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Effectiveness of mRNA COVID-19 Vaccines and Hybrid Immunity in Preventing SARS-CoV-2 Infection and Symptomatic COVID-19 Among Adults in the United States

Leora R. Feldstein,[1] Jasmine Ruffin,[1] Ryan E. Wiegand,[1] Craig B. Borkowf,[1] Jade James-Gist,[1] Tara M. Babu,[2] Melissa Briggs-Hagen,[1] James Chappell,[3] Helen Y. Chu,[2] Janet A. Englund,[4] Jennifer L. Kuntz,[5] Adam S. Lauring,[6] Natalie Lo,[2] Marco Carone,[2] Christina Lockwood,[2] Emily T. Martin,[7] Claire M. Midgley,[1] Arnold S. Monto,[7] Allison L. Naleway,[5] Tara Ogilvie,[2] Sharon Saydah,[1] Mark A. Schmidt,[5] Jonathan E. Schmitz,[3] Ning Smith,[5] Ine Sohn,[3] Lea Starita,[2] H. Keipp Talbot,[3] Ana A. Weil,[2] and Carlos G. Grijalva[3]

[1]Coronavirus and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, Washington; [3]Vanderbilt University Medical Center, Nashville, Tennessee; [4]Department of Pediatrics, University of Washington, Seattle Children's Research Institute, Seattle, Washington; [5]Kaiser Permanente Center for Health Research, Portland, Oregon; [6]Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; and [7]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan

Background. Understanding protection against SARS-CoV-2 infection by vaccine and hybrid immunity is important for informing public health strategies as new variants emerge.

Methods. We analyzed data from 3 cohort studies spanning 1 September 2022 to 31 July 2023 to estimate COVID-19 vaccine effectiveness (VE) against SARS-CoV-2 infection and symptomatic COVID-19 among adults with and without prior infection in the United States. Participants collected weekly nasal swabs irrespective of symptoms, participated in annual blood draws, and completed periodic surveys, which included vaccination status and infection history. Swabs were tested molecularly for SARS-CoV-2. VE was estimated by Cox proportional hazards models for the hazard ratios of infections, adjusting for covariates. VE was calculated considering prior infection and recency of vaccination.

Results. Among 3344 adults, the adjusted VE of a bivalent vaccine against infection was 37.2% (95% CI, 12.3%–55.7%) within 7 to 59 days of vaccination and 21.1% (95% CI, −0.5% to 37.1%) within 60 to 179 days of vaccination when compared with participants who were unvaccinated or had received an original monovalent vaccine dose ≥180 days prior. Overall, the adjusted VE of a bivalent vaccine against infection, in conjunction with prior infection, was 62.2% (95% CI, 46.0%–74.5%) within 7 to 179 days of vaccination and 39.4% (95% CI, 12.5%–61.6%) at ≥180 days when compared with naive participants who were unvaccinated or had received a monovalent vaccine dose ≥180 days prior.

Conclusions. Adults with prior infection and recent vaccination had high protection against infection and symptomatic illness. Recent vaccination alone provided moderate protection.

Keywords. COVID-19; vaccine effectiveness; hybrid immunity; cohort study; prior infection.

Adults are severely affected by COVID-19 illness: >1.2 million COVID-19–related deaths among Americans aged ≥18 years have occurred as of 19 December 2024, accounting for 99.8% of all COVID-19–related deaths in the United States [1]. The original monovalent mRNA COVID-19 vaccines were highly effective at reducing the risk of severe illness and death but waned over time, especially for less severe outcomes, and effectiveness appeared lower against Omicron [2, 3]. To address the diminished protection from vaccination, the Food and Drug Administration authorized use of the bivalent mRNA COVID-19 vaccine, composed of ancestral and Omicron BA.4/BA.5 spike proteins [4]. While previous studies have shown that bivalent mRNA COVID-19 vaccination among adults is effective at reducing COVID-19–related hospitalizations and death [5–7], fewer studies have assessed whether updated vaccines provide protection against infection and milder symptomatic illness [8–15] and examined the impact of prior infection with receipt of the vaccine [8–10, 16, 17].

Understanding how well adults are protected against SARS-CoV-2 infection by vaccine alone and by hybrid immunity is

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Correspondence: Leora Feldstein, PhD, Centers for Disease Control and Prevention, Coronavirus and Other Respiratory Viruses Division, 1600 Clifton Rd NE, Atlanta, GA 30329 (nqw5@cdc.gov); Jasmine Ruffin, MPH, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Atlanta GA 30329 (qpm4@cdc.gov).

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important for informing public health strategies and policies, particularly as new variants continue to emerge. During a period of Omicron XBB variant predominance, this analysis used data from 3 prospective cohort studies to estimate the effectiveness of authorized monovalent and bivalent COVID-19 vaccines (excluding the 2023–2024 monovalent vaccine) and history of infection against laboratory-confirmed SARS-CoV-2 virus infection and symptomatic COVID-19 among adults in the United States.

METHODS

Study Population

We conducted an analysis on data spanning 1 September 2022 to 31 July 2023 from 4 sites in the United States to estimate COVID-19 vaccine effectiveness (VE) among adults aged ≥18 years. Specifically, we combined data from 3 prospective cohort studies: CASCADIA, CoVE (Community Vaccine Effectiveness Against Asymptomatic and Symptomatic SARS-CoV-2 Infection in Michigan), and VIEW (Viruses and Infections in Essential Workers) [18]. CASCADIA enrolled Kaiser Permanente Northwest and University of Washington patients and community members in the metropolitan areas of Portland, Oregon, and Seattle, Washington (children and adults aged 18–49 years). Recruitment strategies included outreach to Kaiser Permanente Northwest health plan members and local school districts and daycares, press releases and social media campaigns, and outreach to community-based organizations and other health care partners [18]. CoVE enrolled children and adults of all ages who live in Michigan and receive health care. Recruitment methods to reach individuals across the state of Michigan included social media campaigns (Facebook/Instagram), the Michigan Medicine searchable study registry (UMhealthresearch.org), and outreach from health systems and partners throughout Michigan. VIEW enrolled adults who are essential workers (non–health care) in Tennessee. Participants in VIEW were recruited through a multipronged approach, including community health care centers, community clinics and organizations, outpatient clinics and settings, specialized recruitment support initiatives such as ResearchMatch, physical and electronic advertisement, social media campaigns and registries of individuals who previously agreed to be contacted for research opportunities, and those who had not opted out of invitations for research opportunities.

For this study, adults living in Washington, Oregon, Michigan, and Tennessee, including individuals from the same household, were eligible for inclusion. Written informed consent was obtained from all participants. This study was reviewed by the US Centers for Disease Control and Prevention, approved by the institutional review boards at participating sites, and conducted consistent with applicable federal law and CDC policy (45 CFR part 46, 21 CFR part 56, 42 USC §241[d], 5 USC §552a, 44 USC §3501 et seq).

Data and Specimen Collection

At enrollment, participants completed a survey that included demographics, household characteristics, chronic medical conditions, COVID-19 vaccination history, and prior SARS-CoV-2 infection; participants were resurveyed at regular intervals to capture up-to-date demographic information. Blood specimens were collected near to the time of enrollment from participants who consented to phlebotomy or by self-collection of blood specimens with Mitra or Tasso+ devices [19]. Weekly surveillance was conducted for COVID-19–like illness symptoms. Participants were asked to self-collect nasal swabs weekly, irrespective of symptoms. To optimally capture symptomatic COVID-19, participants were instructed to collect an additional respiratory specimen upon onset of symptoms if they occurred outside the timing of their regular weekly swab cadence.

Laboratory Testing

All respiratory specimens were tested for SARS-CoV-2 with assays based on real-time reverse transcription polymerase chain reaction (RT-PCR), as detailed in the supplementary materials (Supplementary Table 1). Of note, while the component studies (CASCADIA, CoVE, VIEW) do not fall under the medicolegal auspices of clinical testing, all 3 utilized the same molecular assays employed for patient care. Less than 1% of specimens generated PCR results that would be considered "inconclusive" or "failed" under clinically validated parameters; for the purposes of the present analyses, these specimens were considered negative. Whole genome sequencing was attempted on all SARS-CoV-2–positive specimens with an adequate viral load [20–23].

Available serum specimens were tested for the presence of anti-nucleocapsid (anti-N) IgG with quantitative MesoScale Discovery VPLEX assays (Supplementary Table 1). For the SARS-CoV-2 MesoScale Discovery assay, titers against the N protein were interpolated from a standard calibration curve provided by the manufacturer. Specimens below the lower limit of quantitation per assay insert were set to a value of half the lower limit. Per the assay insert, specimens were determined to have detectable anti-N IgG if they had a titer ≥5000 assigned units per milliliter.

Variables of Interest

COVID-19 vaccination status was captured from enrollment and weekly/monthly surveys (self-report), vaccine cards provided by the participant, and/or queries of the state immunization information systems and electronic medical records (EMRs), when available. Vaccination data included vaccination dates, number of doses, and manufacturer. Information from the EMRs and state immunization information systems was used preferentially over self-reported information in the event that a participant did not report a history of vaccination.

Symptomatic COVID-19 was defined as a positive RT-PCR test result and at least 2 COVID-19–like illness symptoms reported within 7 days before or after the specimen collection date. The list of COVID-19–like illness symptoms varied by the cohort study (Supplementary Table 2).

Prior infection was defined as laboratory-confirmed infection by RT-PCR from a study-collected specimen prior to the analytic period, positive anti-N SARS-CoV-2 antibody at enrollment, or self-report of infection prior to enrollment or 1 September 2022 (whichever occurred later). Time since prior infection was categorized as no prior infection, <4 months, 4 to <6 months, 6 to <12 months, and ≥12 months. Dates of prior infection were imputed for 196 (5.9%) participants who had only serologic results and therefore did not have dates associated with prior infection. Imputation was done with results from linear regression models, in which baseline nucleocapsid blood draw date and numeric nucleocapsid values served as the predictors for the date of prior infection among study participants with known prior infection dates (supplementary methods).

Statistical Analysis

Descriptive statistics compared participants who became infected during the study period with those who remained uninfected and included frequency (proportion) for categorical variables and median (IQR) for continuous variables. *P* values were calculated by χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. The Andersen-Gill extension of the Cox proportional hazards model with time-varying vaccination status was used to estimate hazard ratios of first SARS-CoV-2 infections, comparing participants with receipt of a bivalent dose with participants who either were unvaccinated or had received the original monovalent vaccine ≥180 days prior [24]. Separate VE estimates were produced for SARS-CoV-2 infection (inclusive of asymptomatic and symptomatic infections), symptomatic COVID-19, vaccine valency (original monovalent vs bivalent), and timing of vaccine receipt. VE estimates were stratified by prior infection status and variant period among those with recent bivalent vaccination (within 7–179 days). Additionally, VE estimates were produced for the cohort with vaccination and prior infection, with the reference group consisting of naive participants, defined as those with no evidence of prior infection, who either were unvaccinated or had received the original monovalent vaccine ≥180 days prior.

Multivariable models adjusted for age, sex, race and ethnicity, presence of at least 1 underlying health condition, time since prior infection, geographic site, household size, and 7-day average of COVID-19 cases per 100 000 by site (local incidence: modeled as a continuous linear variable). COVID-19 VE was calculated as (1 – hazard ratio) × 100. Confidence intervals were calculated via the standard estimation methods for the Cox proportional hazards model because the cluster size of participants by household was small [25]. In particular, 32.3% of households had ≥2 adults included in the analysis; note that 1 participant had a missing household identification and was assumed to be the only study participant in the household.

Person-time was calculated as the total number of days under surveillance for a given vaccination status during the analytic period. The surveillance period started on 1 September 2022 and ended on the date of a participant's first positive RT-PCR test result, the participant's study withdrawal date, or the end of the analytic period (31 July 2023), whichever came first. Individuals enrolled after 1 September 2022 began time at risk at the time of surveillance start or 6 weeks after prior infection, if recently infected prior to enrollment. In cases where there was no specimen result for ≥4 consecutive weeks (eg, participant skipped a weekly swab), the surveillance weeks were censored. The 2 weeks following an original monovalent primary vaccine dose and the week following bivalent or original monovalent booster vaccine doses were also excluded from person-time. A sensitivity analysis was conducted by restricting the analysis period to 27 November 2022 to 31 July 2023 to account for the difference in enrollment start dates of the studies (eg, CASCADIA and CoVE began enrollment in July and August 2022, respectively, whereas VIEW started in November 2022) and for the differences in the percentage of participants who received a bivalent vaccine by site (CASCADIA, 66.7%; CoVE, 59.9%; VIEW, 28.4%).

All analyses were conducted with SAS software (version 9.4; SAS Institute) or R Studio software (version 4.1.0; R Foundation).

RESULTS

Study Population

Between 1 September 2022 and 31 July 2023, 3344 participants contributed to person-time in the analysis: 50.0% from CASCADIA, 39.4% from VIEW, and 10.6% from CoVE (Table 1). Overall, 67.2% were female, the median age was 41 years (IQR, 36–46), and the majority were non-Hispanic White (69.3%). Almost half of participants lived in a household with ≥4 individuals (49.4%), and 60.8% of participants reported having at least 1 chronic health condition. Age, sex, race and ethnicity, prevalence of chronic conditions, weekly swab adherence, number of SARS-CoV-2 infections during the study period, prior infection status, and household size varied by site (Supplementary Table 3). Of the 1455 prior infections reported, 12.8% were from self-report only (data not shown). During the study period, 22.5% (n = 751) of participants had a laboratory-confirmed SARS-CoV-2 infection. A higher proportion of participants living in a household with more than 1 other person had SARS-CoV-2 infections compared with those who lived alone (23.1% vs 15.9%). A higher proportion of those with no documented prior infection had a SARS-CoV-2 infection during the study period compared with those with a prior infection (26.5% vs 17.2%).

Table 1. Characteristics of Participants by Laboratory-Confirmed SARS-CoV-2 Status, 1 September 2022–31 July 2023

	Overall		SARS-CoV-2				
			Positive During Study Period		Negative		
	No.	Column %	No.	Row %	No.	Row %	*P* Value[a]
Total	3344		751	22.5	2593	77.5	
Site							.406
CASCADIA: Kaiser Permanente Northwest	854	25.5	186	21.8	668	78.2	
CASCADIA: University of Washington	819	24.5	197	24.1	622	75.9	
CoVE: Michigan	354	10.6	70	19.8	284	80.2	
VIEW: Tennessee	1317	39.4	298	22.6	1019	77.4	
Sex							.781
Female	2246	67.2	504	22.4	1742	77.6	
Male	1088	32.5	246	22.6	842	77.4	
Other	10	0.3	1	10.0	9	90.0	
Age, y, median (IQR)	41	36–46.4	41	37–46	41	36–47	.955
Age group, y							.154
18–49	2881	86.2	663	23.0	2218	77.0	
50–64	385	11.5	74	19.2	311	80.8	
≥65	78	2.3	14	17.9	64	82.1	
Race and ethnicity							.085
Non-Hispanic White	2319	69.3	540	23.3	1779	76.7	
Hispanic or Latino	273	8.2	69	25.3	204	74.7	
Non-Hispanic, multiple races	129	3.9	26	20.2	103	79.8	
Non-Hispanic Black	327	9.8	64	19.6	263	80.4	
Non-Hispanic other[b]	296	8.9	52	17.6	244	82.4	
Chronic conditions[c]							.169
None	1312	39.2	308	23.5	1004	76.5	
≥1	2032	60.8	443	21.8	1589	78.2	
Individuals living in household[d]							.058
1	276	8.3	44	15.9	232	84.1	
2	655	19.6	148	22.6	507	77.4	
3	754	22.7	175	23.2	579	76.8	
≥4	1643	49.4	381	23.2	1262	76.8	
Weekly swab adherence, median (IQR), %	87	76 -93	86	75–93	88	80–93	<.001
Swab adherence							<.001
<80%	1065	31.8	192	18.0	873	82.0	
≥80%	2279	68.2	559	24.5	1720	75.5	
No. of vaccine doses, median (IQR)	4	3–4	3	3–4	4	3–4	.134
Prior infection[e]							<.001
None	1889	56.5	501	26.5	1388	73.5	
≥1	1455	43.5	250	17.2	1205	82.8	
Time since prior infection, mo[f]							.006
No prior infection	1889	56.5	501	26.5	1388	73.5	
<4	500	15.0	79	15.8	421	84.2	
4 to <6	302	9.03	42	13.9	260	86.1	
6 to <12	365	10.9	60	16.4	305	83.6	
≥12	288	8.6	69	24.0	219	76.0	
Symptomatic COVID-19[g]							
No	311	41.4	…	…	…	…	
Yes	440	58.6	…	…	…	…	

Table 1. Continued

	Overall		SARS-CoV-2				
			Positive During Study Period		Negative		
	No.	Column %	No.	Row %	No.	Row %	*P* Value[a]
Predominant variant period of infection[h]							
BA.4/BA.5[i]	245	32.6	…	…	…	…	
XBB[j]	506	67.4	…	…	…	…	

Abbreviation: RT-PCR, reverse transcription polymerase chain reaction.

[a]Fisher exact test, Kruskal-Wallis rank sum test, and Pearson χ^2 test were used to calculate *P* values.

[b]Participants who identified as non-Hispanic American Indian, Alaska Native, Asian, and Native Hawaiian/Pacific Islander.

[c]Chronic conditions for CASCADIA and CoVE included asthma, heart disease, sleep apnea, Down syndrome, diabetes, cancer, autoimmune disease, liver disease, kidney disease, hematologic disease, neurologic or neuromuscular disease, stroke, deep vein thrombosis or pulmonary embolism, anxiety, depression, immunosuppression, hypertension, and thyroid disease. For VIEW: asthma, chronic pulmonary disease, obesity, heart disease, diabetes, liver disease, kidney disease, cancer, arthritis, hematologic disease, neurologic or neuromuscular disease, stroke, deep vein thrombosis or pulmonary embolism, anxiety, depression, immunosuppression, hypertension, and thyroid disease.

[d]Sixteen participants had missing data on the number of individuals in their household.

[e]Prior infection was defined as laboratory-confirmed infection by RT-PCR from a study-collected specimen, positive anti-nucleocapsid SARS-CoV-2 antibody, or self-report of infection prior to enrollment or 1 September 2022.

[f]Time since prior infection was calculated as the date of the prior infection to the first week that each participant was included in the analysis.

[g]Symptomatic COVID-19 was defined as a positive RT-PCR test result and at least 2 COVID-19–like illness symptoms reported within 7 days of the specimen collection date.

[h]Period in which the positive SARS-CoV-2 infection occurred.

[i]BA.4/BA.5–predominant period was defined as 1 September 2022 to 27 January 2023.

[j]XBB-predominant period was defined as 28 January 2023 to 31 July 2023.

Among participants with SARS-CoV-2 infections during the study period, 58.6% reported symptomatic COVID-19. Of the 751 SARS-CoV-2 infections, 480 (64%) had genetic sequencing results; the most prevalent lineages were XBB (61.4%), BQ.1.1 (16.6%), and BA.4/BA.5 (15.5%).

Vaccine Uptake

Half of participants received at least 1 bivalent COVID-19 vaccine dose (49.7%; Table 2). Participants enrolled from the Kaiser Permanent Northwest health plan (Oregon and Washington) had the highest uptake of bivalent vaccine doses (77.0%), whereas those in Tennessee (VIEW) had the lowest (28.4%). Non-Hispanic Black participants had the lowest reported proportion of receiving a bivalent vaccine (30.3%), followed by Hispanic participants (33.7%), as compared with non-Hispanic White participants (55.3%). Those without report of a prior infection had higher uptake of a bivalent vaccine (54.5%) as compared with those with report of a prior infection (46.3%).

VE Against Infection

Of the 751 SARS-CoV-2 infections, 747 were included in the VE analysis (4 were excluded due to missing data on sex and number of individuals in the household). Of the 747 infections, 352 (47.1%) were among participants who were unvaccinated or had received a monovalent vaccine dose ≥180 days prior (1.74 infections per 1000 person-days; 95% CI, 1.56–1.93), and 327 (43.8%) were among those who received a bivalent dose (1.20 infections per 1000 person-days; 95% CI, 1.08–1.34; Tables 2 and 3). The adjusted VE of a bivalent dose received within 7 to 59 days against laboratory-confirmed SARS-CoV-2 infection, as compared with the reference of being unvaccinated/receiving an original monovalent vaccine dose ≥180 days prior, was 37.2% (95% CI, 12.3%–55.7%). When compared with the same reference, the adjusted VE of a bivalent dose received within 60 to 179 days was 21.1% (95% CI, −0.5% to 37.1%), and the adjusted VE of a bivalent dose received ≥180 days prior was 8.3% (95% CI, −17.4% to 30.4%). When stratified by variant period, VE of the bivalent vaccine received within 7 to 179 days was 23.6% (95% CI, −10.6% to 44.5%) for BA.4/BA.5 and 26.1% (95% CI, 3.6%–43.8%) for XBB. When stratified by prior infection status, the adjusted VE of a bivalent dose within 7 to 179 days against infection was 26.5% (95% CI, −2.3% to 39.2%) among those who were naive and 37.7% (95% CI, 9.1%–58.0%) among those with prior infection. The adjusted VE of the original monovalent vaccine within 180 days against laboratory-confirmed SARS-CoV-2 infection, as compared with the same reference group, was 27.1% (95% CI, 2.6%–46.3%).

Hybrid Immunity Against Infection and Symptomatic Illness

The combined protection from bivalent vaccination and prior infection when compared with naive participants who were unvaccinated or had received a monovalent vaccine dose ≥180 days prior was 62.2% (95% CI, 46.0%–74.5%) when vaccination was received within 7 to 179 days and 39.4% (95% CI, 12.5%–61.6%) when received ≥180 days prior (Table 4). For symptomatic COVID-19 illness, combined protection was 73.0% (95% CI, 57.0%–84.2%) when bivalent vaccination was received within 7 to 179 days and 56.7% (95% CI, 31.1%–78.4%) when received ≥180 days prior.

Table 2. Characteristics of Participants by COVID-19 Vaccination Status, 1 September 2022–31 July 2023

	Overall		Unvaccinated or Monovalent Only		Bivalent Dose		
	No.	Column %	No.	Row %	No.	Row %	*P* Value[a]
Total	3344		1642	50.3	1702	49.7	
Site							<.001
CASCADIA: Kaiser Permanente Northwest	854	25.5	196	23.0	658	77.0	
CASCADIA: University of Washington	819	24.5	361	44.1	458	55.9	
CoVE: Michigan	354	10.6	142	40.1	212	59.9	
VIEW: Tennessee	1317	39.4	943	71.6	374	28.4	
Sex							.580
Female	2246	67.2	1117	49.7	1129	50.3	
Male	1088	32.5	520	47.8	568	52.2	
Other	10	0.3	5	50.0	5	50.0	
Age, y, median (IQR)	41	36.0–46.4	40	34.0–46.1	42	38–47	<.001
Age group, y							<.001
18–49	2881	86.2	1388	48.2	1493	51.8	
50–64	385	11.5	223	57.9	162	42.1	
≥65	78	2.3	31	39.7	47	60.3	
Race and ethnicity							<.001
Non-Hispanic White	2319	69.3	1037	44.7	1282	55.3	
Hispanic or Latino	273	8.2	181	66.3	92	33.7	
Non-Hispanic, multiple races	129	3.9	57	44.2	72	55.8	
Non-Hispanic Black	327	9.8	228	69.7	99	30.3	
Non-Hispanic other[b]	296	8.9	139	47.0	157	53.0	
Chronic conditions[c]							.173
None	1312	39.8	625	47.6	687	52.4	
≥1	2032	60.2	1017	50.0	1015	50.0	
Individuals living in household[d]							<.0001
1	276	8.3	158	57.2	118	42.8	
2	655	19.7	389	59.4	266	40.6	
3	754	22.7	337	44.7	406	55.3	
≥4	1643	49.4	744	45.3	899	54.7	
Weekly swab adherence, %, median (IQR)	87	76–93	84	74–92	88	80–95	<.001
Swab adherence							<.001
<80%	1065	37.3	633	59.4	432	40.6	
≥80%	2279	62.7	1009	44.3	1270	55.7	
Prior infection[e]							<.001
None	1889	56.5	860	45.5	1029	54.5	
≥1	1455	43.5	782	53.7	673	46.3	
Time since prior infection, mo[f]							<.001
No prior infection	1889	56.5	860	45.5	1029	54.5	
<4	500	15.0	224	44.8	276	55.2	
4 to <6	302	9.0	163	54.0	139	46.0	
6 to <12	365	10.9	190	52.1	175	47.9	
≥12	288	8.6	205	71.2	83	28.8	
Symptomatic COVID-19[g]							<.001
No	…	…	206	66.2	105	33.8	
Yes	…	…	216	49.1	224	50.9	

Abbreviation: RT-PCR, reverse transcription polymerase chain reaction.

[a]Fisher exact test, Kruskal-Wallis rank sum test, and Pearson χ^2 test were used to calculate *P* values.

[b]Participants who identified as non-Hispanic American Indian, Alaska Native, Asian, and Native Hawaiian/Pacific Islander.

[c]Chronic conditions for CASCADIA and CoVE included asthma, heart disease, sleep apnea, Down syndrome, diabetes, cancer, autoimmune disease, liver disease, kidney disease, hematologic disease, neurologic or neuromuscular disease, stroke, deep vein thrombosis or pulmonary embolism, anxiety, depression, immunosuppression, hypertension, and thyroid disease. For VIEW: asthma, chronic pulmonary disease, obesity, heart disease, diabetes, liver disease, kidney disease, cancer, arthritis, hematologic disease, neurologic or neuromuscular disease, stroke, deep vein thrombosis or pulmonary embolism, anxiety, depression, immunosuppression, hypertension, and thyroid disease.

[d]Sixteen participants had missing data on the number of individuals in their household.

[e]Prior infection was defined as laboratory-confirmed infection by RT-PCR from a study-collected specimen, positive anti-nucleocapsid SARS-CoV-2 antibody, or self-report of infection prior to enrollment or 1 September 2022.

[f]Time since prior infection was calculated as the date of the prior infection to the first week that each participant was included in the analysis.

[g]Symptomatic COVID-19 was defined as a positive RT-PCR test result and at least 2 COVID-19–like illness symptoms reported within 7 days of the specimen collection date.

Table 3. COVID-19 Vaccine Effectiveness Against Laboratory-Confirmed SARS-CoV-2 Infection Among Adults by Vaccine Type, Interval Since Receipt of Dose, Prior Infection Status, and Variant Period

	Contributing Participants[a]	Total PD	Observation Time After Vaccination, D, Median (IQR)	SARS-CoV-2 Infections		VE (95% CI)	
				No.	Crude Incidence Rate per 1000 PD (95% CI)	Unadjusted	Adjusted[b]
Interval since receipt of dose							
Unvaccinated or monovalent vaccine ≥180 d	2013	202 125	446 (311–569)	352	1.74 (1.56, 1.93)	1 [Reference]	1 [Reference]
Monovalent vaccine, <180 d	435	47 775	98 (55–140)	68	1.42 (1.11, 1.80)	38.3 (17.8, 53.7)	27.1 (2.6, 46.3)
Bivalent vaccine, d							
7–59	859	37 058	35 (22–47.8)	40	1.08 (.77, 1.47)	48.1 (26.5, 63.3)	37.2 (12.3, 55.7)
60–179	1338	114 576	123 (93–152)	168	1.47 (1.25, 1.71)	38.7 (23.8, 50.7)	21.1 (−.5, 37.1)
≥180	1356	119 952	236 (208–267)	119	0.99 (.82, 1.19)	22.3 (1.2, 38.9)	8.3 (−17.4, 30.4)
Overall	1695	271 586	165 (95–228)	327	1.20 (1.08, 1.34)	34.7 (22.7, 44.9)	18.5 (2.5, 32.8)
Prior infection status							
Naive[c]							
Unvaccinated or monovalent vaccine ≥180 d	1040	98 518	431 (294–563)	199	2.02 (1.75, 2.32)	1 [Reference]	1 [Reference]
Bivalent vaccine within 7–179 d	835	85 617	104 (60–143)	163	1.90 (1.62, 2.22)	30.9 (11.8, 45.8)	26.5 (−2.3, 39.2)
Prior infection[d]							
Unvaccinated or monovalent vaccine ≥180 d	973	103 607	458 (334–575)	153	1.48 (1.25, 1.73)	1 [Reference]	1 [Reference]
Bivalent vaccine within 7–179 d	566	66 017	103 (61–143)	45	0.68 (.50, .91)	65.9 (51.1, 76.3)	37.7 (9.1, 58.0)
Variant predominance period							
BA.4/BA.5[e]							
Unvaccinated or monovalent vaccine ≥180 d	1101	48 440	349 (309–399)	115	2.37 (1.96, 2.85)	1 [Reference]	1 [Reference]
Bivalent vaccine 7–179 d	948	61 803	61 (36–87)	91	1.47 (1.19, 1.81)	44.9 (22.9, 60.6)	23.6 (−10.6, 44.5)
XBB[f]							
Unvaccinated or monovalent vaccine ≥180 d	1443	153 685	499 (317–599)	237	1.54 (1.35, 1.75)	1 [Reference]	1 [Reference]
Bivalent vaccine 7–179 d	1291	89 831	136 (105–158)	117	1.30 (1.08, 1.56)	39.2 (21.6, 52.9)	26.1 (3.6, 43.8)

Abbreviations: D, days; PD, person-days; RT-PCR, reverse transcription polymerase chain reaction; VE, vaccine effectiveness.

[a]Contributing participants in vaccination categories do not equal the number of participants in the study because participants could contribute to more than 1 vaccination category since vaccination status is time varying. Twenty-six participants, including 4 with SARS-CoV-2 infections during the study period, were excluded from the multivariate models because of missing data on sex or number of individuals in the household.

[b]Adjusted estimates control for coefficient estimates of age, sex, race and ethnicity, presence of at least 1 underlying health condition, time since prior infection, geographic site, household size, and 7-day average of COVID-19 cases per 100 000 by site.

[c]Naive is defined as no evidence of prior infection before 1 September 2022.

[d]Prior infection was defined as laboratory-confirmed infection by RT-PCR from a study-collected specimen, positive anti-nucleocapsid SARS-CoV-2 antibody, or self-report of infection prior to enrollment or 1 September 2022 (whichever occurred later).

[e]BA.4/BA.5–predominant period was defined as 1 September 2022 to 27 January 2023.

[f]XBB-predominant period was defined as 28 January 2023 to 31 July 2023.

The combined protection from monovalent vaccination within 7 to 179 days and prior infection when compared with the same reference group was 59.5% (95% CI, 32.3%–79.0%) against laboratory-confirmed SARS-CoV-2 infection and 80.6% (95% CI, 57.3%–94.4%) against symptomatic COVID-19 illness.

Sensitivity Analysis

In a sensitivity analysis, by limiting the analysis time frame to 27 November 2022 to 31 July 2023, the adjusted VE of a bivalent dose received within 7 to 59 days against infection was 46.2% (95% CI, 19.5%–66.4%); within 60 to 179 days, 23.5% (95% CI, 3.9%–37.5%); and ≥180 days, 8.0% (95% CI, −17.2% to 28.3%; Supplementary Table 4). Overall, the adjusted VE of a bivalent dose, regardless of timing of vaccine receipt, was 19.9% (95% CI, 2.5%–33.1%). When protection from vaccination and prior infection was examined, protection against infection and symptomatic COVID-19 was similar to the main analysis results (Supplementary Table 5).

DISCUSSION

COVID-19 vaccines have been shown to reduce the risk of severe illness and health care utilization following SARS-CoV-2 infection, but there are fewer data available on the impact of vaccination on the overall risk of infection [5–7]. In this multistate prospective community cohort study, adults who were vaccinated with a bivalent mRNA COVID-19 vaccine within the past 59 days were less likely to be infected with SARS-CoV-2 than those who were unvaccinated or had received a monovalent vaccine dose ≥180 days prior regardless of infection history; the overall adjusted VE of a bivalent dose was

Table 4. Hybrid Protection Against Laboratory-Confirmed SARS-CoV-2 Infection Among Adults by Vaccine Type and Interval Since Receipt of Dose

	Contributing Participants[a]	Total PD	Observation Time After Vaccination, D, Median (IQR)	SARS-CoV-2 Infections		VE (95% CI)		Symptomatic SARS-CoV-2 Infections		VE (95% CI)	
				No.	Crude Incidence Rate per 1000 PD (95% CI)	Unadjusted	Adjusted	No.	Crude Incidence Rate per 1000 PD (95% CI)	Unadjusted	Adjusted[b]
Naive[c] and unvaccinated or monovalent vaccine ≥180 d	1040	98 518	431 (294–563)	199	2.02 (1.75–2.32)	1 [Reference]	1 [Reference]	117	1.19 (.98–1.42)	1 [Reference]	1 [Reference]
Prior infection[d]											
Monovalent vaccine ≥180 d	870	92 267	458 (334–575)	133	1.44 (1.21–1.71)	29.2 (11.1–43.6)	28.7 (10.9–42.7)	48	0.52 (.38–.69)	56.2 (37.6–69.3)	56.4 (38.3–70.5)
Bivalent vaccine ≥180 d	571	49 049	233 (206–264)	37	0.75 (.53–1.04)	50.7 (27.8–66.3)	39.4 (12.5–61.6)	21	0.43 (.27–.65)	52.9 (20.6–72.1)	56.7 (31.1–78.4)
Monovalent vaccine <180 d	150	17 192	101 (57–141)	15	0.87 (.49–1.44)	66.5 (41.7–80.8)	59.5 (32.3–79.0)	6	0.35 (.13–.76)	76.0 (44.7–89.6)	80.6 (57.3–94.4)
Bivalent vaccine <180 d	566	66 017	103 (61–143)	45	0.68 (.50–0.91)	74.2 (63.6–81.7)	62.2 (46.0–74.5)	25	0.38 (.25–0.56)	72.6 (56.6–82.7)	73.0 (57.0–84.2)

Abbreviations: D, days; PD, person-days; RT-PCR, reverse transcription polymerase chain reaction; VE, vaccine effectiveness.

[a]Contributing participants in vaccination categories do not equal the number of participants in the study because participants could contribute to more than 1 vaccination category since vaccination status is time varying. Twenty-six participants were excluded from the multivariate models because of missing data on sex or number of individuals in the household.

[b]Adjusted estimates control for coefficient estimates of age, sex, race and ethnicity, presence of at least 1 underlying health condition, prior infection status, geographic site, household size, and 7-day average of COVID-19 cases per 100 000 by site.

[c]Naive is defined as no evidence of prior infection before 1 September 2022.

[d]Prior infection was defined as laboratory-confirmed infection by RT-PCR from a study-collected specimen, positive anti-nucleocapsid SARS-CoV-2 antibody, or self-report of infection prior to enrollment or 1 September 2022 (whichever occurred later).

37% within 7 to 59 days of receipt. Beyond 60 days, protection against infection was lower, regardless of variant period. When hybrid immunity was evaluated, we found that adults with evidence of a prior infection and receipt of a COVID-19 vaccine within 7 to 179 days, regardless of valency, were less likely to be infected with SARS-CoV-2 and less likely experience symptomatic COVID-19 illness than naive individuals who were unvaccinated or had received a monovalent vaccine ≥180 days prior; overall protection was estimated to be 60% to 62% against infection and 73% to 81% against symptomatic illness. In contrast, among adults with no evidence of prior infection, VE was lower (27% against infection when vaccination was received within 7–179 days), although this estimate was less precise due to limited sample size. Also in contrast, among those with evidence of prior infection and receipt of a monovalent vaccine ≥180 days prior, VE was similarly lower at 29% against infection.

These findings suggest that hybrid immunity provided the strongest protection against SARS-CoV-2 infection, with the bivalent vaccine alone providing some protection against SARS-CoV-2 infection; however, VE waned more rapidly than hybrid immunity, and after 6 months there was no measurable protection. Our VE results are consistent with previous bivalent vaccine VE estimates against infection reported from other settings (20%–50%), and some of these studies also found evidence of waning VE against infection [8–10, 13, 15, 26]. Decreased protection over time may reflect waning immunity from the vaccine and/or lower effectiveness of the vaccine against newly circulating variants or subvariants, such as XBB, which constituted the majority of infections in this analysis [3, 27]. Adults with documented prior infection had greater and more durable protection from the original monovalent and bivalent vaccines within 179 days of receipt, which suggests that hybrid immunity against SARS-CoV-2 infection provides better protection than vaccination alone. These findings are consistent with other studies that showed enhanced and longer-lasting protection against infection and symptomatic illness among individuals with prior infection and vaccination but with diminishing protection over time [10, 16, 17].

Limitations

There are several important limitations of this study. First, RT-PCR testing methods and COVID-19–like illness definitions varied by cohort site; therefore, some differences in definition of infection or symptomatic COVID-19 may be present. Second, weekly or symptomatic RT-PCR testing prior to the analytic study start date for estimation of prior infection was available among only a subset of participants. To address this concern, we incorporated serologic data to identify additional prior SARS-CoV-2 infections, but due to anti-N SARS-CoV-2 antibody waning, some prior infections may have been undetected. Third, social desirability or recall bias may have affected self-report of prior infection and vaccination status when

RT-PCR and serologic test results and data from the state immunization information systems and EMRs were unavailable. Fourth, vaccination may be associated with other protective factors that may be difficult to ascertain and account for fully. Additionally, although weekly swab adherence was high, it differed by vaccination status, which could lead to differential misclassification of the outcome; specifically, VE may be underestimated if vaccinated participants were more likely to have reported SARS-CoV-2 infections than unvaccinated participants. Fifth, limited sample sizes resulted in imprecise VE estimates and should be interpreted with caution, as the imprecision may indicate that the actual VE could be substantially different from the point estimates shown. Last, these observations were derived from 3 large prospective cohort studies from different geographic regions and, while internally valid, may not directly generalize to other settings; specifically, participants may have been more likely to be vaccinated and have access to health care.

This study also has many strengths, such as including >3300 participants enrolled from 4 distinct sites in the United States. Participants swabbed weekly, regardless of symptoms, which greatly reduced the risk of missing an asymptomatic SARS-CoV-2 infection. Furthermore, adherence to weekly swabbing was high (median, 85%). Weekly and quarterly surveys, as well as data from the state immunization information systems and EMRs, ensured detailed and complete information on potential confounding variables and vaccination status.

CONCLUSION

Findings from this study demonstrate that during an Omicron-predominant period, hybrid immunity provided the strongest protection against SARS-CoV-2 infection and symptomatic COVID-19. The bivalent COVID-19 vaccine also provided some protection. Protection from both were substantially lower ≥180 days following vaccination. Remaining up-to-date with recommended COVID-19 vaccinations and timing the receipt of vaccination shortly before peak respiratory virus season (presuming that SARS-CoV-2 circulation adopts this typical pattern) may reduce SARS-CoV-2 infections.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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