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Five things to know about: Mixing and matching coronavirus vaccines

Amid global vaccine rollouts, with nearly 1.2 billion doses currently administered, some countries have recommended a mixed-dose approach where a first prime shot is followed by a booster of a second type.

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The measure has been introduced by France and Germany for people who received a first dose of the AstraZeneca vaccine but are in age groups for which that vaccine is no longer recommended in those countries due to rare instances of blood clotting (although the European Medicines Agency (EMA) says the benefits still outweigh the risks).

However, a more widespread policy of mixing different vaccines could also help to ease vaccine supply pressures and may even boost immune response. While the World Health Organisation has said there is currently 'no adequate data' on interchangeability, various trials are now assessing this approach.

Here are five things to know about mixing coronavirus vaccines.

1. **Mix-and-match is nothing new - it started with HIV research**

Mixing different vaccine types is known as a heterologous prime-boost vaccination. It started in the 1990s as a strategy tested by HIV researchers, according to Dr Pierre Meulien, executive director of the Innovative Medicines Initiative (IMI), an EU and European pharmaceutical industry partnership. 'Scientifically, this is not anything new,' he said.

HIV researchers knew that a classical vaccine would not induce the extremely complex immunological mechanisms needed for potential protection from HIV infection. 'People were trying to understand how you could induce both T and B cell immunity,' said Dr Meulien, referring to the critical cells in the adaptive immune system. 'And this was the main driver for that work (mixing vaccines).'

HIV was also the driver for scientists to develop new vaccine platforms to deliver their payload. These platforms include DNA, mRNA, and viral vectors such as the adenovirus, the last two both used in approved Covid-19 vaccines. The raft of new platforms created over the last 30 years is what enabled coronavirus vaccines to be developed so quickly, says Dr Frédéric Martinon an immunologist at the French National Institute of Health and Medical Research (INSERM).

Rodolphe Thiébaut, a professor of public health at France's University of Bordeaux, says the idea behind mixing vaccines is that 'you are basically presenting the antigen (the recognisable part of the pathogen) to the immune system in a different way' which helps the immune system get a better overview of the antigen and tailor its response.

A prime-boost regimen is the only vaccine to ever show efficacy - although not high enough - against HIV infection. In 2012, it was shown to reduce transmission by about 30% in phase 3 human trials. This has led to high expectations around the approach, says Prof. Thiébaut.

2. **Mixing doses can help avoid immunity against a vaccine**

Because some vaccines are delivered into the body using a modified virus, it is possible for the immune system to attack the vaccine itself. Mixing the platforms for the booster could reduce the risk of developing immunity against a viral vector vaccine.

When it comes to Covid-19 vaccines, Russia's Sputnik V, Johnson & Johnson, CanSino Biologics and AstraZeneca's products use a virus, an adenovirus - it usually causes a common cold - modified to express the coronavirus spike protein that the immune system activates against. It is 'replication deficient', so it can't copy itself in the body once injected and give us a cold, explains Pia Dosenovic, an assistant professor in immunology at Karolinska Institutet in Sweden who researches vaccine development through the project VIVA.

But it's possible for the immune system to develop a response against the adenovirus platform. This is not dangerous, says Prof. Dosenovic, but it could dampen the vaccine's effect.

To get around this possible risk, Prof. Dosenovic says Sputnik V uses a different adenovirus in each shot, and AstraZeneca uses one from chimpanzees that our systems have never encountered.

Prof. Dosenovic says getting a third shot - which is possible if vaccines are updated to address variants - with a viral vector vaccine would not be optimal. From this perspective, it makes sense to change platforms to mRNA or one that is protein-based like Novavax.

3. **Mixing vaccines can elicit a stronger/longer-lasting response than a single vaccine regimen**

When it comes to viral vector-based vaccines, a mixed-dose approach may not only stop the immune system from inhibiting a vaccine, but also confer stronger and longer-lasting protection.

'If you give a vector, vector, vector, or you give a vector, vector, protein, then I would expect that you get a stronger antibody response (to the encoded antigen) in the second approach,' said Prof. Dosenovic. 'But to know that you would have to do experiments.'

Again, this is because we want to train the immune system to attack the virus causing the disease rather than the one delivering the vaccine. 'If you mix different types of vaccine, we can imagine that you will increase the (immune) response against the common antigen which is the antigen of interest and not against the vector itself,' said Dr Martinon.

And there is precedent. The Ebola vaccine developed by Johnson & Johnson is an example of a mixed-dose approach being specifically chosen because the immune response could be long-lasting. The first shot uses the same adenovirus as the AstraZeneca coronavirus vaccine, and the second uses an MVA vector – a modified version of a poxvirus – a type that is also under investigation for future Covid-19 vaccines.

Prof. Thiébaut is coordinator of EBOVAC2, a programme assessing the safety and efficacy of this vaccine. He says they have had a 'very good response' with this strategy and predict that the new boost will enable protection to last longer than it would otherwise. 'At least half of the cells that are producing the antibodies will probably stay at least five years,' he said.

4. **The safety and effect of mixing coronavirus vaccines must be assessed**

While experts don't consider the approach of mixing vaccines to be dangerous, they say that we don't have enough data about coronavirus vaccine mixing and that safety should be evaluated as in any new vaccine strategy.

In particular, mixing mRNA vaccines with adenovirus-based vaccines and vice versa has not been done before, says Dr Meulien, as the first instance of mRNA vaccine technology being approved for human use was for Covid-19.

'I think you really need to start from scratch,' he said. 'You have to do dosing regimens and all the usual things that you do in a precautionary way. You will have to do it with these new things because none of them have been tested together before.'

Various trials are underway to test coronavirus vaccine mixing. One anticipated study is that of the Oxford Vaccine Group's Com-Cov trial - launched after the UK in January approved a mixed-dose approach - to study immune responses and any side effects of combinations of four vaccines: AstraZeneca, Pfizer/BioNTech, Moderna, and Novavax. 'What I'm hoping is that we won't rule out any combinations,' chief investigator Professor Matthew Snape told the BBC.

In terms of the research questions that need to be answered, Dr Meulien said: 'I think the types of immune response that are induced, the longevity of response, and then of course, the safety profile would be the three things that I would say would be very important.'

Spain is planning human trials of the effects of following one dose of the AstraZeneca vaccine with a dose of the Pfizer/BioNTech vaccine. Countries that have already taken decisions to mix vaccines are operating by weighing up risks and benefits, according to Dr Meulien.

'This is not brand new thinking,' he said. 'We have decades of experience in pre-clinical and clinical (work), especially in HIV, using these approaches. So it's not as if we're putting populations at risk doing this.'

5. **Mix-and-match could help us fight variants**

For Dr Meulien, the main incentive to mix vaccines is to potentially induce a broader immune response. 'I mean broaden to cover the variants that are now popping up all over the place,' he said.

But there needs to be a real scientific and regulatory justification to mix, he says.

Dr Martinon says vaccines will be improved for different variants such as those that emerged in the UK, Brazil, South Africa, and most recently in India, which is currently facing a surge in cases and a new coronavirus mutation that is potentially making Sars-CoV-2 more contagious and able to reinfect.

The next generation of vaccines will probably be directed against several coronavirus variants, he says, with different vaccines targeting different variants. Mixing these vaccines would give broad collective immunity and make it harder for variants to circulate or for new ones to emerge, according to Dr Martinon.

Periodic shots will be required, he says, although how much time between them is unknown, the hope is it will be years.

From a public health perspective, Prof. Thiébaut says mixing vaccines could help overcome this pandemic by speeding up the vaccination rollout. Obtaining good evaluations of vaccine combinations that show what works well is key.

'It's good news in terms of flexibility of every government to be able to use what they can get as soon as possible,' he said. This flexibility is crucial. 'The best way to fight these variants is to vaccinate as quickly as possible the largest part of the population on Earth.'

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