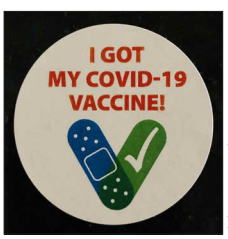
Effectiveness of monovalent and bivalent COVID-19 vaccines



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Lancet Infect Dis 2023

Published Online
July 12, 2023
https://doi.org/10.1016/
S1473-3099(23)00379-1

See Online/Articles
https://doi.org/10.1016/
S1473-3099(23)00365-1

The updated COVID-19 vaccines that are tailored against omicron subvariants BA.1, BA.4, and BA.5 started to be offered to people in late 2022. Immunogenicity studies[1,2] showed promising results: bivalent vaccines were associated with a more than 1·5-times increase in neutralising antibody titres against the omicron variant compared with monovalent vaccines.[1] However, the effectiveness and durability of protection of bivalent vaccines had not been established.

In *The Lancet Infectious Diseases*, Freja Kirsebom and colleagues[3] provide a national overview of the effectiveness of monovalent and bivalent COVID-19 vaccines used in England from June 13, 2022, to Feb 5, 2023. Among people aged 65 years or older, the initially high vaccine effectiveness against hospitalisation provided by three or four doses of monovalent vaccines decreased in the first 6 months, plateauing at an effectiveness of roughly 50% up to 14 months after the last dose. When assessing the additional protection afforded by a booster dose of a bivalent vaccine among people aged 50 years or older who had had at least two doses of a monovalent vaccine, the incremental vaccine effectiveness peaked at 53·0% (95% CI 47·9–57·5) 2–4 weeks after administration. Thereafter the protection waned, falling to 35·9% (31·4–40·1) after 10 weeks. A similar pattern was noted when the effectiveness of four doses of a monovalent vaccine was compared with that of three monovalent doses.

Kirsebom and colleagues' findings are closely related to those of a small study[4] (available only as a preprint at the time of writing) done at one centre in the UK, in which receiving a bivalent vaccine as a fifth vaccine dose offered similar protection to having had only four doses of a monovalent vaccine more than 7 days after the last dose. Furthermore, in the Canadian Immunization Research Network Study (available only as a preprint),[5] protection against hospitalisation was similar in the recipients of monovalent and bivalent boosters—around 80% up to 119 days after the dose.

Kirsebom and colleagues did not assess the vaccines' effectiveness against infection, for which the vaccines were not designed. However, findings from a cohort of 6 million people, in which nearly 1·3 million people received bivalent boosters, suggested only short protection.[6] A possible explanation for the lack of increased protection against infection with bivalent vaccines is immune imprinting against the wild-type variant of SARS-CoV-2. This could impair the production of neutralising antibodies against omicron variants after immunological stimulation with a mix of wild-type and omicron antigens (ie, bivalent vaccines) because production of antibodies against antigens that the immune system had previously been exposed to would be prioritised.[7] This pattern of no protection against mild infection but sustained protection against severe disease was previously reported among children exposed to one strain of influenza, in whom vaccination protected against severe disease caused by new strains but not against mild infection.[8]

However, data suggest that people who experienced multiple breakthrough infections after the emergence of the omicron variant can overcome immune imprinting and produce higher titres of neutralising antibodies against XBB variants.[9] As wild-type SARS-CoV-2 no longer circulates among humans, this finding could suggest the need for a new antigen composition of COVID-19 vaccines, prioritising only variants in circulation, as the WHO Technical Advisory Group on COVID-19 Vaccine Composition recommended.[10]

The fact that monovalent and bivalent doses offer similar protection against severe disease should guide governments' to ensure equitable access to available COVID-19 vaccines. Considering the tremendous inequality in access to COVID-19 vaccine doses—only 30% of people in Africa have received the primary scheme of two doses,[11] whereas many high-income countries have offered five doses to some sections of the population—careful cost–benefit analyses are needed.

The pattern of waning protection against severe illness and low protection against infection of both monovalent and bivalent COVID-19 vaccines reinforces the necessity of new formulations to ensure adequate protection against the ongoing evolution of SARS-CoV-2.

VSB and MB-N are employees of Fiocruz, a federal public institution that manufactures the Oxford–AstraZeneca vaccine (ChAdOx1) in Brazil through a full technology transfer agreement with AstraZeneca. Fiocruz allocates all its manufactured products to Brazil's Ministry of Health for public health use. TC-S declares no competing interests.

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