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Vaccine roll-out

US won't delay second dose

Countries disagree on coronavirus vaccination strategies amid warnings that a long time between shots could create lethal variants, says **Graham Lawton**

THE UK's controversial decision to increase the time between covid-19 vaccine doses has been thrust back under the spotlight after the US hasn't followed suit, amid warnings that the strategy may backfire. However, the UK is no longer alone in its decision, with Canada and Germany both choosing to follow a similar plan.

In December, the UK made the surprise decision to lengthen the interval between doses of the Oxford/AstraZeneca and Pfizer/BioNTech vaccines from the recommended three or four weeks to 12 weeks.

The rationale was that this would maximise the impact of limited supplies of the vaccine. By allowing twice as many people to be given a first dose, it would theoretically produce broader levels of protection across the population.

The decision was based on recommendations from a government advisory body, the Joint Committee on Vaccination and Immunisation (JCVI), which calculated that the level of protection from the first dose was quite high and that a 12-week gap would save 3000 to 4000 more lives per million doses of vaccine.

The strategy appears to be working, with early results from the UK's vaccination programme described as "spectacular". One study of the entire population of Scotland found that by the fifth week after a first dose, the Oxford/AstraZeneca jab reduced the risk of hospitalisation by 94 per cent and the Pfizer/BioNTech vaccine by 85 per cent.

A similar study in Israel found that the first dose of the Pfizer/BioNTech vaccine was 78 per cent effective at preventing hospitalisation after 21 days.

There is growing clamour in the US to pivot to the UK model.

Although the US is managing to roll out about 2 million vaccines a day, it is being limited by vaccine supply, said Nancy Messonnier, director of the National Center for Immunization and Respiratory Diseases (NCIRD), at a JAMA Network webinar on 26 February.

"You see op-eds and talking heads on TV news programmes saying we should be doing what the Brits are doing," says John Moore at Weill Cornell Medicine in New York. But the US won't be changing course, he says.

"There are talking heads on the news saying the US should do what the Brits are doing – but we won't"

On 1 March, the US Centers for Disease Control and Prevention held an online meeting of its own immunisation advisory body, which discussed, among other things, the evidence for and against extending the interval between doses of the mRNA vaccines made by Pfizer/BioNTech and Moderna – both approved in the US. It came down in favour of sticking with the recommended interval, which is three weeks for Pfizer/BioNTech and four weeks for Moderna, and no more than six weeks for either.

At the meeting, Kathleen Dooling at NCIRD laid out the pros and cons of delaying a second dose. On the upside, it could, in theory, protect more people in the short term, she said. But on the downside, it could leave people vulnerable to the new variants and increase the risk of yet more variants emerging.

In addition, the strength and duration of protection from a single dose remain uncertain. On balance, she said, there was "insufficient data to increase the recommended interval".

REUTERS/MARCO BELLO



A healthcare worker gives a coronavirus vaccine to a woman in Miami, Florida

"I completely agree with that," says Moore, who recently wrote an article in the journal *JAMA* specifying the arguments against a longer interval.

He detailed the fact that, even though a single dose of vaccine is protective against the original SARS-CoV-2 virus, it is less so against some of the new variants. Of particular concern are the variants that were first reported in South Africa (named B.1.351) and Brazil (P.1). Both carry a spike protein mutation called E484K, which makes them somewhat resistant to vaccine-induced antibodies, especially at lower antibody concentrations.

"You are going to need the strongest possible antibody response to deal with them," says Moore, and that means giving the second dose to schedule.

94%

Decrease in risk of hospitalisation due to covid-19 in Scotland five weeks after a single dose of the Oxford/AstraZeneca vaccine

One dose of vaccine may be enough for some

Clare Wilson



Experiments in the lab show that a single dose of mRNA vaccine isn't enough to stop these variants from replicating almost unimpeded, he says. "They just blow past it."

"If they start spreading, you're in trouble," says Moore. B.1.351 and P.1 are already present in the UK, and the E484K mutation has also been spotted in the B.1.1.7 variant, first discovered in the UK, which hasn't so far been found to be resistant to vaccines.

Another argument against longer delay is that people who are part-vaccinated are a potential breeding ground for yet more variants, says Moore. A strong antibody response should stop the virus in its tracks, while zero antibody response allows it to replicate with ease. But a half-hearted one would put

selection pressure on the virus to evolve. This hasn't yet been observed, but needs to be considered, says Moore.

John Robertson at the University of Nottingham, UK, agrees. Writing in *The Lancet*, he says: "the UK's delayed second dose could strongly favour the emergence of consequential SARS-CoV-2 variants." This risks perpetuating rather than ending the pandemic, he says. "Why make a short-term decision that could have really bad long-term consequences?" says Moore.

The UK strategy still has its supporters. Immunologist Eleanor Riley at the University of Edinburgh, UK, was a vocal proponent of the decision. "I have not yet seen any data that would persuade me that JCVI should change tack," she says.

She points out that a single dose of either of the vaccines approved in the UK provokes an antibody response at least as strong as that induced by natural infection. "Many previously infected people have weak antibody responses. So, currently, the greatest selection pressure from suboptimal antibody responses is likely

Reminder cards in the UK tell people the date of their second vaccine shot



CHRIS JACKSON/GETTY IMAGES

coming from people who have been infected. Currently there are many, many millions more of them worldwide than there are people who have been vaccinated. So one could argue that the sooner everyone has at least one shot of the vaccine, the better." (For more on the effectiveness of a single dose, see right.)

She also points to the research from Scotland suggesting that the UK vaccine programme is working. "I think the data from across the UK are supporting the rapid roll out of single doses as the fastest way to reduce deaths."

The JCVI is also sticking to its guns. "Data to date demonstrates one dose of either Pfizer or AstraZeneca vaccines are giving high levels of protection against severe disease – hospitalisations and deaths. So currently [we have] no plans to change our advice about delaying the second dose for up to 12 weeks," says JCVI deputy chairman Anthony Harnden at the University of Oxford.

Meanwhile, on 3 March, Canada's National Advisory Committee on Immunization recommended that the interval between the first and second doses of all three two-dose vaccines approved for use in the country should be stretched to a maximum of four months.

The committee acknowledged in a statement that data didn't exist for four months of effectiveness after just one dose, but said "the first two months of real-world effectiveness are showing sustained high levels of protection".

Germany has also opted to recommend an extended interval of six and 12 weeks between the Pfizer/BioNTech and Oxford/AstraZeneca doses, respectively.

Only time will tell which is the right strategy, says Moore. ■

A SINGLE dose of a coronavirus vaccine may be all that is needed for people who have already been infected with covid-19.

A small study suggests that in people receiving the Pfizer/BioNTech vaccine, the body's response to natural infection with SARS-CoV-2 seems to act like a first dose of the vaccine.

Mark Mulligan at New York University and his colleagues tracked antibody levels in 32 people who were given both doses of the vaccine, and one person who had both doses of the Moderna jab. About half had previously contracted covid-19.

About two weeks after a first dose, people who had recovered from covid-19 had antibody levels similar to or higher than those of people who had never been infected but had received both doses. The results were announced on 9 March online at the Conference on Retroviruses and Opportunistic Infections.

A separate study of 109 people in New York who had received either the Pfizer/BioNTech or the Moderna vaccine revealed similar findings.

Alongside antibodies, other aspects of the immune response may still be improved by two doses, such as T-cell activity, says Stephen Evans at the London School of Hygiene & Tropical Medicine. "If you're offered two doses, I would take them even if I thought I had been infected, because it would probably boost my overall response and it might make me more likely to respond to a variant," he says.

The US Centers For Disease Control and Prevention hasn't changed its guidance, which is that people with a confirmed, recent acute covid-19 infection may choose to temporarily delay vaccination, if desired. ■