News in focus

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A health-care worker in Tbilisi, Georgia, fills a syringe with the AstraZeneca vaccine.

WHAT SCIENTISTS DO AND DON'T KNOW ABOUT THE OXFORD–ASTRAZENECA COVID VACCINE

Results confirming that the vaccine provides strong protection against COVID-19 were welcomed after a pause in roll-outs.

By Ewen Callaway & Smriti Mallapaty

The Oxford–AstraZeneca vaccine's rollercoaster ride of uncertainty might have come to a welcome end. A key phase III clinical trial found the vaccine to be 76% effective at preventing COVID-19, the company announced on 25 March, two days after it was accused of misrepresenting interim results, which reported a slightly higher efficacy of 79%. Scientists hope the kerfuffle will not cause lasting damage to the vaccine's reputation, which could be bolstered by scrutiny — and probable approval — by US drug regulators.

"Overall it's a win for the world," says Ann Falsey, a vaccine scientist at the University of Rochester, New York, an investigator on the trial who co-developed its protocol. "The final story is, the results for the final analysis are great. They look very similar to the interim analysis."

"The world, the species, depends on this vaccine. This is 2.5 billion people's worth of vaccine," says Eric Topol, a physician-scientist and director of the Scripps Research Translational Institute in La Jolla, California.

The latest developments highlight issues regarding how trial data are being communicated through press releases, say researchers.

The news came a week after countries across Europe temporarily halted roll-outs to review reports of rare blood-clotting conditions in a handful of vaccinated individuals. The vaccine has since been deemed safe by the European Medicines Agency (EMA) and continues to be recommended by the World Health Organization (WHO).

After all the uncertainty, *Nature* looks at

In the Chilean capital of Santiago, people await their COVID-19 vaccines.

CLAUDIO SANTANA/GETTY

everything we do and don't know about the AstraZeneca vaccine.

What is the vaccine's role in the pandemic?

Unlike many of the vaccines, which are expensive and must be stored at very low temperatures, the Oxford–AstraZeneca vaccine can be kept in an ordinary fridge and costs a few dollars per dose. And, because it is expected to be produced on a huge scale, it could play an essential part in quelling the pandemic.

For the moment, "in many countries, especially on the African continent, the AstraZeneca vaccine is the only one that will be available in substantial quantities", says Shabir Madhi, a vaccinologist at the University of the Witwatersrand in Johannesburg, South Africa.

The vaccine has received regulatory approval in more than 100 countries and should be used with confidence, says Kristine Macartney, director of Australia's National Centre for Immunisation Research and Surveillance in Sydney. But it has not yet been approved in the United States.

More than 20 million doses have been administered in EU countries and the United Kingdom; a further 27 million doses of a version of the vaccine known as Covishield have been administered in India. The vaccine is also being delivered through the COVAX scheme to dozens of low- and middle-income countries: AstraZeneca has committed 170 million doses to COVAX and plans overall to produce 3 billion doses by the end of 2021.

How effective is the vaccine?

On 22 March, the company said in a press release that a preliminary analysis had found two doses to be 79% effective at preventing COVID-19 in a trial of 32,449 adults across the United States, Peru and Chile. No participants who received the vaccine were hospitalized or died from COVID-19, even though 60% had pre-existing conditions associated with increased risk of severe disease, such as diabetes or obesity. Only 141 cases of COVID-19 were reported overall, although the breakdown of cases in people who received the vaccine, and those who did not, has not yet been revealed.

The following day, the US National Institutes of Allergy and Infectious Diseases (NIAID) said that an independent data-safety monitoring board (DSMB) overseeing the trial had concerns that AstraZeneca could have presented "outdated information" that provided an incomplete view of the vaccine's efficacy. In a letter obtained by *The Washington Post*, the DSMB told NIAID that it had urged AstraZeneca to communicate an efficacy of 69–74%, based on more current data.

> **"I think the way that the ship will be righted is by having the FDA's scrutiny."**

In a subsequent statement, AstraZeneca said that its 79% efficacy figure had been based on an interim analysis of early data up to 17 February. On 25 March, it press-released updated trial results reporting an overall efficacy of 76%, which was a little higher than the results of previous trials conducted in the United Kingdom, Brazil and South Africa, involving more than 20,000 participants, which reported efficacies ranging from 60% to 70%. But these were based on pooled results from multiple trials with different dosing regimens – studies that the EMA described as "sub-optimal".

There had been "a lot of claims made on relatively weak data", says Hilda Bastian, an independent scientist who studies evidence-based medicine in Victoria, Australia, but the trial behind the latest efficacy estimates is based on much more robust data. Although impossible to compare directly, the overall figure is close to the 66% efficacy of Johnson & Johnson's COVID-19 vaccine, but lower than the figures for the vaccines made by Pfizer and Moderna, both of which have efficacies higher than 90%.

So far, there has been no evidence of differences in efficacy and safety in people of different ethnicities. The latest announcement stated that 22% of trial participants were Hispanic, 8% were Black and 4% were Native American.

How safe is the vaccine?

This question loomed large several weeks ago in Europe, when more than 20 countries paused the roll-out after scattered reports of rare blood-clotting conditions, mostly in women aged 55 or younger. This was despite the vaccine having been approved and rolled out to millions in the United Kingdom, and the WHO continuing to recommend its use, saying that the benefits outweighed the risks.

An EMA expert committee said on 18 March that the vaccine was safe and was not associated with a higher risk of blood-clotting generally, but it couldn't rule out a link with two very rare and serious clotting conditions, one of which affects blood vessels that drain the brain. It suggested that these potential risks be stated on the product's packaging.

With the release of the interim trial data, AstraZeneca also said that it had not identified any safety concerns, and had found no cases of that specific disorder, which is called cerebral venous sinus thrombosis. "I hope this data is reassuring," says Falsey. But other researchers caution that the condition could be too rare – appearing in one or two people out of a million – to crop up in a trial of tens of thousands.

In unpublished work, scientists in Norway and Germany have reported one possible mechanism by which the vaccine could have caused rare blood-clotting conditions, as well as a possible treatment.

How well does the vaccine work in older people?

The first studies included too few participants aged over 55 for researchers to know whether the vaccine offers the same protection for older people as for younger people. "That was a pretty big hole in the data," says Griffin.

This lack of evidence meant that some countries, including Germany, initially didn't approve the vaccine for those aged 65 or older. But Germany later revised its guidelines to include all adults, after reviewing studies from England and Scotland. Those studies showed

"strong protection against hospitalization, death and disease", says Macartney.

AstraZeneca's interim trial data suggest that the vaccine is 80% effective at preventing COVID-19 among those aged 65 or older, who made up 20% of participants. The press release does not state how many cases of COVID-19 were found in this cohort, but Falsey said there were enough infections in the older age group to enable a statistically significant comparison.

What is the optimal timing of doses?

The optimal dosing schedule has been unclear since the first results were announced in November, revealing that a subset of participants who had accidentally received less vaccine in their first dose were less likely to develop COVID-19. A later analysis suggested that the increased protection resulted not from a dosing error, but from the longer time between doses.

Early trials were originally designed for a one-dose regimen, but researchers decided to add a booster after data showed that a single dose didn't produce a strong enough immune response. They tried a range of intervals between doses, from 4 to 12 weeks.

The interim results from AstraZeneca do not add more clarity on how to optimize dosing, because all participants were given two doses four weeks apart. Falsey says that a longer gap would probably induce a stronger immune response, but a briefer interval is more practical in the middle of a pandemic. The WHO recommends an interval of 8 to 12 weeks.

What will be the impact of this week's confusion on the US roll-out?

Falsey said on Monday that AstraZeneca planned to file for emergency-use authorization with the US Food and Drug Administration (FDA) in the coming weeks, and hopes to gain approval in April.

Stephen Evans, a biostatistician at the London School of Hygiene & Tropical Medicine, hopes that the FDA will put the vaccine's reputation back on track. In contrast to other regulators, the FDA uses raw trial data to conduct its own analysis. "I think the way that the ship will be righted is by having the FDA's scrutiny," says Evans, who expects the agency to authorize the vaccine eventually.

It is unclear whether the vaccine will be widely rolled out in the United States, which is flush with doses of vaccine from Pfizer, Moderna and Johnson & Johnson. But researchers worry that confusion over the AstraZeneca vaccine's efficacy will dent global uptake. "What I'm most distressed about is the effect in low- and middle-income countries — that they will lose confidence," says Evans.

This uncertainty only adds to any fallout from the pauses in Europe last week. "Decisions made in the global north can have substantial consequences," warns Madhi.

How does the Oxford–AstraZeneca vaccine perform against variants?

A big question facing all vaccines since new virus variants started emerging last year — some more transmissible than earlier variants — is how well vaccines work against them. Preliminary analysis in one UK trial of the AstraZeneca vaccine found that it provided a similar level of protection against the B.1.1.7 variant, first detected in the United Kingdom, as it did against pre-existing variants.

But the situation with the variant B.1.351, first detected in South Africa, is more complicated. A small study there, of some 2,000 adults aged under 65, found that it didn't protect against mild-to-moderate COVID-19 from that variant. South Africa has suspended roll-out of the vaccine, but the WHO still recommends it in regions where variants of concern are circulating.

Soon, AstraZeneca will start trials on next-generation vaccines that will work against all current variants of the virus SARS-CoV-2, said Mene Pangalos, the company's executive vice-president of biopharmaceuticals research and development, at a virtual press briefing on 23 March. He added that he hopes they will become available for use in late 2021.

Additional reporting by Heidi Ledford.

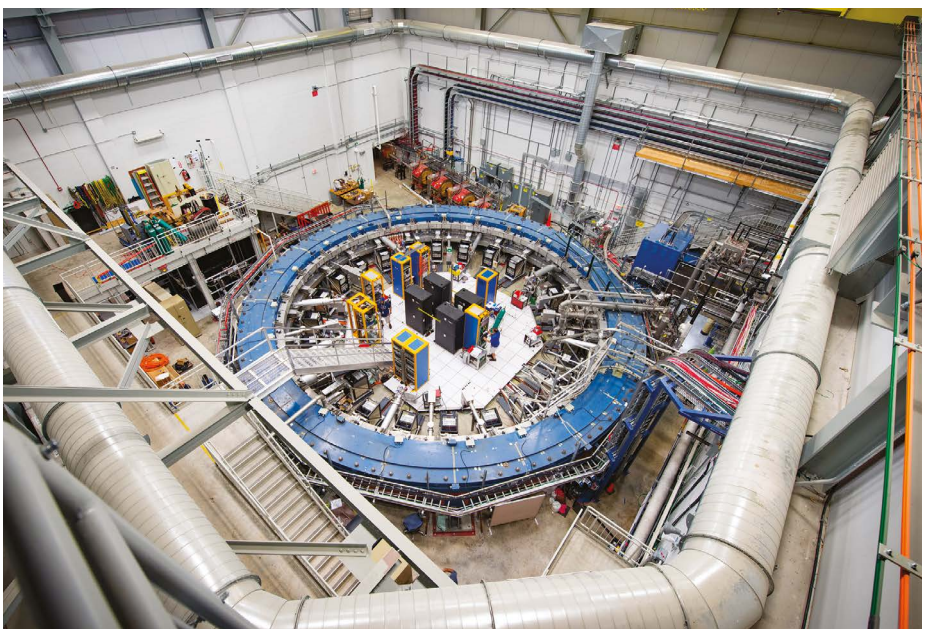
LONG-AWAITED MUON PHYSICS EXPERIMENT NEARS MOMENT OF TRUTH

Results could reveal the existence of new particles, and upend fundamental physics.

By Davide Castelvecchi

After a two-decade wait that included a long struggle for funding and a move halfway across a continent, a rebooted experiment on the muon — a particle similar to the electron but heavier and unstable — is about to unveil its results. Physicists have high hopes that its latest measurement of the muon's magnetism, scheduled to be released on 7 April, will uphold earlier findings that could lead to the discovery of new particles.

The Muon *g*−2 experiment, now based at the Fermi National Accelerator Laboratory (Fermilab) in Batavia, Illinois, first ran between 1997 and 2001 at Brookhaven National Laboratory on Long Island, New York. The original results, announced in 2001 and then finalized in 2006 (ref. 1), found that the muon's magnetic



REIDAR HAHN/FERMILAB

The storage-ring magnet used for the *g*−2 experiment at Fermilab.