variant mostly causes mild disease and is not expected to be the last SARS-CoV-2 variant, the question of whether further booster immunisation should be done or not remains unresolved. Although the paper by van der Kuy and colleagues provides some insights into mRNA vaccine boosters, we believe more studies are needed.

We declare no competing interests.

Andrey V Vasin, Marina A Stukova
vasin_av@spbstu.ru

Smorodintsev Research Institute of Influenza, Saint Petersburg, Russia (AVV, MAS); Institute of Biomedical Systems and Biotechnologies, Peter the Great St Petersburg Polytechnic University, Saint Petersburg, 195251, Russia (AVV)

1 COVID-19 Cumulative Infection Collaborators. Estimating global, regional, and national daily and cumulative infections with SARS-CoV-2 through Nov 14, 2021: a statistical analysis. *Lancet* 2022; **399:** 2351–80.
2 Amicone M, Borges V, Alves MJ, et al. Mutation rate of SARS-CoV-2 and emergence of mutators during experimental evolution. *Evol Med Public Health* 2022; **10:** 142–55.
3 Duong D. Alpha, beta, delta, gamma: what's important to know about SARS-CoV-2 variants of concern? *CMAJ* 2021; **193:** E1059–60.
4 Hachmann NP, Miller J, Collier AY, et al. Neutralization escape by SARS-CoV-2 omicron subvariants BA.2.12.1, BA.4, and BA.5. *N Engl J Med* 2022; **387:** 86–88.
5 Stein C, Nassereldine H, Sorensen RJD, et al. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. *Lancet* 2023; **401:** 1–11.
6 Lau JJ, Cheng SMS, Leung K, et al. Real-world COVID-19 vaccine effectiveness against the Omicron BA.2 variant in a SARS-CoV-2 infection-naive population. *Nat Med* 2023; **29:** 348–57.
7 Andrews N, Stowe J, Kirsebom F, et al. COVID-19 vaccine effectiveness against the omicron (B.1.1.529) variant. *N Engl J Med* 2022; **386:** 1532–46.
8 Chalkias S, Harper C, Vrbicky K, et al. A bivalent omicron-containing booster vaccine against COVID-19. *N Engl J Med* 2022; **387:** 1279–91.
9 Winokur P, Gayed J, Fitz-Patrick D, et al. Bivalent omicron BA.1-adapted BNT162b2 booster in adults older than 55 years. *N Engl J Med* 2023; **388:** 214–27.
10 Tan NG, Geers D, Sablerolles RSG, et al. Immunogenicity of bivalent omicron (BA.1) booster vaccination after different priming regimens in health-care workers in the Netherlands (SWITCH ON): results from the direct boost group of an open-label, multicentre, randomised controlled trial. *Lancet Infect Dis* 2023; published online April 20. https://doi.org/10.1016/S1473-3099(23)00140-8.

Effectiveness of bivalent mRNA booster vaccines against COVID-19: methodological and public health considerations

The decreasing effectiveness of COVID-19-vaccines against the omicron (B.1.1.529) variant of SARS-CoV-2[1,2] was caused by mutations in the spike protein, which made adaptations of the vaccines necessary. In August, 2022, the US Food and Drug Administration approved two bivalent mRNA booster vaccines directed against the wild-type strain as well as omicron BA.4 and BA.5 sublineages.[3] However, because this approval was based on laboratory data rather than clinical effectiveness data, real-world data on effectiveness, especially against public health relevant endpoints (eg, hospitalisation and death), are needed.

In *The Lancet Infectious Diseases*, Ronen Arbel and colleagues[4] report the findings of their study that aimed to evaluate the effectiveness of a bivalent mRNA vaccine booster dose to prevent severe COVID-19 outcomes. In this retrospective cohort study in Israel, 569 519 eligible participants (mean age 75·2 years [SD 7·5], 314 319 [55%] were female, and 255 200 [45%] were male) were identified from Clalit Health Services. Electronic medical records of 134 215 participants who received a Pfizer-BioNTech bivalent mRNA vaccine booster dose were compared with 435 304 participants who did not receive a bivalent booster dose. The adjusted hazard ratio (HR) against hospitalisation due to COVID-19 was 0·28 (95% CI 0·19–0·40), indicating a relative vaccine effectiveness of 72% (95% CI 60–81). The adjusted HR against death due to COVID-19 was 0·32 (95% CI 0·18–0·58), indicating a relative vaccine effectiveness of 68% (95% CI 42–82). HRs were adjusted for a large number of potential confounders, including number of previous COVID-19 vaccine doses, time interval since most recent vaccination, previous SARS-CoV-2 infections, sociodemographic variables, and comorbidities.

As discussed by Arbel and colleagues,[4] these results are broadly similar to those from a US Centers for Disease Control and Prevention (CDC) study based on surveillance data, where relative vaccine effectiveness of a bivalent booster against COVID-19-associated hospitalisation was 73% (95% CI 52 to 85). However, it must be noted that all participants in the CDC study had received at least two monovalent-only mRNA vaccine doses, and participants who had received a bivalent booster additionally were compared with those who had not, which means that the numbers of doses received in the groups were most probably unequal.[5] In a study from North Carolina, USA, which compared participants who had received a monovalent booster with participants who had received a bivalent booster,


Flickr - Montecruz Photo

Published **Online**
April 13, 2023
https://doi.org/10.1016/S1473-3099(23)00187-1

See **Articles** page 914

relative vaccine effectiveness against hospitalisation or death was 49·8% (95% CI −37·5 to 125·8) for the first bivalent booster dose compared with the first monovalent booster dose, and 31·8% (7·3 to 71·1) for the second bivalent booster dose compared with the second monovalent booster dose.[6] A study from several countries in northern Europe compared 3 368 697 participants who had received four vaccine doses with the same number of participants (1:1 matching) who had received three monovalent vaccine doses. The relative vaccine effectiveness against COVID-19 hospitalisation was 80·5% (95% CI 69·5 to 91·5) for vaccines adapted for BA.4 and BA.5 and 74·0% (68·6 to 79·4) for vaccines adapted for BA.1. Compared with vaccines adapted for BA.1, vaccines adapted for BA.4 and BA.5 had a relative vaccine effectiveness of 32·3% (95% CI 10·6 to 53·9) against COVID-19-related hospitalisation.[7]

Most of the currently available evidence shows high effectiveness against hospitalisation and death due to COVID-19 for bivalent mRNA vaccine booster doses as an additional vaccine dose and when compared with a monovalent booster dose. The study by Arbel and colleagues[4] is an important contribution to this evidence base. Furthermore, their study identifies some important methodological issues that should be considered when designing and analysing new studies on vaccine effectiveness against COVID-19. To obtain interpretable estimates of effectiveness for bivalent booster vaccines, it is crucial to compare with—or to adjust for—equivalent number of vaccine doses and time since last vaccination, as the number of vaccine doses and waning of vaccine effectiveness over time can influence estimates substantially. Furthermore, definitions of hospitalisation and death due to COVID-19 are important. Arbel and colleagues used the primary diagnosis in the discharge letter or primary cause of death in the death certificate as reliable surrogates for these endpoints. However, temporal coincidence of SARS-CoV-2 infection and hospitalisation can lead to misclassification, because for the majority of hospitalised patients during the omicron-dominant pandemic wave, SARS-CoV-2 infection was a secondary diagnosis.[8] It is therefore important to thoroughly describe the criteria used to define hospitalisation (or death) due to COVID-19.

To illustrate the public health impact, Arbel and colleagues[4] calculated the respective number needed to vaccinate to prevent one event for both outcomes in their study. While the number needed to vaccinate to prevent one COVID-19-related hospitalisation was high (1118 people, 95% CI 993–1341), it was higher still to prevent one COVID-19-related death (3722 people, 3086–6026). As health-care resources are scarce in many countries, we need to consider the settings and populations in which bivalent booster vaccines are beneficial. Further studies with different populations and health economic evaluations are needed to improve the evidence base for immunisation programmes.

We declare no competing interests.

*Anna Stoliaroff-Pepin, Thomas Harder
stoliaroff-pepina@rki.de

Immunization Unit, Robert Koch Institute, Berlin, Germany (AS-P, TH)

1 Lauring AS, Tenforde MW, Chappell JD, et al. Clinical severity of, and effectiveness of mRNA vaccines against, COVID-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ* 2022; **376:** e069761.

2 Tseng HF, Ackerson BK, Luo Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 omicron and delta variants. *Nat Med* 2022; **28:** 1063–71.

3 US Food and Drug Administration. Coronavirus (COVID-19) update: FDA authorizes Moderna, Pfizer-BioNTechBivalent COVID-19 vaccines for use as a booster dose. Aug 31, 2022. https://www.fda.gov/news-events/pressannouncements/coronavirus-covid-19-update-fda-authorizes-moderna-pfizerbiontech-bivalent-covid-19-vaccines-use (accessed March 13, 2023).

4 Arbel R, Peretz A, Sergienko R, et al. Effectiveness of a bivalent mRNA vaccine booster dose to prevent severe COVID-19 outcomes: a retrospective cohort study. *Lancet Infect Dis* 2023; published online April 13. https://doi.org/10.1016/S1473-3099(23)00122-6.

5 Surie D, DeCuir J, Zhu Y, et al. Early estimates of bivalent mRNA vaccine effectiveness in preventing COVID-19–associated hospitalization among immunocompetent adults aged ≥65 years—IVY Network, 18 states, September 8–November 30, 2022. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 1625–30.

6 Lin D-Y, Xu Y, Gu Y, et al. Effectiveness of bivalent boosters against severe omicron infection. *N Engl J Med* 2023; **388:** 764–66.

7 Andersson NW, Thiesson EM, Baum U, et al. Comparative effectiveness of the bivalent BA.4-5 and BA.1 mRNA-booster vaccines in the Nordic countries. *medRxiv* 2023; published online Jan 19. https://doi.org/10.1101/2023.01.19.23284764 (preprint).

8 Montag K, Kampf G. Acute lower respiratory tract infections have mainly become a secondary diagnosis in 2022 in hospitalized COVID-19 cases in Germany. *Infection* 2023; published online Feb 21. https://doi.org/10.1007/s15010-023-02003-0.