



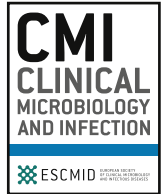
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Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

Effectiveness of first-generation severe acute respiratory syndrome coronavirus 2 mRNA vaccines against the Omicron variant

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ARTICLE INFO

Article history:

Received 7 August 2022

Received in revised form

18 August 2022

Accepted 20 August 2022

Available online xxx

Editor: L Leibovici

Keywords:

COVID-19

mRNA vaccines

Observational data

Omicron

Vaccine effectiveness

The emergence of novel variants, relatively quickly waning immunity following vaccination and possibility of re-infection following recovery have together made the effectiveness of different severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines a 'moving target'. This necessitates constant re-evaluation of vaccine effectiveness (VE) to better inform public policies.

In this issue of *Clinical Microbiology and Infection*, Robilotti et al. [8] estimated the effectiveness of the third dose of a SARS-CoV-2 mRNA vaccine against infection, compared with two doses of the vaccine, in a cohort of health-care workers from a tertiary medical centre in New York during a period dominated by the Omicron variant. Compared with individuals vaccinated twice, they found a modest VE of 33% (95% CI, 29%–38%) in health-care workers who received three doses of the mRNA vaccine. In those previously infected, the effect was similar, with a VE of 34% (95% CI, 7%–41%).

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<https://doi.org/10.1016/j.cmi.2022.08.017>

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The authors additionally described the clinical course of breakthrough infections, finding the majority to be mild.

The authors' results add to an existing body of literature regarding the effectiveness of the first generation of mRNA vaccines against the Omicron variant. For the primary series of the BNT162b2 vaccine, Andrews et al. [1] estimated a VE of 65% soon after the second dose, which later waned to 9%. For the third dose, they estimated a VE of 67% against symptomatic disease soon after boosting, which later waned to 54%. The numbers were similar for the mRNA-1273 vaccine [1]. Asking a similar question, Link-Gelles et al. [2] estimated a VE of 47% for recent two-dose vaccination with either the BNT162b2 vaccine or the mRNA-1273 vaccine against emergency department and urgent care visits because of coronavirus disease 2019 (COVID-19), which later waned to 39%. The VE against hospitalization was better at 68% soon after vaccination, which later waned to 61%. Protection after the third dose was improved, whereas protection against the BA.2 sub-variant was not as good.

The estimates of the effectiveness of the fourth dose (compared with persons who received only three doses) against Omicron were similarly not as high compared to the VE of previous doses against previous variants. For example, Grewal et al. [3] estimated a VE of 19%, 31%, and 40% against infection, symptomatic disease, and more severe outcomes, respectively, of the mRNA-1273 vaccine. Regev-Yochay et al. [4] estimated higher VEs of 30% and 43% against infection and symptomatic disease for the BNT162b2 vaccine, but somewhat lower estimates for the mRNA-1273 vaccine.

There is variance in the different estimates, as would be expected considering the different circumstances under which each was derived (including different populations, study designs, vaccination regimens, etc.). Despite this variability, there is an evident trend of reduced VE of mRNA vaccines, both primary series and boosters, against the Omicron variant (compared with that against previous variants), which further wanes over time. The vaccines also present a trend of improved protection against more severe outcomes. These trends, together with the Omicron variant's increased propensity to cause re-infections in those previously

infected with previous variants, explain the infection surges observed world-wide, including in countries with high vaccine coverage. It should also be noted that the above-mentioned VE estimates were derived during periods in which BA.1 and BA.2 were the pre-dominant sub-variants of Omicron. Today, with the increasing spread of the sub-variant BA.5, the effectiveness might be different.

Although the relatively better effectiveness of vaccines for severe disease caused by the Omicron variant is encouraging, as is the apparent inherent lower virulence of the Omicron variant [5], attaining high protection against infection is still important in order to reduce the amount of community transmission of SARS-CoV-2 and, specifically, to protect vulnerable populations who are at an increased risk of severe disease if infected. The new generation of Omicron-specific vaccines which are currently undergoing clinical trials [6] may provide this needed protection against infections. Indeed, early evidence suggests that they elicit a more vigorous immune response against the now-dominant Omicron variant [7].

The quick pace at which the COVID-19 pandemic changes, including changes in the landscape of variants and introduction of novel mitigation technologies, including vaccines and treatments, emphasizes the need for continuous research efforts to evaluate the effectiveness of these technologies. The work by Robilotti et al., [8] along with the other studies cited in this commentary, provided quick and important evidence regarding the effectiveness of mRNA vaccines against the Omicron variant. This was possible because of the increasing availability of observational data repositories which include COVID-19 data and the increasing experience of various research groups in using them to study causal effects in a reliable and timely manner. Using these resources, the medical community should focus on addressing the most pressing research questions still remaining open, i.e. estimating the clinical effectiveness of novel Omicron-specific vaccines and understanding the long-term effects of Omicron-variant infections, even mild ones. In parallel, and at least until the effectiveness of Omicron-specific vaccines is convincingly proven, societal protection of vulnerable populations must remain a priority.

Transparency declaration

N.D. reports institutional grants to the Clalit Research Institute from Pfizer outside the submitted work and unrelated to COVID-19, with no direct or indirect personal benefits. N.B. reports institutional grants to Sheba Medical Center from Pfizer and Moderna outside the submitted work, with no direct or indirect personal benefits.

Author contributions

N.D. and N.B. participated in the writing and editing of this commentary.

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