CORRESPONDENCE

Effectiveness of Bivalent Boosters against Severe Omicron Infection

TO THE EDITOR: On August 31, 2022, the Food and Drug Administration (FDA) authorized the Moderna and Pfizer–BioNTech bivalent Covid-19 vaccines, each containing equal amounts of mRNA encoding the spike protein from the ancestral strain and the spike protein from the BA.4 and BA.5 strains of the B.1.1.529 (omicron) variant, for emergency use as a single booster dose at least 2 months after primary or booster vaccination.[1] The FDA authorizations were based on nonclinical data for these two bivalent vaccines, safety and immunogenicity data for bivalent vaccines containing mRNA from the BA.1 lineage of the omicron variant, and safety and effectiveness data for the monovalent mRNA Covid-19 vaccines.[1] Since September 1, these two bivalent mRNA vaccines have replaced their monovalent counterparts as booster doses for persons 12 years of age or older in the United States and in other countries. Here, we report data from a large cohort study on the effectiveness of these two bivalent vaccines against severe infection with omicron BA.4.6, BA.5, BQ.1, and BQ.1.1.

The data sources for this study have been described elsewhere.[2-4] We focused on new data collected over 99 days during which bivalent boosters were administered, from September 1 to December 8, 2022, and over the preceding 99 days during which monovalent boosters were administered, from May 25 to August 31, 2022 (see the Supplemental Methods section in the Supplementary Appendix, available with the full text of this letter at NEJM.org). During the period from May 25 to August 31, a total of 292,659 participants among the 6,242,259 who were eligible received monovalent boosters, and 61 of 1896 reported Covid-19–related hospitalizations and 23 of 690 reported Covid-19–related deaths occurred after receipt of the booster; during the period from September 1 to November 3, a total of 1,070,136 participants among the 6,283,483 who were eligible received bivalent boosters, and 57 of 1093 reported Covid-19–related hospitalizations and 17 of 514 reported Covid-19–related deaths occurred after receipt of the booster (Tables S1 and S2 in the Supplementary Appendix).

We fit the Cox regression model with a time-varying hazard ratio for severe infection (defined as infection resulting in hospitalization or death) for a single booster dose (i.e., first booster vs. primary vaccination only, second booster vs. first booster, or third booster vs. second booster) with adjustment for the baseline characteristics shown in Table S1 (see the Supplemental Methods section). We defined vaccine effectiveness as 1 minus the hazard ratio, multiplied by 100. This vaccine effectiveness indicates the additional benefit of receiving a single booster dose rather than the effectiveness as compared with being unvaccinated.

The results are shown in Table 1 and Figures S2 and S3. Booster effectiveness peaked at approximately 4 weeks and waned afterward. For all participants 12 years of age or older, vaccine effectiveness against severe infection resulting in hospitalization over days 15 to 99 after receipt of one monovalent booster dose was 25.2% (95% confidence interval [CI], −0.2 to 44.2), and the corresponding vaccine effectiveness for one bivalent booster dose was 58.7% (95% CI, 43.7 to 69.8); the difference in vaccine effectiveness against this outcome between the bivalent booster and the monovalent booster was 33.5 percentage points (95% CI, 2.9 to 62.1). Vaccine effectiveness against severe infection resulting in hospitalization or death was 24.9% (95% CI, 1.4 to 42.8) for one monovalent booster dose and 61.8% (95% CI, 48.2 to 71.8) for one bivalent booster dose; the difference in vaccine effectiveness against this outcome between the bivalent booster and the monovalent booster was 36.9

Table 1. Estimates of Effectiveness of One Monovalent or Bivalent Booster Dose against Severe Omicron Infection.*

Group	Vaccine Effectiveness against Hospitalization (95% CI)			Vaccine Effectiveness against Hospitalization or Death (95% CI)		
	Monovalent Booster	Bivalent Booster	Difference	Monovalent Booster	Bivalent Booster	Difference
	percent		*percentage points*	*percent*		*percentage points*
All participants	25.2 (–0.2 to 44.2)	58.7 (43.7 to 69.8)	33.5 (2.9 to 62.1)	24.9 (1.4 to 42.8)	61.8 (48.2 to 71.8)	36.9 (12.6 to 64.3)
Age group						
≥18 yr	27.3 (2.6 to 45.8)	59.5 (44.7 to 70.3)	32.2 (2.5 to 60.1)	27.0 (4.2 to 44.4)	62.4 (49.0 to 72.3)	35.4 (11.8 to 62.1)
≥65 yr	21.0 (–7.7 to 42.1)	58.8 (43.0 to 70.2)	37.8 (3.2 to 69.9)	20.3 (–6.0 to 40.1)	61.5 (47.1 to 71.9)	41.2 (9.9 to 71.7)
Primary vaccination with mRNA vaccine	28.0 (2.9 to 46.7)	58.8 (43.8 to 69.9)	30.8 (1.0 to 61.1)	27.2 (4.0 to 44.9)	61.9 (48.3 to 71.9)	34.7 (11.4 to 62.2)
No previous infection	26.3 (–0.3 to 45.8)	61.0 (45.4 to 72.2)	34.7 (6.2 to 69.2)	24.5 (–0.3 to 43.2)	63.1 (48.8 to 73.4)	38.6 (14.8 to 67.3)
Booster vaccine received						
Moderna	28.1 (–8.8 to 52.5)	58.8 (33.8 to 74.3)	30.7 (–17.0 to 79.1)	25.2 (–9.2 to 48.8)	63.8 (41.8 to 77.5)	38.6 (4.2 to 75.8)
Pfizer–BioNTech	22.2 (–16.8 to 48.1)	58.7 (38.7 to 72.2)	36.5 (–1.7 to 78.5)	24.5 (–10.7 to 48.5)	60.4 (42.1 to 73.0)	35.9 (3.7 to 75.5)
Booster dose received						
First	15.8 (–39.5 to 49.1)	54.0 (–6.3 to 80.1)	38.2 (–36.9 to 99.4)	4.2 (–50.1 to 38.8)	54.0 (–0.3 to 78.9)	49.8 (–37.5 to 125.8)
Second	28.0 (–3.2 to 49.8)	61.9 (43.6 to 74.3)	33.9 (0.2 to 68.4)	32.2 (4.5 to 51.8)	64.0 (47.0 to 75.5)	31.8 (7.3 to 71.1)
Third	—	55.7 (12.0 to 77.7)	—	—	63.1 (27.3 to 81.2)	—

* Vaccine effectiveness was defined as (1 – hazard ratio) × 100 and was evaluated for the period from day 15 to day 99 after receipt of the booster dose. CI denotes confidence interval.

percentage points (95% CI, 12.6 to 64.3) (Fig. S3 and Table 1). We obtained similar vaccine effectiveness estimates when the analysis was restricted to participants who were 18 years of age or older or 65 years of age or older, to participants who received an mRNA vaccine as their primary vaccine, or to previously uninfected participants (Table 1). In addition, estimates of vaccine effectiveness were similar for the Moderna and Pfizer–BioNTech boosters and similar among the first, second, and third booster doses (Table 1).

Bivalent boosters provided substantial additional protection against severe omicron infection in persons who had previously been vaccinated or boosted, although the effectiveness waned over time. The effectiveness of bivalent boosters was higher than that of monovalent boosters.

We adjusted for measured confounders, including vaccination history, previous infection, and demographic variables. However, estimates of booster effectiveness would be biased if boosted persons were more likely or less likely to seek Covid-19 testing than nonboosted persons. For this reason, we focused on severe infection, which was more likely to be reported than mild infection. Very strong unmeasured confounders would be required in order to fully explain away the observed effectiveness of bivalent boosters.

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Supported by a grant (R01 AI029168) from the National Institutes of Health.

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

This letter was published on January 25, 2023, at NEJM.org.

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DOI: 10.1056/NEJMc2215471