CORRESPONDENCE

Protection with a Third Dose of mRNA Vaccine against SARS-CoV-2 Variants in Frontline Workers

TO THE EDITOR: Data are needed regarding the effectiveness of a third dose of a messenger RNA (mRNA) vaccine against the B.1.1.529 (omicron) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that are based on scientifically rigorous, population-level surveillance. Health care personnel, first responders, and other essential and frontline workers who are being evaluated in the HEROES-RECOVER cohorts at eight sites in six states across the United States underwent weekly reverse-transcriptase–polymerase-chain-reaction (RT-PCR) testing regardless of the presence or absence of coronavirus disease 2019 (Covid-19) symptoms.[1-3] Here, we report the vaccine effectiveness of two or three doses of an mRNA vaccine against infection caused by the omicron and B.1.617.2 (delta) variants.

Methods for the HEROES-RECOVER studies have been published previously (with details provided in the Supplementary Appendix, available with the full text of this letter at NEJM.org).[1-3] Vaccination was documented by the workers through vaccine cards and medical records or state immunization information systems. Cohort participants could have received three doses of the BNT162b2 vaccine (Pfizer–BioNTech) (administered in 74%), the mRNA-1273 vaccine (Moderna) (in 24%), or a combination of the two vaccines (in 2%); recipients of the Ad26.COV2.S vaccine (Johnson & Johnson–Janssen) were excluded from the analysis.

The study period began on August 26, 2021, shortly after the Food and Drug Administration recommended that recipients of the initial two-dose mRNA vaccination series receive a third (booster) dose. Hazard ratios were estimated with the use of the Andersen–Gill extension of the Cox proportional-hazards model that accounts for time-varying vaccination status. We adjusted the estimates of vaccine effectiveness using inverse-propensity weighting. We performed SARS-CoV-2 whole-genome sequencing using published protocols. The study was reviewed and approved by the institutional review board at each participating study site or under reliance agreements.

From the initiation of the study until January 22, 2022, we detected 202 infections with the delta variant and 419 with the omicron variant in samples obtained from 3241 participants. Among unvaccinated adults, the percentage of asymptomatic infection (no reported symptoms) was higher in infections with the omicron variant than in infections with the delta variant (21% and 8%, respectively), for an odds ratio of 3.10 (95% confidence interval [CI], 0.96 to 9.70). Participants who had symptomatic Covid-19 sought medical care for infection with the omicron variant less frequently than they did for infection with the delta variant (22% and 41%, respectively), for an odds ratio of 0.40 (95% CI, 0.17 to 0.94). Adjusted vaccine effectiveness against delta infection was 65% (95% CI, 49 to 76) after two doses and 91% (95% CI, 84 to 95) after three doses (Table 1). The relative vaccine effectiveness of three doses as compared with two doses against the delta variant was 86% (95% CI, 69 to 94). After adjustment, the vaccine effectiveness against omicron infection was 46% (95% CI, 25 to 61) after two doses and 60% (95% CI, 42 to 72) after three doses, for a relative effectiveness of 60% (95% CI, 40 to 73) for three doses as compared with two doses.

In this prospective cohort of frontline workers, a third mRNA vaccine dose provided strong (91%) protection against delta infection, similar to the findings of a study showing an effectiveness of 89 to 94% for three doses of mRNA vaccine against medically attended Covid-19 during a period when the delta variant was predominant.[4] In contrast, our estimate of vaccine effectiveness of 60% for three doses against omicron infec-

Table 1. Effectiveness of Two or Three Doses of mRNA Vaccine against SARS-CoV-2 Infection among Frontline Workers at Eight Study Sites (August 26, 2021, to January 22, 2022).

Vaccination Status and Timing*	No. of Participants†	Days since Vaccine Dose	Person-Days		SARS-CoV-2 Detected	Vaccine Effectiveness	
						Adjusted‡	Relative§
		median no. (IQR)	*no.*	*median no. (IQR)*	*no.*	*% (95% CI)*	
Predominance of delta variant							
Unvaccinated	343	NA	27,594	85 (35–129)	51	Reference	NA
Second dose	2773	267 (248–301)	204,624	67 (38–124)	134	65 (49–76)	Reference
Third dose	1716	74 (52–93)	110,852	67 (45–87)	20	91 (84–95)	86 (69–94)
Predominance of omicron variant							
Unvaccinated	259	NA	9,072	41 (21–48)	77	Reference	NA
Second dose	1021	330 (272–357)	38,171	48 (29–48)	156	46 (25–61)	Reference
Third dose	1719	93 (70–113)	72,673	48 (41–48)	189	60 (42–72)	60 (40–73)

* A total of 3163 participants were included in the analysis during the period when the delta variant was predominant and 2831 participants were included during the period when the omicron variant was predominant. Although whole-genome sequencing was performed to confirm variant types, data are presented according to the period in which each variant became predominant in the geographic area of the study site. At the time of specimen collection, participants were considered to have received two doses of vaccine at least 14 days after the second dose, to have received three doses at least 7 days after the third dose, or to be unvaccinated if no vaccine doses were received. All other interim periods were considered to be indeterminate, so data that were collected during those periods were excluded from the analysis. NA denotes not applicable. IQR denotes interquartile range.

† Contributing participants in vaccination categories do not equal the number of participants in the study because participants could contribute to more than one vaccination category since vaccination status was time-varying.

‡ In all models, the adjusted vaccine effectiveness was inversely weighted for propensity to be vaccinated and a priori with local virus circulation, study site, and occupation as covariates to adjust for additional bias. After weighting, all covariates that met the balance criteria of a standardized mean difference of less than 0.2 were included in the final model if the estimated effectiveness was changed by at least 5%; all a priori variables were included in the final model regardless of their effect on vaccine effectiveness. For the model of the delta variant, the participant's history regarding occupation and influenza vaccination did not balance, but only occupation changed the calculation of vaccine effectiveness by more than 5%. For the model of the omicron variant, all the covariates met the balance criteria after weighting except study site, occupation, daily medication use, influenza vaccination history, and local virus circulation; influenza vaccination history was found to change the estimate of vaccine effectiveness by at least 5% and was added to the final model.

§ The calculation of the adjusted relative effectiveness of a three-dose vaccine series as compared with a two-dose series was inversely weighted for propensity to be boosted with local virus circulation, study site, occupation, and number of days since the most recent dose as the covariates to adjust a priori for additional bias. For the models of both the delta and omicron variants, all covariates met the balance criteria after weighting.

tion was lower than the corresponding effectiveness of three doses against medically attended Covid-19 (82 to 90%) in the same study. Although in our study a third dose improved protection against omicron infection (relative vaccine effectiveness, 60%), relative protection was much higher against delta infection (86%). Lower vaccine effectiveness against mild or asymptomatic omicron infection is consistent with recent data showing lower protection in the ambulatory care setting and among adults who were tested for SARS-CoV-2 during the periods of circulation of the delta and omicron variants.[5] Despite indicating a decline in vaccine effectiveness, these results show continued effectiveness against clinically severe outcomes related to both variants.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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