

Prevention and Attenuation of COVID-19 by BNT162b2 and mRNA-1273 Vaccines

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ABSTRACT

BACKGROUND: Information is limited on messenger RNA (mRNA) BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) COVID-19 vaccine effectiveness (VE) in preventing SARS-CoV-2 infection or attenuating disease when administered in real-world conditions.

METHODS: Prospective cohorts of 3,975 healthcare personnel, first responders, and other essential and frontline workers completed weekly SARS-CoV-2 testing during December 14 2020—April 10 2021. Self-collected mid-turbinate nasal swabs were tested by qualitative and quantitative reverse-transcription–polymerase-chain-reaction (RT-PCR). VE was calculated as $100\% \times (1 - \text{hazard ratio})$; adjusted VE was calculated using vaccination propensity weights and adjustments for site, occupation, and local virus circulation .

RESULTS: SARS-CoV-2 was detected in 204 (5.1%) participants; 16 were partially (≥ 14 days post-dose-1 to 13 days after dose-2) or fully (≥ 14 days post-dose-2) vaccinated, and 156 were unvaccinated; 32 with indeterminate status (< 14 days after dose-1) were excluded. Adjusted mRNA VE of full vaccination was 91% (95% confidence interval [CI]=76%–97%) against symptomatic or asymptomatic SARS-CoV-2 infection; VE of partial vaccination was 81% (95% CI=64%-90%). Among partially or fully vaccinated participants with SARS-CoV-2 infection, mean viral RNA load (Log_{10} copies/mL) was 40% lower (95% CI=16%-57%), the risk of self-reported febrile COVID-19 was 58% lower (Risk Ratio=0.42, 95% CI=0.18-0.98), and 2.3 fewer days (95% CI=0.8-3.7) were spent sick in bed compared to unvaccinated infected participants.

CONCLUSIONS: Authorized mRNA vaccines were highly effective among working-age adults in preventing SARS-CoV-2 infections when administered in real-world conditions and attenuated viral RNA load, febrile symptoms, and illness duration among those with breakthrough infection despite vaccination.

Messenger RNA (mRNA) BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) COVID-19 two-dose vaccines were highly effective in preventing symptomatic COVID-19 in randomized placebo-controlled Phase III efficacy trials ^{1,2}. Recently, we reported interim estimates of vaccine effectiveness (VE) in preventing symptomatic and asymptomatic SARS-CoV-2 infection that showed similar benefits for mRNA vaccines administered in real-world conditions ³. Less is known about the potentially important secondary benefits of mRNA COVID-19 vaccine, including reductions in severity of disease, viral RNA load, and duration of viral RNA detection.

Using prospective cohorts of healthcare personnel, first responders, and other essential and frontline workers in eight U.S. locations, this report had three aims. First, we estimated VE of partial and full mRNA vaccination in preventing SARS-CoV-2 infections, with adjustments for propensity to be vaccinated and local virus circulation. Second, among participants with laboratory-confirmed SARS-CoV-2 infection, we compared the viral RNA load of participants who were partially or fully vaccinated with those who were unvaccinated. Third, we compared the frequency of febrile symptoms and the duration of COVID-19 among infected participants who were partially or fully vaccinated versus unvaccinated infected participants.

METHODS

Study Population

HEROES-RECOVERⁱ is a network of prospective cohorts in eight locations (Phoenix, Tucson, and other areas in Arizona; Miami, Florida; Duluth, Minnesota; Portland, Oregon; Temple, Texas; and Salt Lake City, Utah) that initiated in July 2020 and share a common protocol, described previously and in [Supplementary Appendix Methods](#). To minimize potential selection biases, participants were invited to join the cohorts using a sampling strategy stratified by site, sex, age group, and occupation. The present analysis was conducted during December 14, 2020-April 10, 2021. All participants provided written consent and both the RECOVER and HEROES studies were reviewed and approved by the Institutional Review Boards at participating sites or under a reliance arrangement.ⁱⁱ

Measures

Socio-demographic and health characteristics were self-reported by electronic surveys at enrollment. Each month, participants reported potential SARS-CoV-2 exposure time and their

use of face masks and other employer recommended personal protective equipment (PPE) with four measures: hours of close contact (within 3 feet) of others at work (co-workers, customers, patients, or the public) in the past 7 days; percent time using PPE during those hours; hours of close contact with someone suspected or confirmed to have COVID-19 at work, home, or the community in the past 7 days; percent time using PPE during this contact.

Active surveillance for symptoms consistent with COVID-19–like illness (defined as fever, chills, cough, shortness of breath, sore throat, diarrhea, muscle aches, or change in smell or taste) occurred through weekly text messages, e-mails, and direct participant or medical record reports. When COVID-19–like illness was identified, participants self-reported the symptom onset date and completed electronic surveys at the beginning and end of illness to indicate symptoms, temperature, days sick in bed for at least half the day, receipt of medical care, and last day symptomatic or ill ([Supplementary Appendix Methods](#)). Febrile COVID-19–like illness was defined as fever, feverishness, chills, or measured temperature >38 degrees Celsius.

Laboratory Methods

Participants self-collected a mid-turbinate nasal swab weekly, regardless of COVID-19–like illness symptoms, and collected an additional nasal swab and saliva specimen at the onset of COVID-19–like illness. Supplies and instructions for participants were standardized across sites. Specimens were shipped weekdays on cold packs and were tested by reverse-transcription-polymerase chain reaction (RT-PCR) assay at Marshfield Clinic Laboratory (Marshfield, Wisconsin). Quantitative RT-PCR was conducted by the Wisconsin State Laboratory of Hygiene (Madison, Wisconsin). SARS-CoV-2 whole genome sequencing was conducted at CDC using previously published protocols⁴ for viruses detected among 22 participants who were ≥ 7 days post dose-1 at infection (through March 3, 2021) and 3-4 unvaccinated participants (71 total) location- and closest-date-matched, as available. Viral lineages were categorized as variants of concern, variants of interest, or other. We compare the percentage of variants of concern (excluding variants of interest) among participants who are at least partially vaccinated (≥ 14 -days post-dose-1) with those unvaccinated. Further details on laboratory methods are in [Supplementary Appendix Methods](#).

Vaccination Status

COVID-19 vaccination status was documented by self-report in electronic and telephone surveys and through direct upload of vaccination card images. Additionally, data from electronic medical records, occupational health records, or state immunization registries were reviewed at the Minnesota, Oregon, Texas, and Utah sites ([Supplementary_Appendix_Methods](#)).

Statistical Analysis

The primary outcome was time to RT-PCR confirmed SARS-CoV-2 infection in vaccinated versus unvaccinated participants. Secondary outcomes included viral RNA load, febrile illness, and illness duration. VE was estimated for full vaccination (≥ 14 -days after mRNA vaccine dose-2) and partial vaccination (≥ 14 -days post-dose-1 and up to 13-days post-dose-2). Days 1-13 following dose-1 were excluded because vaccination status was considered indeterminate.

Hazard ratios were estimated by the Andersen-Gill extension of the Cox proportional hazards model, which accounted for time-varying vaccination status. Unadjusted VE was calculated as $100\% \times (1 - \text{hazard ratio})$. An adjusted VE model accounted for potential confounding in vaccination status using an inverse propensity of treatment weighting (IPTW) approach ⁵.

Generalized boosted regression trees were used to estimate individual propensities to be at least partially vaccinated during each study week conditional on baseline socio-demographic and health characteristics and the most recent reports of virus exposure and PPE use (Table 1 and [Table_S2](#))⁶. Predicted propensities were then used to calculate stabilized IPTW weights. Cox models incorporated these stabilized weights as well as covariates for site and occupation and a daily indicator of local virus circulation (the percentage positive of all SARS-CoV-2 testing for local counties; [Figure_S1](#)). A sensitivity analysis removed person-days among participants with possible misclassification of vaccination or infection and at locations when local SARS-CoV-2 circulation fell below 3% as described in [Supplementary_Appendix_Methods](#).

Due to the relatively small number of breakthrough infections, for evaluation of possible vaccination attenuation effects, participants with RT-PCR-confirmed infections while partially or fully vaccinated were combined into a single vaccinated group and compared to participants who were unvaccinated when infected. The highest viral RNA load (Log_{10} copies/mL) measured during RT-PCR-confirmed infections were compared using a Poisson model adjusted for days from symptom onset to specimen collection and for days in transit to the laboratory.

Dichotomous outcomes were compared using binary log-logistic regression to calculate relative

risks RR). Comparisons of illness duration outcomes in days were made with Student's t-test assuming unequal variances. All analyses were conducted with SAS (version 9.4; SAS Institute) and R (version 4.0.2; R Foundation for Statistical Computing).

RESULTS

Participant Characteristics

After exclusion of 1,147 participants with laboratory documentation of SARS-CoV-2 infection before the start of the study period, the analytic sample consisted of 3,975 participants; CONSORT diagram is [Figure_S2](#). Approximately one-half of the participants (50.8%) were from the three Arizona study sites (Table 1). The majority of participants were female (62.0%), aged 18–49 years (71.6%), White (86.3%), and non-Hispanic (82.8%) and had no chronic medical conditions (68.6%). Participants included primary healthcare providers (20.4%), such as physicians and other clinical leads, nurses and other allied healthcare personnel (33.0%), first responders (20.6%), and other essential and frontline workers (26.1%). Over the 17-week study period, adherence to weekly surveillance reporting and specimen collection was high (median = 100%; interquartile range = 82%–100%).

COVID-19 Vaccination Status

Most (3,179/3,975, 80.0%) of the participants received at least one dose of an authorized mRNA COVID-19 vaccine by April 10, 2021 (Table 1); 2,686/3,179 (84.5%) received both recommended doses; vaccine products were 66.8% Pfizer-BioNTech, 32.7% Moderna, and 0.6% unspecified mRNA vaccine. Too few participants received Johnson & Johnson/Janssen COVID-19 vaccine (n=39) for comparison with mRNA vaccines, and therefore their person-time was censored at vaccination, and they contributed only unvaccinated person-time. Receipt of at least one vaccine dose was higher among participants in Minnesota or Oregon and participants who were female, aged ≥ 50 years, White, non-Hispanic, healthcare personnel, or had ≥ 1 chronic health condition. Mean hours of close contact with people suspected or confirmed to have COVID-19 was lower and the percentage of time using PPE was higher among vaccinated participants (Table 1). Associations with additional covariates included in the vaccination propensity model are presented in [Table_S2](#). Standardized mean differences between vaccinated and unvaccinated were well balanced after propensity weighting with a maximum difference of 0.09 ([Figure_S3](#)).

SARS-CoV-2 RT-PCR-confirmed Infections

SARS-CoV-2 infection was detected by RT-PCR in 204 (5.1%) participants, including 5 fully and 16 partially vaccinated, and 156 unvaccinated; 32 with indeterminate vaccination status (<14 days post-dose-1) were excluded. Of 93 genetically sequenced viruses, 10 were variants of concern (8 B.1.429, 1 B.1.1.7, 1 B.1.427) and 1 was a variant of interest (P.2) ([Table_S3](#)). Excluding 12 viruses among those with indeterminate vaccination, 10 viruses were detected among partially or fully vaccinated participants; of these, 3 (30.0%) were variants of concern (all B.1.429) compared to 7/70 (10.0%) among unvaccinated participants.

RT-PCR-confirmed infection was higher among participants in Arizona, Florida, and Texas or and those who were males, Hispanics, or first responders (Table 1); however, infection outcome did not differ by reported hours of potential virus exposure and PPE use. The majority of RT-PCR-confirmed infections had COVID-19–like illness symptoms before or within 1 day of specimen collection (74.0%) or within 2-14 days after collection (13.2%); the remainder had other symptoms (2.0%) or were asymptomatic within 14 days before and after specimen collection (10.8%). Only 26.0% of PCR-confirmed infections were medically attended, including two hospitalizations among unvaccinated participants; no deaths were reported.

mRNA COVID-19 Vaccine Effectiveness

During the 17-week study period, 3,975 participants contributed a median of 19 (Interquartile Range [IQR]=8-41) unvaccinated days per participant (127,971 total); 156 RT-PCR-confirmed SARS-CoV-2 infections were identified. While partially vaccinated, 3,001 participants contributed a median of 22 (IQR=21-28) days (81,168 total), during which 11 RT-PCR-confirmed infections were identified. While fully vaccinated, 2,510 participants contributed a median of 69 (IQR=53-81) days (161,613 total) during which 5 RT-PCR-confirmed infections were identified. Results of vaccination propensity weight calculations are shown in [Figure_S3](#). Estimated adjusted VE of full vaccination against RT-PCR confirmed infection was 91% (95% confidence interval [CI] = 76%–97%); VE of partial vaccination against RT-PCR confirmed infection was 81% (95% CI=64%–90%) (Table 2). Secondary VE estimates by mRNA vaccine product and age group are available in [Table 2](#). VE point estimates were unchanged in a sensitivity analysis that excluded periods of low local virus circulation ([Table_S4](#)).

Comparisons Between Partially or Fully Vaccinated and Unvaccinated RT-PCR-Confirmed SARS-CoV-2 Infected Participants

Characteristics of 16 participants who were partially or fully vaccinated at SARS-CoV-2 infection and 156 participants who were unvaccinated at the time of infection are listed in [Table_S5](#). The percentage infected while partially or fully vaccinated was higher among participants in Arizona, Minnesota, and Utah and among healthcare personnel; otherwise, there were no other differences by socio-demographic, health, virus exposure, or PPE use ([Table_S5](#)).

Vaccine Attenuation of Viral RNA Load

Mean viral RNA load measured for 155 participants was not associated with participant characteristics, except for somewhat lower viral RNA load among first responders ([Table_S6](#)). The mean viral RNA load (Log_{10} copies/mL) detected for SARS-CoV-2 infections was 3.8 among unvaccinated and 2.3 among partially or fully vaccinated participants; in an adjusted model, this represented 40.2% (95% CI=16.3%-57.3%) lower viral RNA load after at least partial vaccination (Table 3). Examining viral RNA only among those vaccinated, mean viral RNA load detected declined after receipt of dose-1 ([Figure_S4](#)).

The majority of infections among partially or fully vaccinated participants were detected for only a single week (75.0%), while the majority of infections among unvaccinated participants (72.4%) were detected for 2 or more consecutive weeks; this represents a 66% reduction in the relative risk of RT-PCR-detection for ≥ 2 consecutive weeks (Table 3).

Vaccine Attenuation of COVID-19–like Illness and Duration

Measures of COVID-19–like illness severity and duration were not associated with participant characteristics, with the exception of a lower mean of symptom duration at Texas and Utah and a lower percentage of febrile COVID-19–like illness at Florida and Utah sites ([Table_S6](#)). Among participants with RT-PCR-confirmed SARS-CoV-2 infections, only 25.0% of partially or fully vaccinated participants reported febrile COVID-19–like illness compared to 63.1% of unvaccinated participants; this represents a 58% reduction in the relative risk of febrile COVID-19–like illness following at least partial vaccination (Table 3). Vaccinated participants also reported 6.4 fewer (95% CI =0.4-12.3) total days ill or symptomatic and 2.3 fewer (95% CI=0.8-3.7) days sick in bed with COVID-19–like illness than unvaccinated participants.

DISCUSSION

In prospective cohorts of 3,975 healthcare personnel, first responders, and other essential and frontline workers followed over 17 weeks in eight U.S. locations, mRNA COVID-19 vaccines (Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273) were 91% (95% CI = 76%–97%) effective in preventing symptomatic and asymptomatic RT-PCR-confirmed SARS-CoV-2 infection; VE of partial vaccination was 81%. These estimates of VE in real-world conditions are consistent with findings from ^{1,2} and from a similar prospective study of healthcare personnel that also conducts routine SARS-CoV-2 testing ⁷.

Among small number of participants with breakthrough RT-PCR-confirmed SARS-CoV-2 infections despite vaccination, mRNA vaccines appeared to attenuate infection and disease in multiple ways. Specimens from participants who were partially or fully vaccinated at the time of infection had a 40% reduction in viral RNA detected and were less likely to be RT-PCR-positive for more than one week compared to infected, unvaccinated participants. The risk of infected individuals developing febrile COVID-19–like illness was 58% lower and illnesses were on average about 6 days shorter with 2 fewer days sick in bed among partially or fully vaccinated participants compared with unvaccinated participants. Reduced viral RNA presence following mRNA COVID-19 vaccination is consistent with another recent report⁸, and the combination of virologic and clinical effects we observed is consistent with previous findings of lower quantity and duration of viral RNA detection with milder COVID-19 ⁹.

The mechanisms by which COVID-19 vaccination elicits disease attenuation are largely unknown but are likely due to recall of immunologic memory responses that reduce viral replication and accelerate elimination of virally infected cells ¹⁰. The biologic plausibility of these benefits are supported by similar phenomena observed in other studies

^{10,11,12,13,14,15,16,17,18,19}. Our findings are also consistent with reports of lower symptom severity among those with moderate COVID-19 following vaccination with the Ad26.COV2.S COVID-19 vaccine compared to those who received placebo in a randomized controlled trial ²⁰.

Among this study's strengths are the focus on working-age adults without prior laboratory-documented SARS-CoV-2 infections, use of weekly testing for SARS-CoV-2 infection and illness with high surveillance adherence, multi-method documentation of vaccination status, and estimation of VE using vaccination propensity weighting, continuous local virus circulation

updates, potential virus exposure, and PPE use. The study's use of a standard synthetic RNA to conduct quantitative RT-PCR improves upon most prior studies that have relied upon cycle thresholds from real-time RT-PCR as a proxy for viral RNA load⁹.

This study also has at least seven limitations. First, although our estimate of 81% VE for partial vaccination is similar to other reports^{1,2,7,21,22}, this estimate is based on a relatively brief period of follow-up (median of 19 days partially vaccinated versus 69 days fully vaccinated per participant). Second, we may have overestimated VE if we disproportionately failed to detect infections among vaccinated participants due to vaccine attenuation of viral RNA load or reductions in RT-PCR sensitivity due to self-collection and shipping of specimens²³. Third, the study has not completed genetic sequencing for all viruses. Fourth, due to the relatively small number of breakthrough infections observed, we could not differentiate attenuation effects associated with partial versus full vaccination. Similarly, sparse data reduced the precision of estimates, though the consistency of trends across measures affirms the direction of the overall effect. Fifth, due to sparse data and limited racial and ethnic diversity, we were also unable to fully examine or adjust for potential confounders of vaccine attenuation effects. Nonetheless, we stratified our participant recruitment to ensure a combination of participant characteristics by occupation, age, and sex; we did not observe consistent associations between socio-demographic, health, virus exposure, or PPE use with either vaccination status, viral RNA load, or illness duration. Sixth, febrile symptoms and illness duration were measured using self-report, which can be subject to recall and confirmation biases. Yet, these findings are consistent with our virologic findings of reduced viral load and duration of detection. Finally, detection of viral RNA is not equivalent to isolation of infectious virus; however, lower RT-PCR cycle thresholds have been associated with the ability to isolate SARS-CoV-2 in culture⁹, and both viral quantity and duration of viral RNA detection are associated with infectivity and transmission in other viral infections^{19,24-26}.

If further data confirms that mRNA vaccination reduces the number of viral RNA particles and the duration of detection and this in turn blunts the infectivity of SARS-CoV-2, then mRNA vaccines are not only highly effective in preventing SARS-CoV-2 infection, but they may also mitigate the impact of breakthrough infections, which is especially important to essential and frontline workers given their potential to transmit the virus through frequent close contacts with patients, co-workers, and the public.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](https://www.nejm.org).

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Table 1. Characteristics of healthcare personnel (HCP), first responders, and other essential and frontline workers in prospective cohorts and percentage with RT-PCR-confirmed SARS-CoV-2 infections and percentage receiving ≥1 dose of messenger RNA COVID vaccine during the study period

	Unique Participants				SARS-CoV-2 RT-PCR-Negative				SARS-CoV-2 RT-PCR-Positive				Unvaccinated				Vaccinated with ≥1 Dose			
	N	(	Col. %	)	N	(	Row %	)	N	(	Row %	)	N	(	Row %	)	N	(	Row %	)
All participants [†]	3975				3771	(	94.9	)	204	(	5.1	)	796	(	20.0	)	3179	(	80.0	)
<u>Socio-demographic characteristics</u>																				
Cohort location ^{‡,§}																				
Phoenix, AZ	504	(	12.7	)	461	(	91	)	43	(	9	)	105	(	21	)	399	(	79	)
Tucson, AZ	1223	(	30.8	)	1148	(	94	)	75	(	6	)	274	(	22	)	949	(	78	)
Other, AZ	291	(	7.3	)	276	(	95	)	15	(	5	)	70	(	24	)	221	(	76	)
Miami, FL	239	(	6.0	)	216	(	90	)	23	(	10	)	111	(	46	)	128	(	54	)
Duluth, MN	456	(	11.5	)	445	(	98	)	11	(	2	)	32	(	7	)	424	(	93	)
Portland, OR	491	(	12.4	)	486	(	99	)	5	(	1	)	44	(	9	)	447	(	91	)
Temple, TX	302	(	7.6	)	284	(	94	)	18	(	6	)	66	(	22	)	236	(	78	)
Salt Lake City, UT	469	(	11.8	)	455	(	97	)	14	(	3	)	94	(	20	)	375	(	80	)
Sex																				
Female [□]	2464	(	62.0	)	2349	(	95	)	111	(	5	)	423	(	17	)	2037	(	83	)
Male	1511	(	38.0	)	1422	(	94	)	93	(	6	)	373	(	25	)	1142	(	75	)
Age (Years)																				
18-49	2847	(	71.6	)	2705	(	95	)	142	(	5	)	602	(	21	)	2245	(	79	)
≥50	1128	(	28.4	)	1066	(	95	)	62	(	5	)	194	(	17	)	934	(	83	)
Race																				
White	3431	(	86.3	)	3253	(	95	)	178	(	5	)	659	(	19	)	2772	(	81	)
Other	544	(	13.7	)	518	(	95	)	26	(	5	)	137	(	25	)	407	(	75	)
Ethnicity																				
Hispanic/Latinx	685	(	17.2	)	625	(	91	)	60	(	9	)	198	(	29	)	487	(	71	)
Other	3290	(	82.8	)	3146	(	96	)	144	(	4	)	598	(	18	)	2692	(	82	)
Occupation [¶]																				
Primary HCP	809	(	20.4	)	793	(	98	)	16	(	2	)	45	(	6	)	764	(	94	)
Nurses and other allied HCP	1310	(	33.0	)	1244	(	95	)	66	(	5	)	204	(	16	)	1106	(	84	)

First Responders	818	(	20.6	)	745	(	91	)	73	(	9	)	257	(	31	)	561	(	69	)
Essential and other frontline	1038	(	26.1	)	989	(	95	)	49	(	5	)	290	(	28	)	748	(	72	)
Chronic Condition																				
None**	2728	(	68.6	)	2589	(	95	)	139	(	5	)	582	(	21	)	2146	(	79	)
1 or more	1247	(	31.4	)	1182	(	95	)	65	(	5	)	214	(	17	)	1033	(	83	)
<u>Potential virus exposures and use of PPE, Median (IQR) of the Average from Monthly Updates per Participant</u> ^{††}																				
Hours within 3 feet of others at work	27	(	20.0-35.3	)	27	(	20.0-35.2	)	25	(	20.0-37.9	)	26	(	20.0-35.6	)	27	(	20.0-35.2	)
While in close contact at work, percent time using PPE ^{‡‡}	99	(	90.0-100.0	)	99	(	90.0-100.0	)	100	(	89.0-100.0	)	96	(	78.6-100.0	)	99	(	99.4-100.0	)
Hours within 3 feet of those suspected or confirmed to have COVID-19 at work, home, or community	8	(	2.2-24.0	)	8	(	2.2-24.0	)	6	(	2.0-23.2	)	10	(	3.1-26.7	)	7	(	2.0-23.4	)
For those in close contact with COVID-19, percent time using PPE ^{‡‡}	100	(	96.7-100.0	)	100	(	96.7-100.0	)	100	(	95.0-100.0	)	100	(	90.0-100.0	)	100	(	98.0-100.0	)

Abbreviations: Interquartile range (IQR), Healthcare personnel (HCP), COVID-19-like illness (CLI); Messenger RNA (mRNA); Personal protective equipment (PPE)

† Analytic sample excludes 1,147 participants with documented SARS-CoV-2 infection before enrollment or as part of surveillance.

§ Comparison of those who were vaccinated with at least one dose and those who were not, cohort locations for Portland, OR, Duluth, MN, Salt Lake City UT were combined compared to

□ For 15 participants missing biological sex, it was imputed as the more common category (female).

¶ Occupation categories: Primary HCP (physicians, physician assistants, nurse practitioners, dentists), Other allied HCP (nurses, therapists, technicians, medical assistants, orderlies and all others providing clinical support in inpatient or outpatient settings), first responders (FR; firefighters, law enforcement, corrections, emergency medical technicians), essential and frontline workers (EFW; workers in hospitality, delivery, and retail; teachers; all other occupations that require contact within 3 feet of the public, customers, or co-workers as a routine part of their job).

** For 77 participants, who did not respond to the self-report question, they were imputed as none, pending further verification.

†† Each month, participants were asked about close contacts and PPE use during the past 7 days. The mean of monthly responses during the study period were calculated.

‡‡ Only applicable for participants indicating a potential exposure during the past 7 days.

Table 2. Contributing participants, person-days, and the number of RT-PCR confirmed SARS-CoV-2 infections by vaccination status with estimates of messenger RNA (mRNA) vaccine effectiveness (VE) for partial and full vaccination in preventing infection among 3,975 healthcare personnel, first responders, and essential and frontline workers

	Contributing Participants [*]	Total Person- Days	Median (IQR) Days	SARS-CoV-2 Infections [*]	Unadjusted VE % (95% CI)	Adjusted VE [†] % (95% CI)
<u>mRNA COVID-19 vaccination status</u>						
Unvaccinated	3,964	127,971	19 (8 - 41)	156		
Partially vaccinated (≥14-days post dose-1 to day 13 post dose-2)	3,001	81,168	22 (21 - 28)	11	86 (74 - 93)	81 (64 - 90)
Fully vaccinated (≥14-days post dose-2)	2,510	161,613	69 (53 - 81)	5	92 (80 - 97)	91 (76 - 97)
<u>Pfizer-BioNTech</u>						
Unvaccinated	3,964	127,971	19 (8 - 41)	156		
Partially vaccinated (≥14-days post dose-1 to day 13 post dose-2)	2,005	49,516	21 (21 - 22)	8	85 (69 - 93)	80 (60 - 90)
Fully vaccinated (≥14-days post dose-2)	1,731	120,653	77 (64 - 82)	3	94 (82 - 98)	93 (78 - 98)
<u>Moderna</u>						
Unvaccinated	3,964	127,971	19 (8 - 41)	156		
Partially vaccinated (≥14-days post dose-1 to day 13 post dose-2)	982	31,231	28 (28 - 31)	3	88 (61 - 96)	83 (40 - 95)
Fully vaccinated (≥14-days post dose-2)	770	40,394	58 (44 - 66)	2	84 (31 - 96)	82 (20 - 96)
<u>Age < 50</u>						
Unvaccinated	2,838	90,768	18 (8 - 42)	107		
Partially vaccinated (≥14-days post dose-1 to day 13 post dose-2)	2,116	57,064	22 (21 - 28)	8	87 (72 - 94)	81 (59 - 91)
Fully vaccinated (≥14-days post dose-2)	1,760	114,676	72 (55 - 81)	4	91 (75 - 97)	90 (69 - 97)
<u>Age ≥ 50</u>						

Unvaccinated	1,126	37,203	21 (9 - 40)	49			
Partially vaccinated (≥ 14 -days post dose-1 to day 13 post dose-2)	885	24,104	22 (21 - 28)	3	84 (46 - 95)	78 (28 - 93)	
Fully vaccinated (≥ 14 -days post dose-2)	750	46,937	68 (50 - 80)	1	95 (59 - 99)	94 (51 - 99)	

Abbreviations: Messenger RNA (mRNA), Vaccine effectiveness (VE), Interquartile range (IQR)

* Contributing participants in vaccination categories do not equal the number of vaccination doses because participants must be in active surveillance and have met the vaccination criteria. Person-days during days 1-13 following dose-1 and the 32 associated RT-PCR-confirmed infections are excluded from this model because immunity was considered indeterminate.

† Adjusted VE is inversely weighted for propensity to be vaccinated with doubly robust adjustment for local virus circulation, study location, and occupation (Supplementary_Appendix_Methods)

Table 3. Comparisons between Unvaccinated and Partial or Fully mRNA Vaccine Vaccinated Participants with RT-PCR-Confirmed SARS-CoV-2 Infections in Viral RNA

	No.	Unvaccinated	No.	Partial or Fully Vaccinated	Comparison of Vaccinated versus Unvaccinated RT-PCR-Confirmed SARS-CoV-2 Infections
Mean Viral RNA Load, Log ₁₀ Copies/mL (SD) *	155 [†]	3.8 (1.7)	16	2.3 (1.7)	40.2% lower (95% CI = 16.3%-57.3%) [‡]
SARS-CoV-2 Detected by RT-PCR for ≥2 Consecutive Weeks, No. (%)	156	113 (72.4)	16	4 (25.0)	66% lower (RR = 0.34, 95% CI = 0.15-0.81)
Duration of Viral RNA Detection, Mean Days (SD)	155	8.9 (10.2)	16	2.7 (3.0)	6.2 fewer (95% CI =4.0-8.4) days
Febrile COVID-19 (vs. Afebrile or Asymptomatic), No. (%) ^{§□}	149	94 (63.1)	16	4 (25.0)	58% lower (RR = 0.42, 95% CI = 0.18-0.98)
Duration of Illness, Mean Days (SD) [□]	148	16.7 (15.7)	16	10.3 (10.3)	6.4 fewer (95% CI = 0.4-12.3) days
Days Sick in Bed, Mean Days (SD) ^{□ **}	147	3.8 (5.9)	15	1.5 (2.1)	2.3 fewer (95% CI = 0.8-3.7) days

Abbreviations: Standard deviation (SD); Relative risk (RR); Confidence interval (CI)

* Maximum viral load measured among all mid-turbinate nasal swabs collected for each RT-PCR-confirmed SARS-CoV-2 infection

[†] One specimen could not be tested due to insufficient volume

[‡] Poisson model adjusted for days from symptom onset to specimen collection and days of shipping to laboratory

[§] Febrile illness defined as self-reported fever, feverishness, chills, or measured temperature >38 degrees Celsius

[□] For illness indicators among unvaccinated participants, the denominator for febrile versus afebrile/asymptomatic excludes 7 participants with confirmed COVID-like illness (CLI) but who did not complete an illness survey to document symptoms (or 156-7=149); for illness duration, the same 7 participants do not have total illness duration due to the missing illness survey and an additional participant had an illness without resolution by 4/10/21 (or 149-1=148); for days sick in bed, one additional participant completed an illness survey but was missing an answer to this item (or 148-1=147)

** For illness indicators among vaccinated participants, 1 participant with confirmed CLI completed an illness survey but was missing an answer to days sick in bed (or 16-1=15)

ⁱ Arizona Healthcare, Emergency Response and Other Essential Workers Surveillance Study (HEROES); Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel (RECOVER).

ⁱⁱ See 45 C.F.R. part 46; 21 C.F.R. part 56