JAVIER TORRES/AFP/GETTY

Health-care workers receive a fourth dose of the Pfizer–BioNTech vaccine in Santiago, Chile.

THREE, FOUR OR MORE: WHAT'S THE MAGIC NUMBER FOR BOOSTERS?

Endless boosting with COVID vaccines might not be a practical or sustainable strategy.

By Clare Watson

Late last year, studies showed that third shots of COVID-19 vaccines — boosters — were effective at providing a little extra protection from infection, particularly in the face of the Omicron variant. Some countries are now offering fourth doses, but scientists say that endless boosting might not be a viable strategy.

This is "uncharted territory for vaccinology", says Danny Altmann, an immunologist at Imperial College London. "We've stumbled into a de facto programme of frequent mRNA boosters as an emergency measure, but this really doesn't feel like the way to go."

In early January, Israel began offering fourth doses to older people, those with compromised immune systems and health workers, hoping to shield vulnerable groups from a wave of Omicron infections, says Ran Balicer, a public-health physician at the Clalit Health Institute in Tel Aviv. Last week, preliminary data from Israel revealed that a fourth dose reduces the risk of infection and severe disease.

But researchers are debating whether a third dose will be enough to confer lasting immunity against Omicron and emerging variants in most people — or whether a fourth dose, or even regular boosters, will be needed, as they are for influenza.

Some researchers say that the answer depends on the desired effect — whether boosters are intended to prevent infections and slow viral transmission, or whether the goal is to reduce severe disease and keep people out of hospital. Others point to evidence that extra doses could broaden the immune response enough to recognize new variants. Most agree that we need new vaccines that offer wider protection against future variants.

Limitations of the process

Omicron changed the thinking around boosters, says Alejandro Balazs, an immunologist at the Ragon Institute in Cambridge, Massachusetts. That's because, faced with the variant, people previously regarded as fully vaccinated now have "an antibody response that is insufficient to prevent infections", he says.

As Omicron outbreaks have spread, boosters have been used to ramp up levels of neutralizing antibodies, curbing cases and easing strain on hospitals[1,2]. But the concern is that boosters don't block infections for long.

Data from Israel, collected between June and November last year — when the Delta variant was dominant — and published online ahead of peer review, indicate that the immunity from a third shot of an mRNA vaccine wanes within months, mirroring the decline after two doses[3].

Real-world data from the United Kingdom, collected in late 2021, suggest that immunity from boosters might decrease even faster against Omicron than against Delta. However, another laboratory study, posted as a preprint that has yet to be peer reviewed, suggests that neutralizing antibodies elicited by a third dose could sustain protection against Omicron infections for up to four months[4].

Because protection from boosters might be short-lived, rolling out endless doses — potentially at the expense of immunizing unvaccinated people in low-income nations — is not a "viable or reasonable" long-term global strategy, says Kanta Subbarao, a virologist at the Peter Doherty Institute for Infection and Immunity in Melbourne, Australia.

And, in a statement released on 11 January, the World Health Organization warned that "a vaccination strategy based on repeated booster doses of the original vaccine composition is unlikely to be appropriate or sustainable".

Repeated booster doses of existing vaccines also probably offer only diminishing returns in terms of protection against future strains, says Miles Davenport, a computational immunologist at the University of New South Wales in Sydney, Australia. New vaccines that target specific variants are likely to be much more effective, he adds.

Whether a fourth shot boosts levels of infection-blocking antibodies any higher than a third dose remains to be seen, Davenport says, but that hasn't deterred nations including Chile, Cambodia, Denmark and Sweden from offering fourth doses to specific groups.

The preliminary data released from Israel last week, on study participants aged over 60, does, however, suggest that a fourth dose administered four months after the third shot revives antibody levels, doubles resistance against Omicron infection and triples protection against hospitalization, compared with only three shots.

Other studies, which looked at different parts of the body's immune response, suggest that a third shot might already provide long-lasting immunity in most cases. Protection against severe illness seems more durable and is probably due to memory B cells and T cells, which remain capable of battling Omicron even as antibody defences decline[5,6].

Real-world data from the United States, the United Kingdom and Israel show that a third (booster) shot of an mRNA vaccine protects most people against hospitalization for up to five months against Delta — and for three months or more against Omicron[7–9]. This more durable immunity "also wanes, but to a lesser extent", says Balicer, meaning that a third shot alone might be enough to prevent people getting critically ill.

Work led by Balazs further suggests that a third dose of an mRNA vaccine (a type used mostly in the West) not only restores antibody levels, but also potentially broadens responses to variants[10]. After that booster, "the antibodies actually see Omicron now, where they effectively didn't see it before", he says.

"Hopefully, this third shot is enough" to prevent severe disease for most people, and to offer some protection against infection, Balazs adds. But some studies suggest that people who are immunized with inactivated-virus vaccines — such as China's CoronaVac and Sinopharm jabs — might need two additional doses of an mRNA vaccine to combat Omicron.

Altmann says that, with differing levels of immunity from past infections in communities, and with people having had many combinations of vaccines, "we may need to take a deep breath and re-evaluate which approaches really give the most enduring immunity when overlaid on what we have so far".

Rather than administering endless booster shots, says Balicer, a better way to slow the pandemic would be to develop new vaccines that "have a longer, enduring effect, and that allow adequate protection against multiple existing and emerging strains".

The first data on Omicron-specific vaccines are expected within months — although even that might be too late, given how quickly the variant spreads. A pan-coronavirus vaccine that covers all strains, as well as related viruses, would be preferable, but "whether this will be possible isn't yet clear", says disease ecologist Marm Kilpatrick at the University of California, Santa Cruz. "There is always substantial uncertainty when dealing with viral evolution."

Peter McIntyre, an infectious-disease specialist at the University of Otago in Dunedin, New Zealand, argues that, until we have new vaccines, strategies should prioritize protecting individuals against severe illness, boosting to shield vulnerable groups and using antivirals to keep people out of hospital.

"We need to keep our focus very firmly on protection against severe disease," he says. "That is the yardstick we should be judging ourselves by."

1. Gardner, B. J. & Kilpatrick, M. Preprint at medRxiv https://doi.org/10.1101/2021.12.10.21267594 (2021).
2. Belik, M. *et al*. Preprint at Research Square https://doi.org/10.21203/rs.3.rs-1199296/v1 (2022).
3. Levine-Tiefenbrun, M. *et al*. Preprint at medRxiv https://doi.org/10.1101/2021.12.27.21268424 (2021).
4. Xia, H. *et al*. Preprint at bioRxiv https://doi.org/10.1101/2022.01.21.476344 (2022).
5. Goel, R. G. *et al*. Science https://doi.org/10.1126/science.abm0829 (2021).
6. Naranbhai, V. *et al*. Preprint at medRxiv https://doi.org/10.1101/2022.01.04.21268586 (2022).
7. Barda, N. *et al. Lancet* https://doi.org/10.1016/S0140-6736(21)02249-2 (2021).
8. Andrews, N. *et al. Nature Med*. https://doi.org/10.1038/s41591-022-01699-1 (2022).
9. Arbel, R. *et al. N. Engl. J. Med*. https://doi.org/10.1056/NEJMoa2115624 (2021).
10. Garcia-Beltran, W. F. *et al. Cell* https://doi.org/10.1016/j.cell.2021.12.033 (2021).

BIG DOG, LITTLE DOG: MUTATION EXPLAINS RANGE OF CANINE SIZES

The genetic variant probably came from ancient wolves.

By Ewen Callaway

From chihuahuas to great Danes, dogs differ more in size than any other mammal species on Earth. A mutation behind such variation has been traced to an unexpected source: ancient wolves.

The mutation lies near a gene called *IGF1*, which researchers flagged 15 years ago as having a role in the size variation of domestic dogs. It was the first of around two dozen such genes identified. But efforts to pinpoint the gene variant responsible had come up empty.

"*IGF1* has been a thorn in our side," says Elaine Ostrander, a geneticist at the US National Human Genome Research Institute in Bethesda, Maryland, who led the 2007 study that first identified *IGF1*'s role in dog size (N. B. Sutter *et al*. *Science* **316**, 112–115; 2007), as well as the 27 January study in *Current Biology* that now fulfils the quest (J. Plassais *et al*. *Curr. Biol*. https://doi.org/hfdp; 2021).

Ancient dogs, domesticated from wolves in the past 30,000 years, differed in size to some extent. But the current extreme size differences — the largest breeds are up to 40 times bigger than the smallest — has emerged in the past 200 years, as humans established modern breeds.

Ostrander and her colleagues, including geneticist Jocelyn Plassais at INSERM-University of Rennes, France, analysed the genomes of more than 1,400 canids, including ancient dogs, wolves, coyotes and 230 modern dog breeds.

Dogs differ in size more than any other mammal.

BILDAGENTUR ZOONAR GMBH/SHUTTERSTOCK

When they compared variation in the region around the *IGF1* gene with body size in dogs and wild canids, one variant stood out. It lies in a stretch of DNA that encodes a molecule — of a type called a long non-coding RNA — that is involved in controlling levels of the IGF1 protein, a potent growth hormone.

The researchers identified two versions, or alleles, of the variant. Across all breeds, dogs with two copies of one allele tended to weigh less than 15 kilograms, whereas those with two copies of the other version were more likely to weigh more than 25 kilograms. Dogs with one copy of each allele tended to be intermediate in size, says Ostrander. Canines with two copies of the large-bodied allele also had higher levels of the IGF1 protein in their blood, compared with those with two copies of the 'small' allele.

When the researchers looked at the genomes of other canids, they found a similar relationship. "This wasn't just a dog story. This was a wolf story and a fox story and a coyote story and everything story. It was canine-wide," says Ostrander.

Diminutive ancestors

The researchers think that the allele linked to small bodies is, evolutionarily, much older than the large-bodied version. Coyotes, jackals, foxes and most other canids they analysed had two copies of the 'small' version, suggesting that this version was present in a common ancestor of these animals.

It's not clear when the large-bodied allele evolved. The researchers found that an ancient wolf that lived in Siberia around 53,000 years ago carried one copy of this version. Other ancient wolves and modern grey wolves tend to have two, suggesting that the large-bodied allele might have been beneficial to wolves.

The prevailing view among scientists used to be that small body size was probably linked to relatively new genetic changes, potentially unique to domestic dogs, says Robert Wayne, an evolutionary biologist at the University of California, Los Angeles. "This turns the whole story on its head. That's what's marvellous about the whole thing."