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As more COVID-19 vaccines become available, researchers are testing the impact of pairing different products that require two shots. BEATA ZAWRZEL/NURPHOTO VIA GETTY IMAGES

Should you mix and match COVID-19 vaccines? Scientists are seeking answers

By [Jon Cohen](#) | Feb. 12, 2021 , 9:00 AM

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With nine vaccines now showing they can powerfully prevent severe illness and death from COVID-19—and vaccines in short supply—researchers are mulling an issue that, even a few months ago, was only hypothetical: Should people mix and match vaccines that require two shots?

If some combinations work, they may provide needed flexibility whenever production of a vaccine falters, as often happens. And there's even a chance that mixing doses of two different vaccines may boost the protection against COVID-19.

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One mixed vaccine trial is already underway: It is examining matching a dose of the Sputnik V vaccine made by Russia's Gamaleya Research Institute of Epidemiology and Microbiology with a booster dose of a similar vaccine made by AstraZeneca and the University of Oxford. A second trial, examining a combination of the AstraZeneca-Oxford and Pfizer-BioNTech vaccines, which mixes two different technologies, is just getting started, and others are under discussion.

Until these trials produce results, however, health officials are urging caution. The U.S. Centers for Disease Control and Prevention has discouraged people from mixing vaccines unless there are "exceptional situations," such as a shortage of the vaccine they received first because of production or distribution hiccups. In the United Kingdom, Public Health England has taken a similar position.

But the scarcity of COVID-19 vaccines—and the urgency of stepping up vaccination rates—is pushing the mix-and-match issue to the fore. "As we have more products that are the interchangeable, that's going to have a huge implications for the conduct of this mass vaccination campaign in a setting of uncertain supplies," says Bruce Gellin, who heads global immunization for the nonprofit Sabin Vaccine Institute.

"There are definite advantages to having data that could support a more flexible immunization program, if needed and if approved by the medicines regulator," said Jonathan Van-Tam, the United Kingdom's deputy chief medical officer, in announcing the trial combining the [AstraZeneca-Oxford and Pfizer-BioNTech vaccines](#).

Researchers have past experience with mix-and-match vaccine trials. For more than 20 years, the long-struggling HIV vaccine field has tried to combine different vaccine strategies to elicit more powerful immune responses, but none has succeeded. Johnson & Johnson brought an [Ebola vaccine](#) to market in the European Union that combines its preparation with one that uses a completely

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different formulation made by Bavarian Nordic. Similarly, to trigger more robust protection in the elderly, a shot of a **pneumococcal conjugate vaccine** is boosted by one that contains a pneumococcal polysaccharide. The **inactivated polio vaccine**, for safety reasons, has also been given before one made with live attenuated virus, which can sometimes cause the disease if the virus mutates. But there are few other examples of using two vaccines approved for market in a one-two punch.

Mixing and matching COVID-19 vaccines raises several potential complications. One is regulatory: What if, say, only one is authorized for emergency use? Another is immunological: Whereas some vaccines share the same underlying technology platforms—such as the messenger RNA technology used by both the Pfizer-BioNTech collaboration and Moderna—others do not.

Different platforms may, on the other hand, turn on different arms of the immune system. And pairing matched platforms may dodge unwanted immune responses. For example, both **Gamaleya's Sputnik V vaccine and the AstraZeneca-Oxford** vaccine employ different adenovirus (Ad) vectors to deliver a key gene to human cells. Both require a prime shot followed by a booster. *The Lancet* has published efficacy data for each vaccine, and they have received emergency use authorizations in several countries.

Gamaleya uses two different Ad vectors that contain the spike gene for its priming and booster shots: Ad26 followed by Ad5.

AstraZeneca and Oxford use the same chimpanzee adenovirus (ChAd) for both its prime and booster. In theory, AstraZeneca's use of the same vector for both shots means the immune response triggered by the first shot could cripple the booster. That potential problem could be avoided by pairing the AstraZeneca shot with the Sputnik V one, presumably in either order.

Gamaleya, in turn, might benefit from using the AstraZeneca-Oxford vaccine as a booster because the institute, according to a Bloomberg report, has had problems making the Ad5 vector. (Sputnik V representatives told *Science* they had no comment about the Bloomberg report, but said delays in supplies to Latin America could occur as they upgrade manufacturing facilities.) And many researchers have criticized Gamaleya for choosing Ad5 because of disastrous trials in 2007 with an Ad5-based HIV vaccine that somehow *increased* the risk of infection with the AIDS virus. So an Ad26-ChAd combination gets around that concern.

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Sputnik V's financial backers also contacted CanSino Biologics, a Chinese company that makes an Ad5 spike vaccine that's used as a single shot, to discuss pairing their vaccines, CEO Yu Xuefeng told *Science*. But they have not negotiated a deal as of yet. CanSino has not reported efficacy data. (A health adviser to Pakistan's prime minister tweeted on 8 February that the CanSino candidate worked in a trial there and in other countries. Yu said he couldn't confirm the report because the company has not seen the data, but believes it is accurate.)

The United Kingdom's National Immunisation Schedule Evaluation Consortium is moving ahead with an elaborate mix-and-match study of the AstraZeneca-Oxford and Pfizer-BioNTech vaccines. It has eight different strategies that will involve giving the vaccines in different orders and at different intervals. Van-Tam hopes the trial will produce "greater insight into how we can use vaccines to stay on top of this nasty disease."

Gellin, for one, is frustrated that more mix-and-match trials aren't already up and running. "It's got to be a top priority for someone," he says. But Gellin concedes the regulatory issues are daunting. "This is something that companies should do, and maybe they'll be able to do it," he says. "But they'll probably require more lawyers than volunteers."

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