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Vaccine makers say they will act quickly to redesign and roll out COVID-19 jabs if needed.

COVID VACCINE MAKERS BRACE FOR A VARIANT WORSE THAN DELTA

Companies are updating and testing jabs to prepare for whatever comes next in the pandemic.

By Emily Waltz

Pfizer's chief executive, Albert Bourla, made a bold promise in June. Standing next to US President Joe Biden at a press conference in St Ives, UK, just before the summit meeting of the G7 group of wealthy nations, Bourla said that, should the need arise for a new COVID-19 vaccine, his company could get one ready within 100 days.

The need he was referring to is the possible emergence of an 'escape variant' — a dominant strain of SARS-CoV-2 that evades the fledgling immunity established through vaccines and previous infections. No such strain has yet been identified, but Pfizer and other leading COVID-19 vaccine makers are gearing up for that scenario.

What does it take to be nimble enough to design and test an updated vaccine against an unknown viral strain, in record time? *Nature* spoke to three COVID-19 vaccine makers — Pfizer, Moderna and AstraZeneca — to find out exactly how they are preparing.

Over the past few months, all three companies have been running dress rehearsals by practising on known SARS-CoV-2 variants. This involves updating their vaccines to match variants such as Beta and Delta, testing them in clinical studies, tuning internal workflows and coordinating with regulators. Their goal is to learn from these warm-up trials and to smooth out kinks in their processes, so that they can move fast if, or when, a true escape variant emerges.

"At some point, inevitably, we're going to have to make variant vaccines — if vaccines are the way population immunity will be maintained — but we're not at the point where we can confidently predict the evolution of the virus," says Paul Bieniasz, a virologist at the Rockefeller University in New York City. "Practising with existing variants seems like a reasonable approach."

Dress rehearsal

The first generation of COVID-19 vaccines seems to be holding up against Delta and other known variants, at least in preventing severe disease and hospitalization. Pfizer, Moderna and AstraZeneca say that their vaccines, which are based on the original SARS-CoV-2 strain that was first detected in Wuhan, China, still offer the best protection against all known variants. "There really isn't a need at this time to make a new vaccine that will be more effective, because it looks like the old ones work very well [against] the Delta variant," says Kathryn Edwards, scientific director of the Vanderbilt Vaccine Research Program at Vanderbilt University Medical Center in Nashville, Tennessee.

If an escape variant emerges, RNA vaccine makers such as Pfizer and Moderna could probably design and synthesize an initial prototype jab against it in a few days. Viral-vector vaccines, such as AstraZeneca's, could follow closely behind. Making an RNA vaccine typically involves generating a new genetic sequence and encapsulating it in a fatty substance such as a lipid. Viral-vector vaccines are generated by inserting the key genetic sequence into a harmless carrier virus, culturing large quantities of the virus in a bioreactor, and purifying them.

But before these shots can be deployed, they will have to be tested in humans, and that will take time. So pharma companies are doing dry runs. Pfizer, with its partner BioNTech, based in Mainz, Germany, is testing a Beta-specific RNA vaccine in a randomized, placebo-controlled clinical trial with up to 930 participants. In August, the companies began a trial of a multivalent vaccine that targets both the Delta and Alpha variants.

"We're not doing that because we actually think we need a new vaccine for those strains," says Philip Dormitzer, vice-president and chief scientific officer of viral vaccines and mRNA at Pfizer, based in New York City. "We want to practise all aspects of executing a strain change — the preclinical research, the manufacturing, the clinical testing and the regulatory submissions — so that if we do see a variant out there that truly escapes vaccine immunity, we're ready to go fast." Dormitzer says Pfizer currently has no plans to deploy its Beta or Delta vaccines among the public.

Moderna, based in Cambridge, Massachusetts, is recruiting cohorts of 300–500 participants to test new RNA vaccines against Beta, Delta and a combination of Beta and the original strain. The company also plans to test a Beta–Delta multivalent vaccine. The purpose is to submit test cases to the US Food and Drug Administration and "establish a process by which this could happen more quickly in the future", says Jacqueline Miller, a senior vice-president and head of infectious-disease research at Moderna.

Beta is a particular focus because it carries mutations that make it more resistant than any other known variant to neutralization by antibodies created in a person's body after they've been vaccinated. "If there's another strain that evolves those mutations in the future, we can capitalize on what we've already learned from studying the Beta variant," Miller says.

AstraZeneca, based in Cambridge, UK, has begun a large study of a Beta-specific viral-vector vaccine. Launched in June, the study is enrolling more than 2,800 participants, many of whom have already been vaccinated with

either an mRNA vaccine or AstraZeneca's first-generation viral-vector vaccine. "We're definitely practising with this one, but we are also developing it, and if it's successful, we will have it ready to use," says Mene Pangalos, executive vice-president of biopharmaceuticals research and development at AstraZeneca.

EMBL PHOTOLAB

Real-world effectiveness

Determining the true efficacy of variant vaccines will be difficult. In regions where COVID-19 vaccine trials are well established, it can be hard to find volunteers who have not yet received a vaccine, yet are willing to enrol in an experimental trial of a new one. There might also be ethical concerns around recruiting placebo groups for randomized controlled trials, given that effective vaccines are available.

"If we're not going to do randomized controlled trials for efficacy, one alternative would be to do immunogenicity studies, plus really robust, well-designed real-world effectiveness studies," says Matthew Hepburn, who until August was the director of COVID-19 vaccine development at the US government's Countermeasures Acceleration Group (formerly Operation Warp Speed) and is now a special adviser at the White House Office of Science and Technology Policy.

Immunogenicity studies would measure the immune responses triggered by variant vaccines — for instance, an increase in antibody or B-cell levels — and compare those with the effects of the first-generation vaccine. That seems to be where some vaccine makers are heading: on the basis of guidance from European regulators, AstraZeneca will use this approach in its Beta-vaccine trial.

Moderna is also focusing on immunogenicity data, and is collaborating with a hospital system in Southern California to collect real-world data on vaccine effectiveness. In these observational studies, participants can choose whether they get a vaccine or not, and researchers monitor the two groups to see how they fare. Such studies "aren't perfect", concedes Miller, because the two groups might have different behaviours and risk factors.

How public-health authorities will determine that a variant has escaped — and therefore that the world needs a new COVID-19 vaccine — isn't yet clear. Pangalos offers one way to measure that: "If we start to see lots of people going into the hospital that have been vaccinated, then we have a problem," he says. "But right now, we're nowhere near that."

Miller hopes that the process of updating a COVID-19 vaccine will eventually become as streamlined as changing an influenza vaccine, which typically doesn't require much in the way of clinical studies. And because RNA vaccines can be manufactured more quickly than can conventional jabs, she adds, "the idea would be to make that switch even more rapidly than we're able to do with flu".

Q&A

'Politicians shouldn't meddle': new chief of Europe's major research funder

On 1 November, developmental geneticist Maria Leptin will become president of the European Research Council (ERC), Europe's premier funding agency for basic research.

What are your top priorities as incoming president?
The ERC is a fantastic organization with fantastic aims and a fantastic staff. I wouldn't dream of coming in and saying we have to change everything. My first aim will be to keep the ERC stable and emphasize its strength. Of course, there are always things that can be improved, such as attaining broader public engagement. The ERC's service to the scientific community might need tweaking, because different fields have different needs.

The ERC aims to be independent from politics. What is your plan to keep the ERC true to its founding mission?
I'm hoping this doesn't need a plan. We have sufficient examples to remind people of how important it is not to meddle with the autonomy of basic research. Everybody recognizes that COVID-19 vaccines were developed so fast because a range of fields, which had been receiving basic-research funding for a long time, suddenly came together. It illustrates that necessary and topical science comes bottom-up from the best scientists.

How will you promote the value of basic research?
That's really not easy, and I wouldn't say I have a recipe. The ERC budget is decided by European Union member states and the European Parliament, and parliamentarians listen strongly to their home constituencies. It's clear that the public needs to realize what basic research is about and what it does for them. We will have to think very hard about new routes to get to the public — and it's not just going to be senior people giving lectures. One way to get there is working with locally engaged media experts to reach the people who need to be reached.

Do you envision special ERC programmes, such as on climate or COVID-19 research?
I would not go for top-down research. We have programmes for that, including the European Innovation Council and the rest of Horizon Europe, the EU's seven-year research programme.

ERC funding is very sought after by early-career scientists, but success rates for starting grants are low (13.5% in 2020). How will you keep young researchers happy?
Well, I think all researchers should be kept happy. Of course I'd like to be able to fund more of them. I also would like to not let them fall off a cliff after getting their first starting grant, when they apply for consolidator or advanced grants and find out that it's even tougher to get one (2020 success rates were 13% and 8%, respectively). For every funding call, there are lots of good proposals that cannot be funded. I really would like the award rates to go up, but there's only two ways to do this: either fewer applications or more money.

The United Kingdom and Switzerland are still negotiating access to Horizon Europe. What does this mean for grant applicants from these countries?
We are all desperately hoping that Switzerland and the United Kingdom will associate with Horizon Europe. We care about our colleagues in these countries and their science, and we want them in the ERC. At the moment, UK-based researchers can apply for funding, but grants can be awarded only once the association agreements have been signed.

Do you think it would be better to keep politics out of science?
It's the prerogative of elected governments to determine what goes on in their constituencies, and if science is part of that, they should have a say. But politicians who are not trained in science should not meddle in our day-to-day business, or tell scientists what's right or wrong. I would see it as my duty to explain to politicians what's best, and to get them to realize that. They distribute the money, so we have to make them understand what's good for people, rather than say, "Just stay out."

Interview by Quirin Schiermeier
This interview has been edited for length and clarity.