CORRESPONDENCE

Durability of Bivalent Boosters against Omicron Subvariants

TO THE EDITOR: On September 1, 2022, the Moderna and Pfizer–BioNTech bivalent vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) containing equal amounts of spike messenger RNA from the ancestral and omicron BA.4–BA.5 subvariants replaced their monovalent counterparts as booster doses for persons who are 12 years of age or older in the United States. We previously reported surveillance data from North Carolina on the effectiveness of these two bivalent boosters against coronavirus disease 2019 (Covid-19) during the first 3 months after deployment (September 1 to December 8, 2022); the BA.4–BA.5 subvariants were predominant during the first 2.5 months of this period.[1] Here, we present two additional months of data that were obtained during a period when the omicron BQ.1–BQ.1.1 and XBB–XBB.1.5 subvariants had become predominant to show the durability of protection conferred by these two bivalent boosters against a wider range of clinical outcomes than were included in our previous report.

The data sources and study design have been described previously,[1-3] and updated information is provided in the Methods section of the Supplementary Appendix, available with the full text of this letter at NEJM.org. The current study used data regarding booster doses and clinical outcomes from September 1, 2022, to February 10, 2023, for all North Carolina residents who were 12 years of age or older. During this period, a total of 6,306,311 residents were eligible to receive bivalent boosters; of these residents, 1,279,802 received the injections. A total of 19,462 of the 154,581 SARS-CoV-2 infections, 253 of the 2208 Covid-19–related hospitalizations, and 79 of the 867 Covid-19–related deaths occurred after receipt of the bivalent booster (Table S1 in the Supplementary Appendix).

We considered four outcome measures: infection, severe infection resulting in hospitalization, severe infection resulting in hospitalization or death, and severe infection resulting in death. We fit the Cox regression model with a time-varying hazard ratio for severe infection and fit the proportional-rates model with a time-varying rate ratio for recurrent infection for each additional booster dose that was received (i.e., first booster vs. primary vaccination, second booster vs. first booster, or third booster vs. second booster); all measures were adjusted for the baseline characteristics shown in Table S1. We estimated the booster effectiveness on a particular day as 1 minus the hazard ratio or rate ratio on that day multiplied by 100%.

The estimation results are shown in the left column of Figure 1 and in Table S2. Effectiveness against severe infection resulting in hospitalization or death reached a level of 67.4% (95% confidence interval [CI], 46.2 to 80.2) after 2 weeks and decreased to 47.5% (95% CI, 32.6 to 59.2) after 4 weeks, to 44.3% (95% CI, 35.7 to 51.7) after 10 weeks, and to 38.4% (95% CI, 13.4 to 56.1) after 20 weeks. Effectiveness against severe infection resulting in hospitalization was slightly lower, and effectiveness against infection was much lower. The effectiveness against severe infection resulting in death was the highest despite uncertainty because of the small number of events.

We also analyzed the data separately for participants who received bivalent boosters before November 1, 2022 (when the BA.4–BA.5 subvariants were predominant) and after November 1, 2022 (when the BQ.1–BQ.1.1 subvariants were more prevalent and then were gradually replaced by the XBB–XBB.1.5 subvariants). The results are shown in the right column of Figure 1 and in Tables S3 and S4. The effectiveness was broadly similar between the two booster cohorts.

Finally, we performed subgroup analyses according to the participant's age and previous infection status and according to the manufacturers of the bivalent vaccine and the previous vaccine. Effectiveness against infection was higher for the Moderna bivalent vaccine than for the

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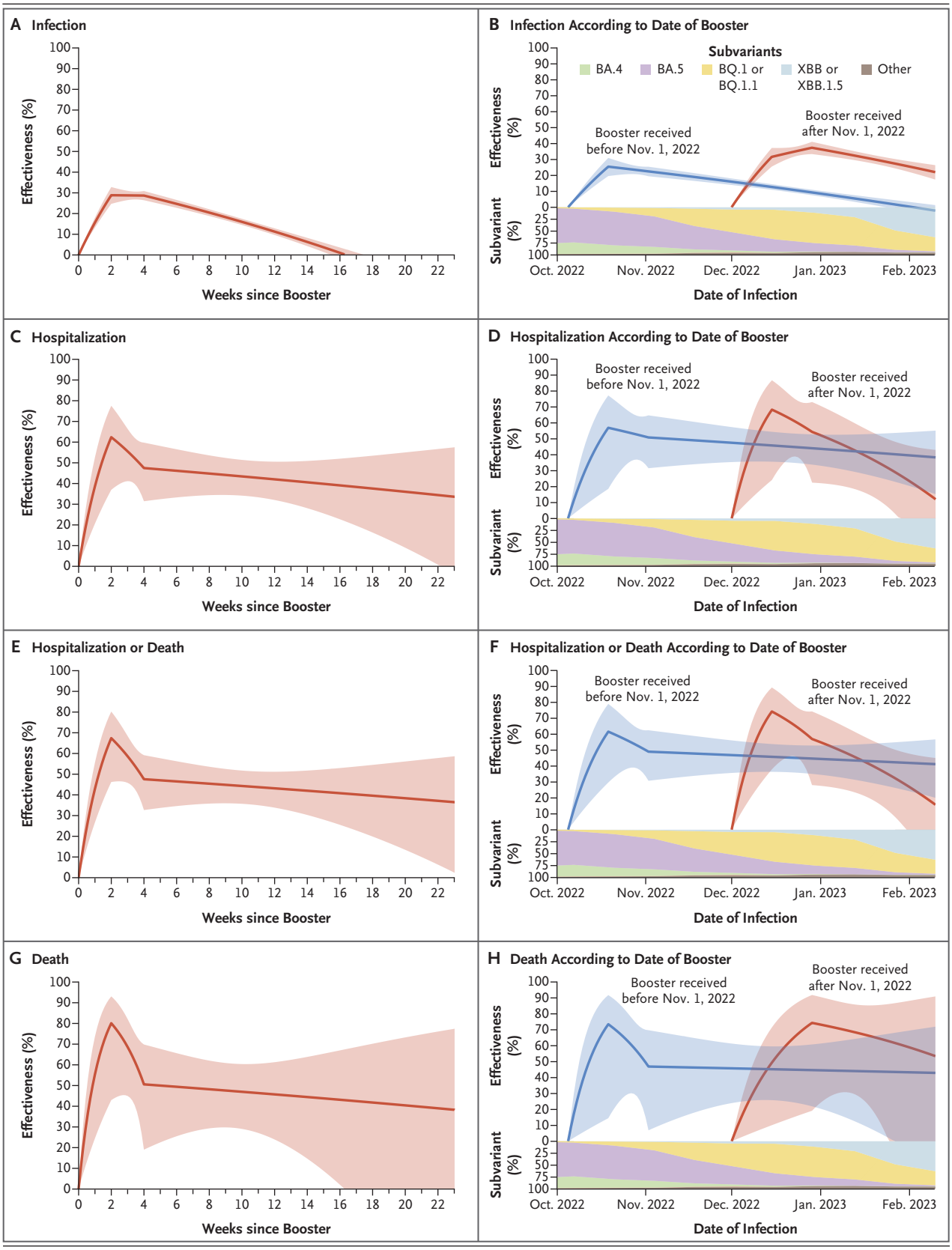

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Figure 1 (facing page). Effectiveness of Bivalent Boosters According to the Interval since Administration.

Shown is the pooled effectiveness of the two bivalent boosters that were evaluated in the study regarding the end points of infection (Panels A and B), severe infection resulting in hospitalization (Panels C and D), severe infection resulting in hospitalization or death (Panels E and F), and severe infection resulting in death (Panels G and H). The left column shows the results of the analysis of all bivalent booster doses, and the right column shows the stratified analysis according to the date of administration. The solid curves show the estimates of booster effectiveness, and the shaded bands indicate 95% confidence intervals. In the right column, each curve starts at the median date of booster administration for participants in that date cohort; the proportions of BA.4, BA.5, BQ.1–BQ.1.1, XBB–XBB.1.5, and other subvariants are indicated below the effectiveness graph.

Pfizer–BioNTech bivalent vaccine and higher among previously infected participants than among those with no previous infection (Fig. S1).

The two types of bivalent boosters were associated with an additional reduction in the incidence of omicron infection among participants who had previously been vaccinated or boosted. Although the two bivalent vaccines were designed to target the BA.4–BA.5 subvariants, they were also associated with a lower risk of infection or severe infection with the BQ.1–BQ.1.1 and XBB–XBB.1.5 subvariants. The effectiveness was higher against hospitalization and death than against infection and waned gradually from its peak over time.

Dan-Yu Lin, Ph.D.
Yangjianchen Xu, B.S.
Yu Gu, B.S.
Donglin Zeng, Ph.D.

University of North Carolina Gillings School of Global Public Health
Chapel Hill, NC
lin@bios.unc.edu

Shadia K. Sunny, M.D., Ph.D.
Zack Moore, M.D., M.P.H.

North Carolina Department of Health and Human Services
Raleigh, NC

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1. Lin D-Y, Xu Y, Gu Y, et al. Effectiveness of bivalent boosters against severe omicron infection. N Engl J Med 2023;388:764-6.
2. Lin D-Y, Gu Y, Wheeler B, et al. Effectiveness of Covid-19 vaccines over a 9-month period in North Carolina. N Engl J Med 2022;386:933-41.
3. Lin D-Y, Gu Y, Xu Y, et al. Association of primary and booster vaccination and prior infection with SARS-CoV-2 infection and severe COVID-19 outcomes. JAMA 2022;328:1415-26.

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