ORIGINAL ARTICLE

Effectiveness of mRNA Covid-19 Vaccine among U.S. Health Care Personnel

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ABSTRACT

BACKGROUND

The prioritization of U.S. health care personnel for early receipt of messenger RNA (mRNA) vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), allowed for the evaluation of the effectiveness of these new vaccines in a real-world setting.

METHODS

We conducted a test-negative case–control study involving health care personnel across 25 U.S. states. Cases were defined on the basis of a positive polymerase-chain-reaction (PCR) or antigen-based test for SARS-CoV-2 and at least one Covid-19–like symptom. Controls were defined on the basis of a negative PCR test for SARS-CoV-2, regardless of symptoms, and were matched to cases according to the week of the test date and site. Using conditional logistic regression with adjustment for age, race and ethnic group, underlying conditions, and exposures to persons with Covid-19, we estimated vaccine effectiveness for partial vaccination (assessed 14 days after receipt of the first dose through 6 days after receipt of the second dose) and complete vaccination (assessed ≥7 days after receipt of the second dose).

RESULTS

The study included 1482 case participants and 3449 control participants. Vaccine effectiveness for partial vaccination was 77.6% (95% confidence interval [CI], 70.9 to 82.7) with the BNT162b2 vaccine (Pfizer–BioNTech) and 88.9% (95% CI, 78.7 to 94.2) with the mRNA-1273 vaccine (Moderna); for complete vaccination, vaccine effectiveness was 88.8% (95% CI, 84.6 to 91.8) and 96.3% (95% CI, 91.3 to 98.4), respectively. Vaccine effectiveness was similar in subgroups defined according to age (<50 years or ≥50 years), race and ethnic group, presence of underlying conditions, and level of patient contact. Estimates of vaccine effectiveness were lower during weeks 9 through 14 than during weeks 3 through 8 after receipt of the second dose, but confidence intervals overlapped widely.

CONCLUSIONS

The BNT162b2 and mRNA-1273 vaccines were highly effective under real-world conditions in preventing symptomatic Covid-19 in health care personnel, including those at risk for severe Covid-19 and those in racial and ethnic groups that have been disproportionately affected by the pandemic. (Funded by the Centers for Disease Control and Prevention.)

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HEALTH CARE PERSONNEL ARE AT increased risk for exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), through interactions in the workplace related to care and proximity to patients, in addition to household and community interactions.[1] In December 2020, two messenger RNA (mRNA) vaccines, the BNT162b2 vaccine from Pfizer–BioNTech and the mRNA-1273 vaccine from Moderna, were approved by the Food and Drug Administration under Emergency Use Authorization for use among persons 16 years of age or older (for the BNT162b2 vaccine) or among those 18 years or older (for the mRNA-1273 vaccine).[2-4] The U.S. Advisory Committee on Immunization Practices recommended the prioritization of health care personnel during early-phase distribution of these vaccines[5] to ensure that critical services were maintained and that the spread of infection in health care settings was reduced.[5] Vaccination of health care personnel in the United States was initiated in December 2020, and by early March 2021, more than half the frontline health care personnel in the United States had been vaccinated with Covid-19 vaccines.[6]

Phase 3 clinical trials showed the safety and efficacy of the mRNA vaccines,[7,8] and early data from observational studies[9-11] have supported the clinical trial results. Real-world data on vaccine effectiveness are useful for building on evidence from clinical trials and continuing to inform Covid-19 vaccine policy. The randomized, controlled trials were not powered to evaluate efficacy among persons with chronic illness or among those in racial and ethnic minority groups that have been disproportionately affected by Covid-19.

To evaluate the effectiveness of mRNA vaccines in preventing Covid-19 among health care personnel in the United States, we conducted a multisite, test-negative case–control study involving health care personnel who had been tested for SARS-CoV-2. The interim results of this study showing the effectiveness of the receipt of either mRNA vaccine have been published previously.[12] Here, we report the full study results with the extended enrollment through May 2021. We evaluated effectiveness according to vaccine product for partial and complete vaccination and in subgroups defined according to age, race and ethnic group, presence of underlying conditions, estimated level of patient contact, and the time from receipt of two vaccine doses.

METHODS

STUDY POPULATION

Our study population included health care personnel who had been tested for SARS-CoV-2. Participants were enrolled from December 28, 2020 (2 weeks after the introduction of a Covid-19 vaccine), through May 19, 2021, at 33 sites across 25 U.S. states, representing more than 500,000 health care personnel (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The majority (68%) of the participating facilities were acute care hospitals (with or without affiliated outpatient and urgent care clinics), and 32% were long-term care facilities. Covid-19 vaccines were introduced at the participating facilities in December 2020, and the vaccine coverage among health care personnel at these facilities reached 55 to 98% for the receipt of at least one dose of vaccine and 51 to 94% for the receipt of two vaccine doses during the study period.

The study protocol was reviewed by the Centers for Disease Control and Prevention and the institutional review board at each participating medical center and was conducted in accordance with federal laws and institutional policies. The authors vouch for the accuracy and completeness of the data reported and for the fidelity of the study to the protocol.

STUDY DESIGN

We conducted a test-negative case–control study involving health care personnel, a group that comprised all paid and unpaid health care personnel with the potential for direct exposure to patients or the potential for indirect exposure to infectious materials at the workplace.[13] Testing for SARS-CoV-2 was based on occupational health practices at each facility and was leveraged to identify cases and controls for this study. Case participants were defined as health care personnel who had at least one Covid-19–like symptom and a positive result for SARS-CoV-2 on polymerase-chain-reaction (PCR) testing, other nucleic acid amplification testing, or antigen-based testing.[14] The index test date (date that the specimen was obtained) for cases was the first SARS-CoV-2–positive test for the episode of Covid-19–

like illness for which case participants were enrolled. The illness was defined as symptomatic if the participant had at least one of the following symptoms present within 14 days before or after the index test date: fever (a body temperature documented at ≥38°C or subjective fever), chills, cough (dry or productive), shortness of breath, chest pain or tightness, fatigue or malaise, sore throat, headache, runny nose, congestion, muscle aches, nausea or vomiting, diarrhea, abdominal pain, altered sense of smell or taste, loss of appetite, or red or bruised toes or feet.

Persons who tested negative on PCR or other laboratory-based nucleic acid amplification testing, regardless of symptoms, were eligible for inclusion as controls. Control participants were matched to case participants according to site of enrollment and week of test date. Within any given week and study site, any participants who tested positive for SARS-CoV-2 (cases) and those who tested negative (controls) and agreed to complete a survey or to be interviewed were matched, with a target ratio of three controls per case. Persons with previous infection, defined as a positive SARS-CoV-2 test (on PCR or antigen testing) that had occurred more than 60 days before the index test date, were excluded.

Information on the participants' demographic characteristics, symptoms of Covid-19–like illness, underlying conditions and risk factors associated with severe Covid-19,[15] and medical care received was collected by means of interviews or participant-completed surveys. The interviews and surveys also included information on potential confounders related to workplace and community behaviors. Medical records were reviewed in order to collect information about the SARS-CoV-2 test, including the date, test type, and result, and about the medical care sought during the Covid-19–like illness. Information on Covid-19 vaccination dates and products received was obtained from occupational health clinics, vaccine cards, state registries, or medical records.

VACCINATION STATUS

Vaccination status of the participants was determined at the time of their SARS-CoV-2 test date. Participants were considered to be unvaccinated if they had not received any dose of Covid-19 vaccine as of the test date. We defined the interval from days 0 through 13 after receipt of the first dose as the time before effectiveness from a single dose is expected. We further stratified this interval to evaluate for a potential early effect of the first dose by measuring vaccine effectiveness at 0 to 9 days and at 10 to 13 days after receipt of the first dose, on the basis of the cutoff when vaccine effectiveness after the first dose was measured both in this study and in clinical trials.[1,7]

The effectiveness of a single vaccine dose was measured from 14 days after receipt of the first dose through 6 days after receipt of the second dose (partially vaccinated). We conducted a sensitivity analysis to evaluate the effectiveness of a single vaccine dose before receipt of the second dose to exclude potential early effects after receipt of the second dose. In an additional sensitivity analysis that evaluated the potential influence of vaccine-related reactions leading to the testing of health care personnel, we excluded participants who had been tested within 0 to 2 days after receipt of the second dose. The effectiveness of two doses of vaccine was measured at 7 days or more after receipt of the second dose (complete vaccination), which was consistent with the Pfizer–BioNTech clinical trial.[7] In a sensitivity analysis, we also evaluated the effectiveness of two doses of vaccine at 14 days or more after receipt of the second dose, which was consistent with the Moderna trial.[8]

STATISTICAL ANALYSIS

We used conditional logistic regression to estimate vaccine effectiveness as 1 minus the matched odds ratio (×100%) for partial vaccination or complete vaccination as compared with no vaccination. We evaluated the influence of age, race and ethnic group, presence of underlying medical conditions or risk factors for severe Covid-19, and other factors related to community and workplace behaviors, such as the use of personal protective equipment and receipt of influenza vaccine during the current respiratory season, as potential confounders for vaccine effectiveness by including each variable with vaccination status in the model and then retaining variables that resulted in a change of more than 10% in the model estimate for vaccination status.

In the final model, we adjusted for age, race and ethnic group, presence of at least one underlying condition or risk factor for severe Covid-19, and close contact with patients with Covid-19 in the workplace or with persons with Covid-19

outside the workplace. We evaluated vaccine effectiveness according to vaccine product and in subgroups defined according to participants' age (<50 years or ≥50 years), race and ethnic group, presence of underlying conditions, health care job categories, and clinical case definitions that were consistent with those used in the clinical trials. We examined the adjusted vaccine effectiveness according to 2-week intervals of follow-up after receipt of the second dose (as compared with unvaccinated participants) to assess for waning of vaccine effect. All the statistical analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

CHARACTERISTICS OF HEALTH CARE PERSONNEL

During the study period of December 28, 2020, through May 19, 2021, a total of 109,865 health care personnel were tested across the participating sites; of these persons, 8365 (7.6%) tested positive for SARS-CoV-2. A total of 1482 participants with a positive test and at least one Covid-19–like symptom (cases) and 3449 with a negative test (controls) were enrolled. Among the enrolled health care personnel, 69% worked at acute care hospitals (including emergency departments), 31% in outpatient or specialty clinics, 1% in urgent care clinics, and 1% in long-term care facilities.

The characteristics of the enrolled participants are shown in Tables 1 and 2. More than three quarters of the participants (76% of the cases and 75% of the controls) reported having at least one underlying condition associated with an increased risk of severe Covid-19, and no differences were noted in the distribution of individual conditions or risk factors between cases and controls, with the exception of obesity (more common among case participants) and asthma (more common among control participants) (Table S2). We identified 62 cases among pregnant women; the median gestational age at the time of the index test date was 23 weeks (range, 3 to 41). The most common underlying conditions were obesity (in 36% of the case participants and in 31% of the control participants), overweight (in 29% and 28%, respectively), asthma (in 14% and 18%), and hypertension (in 15% and 14%). Only 2% of case participants were hospitalized during their illness; 1% of control participants

were hospitalized during a non–Covid-19–related illness. No deaths were reported among the participants included in this study.

A total of 45% of the case participants and 74% of the control participants had received at least one dose of Covid-19 vaccine at any time before the test date. Among vaccinated participants, 78% of the cases and 79% of the controls had received the BNT162b2 vaccine; 21% and 20%, respectively, had received the mRNA-1273 vaccine. The remaining participants had received the ChAdOx1 nCoV-19 vaccine from AstraZeneca (in 2 cases and 1 control) or the Ad26.COV2.S vaccine from Johnson & Johnson (in 8 cases and 28 controls) and were excluded from the analyses of vaccine effectiveness. A higher proportion of control participants than case participants had received one vaccine dose at least 14 days before their test date and had received two doses at least 7 days before their test date.

We identified 167 cases among completely vaccinated participants and 140 cases among partially vaccinated participants (Table 3). The characteristics of the completely and partially vaccinated case participants and the unvaccinated case participants are shown in Table S3. Among completely vaccinated case participants, the median length of time after receipt of the second dose to the index test date was 41 days (range, 7 to 165); the median interval between the two doses was 21 days (range, 17 to 42) for the BNT162b2 vaccine and 28 days (range, 24 to 32) for the mRNA-1273 vaccine. The proportion of participants who had severe symptoms or were hospitalized was higher among unvaccinated case participants than among partially or completely vaccinated case participants.

VACCINE EFFECTIVENESS

For the period of 0 to 9 days after receipt of the first dose, the vaccine effectiveness was 12.8% (95% confidence interval [CI], −9.4 to 30.5). Vaccine effectiveness at 10 to 13 days after receipt of the first dose was 36.8% (95% CI, 14.8 to 53.1). The adjusted effectiveness for partial vaccination with any vaccine was 79.7% (95% CI, 74.1 to 84.1) and was similar with both the BNT162b2 vaccine (77.6%; 95% CI, 70.9 to 82.7) and the mRNA-1273 vaccine (88.9%; 95% CI, 78.7 to 94.2) (Table 3). Results of sensitivity analyses for partial vaccination were similar when effectiveness was measured before receipt of the

Table 1. Demographic Characteristics of Health Care Personnel Who Tested Positive for SARS-CoV-2 and Had One or More Symptoms of Covid-19–like Illness (Case Participants) and Those Who Tested Negative (Control Participants) at 33 U.S. Sites, January to May 2021.*

Characteristic	Case Participants (N = 1482)	Control Participants (N = 3449)	Standardized Difference†
Age			
Median (range) — yr	37 (18–69)	37 (18–78)	0.0831
Distribution — no. (%)			
18–49 yr	1134 (77)	2590 (75)	0.0333
50–64 yr	318 (21)	743 (22)	0.0021
≥65 yr	17 (1)	80 (2)	0.0899
Missing data	13 (1)	36 (1)	0.0171
Sex — no. (%)			
Male	250 (17)	574 (17)	0.0061
Female	1222 (82)	2863 (83)	0.0146
Other	10 (1)	12 (<1)	0.0458
Race and ethnic group — no. (%)‡			
White, non-Hispanic	980 (66)	2502 (73)	0.1395
Black, non-Hispanic	188 (13)	259 (8)	0.1724
Hispanic or Latino	160 (11)	284 (8)	0.0874
Asian or Pacific Islander, non-Hispanic	84 (6)	269 (8)	0.0851
American Indian or Alaska Native, non-Hispanic	34 (2)	47 (1)	0.0696
Multiple or other, non-Hispanic	17 (1)	38 (1)	0.0043
Unknown	19 (1)	50 (1)	0.0144
Educational level — no. (%)			
High school or less	107 (7)	125 (4)	0.1593
Undergraduate or technical degree	1029 (69)	1923 (56)	0.2855
Graduate or professional degree	335 (23)	1383 (40)	0.3840
Unknown	11 (1)	18 (1)	0.0278
Health insurance — no. (%)			
Private	1255 (85)	2733 (79)	0.1419
Government	82 (6)	162 (5)	0.0380
None	19 (1)	20 (1)	0.0732
Unknown	126 (9)	534 (15)	0.2161

* Percentages may not total 100 because of rounding. Covid-19 denotes coronavirus disease 2019, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† The standardized difference shows the difference in means in units of the pooled standard deviation (Section E in the Supplementary Appendix).
‡ Race and ethnic group were reported by participants.

second dose (74.0%; 95% CI, 66.1 to 80.1) and when the analyses excluded the period of 0 to 2 days after receipt of the second dose (76.3%; 95% CI, 69.6 to 81.5). The adjusted effectiveness for complete vaccination was 90.4% (95% CI, 87.0 to 92.9) and was similar with either of the two mRNA vaccines; effectiveness that was as-sessed at 14 days or more after receipt of the second dose also showed similar results (88.9%; 95% CI, 84.7 to 92.0).

Sensitivity analyses that excluded asymptom-atic controls resulted in estimates of vaccine ef-fectiveness for partial vaccination of 82.1% (95% CI, 76.6 to 86.3) and for complete vaccination of

Table 2. Workplace and Community Behaviors of Health Care Personnel Who Tested Positive for SARS-CoV-2 and Had One or More Symptoms of Covid-19–like Illness (Case Participants) and Those Who Tested Negative (Control Participants).

Variable	Case Participants (N = 1482)	Control Participants (N = 3449)	Standardized Difference*
Anticipated level of patient contact, assessed on the basis of job category — no. (%)†			
Substantial direct patient contact	918 (62)	2227 (65)	0.0545
Moderate direct patient contact	168 (11)	394 (11)	0.0028
Minimal direct patient contact	340 (23)	702 (20)	0.0629
Undefined patient contact	56 (4)	126 (4)	0.0066
Community behaviors 14 days before symptom-onset date or test date — no. (%)			
Had close contact with a person with Covid-19 outside the health care setting‡	665 (45)	638 (18)	0.5911
Had close contact with any ill person outside a health care facility‡	518 (35)	731 (21)	0.3098
Attended a gathering that included persons other than household members	390 (26)	753 (22)	0.1050
Used public or shared transportation	225 (15)	650 (19)	0.0976
Attended or worked at a school or day care	72 (5)	201 (6)	0.0431
Had a household member who attended school or day care	367 (25)	998 (29)	0.0942
Workplace behaviors			
Had close contact with a person with Covid-19 who was not a patient — no. (%)	250 (17)	624 (18)	0.0322
Had close contact with a patient with Covid-19 during work in health care facility — no. (%)	479 (32)	1142 (33)	0.0168
Used personal protective equipment appropriately — no./total no. (%)§¶	206/479 (43)	519/1142 (45)	0.0326
Participated in aerosol-generating procedures for patients with Covid-19 — no./total no. (%)§‖	180/479 (38)	434/1142 (38)	0.0133
Had exposure to patients with Covid-19 who were not intubated or wearing face coverings — no./total no. (%)§			
All or most of the time	129/479 (27)	308/1142 (27)	0.0080
Sometimes	60/479 (13)	170/1142 (15)	0.0425
Rarely or never	83/479 (17)	250/1142 (22)	0.0672
Not sure	207/479 (43)	414/1142 (36)	0.0585
Reason for SARS-CoV-2 test — no. (%)**			
Occupational exposure in the workplace	192 (13)	493 (14)	0.0390
Exposure outside the workplace	327 (22)	449 (13)	0.2396
Routine screening, with no symptoms	63 (4)	541 (16)	0.3888
Presence of symptoms	1182 (80)	2229 (65)	0.3426
Other**	14 (1)	97 (3)	0.1379
Reported previous positive result of serologic test during study interview — no. (%)	17 (1)	14 (<1)	0.0845

* The standardized difference shows the difference in means in units of the pooled standard deviation (Section E in the Supplementary Appendix).

† Job categories that were associated with anticipated substantial direct patient contact included the following: physician, physician assistant, nurse practitioner, registered nurse, licensed practical nurse, other nurse, certified nursing assistant, patient care technician or assistant, medical assistant, coronavirus disease 2019 (Covid-19) tester, phlebotomist, home health personnel, emergency medical services provider, physical therapist or assistant, rehabilitation aide, occupational therapist, speech–language pathologist, respiratory therapist, radiology technician, dental health care provider, and surgical, medical, or emergency technician. Job categories that were associated with anticipated moderate direct patient contact included the following: environmental services personnel, food services personnel, patient transport personnel, nonphysician behavioral health provider, chaplain, care coordinator, translator, health educator, genetic counselor, dietitian, and research personnel. Job categories that were associated with minimal patient contact included the following: administrative or ward clerk, symptom checker, telehealth trainer, facilities maintenance equipment and sterile technician, medical equipment salesperson, laboratory personnel, and pharmacist. Undefined patient contact included other health care personnel who could not be classified into any of the above categories and those with missing information.

‡ Close contact was defined as being within approximately 6 ft (approximately 2 m) of a person with Covid-19 for at least 15 minutes or having unprotected direct contact with potentially infectious secretions or excretions.

§ This measure was assessed among participants who reported close contact with patients with Covid-19 during work.

¶ Appropriate use of personal protective equipment during care for patients with Covid-19 was defined as the wearing of an N95 mask or powered air-purifying respirator, gown, gloves, and face shield or goggles at all times.

‖ Aerosol-generating procedures were defined as follows: airway suctioning, breaking the ventilation circuit (intentionally or unintentionally), bronchoscopy, chest physiotherapy, cardiopulmonary resuscitation, high-flow oxygen delivery (whether by nasal cannula or mask), high-frequency oscillatory ventilation, intubation, mini–bronchoalveolar lavage, manual (bag) ventilation, nebulizer treatments, noninvasive positive-pressure ventilation (e.g., bilevel positive airway pressure or continuous positive airway pressure), sputum induction, and other procedures that might result in the generation of aerosols.

** Reasons for testing are not mutually exclusive. Other reasons for testing included screening before or after travel, testing because of symptoms after receipt of a Covid-19 vaccine, or not specified.

Table 3. Estimated Effectiveness of mRNA Vaccines among Health Care Personnel, According to Covid-19 Vaccination Status among Case and Control Participants.*

Variable	Case Participants (N=1472)	Control Participants (N=3420)	Vaccine Effectiveness (95% CI)	
			Unadjusted Analysis	Adjusted Analysis†
	number (percent)		*percent*	
Receipt of any Covid-19 vaccine				
One dose <10 days before test date	249 (17)	375 (11)	25.0 (7.3 to 39.3)	12.8 (−9.4 to 30.5)
One dose 10–13 days before test date	104 (7)	220 (6)	44.1 (26.2 to 57.7)	36.8 (14.8 to 53.1)
Partial vaccination	140 (10)	863 (25)	81.3 (76.5 to 85.1)	79.7 (74.1 to 84.1)
Complete vaccination	167 (11)	1072 (31)	90.2 (87.0 to 92.6)	90.4 (87.0 to 92.9)
BNT162b2 vaccine				
Partial vaccination	122 (8)	707 (21)	79.4 (73.7 to 83.9)	77.6 (70.9 to 82.7)
Complete vaccination	149 (10)	882 (26)	88.9 (85.1 to 91.7)	88.8 (84.6 to 91.8)
mRNA-1273 vaccine				
Partial vaccination	18 (1)	156 (5)	89.8 (81.1 to 94.4)	88.9 (78.7 to 94.2)
Complete vaccination	18 (1)	190 (6)	95.7 (90.4 to 98.0)	96.3 (91.3 to 98.4)

* Effectiveness of the messenger RNA (mRNA) vaccines was calculated as 1 minus the matched odds ratio (×100%) for partial or complete vaccination, as compared with no vaccination, and was estimated with the use of a conditional logistic-regression model with accounting for matching according to site of enrollment and week of test date. Vaccine effectiveness for all categories was estimated with the use of unvaccinated participants as a reference group. For partial vaccination, the effectiveness of a single dose was assessed during the interval from 14 days after receipt of the first dose through 6 days after receipt of the second dose. For complete vaccination, the effectiveness of two doses was assessed at least 7 days after receipt of the second dose (consistent with the Pfizer–BioNTech clinical trial[7]). CI denotes confidence interval.

† The odds ratio was adjusted for age, race and ethnic group, presence of underlying conditions, and close contact with patients with Covid-19 in the workplace or persons with Covid-19 outside the workplace.

90.9% (95% CI, 87.2 to 93.5), results that were similar to those of the primary analysis. The exclusion of case and control participants who reported positive serologic (antibody) test results during the interview did not change the vaccine effectiveness for partial vaccination (79.7%; 95% CI, 74.1 to 84.1) or complete vaccination (90.5%; 95% CI, 87.1 to 93.0).

We evaluated vaccine effectiveness according to subgroup and according to clinical case definition (Tables 4 and S4). The adjusted effectiveness for partial vaccination or complete vaccination was similar in subgroups defined according to age (<50 years and ≥50 years), race and ethnic group, presence of underlying conditions, and level of patient contact. Owing to the limited number of pregnant participants, vaccine effectiveness was estimated in a subgroup that included both partially and completely vaccinated participants (77.1%; 95% CI, 32.2 to 92.2). In a combined group of partially and completely vaccinated participants with immunocompromis-

ing conditions, vaccine effectiveness was 39.1% (95% CI, −45.0 to 74.4).

To evaluate evidence of waning of vaccine effect, we estimated effectiveness every 2 weeks during the 14 total weeks of follow-up available immediately after receipt of the second dose (Fig. 1). The point estimate of vaccine effectiveness, assessed in 2-week intervals, was highest during weeks 3 and 4 after receipt of the second dose (96.3%; 95% CI, 92.5 to 98.2). The point estimates were lower during weeks 9 through 14, but the 95% confidence intervals were wide and overlapping.

DISCUSSION

In this multisite, test-negative case–control study, we found that both the BNT162b2 and mRNA-1273 vaccines were highly effective against symptomatic Covid-19 among health care personnel. The effectiveness estimates were similar across racial and ethnic groups, among persons with under-

lying conditions and risk factors associated with an increased risk of severe Covid-19, and in subgroups defined according to various levels of patient contact, including substantial direct contact with patients. Our results showed that the effectiveness of a two-dose regimen with the BNT162b2

vaccine was 89% and that with the mRNA-1273 vaccine was 96%, findings that are consistent with efficacy results from phase 3 trials.[7,8]

Evidence from postintroduction effectiveness studies has been accruing rapidly. These studies have shown that in a real-world setting, both of

Table 4. Estimated Effectiveness of mRNA Vaccines among Health Care Personnel in Subgroups Defined According to Risk Factors, Age Group, and Race and Ethnic Group.*

Variable	Case Participants (N=1472)	Control Participants (N=3420)	Vaccine Effectiveness (95% CI)	
			Unadjusted Analysis	Adjusted Analysis†
	no./total no. (%)		*percent*	
Risk factors				
Underlying condition or risk factor that increases risk of severe Covid-19‡				
≥1 Underlying condition or risk factor				
Partial vaccination	110/1126 (10)	627/2561 (24)	79.3 (73.2 to 84.0)	76.4 (69.0 to 82.0)
Complete vaccination	118/1126 (10)	784/2561 (31)	90.1 (85.8 to 92.7)	90.3 (86.4 to 93.0)
≥2 Underlying conditions or risk factors				
Partial vaccination	69/697 (10)	409/1639 (25)	81.1 (72.7 to 85.5)	76.7 (67.4 to 83.3)
Complete vaccination	80/697 (11)	500/1639 (31)	88.8 (84.0 to 92.2)	88.5 (83.2 to 92.2)
≥3 Underlying conditions or risk factors				
Partial vaccination	43/407 (11)	235/944 (25)	79.6 (69.5 to 86.4)	76.1 (63.4 to 84.3)
Complete vaccination	50/407 (12)	298/944 (32)	89.5 (83.7 to 93.3)	89.4 (83.1 to 93.4)
No underlying condition or risk factor				
Partial vaccination	30/346 (9)	236/859 (27)	87.0 (79.4 to 91.8)	87.5 (79.7 to 92.3)
Complete vaccination	49/346 (14)	288/859 (34)	91.0 (85.8 to 94.3)	91.1 (85.5 to 94.6)
Any immunocompromising condition, assessed for partial and complete vaccination§¶	23/64 (36)	58/124 (47)	52.4 (−6.4 to 78.7)	39.1 (−45.0 to 74.4)
Obesity‖				
Partial vaccination	47/529 (9)	254/1068 (24)	81.6 (72.9 to 87.5)	80.2 (70.3 to 86.8)
Complete vaccination	49/529 (9)	321/1068 (30)	91.2 (86.6 to 94.2)	92.1 (87.6 to 95.0)
Obesity or overweight‖				
Partial vaccination	97/954 (10)	490/2022 (24)	78.2 (71.2 to 83.5)	76.5 (68.4 to 82.5)
Complete vaccination	93/954 (10)	633/2022 (31)	90.7 (87.0 to 93.4)	91.0 (87.0 to 93.7)
Hypertension				
Partial vaccination	17/215 (8)	120/485 (25)	85.8 (74.1 to 92.2)	83.1 (68.1 to 91.0)
Complete vaccination	22/215 (10)	148/485 (31)	91.3 (83.7 to 95.3)	91.8 (83.9 to 95.8)
Asthma				
Partial vaccination	20/207 (10)	155/616 (25)	81.8 (67.6 to 89.7)	77.8 (59.5 to 87.8)
Complete vaccination	21/207 (10)	175/616 (28)	90.7 (82.8 to 94.9)	90.5 (81.9 to 95.0)
Diabetes				
Partial vaccination	4/69 (6)	42/159 (26)	89.0 (64.9 to 96.5)	85.5 (52.3 to 95.6)
Complete vaccination	10/69 (14)	42/159 (26)	79.2 (48.2 to 91.7)	80.2 (45.8 to 92.7)
Pregnancy, assessed for partial and complete vaccination¶	6/62 (10)	28/91 (31)	83.8 (54.5 to 94.2)	77.1 (32.2 to 92.2)

Table 4. (Continued.)

Variable	Case Participants (N = 1472)	Control Participants (N = 3420)	Vaccine Effectiveness (95% CI)	
			Unadjusted Analysis	Adjusted Analysis†
	no./total no. (%)		*percent*	
Age				
<50 yr				
Partial vaccination	106/1128 (9)	644/2568 (25)	81.5 (76.1 to 85.7)	80.3 (74.2 to 85.0)
Complete vaccination	130/1128 (12)	810/2568 (32)	90.2 (86.6 to 92.7)	90.3 (86.5 to 93.0)
≥50 yr				
Partial vaccination	34/331 (10)	205/816 (25)	78.6 (66.1 to 86.5)	77.0 (62.7 to 85.8)
Complete vaccination	36/331 (11)	256/816 (31)	89.0 (82.0 to 93.3)	90.7 (84.2 to 94.6)
Race and ethnic group				
White, non-Hispanic				
Partial vaccination	103/973 (11)	641/2478 (26)	79.7 (73.4 to 84.5)	79.3 (72.5 to 84.4)
Complete vaccination	127/973 (13)	815/2478 (33)	89.5 (85.5 to 92.3)	90.1 (86.2 to 93.0)
Black, non-Hispanic				
Partial vaccination	7/188 (4)	40/259 (15)	85.3 (64.9 to 93.9)	85.7 (64.7 to 94.2)
Complete vaccination	6/188 (3)	44/259 (17)	94.4 (82.7 to 98.2)	94.8 (83.3 to 98.4)
Hispanic or Latino				
Partial vaccination	12/157 (8)	69/281 (25)	81.3 (61.1 to 91.0)	81.6 (60.5 to 91.5)
Complete vaccination	16/157 (10)	74/281 (26)	86.4 (73.1 to 93.1)	89.4 (78.0 to 94.9)
Asian or Pacific Islander, non-Hispanic				
Partial vaccination	9/84 (11)	74/268 (28)	80.5 (54.3 to 91.7)	79.6 (50.4 to 91.6)
Complete vaccination	11/84 (13)	99/268 (37)	90.3 (77.4 to 95.9)	89.3 (74.2 to 95.6)
American Indian or Alaska Native, non-Hispanic				
Partial vaccination	5/34 (15)	13/47 (28)	78.3 (5.8 to 95.0)	75.9 (−7.7 to 94.6)
Complete vaccination	6/34 (18)	1/47 (2)	91.0 (57.3 to 98.1)	93.7 (69.4 to 98.7)

* Vaccine effectiveness was calculated as 1 minus the matched odds ratio (×100%) for partial or complete vaccination, as compared with no vaccination, and was estimated with the use of a conditional logistic-regression model with accounting for matching according to site of enrollment and week of test date. The reference group in the analysis of effectiveness in all categories was the group of unvaccinated participants. For partial vaccination, the effectiveness of a single dose was assessed during the interval from 14 days after receipt of the first dose through 6 days after receipt of the second dose. For complete vaccination, the effectiveness of two doses was assessed at least 7 days after the receipt of the second dose (consistent with the Pfizer–BioNTech clinical trial[7]).

† The odds ratio was adjusted for age, race and ethnic group, presence of underlying conditions, and close contact with patients with Covid-19 in the workplace or persons with Covid-19 outside the workplace.

‡ We defined conditions as being associated with a definite or potential increased risk of severe Covid-19 according to the definitions of the Centers for Disease Control and Prevention (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html).

§ Immunocompromising conditions included receipt of immunosuppressive medication (e.g., glucocorticoids, chemotherapy, or other immunosuppressive medication), solid-organ transplantation, hematopoietic stem-cell transplantation, human immunodeficiency virus infection, or active cancer (current cancer or treatment for cancer or receipt of diagnosis in the preceding 12 months).
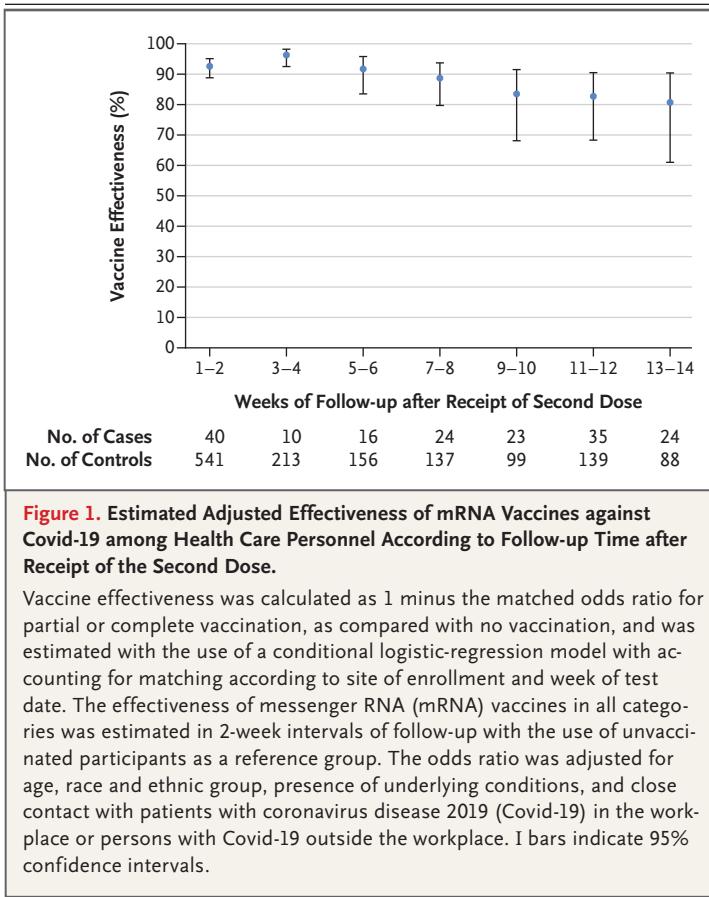
¶ The sample size was limited for the evaluation of effectiveness according to vaccination status. Therefore, vaccine effectiveness was assessed in the interval from at least 14 days after receipt of the first dose through the receipt of the second dose or later.

‖ Obesity was defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher, and overweight as a BMI of 25 to 29.

these mRNA vaccines work well, and the effectiveness of these vaccines among persons who are completely vaccinated is consistent across observational studies involving different populations[16,17] and using different study designs[9,18,19] and case definitions.[20,21]

Although Covid-19 vaccines have been recommended for adults with chronic medical condi-

Figure 1. Estimated Adjusted Effectiveness of mRNA Vaccines against Covid-19 among Health Care Personnel According to Follow-up Time after Receipt of the Second Dose.

Vaccine effectiveness was calculated as 1 minus the matched odds ratio for partial or complete vaccination, as compared with no vaccination, and was estimated with the use of a conditional logistic-regression model with accounting for matching according to site of enrollment and week of test date. The effectiveness of messenger RNA (mRNA) vaccines in all categories was estimated in 2-week intervals of follow-up with the use of unvaccinated participants as a reference group. The odds ratio was adjusted for age, race and ethnic group, presence of underlying conditions, and close contact with patients with coronavirus disease 2019 (Covid-19) in the workplace or persons with Covid-19 outside the workplace. I bars indicate 95% confidence intervals.

tions,[22] little has been known about the effectiveness of vaccines among adults with individual risk factors for severe outcomes of Covid-19.[15] Phase 3 trials showed vaccine efficacy in a group of adults with at least one at-risk condition,[7,8] and few observational studies[9,23] to date have been powered to evaluate effectiveness among persons with specific underlying conditions. Our study results showed that complete vaccination with mRNA vaccines was effective in adults with more than one risk factor for severe Covid-19; in adults with obesity, hypertension, asthma, or diabetes; and in adults 50 years of age or older. Among health care personnel with immunocompromising conditions, the estimated vaccine effectiveness was low and had confidence intervals that included the null value; these results are consistent with recent studies showing a poor immune response to mRNA vaccines in immunocompromised persons.[24,25]

Our study showed that mRNA vaccines were effective in pregnant women who were com-

pletely or partially vaccinated; the effectiveness among completely vaccinated pregnant women is probably higher than the estimate in our study. Older persons, those with chronic medical conditions, and pregnant women have been recognized during this pandemic as groups at increased risk for severe outcomes of Covid-19,[26] and the availability of highly effective vaccines has the potential of reducing mortality and the incidence of hospitalization associated with Covid-19 in these populations.

The effectiveness of partial vaccination, estimated in this study at 78% with the BNT162b2 vaccine and at 89% with the mRNA-1273 vaccine, was higher than the estimates from the respective phase 3 trials.[7,8] Although 90% and 94% of the case participants who were included in this study would meet the case definitions of the Pfizer–BioNTech and Moderna phase 3 trials, respectively, our study population was younger (76% of the participants were <50 years of age) and the proportion of participants with chronic underlying conditions was lower than those in the trial populations.[7,8] In addition, when the efficacy data for a single dose of the BNT162b2 vaccine were reanalyzed with restriction to cases that occurred at least 14 days after receipt of the first dose (instead of at ≥0 days after receipt of the first dose, as in the initial trial analysis), the efficacy was measured at 92.6%.[27] Several cohort studies involving health care personnel have shown effectiveness estimates of partial vaccination with two mRNA vaccines that are consistent with our findings.[19,28-33] The high effectiveness of partial vaccination in our study should be interpreted with caution owing to the short window of risk after the receipt of a single dose, given that overall adherence to the recommended administration interval was high (i.e., 21 days for the BNT162b2 vaccine and 28 days for the mRNA-1273 vaccine).[34]

The effectiveness estimates in our study and in other studies were based on a relatively short follow-up; it is unknown how long this level of protection from either vaccine will last, especially among persons with immunocompromising conditions or among older persons. In this relatively young population of health care personnel, we did not find strong evidence of decreasing effectiveness during the 14 weeks of observation after receipt of the second dose. Although effectiveness estimates during weeks 9 through 14

were lower than the maximum vaccine effectiveness that was observed during weeks 3 and 4, wide and overlapping confidence intervals do not support a conclusion of waning immunity but do warrant longer-term monitoring of vaccine effects.

The findings of this study are subject to limitations. First, the testing of health care personnel for SARS-CoV-2 was based on occupational health practices at each facility. Although participating sites did not report any changes in routine testing practices after the introduction of vaccines, if vaccinated health care personnel were less likely to seek testing than those who were unvaccinated, the vaccine effectiveness could be underestimated. Alternatively, if post-vaccination systemic reactions led to vaccinated health care personnel being more likely to seek testing, vaccine effectiveness could be overestimated. A sensitivity analysis that excluded the time window when most postvaccination reactions are expected to occur (0 to 2 days after receipt of the second dose) resulted in estimates of vaccine effectiveness similar to those in the primary analysis. Second, although the study excluded health care personnel with a known history of acute SARS-CoV-2 infection, persons with unknown previous infection could not be excluded. A sensitivity analysis that excluded participants who reported having a positive result for SARS-CoV-2 on serologic testing resulted in estimates of vaccine effectiveness similar to those in the primary analysis, although the number of participants reporting positive serologic tests was small.

Strengths of the study include its large sample size, which allowed for adjustment of confounding and for estimation of vaccine effectiveness in various subgroups of health care personnel, and broad geographic coverage representing the U.S. population. Although we controlled for potential confounders by carefully selecting factors that are common causes of exposure and SARS-CoV-2 infection and, in the final model, selecting from those on the basis of a "change in estimate" approach, there are limitations to this method.[35] We had small sample sizes in subgroups of participants with selected underlying conditions, and it will be useful to investigate the reproducibility of these results in future studies. Studies focusing on persons with immunocompromising conditions are needed to understand how well Covid-19 vaccines work in these groups of persons at high risk for severe outcomes of Covid-19. Studies with longer follow-up are necessary for understanding the long-term duration of vaccine effect.

Our study showed that vaccination with either the BNT162b2 or mRNA-1273 vaccine was highly effective in preventing symptomatic Covid-19, a finding that is consistent with the results of phase 3 trials.[7,8] Our study also provided additional support to the evidence accruing from observational studies. In this population of health care personnel, vaccine effectiveness was similar among persons with underlying medical conditions or other risk factors for severe Covid-19, including pregnancy; in different subgroups of health care personnel defined according to job category; and in racial and ethnic groups that have been disproportionately affected by the pandemic. The long-term duration of protection and the effectiveness of these vaccines against emerging variants is unknown and should be monitored to indicate whether changes to vaccine composition or vaccine policy are needed.

APPENDIX

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