ORIGINAL ARTICLE

Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines

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ABSTRACT

BACKGROUND

Information is limited regarding the effectiveness of the two-dose messenger RNA (mRNA) vaccines BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) in preventing infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and in attenuating coronavirus disease 2019 (Covid-19) when administered in real-world conditions.

METHODS

We conducted a prospective cohort study involving 3975 health care personnel, first responders, and other essential and frontline workers. From December 14, 2020, to April 10, 2021, the participants completed weekly SARS-CoV-2 testing by providing mid-turbinate nasal swabs for qualitative and quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) analysis. The formula for calculating vaccine effectiveness was 100% × (1 − hazard ratio for SARS-CoV-2 infection in vaccinated vs. unvaccinated participants), with adjustments for the propensity to be vaccinated, study site, occupation, and local viral circulation.

RESULTS

SARS-CoV-2 was detected in 204 participants (5%), of whom 5 were fully vaccinated (≥14 days after dose 2), 11 partially vaccinated (≥14 days after dose 1 and <14 days after dose 2), and 156 unvaccinated; the 32 participants with indeterminate vaccination status (<14 days after dose 1) were excluded. Adjusted vaccine effectiveness was 91% (95% confidence interval [CI], 76 to 97) with full vaccination and 81% (95% CI, 64 to 90) with partial vaccination. Among participants with SARS-CoV-2 infection, the mean viral RNA load was 40% lower (95% CI, 16 to 57) in partially or fully vaccinated participants than in unvaccinated participants. In addition, the risk of febrile symptoms was 58% lower (relative risk, 0.42; 95% CI, 0.18 to 0.98) and the duration of illness was shorter, with 2.3 fewer days spent sick in bed (95% CI, 0.8 to 3.7).

CONCLUSIONS

Authorized mRNA vaccines were highly effective among working-age adults in preventing SARS-CoV-2 infection when administered in real-world conditions, and the vaccines attenuated the viral RNA load, risk of febrile symptoms, and duration of illness among those who had breakthrough infection despite vaccination. (Funded by the National Center for Immunization and Respiratory Diseases and the Centers for Disease Control and Prevention.)

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The two-dose messenger RNA (mRNA) vaccines BNT162b2 (Pfizer–BioNTech) and mRNA-1273 (Moderna) were shown to be highly effective in preventing symptomatic infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in randomized, placebo-controlled, phase 3 efficacy trials.[1,2] Recently, we reported interim estimates of the effectiveness of mRNA vaccines in preventing symptomatic and asymptomatic SARS-CoV-2 infection when administered in real-world conditions, which showed benefits similar to those observed in the efficacy trials.[3] Less is known about the potentially important secondary benefits of mRNA vaccines, including possible reductions in the severity of coronavirus disease 2019 (Covid-19), viral RNA load, and duration of viral RNA detection.

In conducting a prospective cohort study involving health care personnel, first responders, and other essential and frontline workers in six U.S. states, we had three aims. First, we estimated the effectiveness of mRNA vaccines in preventing SARS-CoV-2 infection with partial and full vaccination, with adjustments for the propensity to be vaccinated and local viral circulation. Second, among participants with laboratory-confirmed SARS-CoV-2 infection, we compared the mean viral RNA load in participants who were partially or fully vaccinated with the level in participants who were unvaccinated. Third, among participants with SARS-CoV-2 infection, we compared the frequency of febrile symptoms and the duration of illness in partially or fully vaccinated participants with those outcomes in unvaccinated participants.

Methods

Study Population

The HEROES-RECOVER network includes prospective cohorts from two studies: HEROES (the Arizona Healthcare, Emergency Response, and Other Essential Workers Surveillance Study) and RECOVER (Research on the Epidemiology of SARS-CoV-2 in Essential Response Personnel). The network was initiated in July 2020 and has a shared protocol, described previously and outlined in the Methods section of the Supplementary Appendix (available with the full text of this article at NEJM.org). Participants were enrolled in six U.S. states: Arizona (Phoenix, Tucson, and other areas), Florida (Miami), Minnesota (Duluth), Oregon (Portland), Texas (Temple), and Utah (Salt Lake City). To minimize potential selection biases, recruitment of participants was stratified according to site, sex, age group, and occupation. The data for this analysis were collected from December 14, 2020, to April 10, 2021. All participants provided written informed consent. The individual protocols for the RECOVER study and the HEROES study were reviewed and approved by the institutional review boards at participating sites or under a reliance agreement.

Participant-Reported Outcome Measures

Sociodemographic and health characteristics were reported by the participants in electronic surveys completed at enrollment. Each month, participants reported their potential exposure to SARS-CoV-2 and their use of face masks and other employer-recommended personal protective equipment (PPE) according to four measures: hours of close contact with (within 3 feet [1 m] of) others at work (coworkers, customers, patients, or the public) in the previous 7 days; the percentage of time using PPE during those hours of close contact at work; hours of close contact with someone suspected or confirmed to have Covid-19 at work, at home, or in the community in the previous 7 days; and the percentage of time using PPE during those hours of close contact with the virus.

Active surveillance for symptoms associated with Covid-19 — defined as fever, chills, cough, shortness of breath, sore throat, diarrhea, muscle aches, or a change in smell or taste — was conducted through weekly text messages, emails, and reports obtained directly from the participant or from medical records. When a Covid-19–like illness was identified, participants completed electronic surveys at the beginning and end of the illness to indicate the date of symptom onset, symptoms, temperatures, the number of days spent sick in bed for at least half the day, the receipt of medical care, and the last day of symptoms. Febrile symptoms associated with Covid-19 were defined as fever, feverishness, chills, or a measured temperature higher than 38°C.

Laboratory Methods

Participants provided a mid-turbinate nasal swab weekly, regardless of whether they had symptoms associated with Covid-19, and provided an additional nasal swab and saliva specimen at the onset of a Covid-19–like illness. Supplies and instructions for participants were standardized across sites. Specimens were shipped on weekdays

on cold packs and were tested by means of qualitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay at the Marshfield Clinic Research Institute (Marshfield, WI). Quantitative RT-PCR assays were conducted at the Wisconsin State Laboratory of Hygiene (Madison, WI). SARS-CoV-2 whole-genome sequencing was conducted at the Centers for Disease Control and Prevention, in accordance with previously published protocols,[4] for viruses detected in 22 participants who were infected at least 7 days after vaccine dose 1 (through March 3, 2021), as well as for viruses detected in 3 or 4 unvaccinated participants matched to each of those 22 participants in terms of site and testing date, as available (71 total matched participants). Viral lineages were categorized as variants of concern, variants of interest, or other. We compared the percentage of variants of concern (excluding variants of interest) in participants who were at least partially vaccinated (≥14 days after dose 1) with the percentage in participants who were unvaccinated.

VACCINATION STATUS

Covid-19 vaccination status was reported by the participants in electronic and telephone surveys and through direct upload of images of vaccination cards. In addition, data from electronic medical records, occupational health records, or state immunization registries were reviewed at the sites in Minnesota, Oregon, Texas, and Utah. At the time of specimen collection, participants were considered to be fully vaccinated (≥14 days after dose 2), partially vaccinated (≥14 days after dose 1 and <14 days after dose 2), or unvaccinated or to have indeterminate vaccination status (<14 days after dose 1).

STATISTICAL ANALYSIS

The primary outcome was the time to RT-PCR–confirmed SARS-CoV-2 infection in vaccinated participants as compared with unvaccinated participants. Secondary outcomes included the viral RNA load, frequency of febrile symptoms, and duration of illness among participants with SARS-CoV-2 infection.

The effectiveness of mRNA vaccines was estimated for full vaccination and partial vaccination. Participants with indeterminate vaccination status were excluded from the analysis. Hazard ratios for SARS-CoV-2 infection in vaccinated participants as compared with unvaccinated participants were estimated with the Andersen–Gill extension of the Cox proportional hazards model, which accounted for time-varying vaccination status. Unadjusted vaccine effectiveness was calculated with the following formula: 100% × (1 − hazard ratio). An adjusted vaccine effectiveness model accounted for potential confounding in vaccination status with the use of an inverse probability of treatment weighting approach.[5] Generalized boosted regression trees were used to estimate individual propensities to be at least partially vaccinated during each study week, on the basis of baseline sociodemographic and health characteristics and the most recent reports of potential virus exposure and PPE use (Table 1 and Table S2 in the Supplementary Appendix).[6] Predicted propensities were then used to calculate stabilized weights. Cox proportional hazards models incorporated these stabilized weights, as well as covariates for site, occupation, and a daily indicator of local viral circulation, which was the percentage positive of all SARS-CoV-2 tests performed in the local county (Fig. S1). A sensitivity analysis removed person-days when participants had possible misclassification of vaccination status or infection or when the local viral circulation fell below 3%.

Because there was a relatively small number of breakthrough infections, for the evaluation of possible attenuation effects of vaccination, participants with RT-PCR–confirmed SARS-CoV-2 infection who were partially vaccinated and those who were fully vaccinated were combined into a single vaccinated group, and results for this group were compared with results for participants with SARS-CoV-2 infection who were unvaccinated. Means for the highest viral RNA load measured during infection were compared with the use of a Poisson model adjusted for days from symptom onset to specimen collection and for days with the specimen in transit to the laboratory. Dichotomous outcomes were compared with the use of binary log-logistic regression for the calculation of relative risks. Means for the duration of illness were compared with the use of Student's t-test under the assumption of unequal variances. All analyses were conducted with SAS software, version 9.4 (SAS Institute), and R software, version 4.0.2 (R Foundation for Statistical Computing).

RESULTS

PARTICIPANT CHARACTERISTICS

After the exclusion of 1147 participants who had laboratory documentation of SARS-CoV-2 infection before the start of the study period, the study sample consisted of 3975 participants (Fig. S2). Approximately half the participants (51%) were from the three study sites in Arizona (Table 1). Most participants were female (62%), 18 to 49 years of age (72%), White (86%), and non-Hispanic (83%) and had no chronic medical conditions (69%). The participants included primary health care providers (20%), such as physicians and other clinical leads; nurses and other allied health care personnel (33%); first responders (21%); and other essential and frontline workers (26%). Over the 17-week study period, adherence to weekly surveillance reporting and specimen collection was high (median, 100%; interquartile range, 82 to 100).

VACCINATION

A total of 3179 participants (80%) had received at least one dose of an authorized mRNA vaccine by April 10, 2021 (Table 1), and 2686 of those participants (84%) had received both recommended doses. Of the vaccine products administered, 67% were the BNT162b2 vaccine, 33% were the mRNA-1273 vaccine, and less than 1% were an unspecified mRNA vaccine. Because only 39 participants received the Ad26.COV2.S vaccine (Johnson & Johnson–Janssen), results for those participants could not be compared with results for participants who received the mRNA vaccines; therefore, person-time for those 39 participants was censored at vaccination, and they contributed only person-time associated with unvaccinated status. Participants most likely to have received at least one vaccine dose were located in Minnesota or Oregon, female, 50 years of age or older, White, non-Hispanic, or health care personnel or had at least one chronic medical condition. The mean number of hours of close contact with someone 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-probability model are shown in Table S2. Standardized mean differences between vaccinated and unvaccinated participants for all covariates were well balanced after propensity weighting, with a maximum difference of 0.09 (Fig. S3).

SARS-COV-2 INFECTIONS CONFIRMED BY RT-PCR ASSAY

SARS-CoV-2 infection was detected by means of RT-PCR assay in 204 participants (5%), of whom 5 were fully vaccinated, 11 partially vaccinated, and 156 unvaccinated; the 32 participants with indeterminate vaccination status were excluded. Of the 93 genetically sequenced viruses, 12 were detected in participants with indeterminate vaccination status and were excluded. Of the remaining viruses, 10 were variants of concern (8 were the B.1.429 variant and 1 was the B.1.427 variant [epsilon] and 1 was the B.1.1.7 variant [alpha]); 1 was a variant of interest (the P.2 variant [zeta]) (Table S3). There were 10 genetically sequenced viruses detected in partially or fully vaccinated participants; 3 of these 10 viruses (30%) were variants of concern (all the B.1.429 variant [epsilon]), as compared with 7 of the 70 viruses (10%) detected in unvaccinated participants (excluding the variant of interest).

RT-PCR–confirmed SARS-CoV-2 infection was most frequently detected in participants who were located in Arizona, Florida, or Texas or were male, Hispanic, or a first responder (Table 1). However, the frequency of infection did not differ according to reported hours of potential virus exposure or PPE use. Most participants with RT-PCR–confirmed SARS-CoV-2 infection had symptoms associated with Covid-19 before or within 1 day after specimen collection (74%) or within 2 to 14 days after specimen collection (13%); the remainder had other symptoms (2%) or were asymptomatic within the 14 days before and after specimen collection (11%). Only 26% of the participants with RT-PCR–confirmed infection received medical care, including 3 unvaccinated participants who were hospitalized; no deaths were reported.

Characteristics of the 16 participants who were partially or fully vaccinated at the time of SARS-CoV-2 infection and the 156 participants who were unvaccinated at the time of infection are shown in Table S5. The percentage who were infected while partially or fully vaccinated was highest among participants in Arizona, Minnesota, and Utah and among health care personnel; there

Table 1. Characteristics of the Participants According to SARS-CoV-2 Test Results and Vaccination Status.*

Characteristic	Overall†	Results of RT-PCR Assay for SARS-CoV-2		Vaccination Status	
		Negative	Positive	Unvaccinated	Received ≥1 Dose of mRNA Vaccine
Total participants — no. (%)	3975 (100)	3771 (95)	204 (5)	796 (20)	3179 (80)
Cohort location — no. (%)‡					
Phoenix, AZ	504 (13)	461 (91)	43 (9)	105 (21)	399 (79)
Tucson, AZ	1223 (31)	1148 (94)	75 (6)	274 (22)	949 (78)
Other areas in Arizona	291 (7)	276 (95)	15 (5)	70 (24)	221 (76)
Miami, FL	239 (6)	216 (90)	23 (10)	111 (46)	128 (54)
Duluth, MN	456 (11)	445 (98)	11 (2)	32 (7)	424 (93)
Portland, OR	491 (12)	486 (99)	5 (1)	44 (9)	447 (91)
Temple, TX	302 (8)	284 (94)	18 (6)	66 (22)	236 (78)
Salt Lake City, UT	469 (12)	455 (97)	14 (3)	94 (20)	375 (80)
Sex — no. (%)§					
Female	2464 (62)	2349 (95)	111 (5)	423 (17)	2037 (83)
Male	1511 (38)	1422 (94)	93 (6)	373 (25)	1142 (76)
Age group — no. (%)					
18–49 yr	2847 (72)	2705 (95)	142 (5)	602 (21)	2245 (79)
≥50 yr	1128 (28)	1066 (95)	62 (5)	194 (17)	934 (83)
Race — no. (%)¶					
White	3431 (86)	3253 (95)	178 (5)	659 (19)	2772 (81)
Other	544 (14)	518 (95)	26 (5)	137 (25)	407 (75)
Ethnic group — no. (%)¶					
Hispanic	685 (17)	625 (91)	60 (9)	198 (29)	487 (71)
Non-Hispanic	3290 (83)	3146 (96)	144 (4)	598 (18)	2692 (82)
Occupation — no. (%)‖					
Primary health care provider	809 (20)	793 (98)	16 (2)	45 (6)	764 (94)
Nurse or other allied health care personnel	1310 (33)	1244 (95)	66 (5)	204 (16)	1106 (84)
First responder	818 (21)	745 (91)	73 (9)	257 (31)	561 (69)
Other essential or frontline worker	1038 (26)	989 (95)	49 (5)	290 (28)	748 (72)
Chronic conditions — no. (%)**					
None	2728 (69)	2589 (95)	139 (5)	582 (21)	2146 (79)
≥1	1247 (31)	1182 (95)	65 (5)	214 (17)	1033 (83)
Potential virus exposure and use of PPE — median (IQR) per participant					
Hours within 3 ft (1 m) of others at work in previous 7 days	27 (20–35)	27 (20–35)	25 (20–38)	26 (20–36)	27 (20–35)
Percentage of time using PPE among those reporting close contact at work	99 (90–100)	99 (90–100)	100 (89–100)	96 (79–100)	99 (99–100)
Hours within 3 ft of someone suspected or confirmed to have Covid-19 at work, at home, or in the community in previous 7 days	8 (2–24)	8 (2–24)	6 (2–23)	10 (3–27)	7 (2–23)
Percentage of time using PPE among those reporting close contact with the virus	100 (97–100)	100 (97–100)	100 (95–100)	100 (90–100)	100 (98–100)

Table 1. (Continued.)

* Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, IQR interquartile range, mRNA messenger RNA, RT-PCR reverse-transcriptase–polymerase-chain-reaction, PPE personal protective equipment, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

† The percentages in this column are based on the total number of participants in the study; all other percentages are based on the total number of participants with the given characteristic, which is provided in this column. The study sample excluded 1147 participants with laboratory documentation of SARS-CoV-2 infection before the start of the study period.

‡ The percentage of participants who received at least one dose of vaccine across sites with the highest observed vaccination rates (Portland, OR, Duluth, MN, and Salt Lake City, UT) was compared with the percentage across sites with the lowest observed vaccination rates (Phoenix, AZ, Tucson, AZ, other areas in Arizona, Miami, FL, and Temple, TX), with a chi-square value of 88.3 ($P<0.001$).

§ For the 15 participants with missing data regarding biologic sex, the data were imputed as the most common category (female).

¶ Race and ethnic group were reported by the participant.

‖ Primary health care providers included physicians, physician assistants, nurse practitioners, and dentists; allied health care personnel included nurses, therapists, technicians, medical assistants, orderlies, and all others providing clinical support in inpatient or outpatient settings; first responders included firefighters, law enforcement, corrections officers, and emergency medical technicians; and other essential and frontline workers included teachers and hospitality, delivery, and retail workers, as well as all other occupations that require routine close contact with the public, customers, or coworkers.

** For the 77 participants who did not provide a response, the data were imputed as none, pending further verification.

were no substantial differences according to other sociodemographic or health characteristics or according to potential virus exposure or PPE use.

EFFECTIVENESS OF MRNA VACCINES AGAINST SARS-COV-2 INFECTION

During the 17-week study period, a total of 3964 participants contributed a median of 19 unvaccinated days per participant (interquartile range, 8 to 41; total days, 127,971), during which 156 RT-PCR–confirmed SARS-CoV-2 infections were identified. A total of 3001 participants contributed a median of 22 partially vaccinated days (interquartile range, 21 to 28; total days, 81,168), during which 11 RT-PCR–confirmed infections were identified. A total of 2510 participants contributed a median of 69 fully vaccinated days (interquartile range, 53 to 81; total days, 161,613), during which 5 RT-PCR–confirmed infections were identified. Results of vaccination-propensity weight calculations are shown in Figure S3.

Estimated adjusted vaccine effectiveness against RT-PCR–confirmed SARS-CoV-2 infection was 91% (95% confidence interval [CI], 76 to 97) with full vaccination and 81% (95% CI, 64 to 90) with partial vaccination (Table 2). Estimates of vaccine effectiveness according to mRNA vaccine product and age group are shown in Table 2. Point estimates of vaccine effectiveness were unchanged in a sensitivity analysis that excluded periods of low local viral circulation (Table S4).

ATTENUATION OF VIRAL RNA LOAD WITH VACCINATION

There were no substantial associations between the mean viral RNA load and participant characteristics, except for a somewhat lower viral RNA load among first responders (Table S6). The mean viral RNA load was 3.8 $\log_{10}$ copies per microliter among unvaccinated participants and 2.3 $\log_{10}$ copies per microliter among partially or fully vaccinated participants; in an adjusted model, the viral RNA load was 40% lower (95% CI, 16.3 to 57.3) with at least partial vaccination than with no vaccination (Table 3). Among vaccinated participants, the mean viral RNA load decreased after receipt of dose 1 (Fig. S4). Viral RNA was detected for only 1 week in most partially or fully vaccinated participants (75%) and was detected for more than 1 week in most unvaccinated participants (72%); the risk of viral RNA detection for more than 1 week was 66% lower with at least partial vaccination (Table 3).

ATTENUATION OF FEBRILE SYMPTOMS AND DURATION OF ILLNESS WITH VACCINATION

There were no substantial associations between measures of the severity and duration of Covid-19 and participant characteristics, except for a lower mean duration of illness among participants located in Texas and Utah and a lower frequency of febrile symptoms among participants located in Florida and Utah (Table S6). Among participants with RT-PCR–confirmed SARS-CoV-2 infection, only 25% of those who were partially or fully vaccinated reported febrile symptoms, as compared with 63% of those who were unvaccinated; the risk of febrile symptoms was 58% lower with at least partial vaccination (Table 3). Vaccinated participants also reported 6.4 fewer total days of symptoms (95% CI, 0.4 to 12.3) and 2.3 fewer

Table 2. Effectiveness of mRNA Vaccines in Preventing SARS-CoV-2 Infection with Full and Partial Vaccination.*

Characteristic and Vaccination Status	Contributing Participants†	Person-Days		SARS-CoV-2 Infections	Vaccine Effectiveness‡	
					Unadjusted	Adjusted
	no.	*total no.*	*median (IQR)*	*no.*	*percent (95% CI)*	
Overall						
Unvaccinated	3964	127,971	19 (8–41)	156	—	—
Partially vaccinated	3001	81,168	22 (21–28)	11	86 (74–93)	81 (64–90)
Fully vaccinated	2510	161,613	69 (53–81)	5	92 (80–97)	91 (76–97)
mRNA vaccine product						
BNT162b2 vaccine						
Unvaccinated	3964	127,971	19 (8–41)	156	—	—
Partially vaccinated	2005	49,516	21 (21–22)	8	85 (69–93)	80 (60–90)
Fully vaccinated	1731	120,653	77 (64–82)	3	94 (82–98)	93 (78–98)
mRNA-1273 vaccine						
Unvaccinated	3964	127,971	19 (8–41)	156	—	—
Partially vaccinated	982	31,231	28 (28–31)	3	88 (61–96)	83 (40–95)
Fully vaccinated	770	40,394	58 (44–66)	2	84 (31–96)	82 (20–96)
Age group						
<50 yr						
Unvaccinated	2838	90,768	18 (8–42)	107	—	—
Partially vaccinated	2116	57,064	22 (21–28)	8	87 (72–94)	81 (59–91)
Fully vaccinated	1760	114,676	72 (55–81)	4	91 (75–97)	90 (69–97)
≥50 yr						
Unvaccinated	1126	37,203	21 (9–40)	49	—	—
Partially vaccinated	885	24,104	22 (21–28)	3	84 (46–95)	78 (28–93)
Fully vaccinated	750	46,937	68 (50–80)	1	95 (59–99)	94 (51–99)

* At the time of specimen collection, participants were considered to be fully vaccinated (≥14 days after dose 2), partially vaccinated (≥14 days after dose 1 and <14 days after dose 2), or unvaccinated or to have indeterminate vaccination status (<14 days after dose 1). The 32 participants with SARS-CoV-2 infection who had indeterminate vaccination status were excluded, as were all person-days associated with indeterminate vaccination status.

† The number of contributing participants does not equal the total number of participants in the study because contributing participants were required to be in active surveillance and to have met the vaccination criteria.

‡ Vaccine effectiveness was calculated with the following formula: 100% × (1 − hazard ratio for SARS-CoV-2 infection in vaccinated vs. unvaccinated participants). Adjusted vaccine effectiveness was inversely weighted for the propensity to be vaccinated, with doubly robust adjustment for local viral circulation, site, and occupation.

days spent sick in bed with Covid-19 (95% CI, 0.8 to 3.7) than unvaccinated participants.

DISCUSSION

In a prospective cohort study involving 3975 health care personnel, first responders, and other essential and frontline workers followed over 17 weeks in six U.S. states, the effectiveness of the mRNA vaccines BNT162b2 and mRNA-1273 in preventing symptomatic and asymptomatic RT-PCR–confirmed SARS-CoV-2 infection was 91% (95% CI, 76 to 97) with full vaccination; vaccine effectiveness was 81% with partial vaccination. These estimates of vaccine effectiveness in real-world conditions are consistent with findings from efficacy trials[1,2] and from a similar prospective study involving health care personnel in which routine SARS-CoV-2 testing was also conducted.[7]

Table 3. Viral RNA Load, Duration of Viral RNA Detection, Frequency of Febrile Symptoms, and Duration of Illness in Vaccinated and Unvaccinated Participants with SARS-CoV-2 Infection.*

Variable	Unvaccinated	Partially or Fully Vaccinated	Difference (95% CI)
Viral RNA load			
No. assessed	155	16	—
Mean — $\log_{10}$ copies/μl†	3.8±1.7	2.3±1.7	40.2 (16.3–57.3)‡
Duration of viral RNA detection			
No. assessed	155	16	—
Mean — days	8.9±10.2	2.7±3.0	6.2 (4.0–8.4)
Detection of viral RNA for >1 week — no./total no. (%)	113/156 (72.4)	4/16 (25.0)	0.34 (0.15–0.81)§
Febrile symptoms — no./total no. (%)¶	94/149 (63.1)	4/16 (25.0)	0.42 (0.18–0.98)‖
Total days of symptoms			
No. assessed	148	16	—
Mean — days	16.7±15.7	10.3±10.3	6.4 (0.4–12.3)
Days spent sick in bed			
No. assessed	147	15	—
Mean — days	3.8±5.9	1.5±2.1	2.3 (0.8–3.7)

* Plus–minus values are means ±SD. The following unvaccinated participants were excluded from the total number assessed: 1 participant for viral RNA load and duration of viral RNA detection (the specimen could not be tested because of insufficient volume), 7 for febrile symptoms (they did not complete an illness survey to document symptoms), 8 for total days of symptoms (7 did not complete an illness survey and 1 had an illness that had not resolved by April 10, 2021), and 9 for days spent sick in bed (7 did not complete an illness survey, 1 had an illness that had not resolved by April 10, 2021, and 1 did not provide a response on the illness survey). In addition, 1 vaccinated participant was excluded from the total number assessed for days spent sick in bed (that person did not provide a response on the illness survey).

† Means were based on the maximum viral load measured among all mid-turbinate nasal swabs from each participant with RT-PCR–confirmed SARS-CoV-2 infection and were compared with the use of a Poisson model adjusted for days from symptom onset to specimen collection and days with the specimen in transit to the laboratory.

‡ The value is a relative difference (percent).

§ The value is a relative risk, indicating 66% lower risk in vaccinated participants.

¶ Febrile symptoms were defined as fever, feverishness, chills, or a measured temperature higher than 38°C.

‖ The value is a relative risk, indicating 58% lower risk in vaccinated participants.

Among the small number of participants with breakthrough RT-PCR–confirmed SARS-CoV-2 infection despite vaccination, the mRNA vaccines appeared to attenuate infection and disease in multiple ways. Participants who were partially or fully vaccinated at the time of infection had a 40% lower viral RNA load and a 66% lower risk of viral RNA detection for more than 1 week than participants who were unvaccinated at infection. Partially or fully vaccinated participants also had a 58% lower risk of febrile symptoms and a shorter duration of illness, with approximately 6 fewer days of symptoms and 2 fewer days spent sick in bed, than unvaccinated participants. The observed presence of a reduced viral RNA load after the administration of mRNA vaccines is consistent with findings in a recent report,[8] and the observed combination of virologic and clinical effects is consistent with previous findings of a lower level and shorter duration of viral RNA detection with milder Covid-19.[9]

The mechanisms by which vaccination attenuates Covid-19 are largely unknown, but the effect is probably due to recall of immunologic memory responses that reduce viral replication and accelerate the elimination of virally infected cells.[10] The biologic plausibility of these benefits is supported by the observation of similar phenomena in studies of other vaccines.[10-19] Our findings are also consistent with reports of less severe symptoms in patients with moderate Covid-19 who received the Ad26.COV2.S vaccine

than in those who received placebo in a randomized, controlled trial.[20]

Strengths of this study include the focus on working-age adults without previous laboratory-documented SARS-CoV-2 infection, the use of weekly testing for SARS-CoV-2 infection and illness with high adherence to surveillance, the multimethod documentation of vaccination status, and the estimation of vaccine effectiveness with vaccination-propensity weighting, continuous updates regarding local viral circulation, and reports of potential virus exposure and PPE use. The use of a standard synthetic RNA to conduct quantitative RT-PCR assays improves on the methods used in many previous studies, which relied on cycle thresholds from real-time RT-PCR assays as a proxy for viral RNA loads.[9]

This study also has several limitations. First, although our estimate of 81% vaccine effectiveness with partial vaccination is similar to results provided in other reports,[1,2,7,21,22] this estimate is based on a relatively brief follow-up period (with a median of 22 partially vaccinated days, as compared with 69 fully vaccinated days, per participant). Second, we could have overestimated vaccine effectiveness if we disproportionately failed to detect infections among vaccinated participants because of attenuation of viral RNA load after vaccination or because of reductions in the sensitivity of RT-PCR assays associated with specimen collection by participants and shipping of specimens.[23] Third, we have not completed genetic sequencing for all viruses. Fourth, because there was a relatively small number of breakthrough infections, we could not differentiate attenuation effects associated with partial vaccination from effects associated with full vaccination. Similarly, sparse data reduced the precision of estimates, although the consistency of trends across measures affirms the direction of the overall effect. Fifth, because of the sparse data and limited racial and ethnic diversity among participants, we were 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 according to occupation, age, and sex; we did not observe consistent associations of sociodemographic or health characteristics or reported virus exposure or PPE use with vaccination status, viral RNA load, or duration of illness. Sixth, results for febrile symptoms and duration of illness were based on participant-reported data, which can be subject to recall and confirmation biases. Yet, the findings for these measures were consistent with the virologic findings of a reduced viral RNA load and duration of viral RNA detection among vaccinated participants. Finally, the detection of viral RNA is not equivalent to isolation of an infectious virus; however, low cycle thresholds on RT-PCR assay have been associated with the ability to isolate SARS-CoV-2 in culture,[9] and both the level and the duration of viral RNA detection are associated with infectivity and transmission in other viral infections.[19,24-26]

If further data confirm that the administration of mRNA vaccines reduces the number of viral RNA particles and the duration of viral RNA detection, thereby blunting the infectivity of SARS-CoV-2, then the overall results support that mRNA vaccines not only are highly effective in preventing SARS-CoV-2 infection but also may mitigate the effects of breakthrough infections — a finding that is especially important to essential and frontline workers, given their potential to transmit the virus through frequent close contact with patients, coworkers, and the public.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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APPENDIX

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