LEON NEAL/GETTY

A man in London is given the Pfizer–BioNTech COVID-19 vaccine.

SCIENTISTS DIVIDED OVER COVID VACCINE DOSING STRATEGIES

Researchers worry that efforts to stretch limited vaccine supplies are driven by desperation, not data.

By Heidi Ledford

Amid skyrocketing coronavirus infections, some countries are attempting to stretch limited supplies of COVID-19 vaccines by reducing doses or changing vaccination schedules from those shown to be effective in clinical trials. But data are scarce on the impact of such measures, and scientists are split over whether they are worth the risks.

"It might be fine," says virologist Dan Barouch at Harvard Medical School in Boston, Massachusetts. "But we should stick with what's been proven to work."

On 30 December, the United Kingdom announced that it would allow doses of two coronavirus vaccines to be administered as many as 12 weeks apart, even though, in clinical trials, the two doses of the vaccine made by Pfizer of New York City and BioNTech of Mainz, Germany, were given to participants about three weeks apart. By delaying the second jab, the government hopes to free up doses to inoculate more people with their first shot during the current surge in cases.

Similar changes have been discussed in other countries, including the United States. Current US policy is to hold doses of the vaccine in reserve to guarantee recipients a second shot. The transition team of president-elect Joe Biden is reportedly considering an end to that. But Stephen Hahn, chief of the US Food and Drug Administration (FDA), said in a statement released on 4 January that, "at this time, suggesting changes to the FDA-authorized dosing or schedules of these vaccines is premature and not rooted solidly in the available evidence".

Delayed boosters

Many vaccines consist of multiple jabs — the first to trigger an initial immune response to certain proteins produced by a pathogen, and later booster shots calling the immune system's memory cells into action. It usually takes weeks for these memory cells to be generated. Over time, the immune system also broadens its response, developing memory cells capable of responding not only to specific proteins, but also to some variants of them. This means that a later booster shot is sometimes more effective, says immunologist Akiko Iwasaki at Yale University in New Haven, Connecticut. "Immunologically speaking, it may even help to delay a little."

This might be especially true for vaccines that use harmless viruses to shuttle the genetic code for coronavirus proteins into cells, including Russia's Sputnik V, as well as the vaccine developed by AstraZeneca of Cambridge, UK, and the University of Oxford, UK. Cells read the code and make the coronavirus protein, triggering immune responses against it. But the immune system might also generate antibodies against the harmless vector virus. If the booster is administered while levels of those antibodies remain high, the vector could be neutralized before it has a chance to deliver its cargo.

This kind of vaccine can also cause cells to express the coronavirus protein for weeks after vaccination. A booster given too soon could arrive while the immune system's initial response is still raging and memory cells are not yet established.

Resistance fears

But it is less clear how a longer interval might change the effectiveness of RNA vaccines such as that made by Pfizer, and another produced by biotech firm Moderna in Cambridge, Massachusetts. These vaccines do not use viral vectors, and they cause cells to produce the coronavirus protein for only a few days. Trial data suggest that recipients derive significant protection from the first dose, but most study participants received their second shot within a month, and little is known about the length of the immune response in the few who did not.

Some researchers are also worried about the impact of longer dosing intervals on the virus itself. Immunologist Florian Krammer at the Icahn School of Medicine at Mount Sinai in New York City says that people who receive a single dose of an RNA vaccine produce relatively low levels of antibodies, and he fears that this could encourage the emergence of viral variants that are resistant to vaccines. It is unclear how high the risk of that is. The virus SARS-CoV-2 mutates more slowly than the influenza virus, for example, which changes so rapidly that new vaccines are needed each flu season. "But at this point, I wouldn't take the risk," Krammer says.

Not everyone agrees. Sarah Cobey, who studies the evolution of viruses and immunity at the University of Chicago in Illinois, points out that natural infections can also generate fairly low antibody levels. If single doses of vaccine can reduce the number of natural infections, they might cut the risk of resistance evolving, she says. And although some variants might be partially resistant to vaccines, Cobey adds, they are unlikely to render the shots completely ineffective. The body produces a mix of antibodies targeting different regions of a foreign protein; it will be difficult for a slowly evolving virus such as SARS-CoV-2 to mutate so that none of those antibodies recognize it while still retaining its ability to infect human cells.

Meanwhile, other vaccines currently in the pipeline could provide fresh weapons against future variants. "It's a very serious thing to be sacrificing people now because you're afraid that you won't be able to handle a strain in the future," says Cobey. "If I were to place a bet, I would be doing what the UK is doing."