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Omicron-targeted vaccines do no better than original jabs in early tests

Experiments in animals show that boosters customized for the fast-spreading COVID variant offer little advantage over standard jabs.

Emily Waltz

Ambulances queue at a London hospital during a COVID-19 surge driven by the Omicron variant. Credit: Mark Thomas/Shutterstock

As the Omicron variant of SARS-CoV-2 continues its global rampage, vaccine makers are pouring resources into clinical trials of COVID-19 shots tailored to the highly

transmissible variant. But a raft of early animal studies suggest that Omicron-specific boosters offer no advantage over a third dose of current vaccines[1–4].

Most of the studies involved only a small number of animals — just eight primates, in one case — and none has been peer reviewed. But they offer early hints that a single dose of a customized vaccine won't change the game against Omicron.

"What we're seeing coming out of these preclinical studies in animal models is that a boost with a variant vaccine doesn't really do any better than a boost with the current vaccine," says David Montefiori, director of the Laboratory for AIDS Vaccine Research and Development at Duke University Medical Center in Durham, North Carolina, who has been studying COVID-19 vaccines.

Quest for a bespoke vaccine

Since it was first identified in November, Omicron has become the dominant variant globally. Its biology differs significantly from that of the original 'ancestral' strain of SARS-CoV-2, on which currently approved vaccines are based. The differences might explain why three doses of existing vaccines are less potent against Omicron than they are against other variants.

The changes in the virus compelled the manufacturers of the widely used mRNA-based vaccines to develop Omicron-matched formulations. Both Pfizer and Moderna announced in late January that they had initiated clinical trials of their Omicron-specific jabs. These should yield data in the coming months.

As scientists await the results, animal studies published as preprints offer an early glimpse of the potential utility of these updated vaccines.

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One study[1] examined the immune responses of eight rhesus macaques (*Macaca mulatta*) that received three doses of vaccine: two doses of Moderna's original vaccine and a booster of either the same shot or a version that incorporated Omicron's heavily mutated

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spike protein, which the virus uses to enter human cells. The authors found that monkeys boosted with either vaccine mounted a broad antibody response against all variants of concern, including Omicron.

Importantly, the boosters also had a positive effect on memory B cells, which are responsible for cranking out antibodies to fend off a virus. Both the original vaccine and the updated jab prompted a rise in the animals' levels of 'cross-reactive' memory B cells — those that target many variants, not just the one in the vaccine.

"For now, that's a very good thing," says Robert Seder, a co-author of the paper and an immunologist at the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland. "It means we're still able to cover all known variants with a boost" of the current vaccines. However, he cautions that the study only examined immune responses up to four weeks after the boost, and says that it is not clear how long the increase in antibody production will last.

Booster versus booster

Seder's group also exposed animals boosted with either the original vaccine or the Omicron-matched version to Omicron. "Either boost completely shut down viral replication within two days," he says. In both this experiment and the one analysing memory B-cell responses, the Omicron-specific vaccine showed no significant advantage over the original.

A study of eight animals isn't definitive. But given the condensed pandemic-style timescale, the study has value, says Montefiori.

Consistent with the primate results, a study[2] in mice found that giving an Omicron-matched booster after two doses of mRNA-based vaccine offered no more benefit than a standard booster. The study also looked at the Omicron-specific vaccine in 'naive' mice — those that had not previously been immunized — and found that the rodents produced high levels of potent antibodies against Omicron. But those antibodies had a limited ability to inhibit other key variants of COVID-19. A separate

study[3] in naive mice immunized with an Omicron-matched mRNA vaccine reported similar results.

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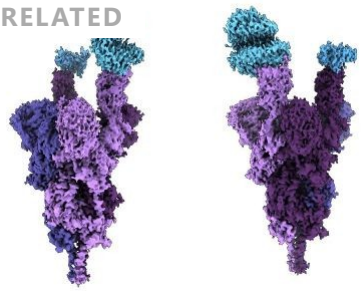

Omicron's molecular structure could help explain its global takeover

A fourth study[4] investigated a 'replicating RNA' vaccine. In contrast to the widely used mRNA vaccines, this encodes both a snippet of the virus and an enzyme to amplify the expression of that snippet. Scientists gave three doses of the replicating RNA vaccine, made by HDT Bio in Seattle, Washington, to mice: two doses based on the ancestral SARS-CoV-2 strain followed by a single Omicron-specific booster.

The third dose did not produce an elevated immune response against Omicron. But such a response was seen in mice that received one dose of vaccine based on the ancestral strain and two doses of the Omicron-specific vaccine.

"What these studies are teaching us are the rules of engagement of the immune system when you boost with a variant vaccine," says Montefiori. Those rules suggest that single boost of a variant-matched vaccine probably isn't the solution, he says. "There are important questions that still need to be addressed. Hopefully Pfizer and Moderna's Omicron studies in humans will do that".

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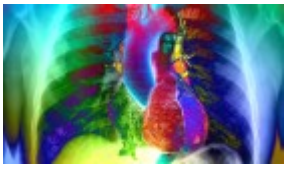

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