, including an increase in, and adaptation of, anti-receptor binding domain specific memory B cells, providing biologic plausibility for increased vaccine effectiveness after a booster dose even with the highly divergent omicron variant.[22 34-36] Our data from healthy adult volunteers suggested statistically significant increases in anti-receptor binding domain and anti-spike antibody levels 2-6 weeks after receiving one booster dose, consistent with observed differences in vaccine effectiveness between those who received a booster dose compared with a primary series only.

In our study, vaccine effectiveness against the BA.2 lineage was lower than against the BA.1 lineage, consistent with a recent US based electronic health record study,[15] but different from recent studies from the United Kingdom and the Netherlands that suggested similar vaccine effectiveness against BA.2 and BA.1.[37 38] The use of viral whole genome sequencing in the current study enabled genetic characterization of many of the viruses. Importantly, 56% of the sequenced BA.2 viruses in this study had a BA.2.12.1 sequence, which has enhanced immune

escape features compared with earlier omicron lineages.[39] Vaccinated participants in this study also tended to have longer time delays between their most recent vaccine dose and symptom onset in the BA.2 period (median 241 days from primary series) compared with the BA.1 period (median 197 days from primary series). Hence, the observed lower vaccine effectiveness in the BA.2 period might be due to a combination of greater immune evasion of the BA.2.12.1 lineage and the effects of waning immunity.

We also observed that vaccinated patients admitted to hospital with covid-19 experienced less severe outcomes than unvaccinated patients admitted to hospital with covid-19, suggesting that covid-19 vaccines result in disease attenuation and providing further rationale for covid-19 vaccination.[30 31] In this analysis, although patients who received boosted vaccine regimens were less likely to be admitted to hospital with covid-19 than those who received a primary series alone, in-hospital outcomes were similar between those who received boosted regimens and a primary series alone. Additional study will be required to understand if booster doses lead to incremental disease attenuation beyond a primary series among patients with vaccine breakthrough.

Our findings also suggest lower effectiveness for the adenovirus vector vaccine Ad26.COV2, both as a primary vaccine series and as a booster dose compared with mRNA vaccines. Although mechanisms of protection against SARS-CoV-2 have not yet been established, binding antibodies correlate with protection against SARS-CoV-2, allowing for contextualization of findings from observational data.[28 40 41] In this analysis, the persistently low levels of anti-spike and anti-receptor binding domain after a primary series dose and before a first booster dose for recipients of Ad26.COV2 compared with recipients of mRNA vaccines provide complementary understanding of the reduced effectiveness of this vaccine relative to mRNA vaccines. These findings support preferential use of mRNA vaccines both for a primary series and for booster doses, regardless of which vaccine product was used for the primary series.[22]

Strengths and limitations of this study

Important strengths of this study included enrollment of patients with active covid-19 symptoms ascertained at the bedside in real time, and laboratory confirmed SARS-CoV-2 infection; these methods facilitated calculations of vaccine effectiveness to prevent symptomatic, laboratory confirmed hospital admission with covid-19. Additionally, ascertainment of vaccination status was robust, with patient interviews combined with systematic searches of medical records and vaccines registries, which enabled precise classification of each patient's vaccination status, including the receipt of booster doses. Furthermore, respiratory tract samples with SARS-CoV-2 detected underwent viral sequencing, which enabled exclusion of patients infected with a variant other than omicron.

This analysis also had limitations. First, although we evaluated several relevant confounders, residual or unmeasured confounding is possible. In particular, increases in the proportion of individuals with previous SARS-CoV-2 infection, which is associated with a degree of protection against reinfection, may have led to the lower vaccine effectiveness observed in this study compared with studies from earlier in the pandemic when fewer unvaccinated patients had had a previous natural infection.[42-44] Second, although binding antibodies likely correlate with protection against SARS-CoV-2 infection, other immune responses, including neutralizing antibodies and cellular immunity, were not evaluated. Third, patients included in the antibody analysis were healthy adult volunteers and may not fully represent the clinical and demographic characteristics of those included in vaccine effectiveness analyses. Fourth, the modest sample size in some subgroups limited precision of some estimates, including waning of vaccine effectiveness >120 days after two booster doses and effectiveness of Ad26.COV2, and prevented estimates for effectiveness of second booster doses in immunocompromised patients. Fifth, although the test negative design is a preferred method for evaluating vaccine effectiveness with observational data and is the method recommended by WHO for covid-19 vaccine effectiveness studies, potential limitations of the test negative design should be considered.[19 45] These limitations include collider bias, which can occur when attenuation of disease severity from vaccination results in different healthcare seeking behavior, leading to differences in testing or hospital admission between cases and controls.[46 47] However, the impact of collider bias is likely to be lower in this study than in outpatient vaccine effectiveness studies owing to our focus on severe covid-19 in hospitals, where a high proportion of patients with covid-19 should be detected owing to near universal testing for SARS-CoV-2 (regardless of disease severity) among adults admitted to hospital in the US during the period of this study.

Conclusion

Vaccination with a primary covid-19 vaccine series plus booster doses was statistically significantly more effective than a primary series alone in preventing covid-19 associated hospital admission during the omicron period in the US. Additionally, mRNA vaccines were more effective than the Ad26.COV2 vaccine, both as a primary series vaccine and as booster doses. Serology results support these findings by showing substantial increases in anti-SARS-CoV-2 antibody titers after booster vaccine doses, particularly with mRNA vaccines. These findings support recommendations for all eligible adults aged ≥18 years to receive booster doses of an mRNA vaccine.

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Contributors: KA, JPR, and DS contributed equally to this work as lead author. WHS and MWT contributed equally to this work as senior author. Guarantors of this work include WHS (protocol and data integrity), KA (statistical analysis), ASL (viral sequencing laboratory methods), JDChappell (reverse transcription polymerase chain reaction laboratory methods), and NJT (antibody measurement methods). WHS was responsible for the decision to submit the manuscript, KA, JPR, DS, MWT, and WHS drafted the initial manuscript (without outside assistance). KA, JPR, DS, MG, AAG, TM, SG, BH, KT, JDCasey, NM, AZ, NIS, KWG, DCF, MH, DNH, HA, MP, AEF, MCE, MG, AM, NJJ, VS, JSS, IDP, SMB, ETM, AM, ASL, AK, CLH, LWB, CtL, AD, JGW, AJG, NQ, SYC, CM, CR, HB, JHK, JDChappell, NH, CGG, TR, WBS, AB, CJL, KH, SNL, NJT, SP, MLM, MMP, MWT, and WHS conceptualized the study methods. KA, MWT, CJL, KH, and YZ were responsible for statistical analysis and data management. WHS acquired funding. KA, JPR, DS, MG, AAG, TM, SG, DH, HKT, JDCasey, NM, AZ, NIS, KWG, DCF, MH, DNH, HA, MP, AEF, MCE, MG, AM, NJJ, VS, JSS, IDP, SMB, ETM, AM, ASL, AK, CLH, LWB, CtL, AD, JGW, AJG, NQ, SYC, CM, CR, HB, JHK, JDChappell, NH, CG, TR, WBS, AB, CJL, KH, SNL, NJT, SP, MLM, MMP, MWT, and WHS critically reviewed the manuscript for important intellectual content. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: No additional data available.

The corresponding author (WHS) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. WHS led the development of the study protocol and participant enrollment. KA led statistical analysis. ASL led viral sequencing work. JDChappell led reverse transcription polymerase chain reaction work. NJT led the antibody measurement work. WHS takes responsibility for the work overall.

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Supplementary information: appendices A-C