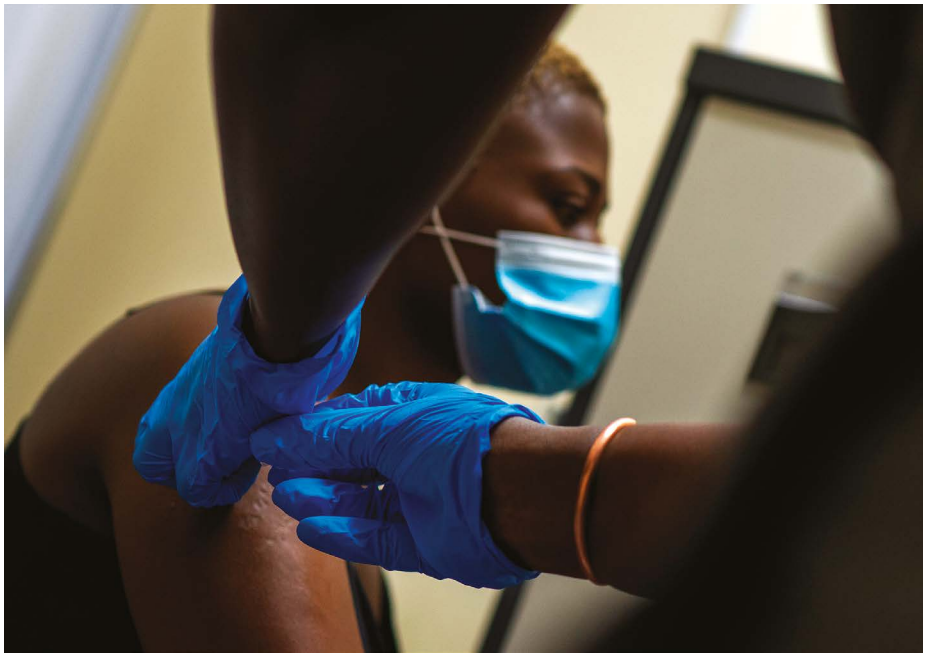

JEROME DELAY/AP/SHUTTERSTOCK

Large-scale trials of COVID-19 vaccines have been conducted at an unprecedented speed.

# COVID VACCINES: WHAT SCIENTISTS NOW WANT TO KNOW

UK approves Pfizer–BioNTech vaccine. Researchers are watching how it and others will perform.

**By Heidi Ledford, David Cyranoski & Richard Van Noorden**

With striking speed, the United Kingdom has become the first country to approve a COVID-19 vaccine that has been tested in a large clinical trial. On 2 December, UK regulators granted emergency-use authorization to a vaccine from drug firms Pfizer and BioNTech, just seven months after the start of clinical trials. Hospitals have already administered the first doses; front-line health-care workers, care-home staff and residents are at the head of the queue.

China and Russia have approved vaccines already, but without waiting for the immunizations to complete the final round of tests in people. Regulators in the United States and the European Union are expected to issue their decisions on the Pfizer vaccine in the coming weeks.

Tests on more than 43,000 people have shown that it is 95% effective at preventing disease when measured a week after participants are given their second dose, the New York City-based firm said in November when it and BioNTech, in Mainz, Germany, submitted a request for emergency approval to the US Food and Drug Administration. The trial has so far gathered data from only 170 cases of COVID-19 across its control and intervention arms, and real-world efficacy might be lower than in a trial, but it is still an extraordinarily promising result, says immunologist Danny Altmann at Imperial College London: "This is brilliant news."

The approval is a historic moment. But scientists still have many questions about how this and other vaccines will perform as they're rolled out to millions of people.

## Do the vaccines prevent transmission of SARS-CoV-2?

In addition to the Pfizer vaccine, regulators are poring over data from a similar vaccine made by Moderna of Cambridge, Massachusetts, and a third produced by AstraZeneca of Cambridge, UK, and the University of Oxford, UK. All three have been tested in large clinical trials, and have shown promise in preventing disease symptoms.

But none has demonstrated that it prevents infection altogether, or reduces the spread of the virus in a population. This leaves open the chance that those who are vaccinated could remain susceptible to asymptomatic infection – and could transmit that infection to others who remain vulnerable. "In the worst-case scenario, you have people walking around feeling fine, but shedding virus everywhere," says virologist Stephen Griffin at the University of Leeds, UK.

Pfizer has said that its scientists are looking at ways to assess virus transmission in future studies. For now, AstraZeneca and the University of Oxford might be able to provide the first hints as to whether a vaccine can protect against such transmission. Although they have yet to publish complete results, their trial did routinely test participants for SARS-CoV-2, allowing investigators to track whether people became infected without developing symptoms. Early indications are that the vaccine might have reduced the frequency of such infections, which would suggest that transmission might also be reduced.

## How long will vaccine-induced immunity last?

There is no quick way to determine how long immunity to the SARS-CoV-2 virus will last, and researchers will need to monitor this closely in the coming months and years.

There have been some reports that people who have had one bout of COVID-19 and developed antibodies against it can experience falling antibody levels and even reinfection months later, but it is still unclear how prevalent reinfection is. There are signs that the immune system preserves a memory of coronavirus infection in the form of specialized memory cells that could kick into action rapidly if the virus is encountered again. And vaccines, Altmann says, are deliberately designed to provoke strong responses from the immune system.

Still, it will be important for public-health officials to monitor immunity – and to know when it begins to wane. One way to do that, in addition to keeping track of infections among people who have received the shots, is to assess their levels of antibodies and immune cells periodically. Tracking how these immune responses change could give an early indication of when they are waning to worrisome levels, says Altmann. But the wide variation in people's immune responses could make it a challenge to understand the circumstances in which a vaccine doesn't work, and such studies will need to track many people. "You need to have a good stab at some high-level population analysis to work out whether you're winning or losing," says Altmann. "Otherwise, you might be a government kidding yourself in years' time."

## How well do the vaccines work in older people and other groups?

The major vaccine trials so far have enrolled tens of thousands of people, but for each one,

conclusions about effectiveness are drawn from fewer than 200 people who have developed disease. As a result, it can be difficult to break up the data to look at efficacy in different groups — such as people who are obese or elderly — without losing statistical power. More data are needed across demographics, says Michael Head, an infectious-disease researcher at the University of Southampton, UK.

There are early indications that the three leading vaccines protect people over 65. But researchers will probably need real-world data from large numbers of vaccinated people before they can get the demographic granularity necessary to ensure that parts of the population aren't left unprotected.

There are no data yet on how the vaccines fare in children and pregnant women. On 2 December, Moderna unveiled plans to test its vaccine in adolescents.

### How do the vaccines stack up against each other?

All three leading vaccines have probably beaten the goal of achieving 50% efficacy, and all seem to be safe, on the basis of the clinical-trial data so far. But there might be differences in how well they work.

The vaccines from Pfizer and Moderna rely on RNA encased in a lipid particle that ferries it into cells, where it helps to generate a viral protein that stimulates the immune system. AstraZeneca's vaccine uses DNA that is shuttled into cells inside a harmless virus.

Early data suggest that the RNA approach might be more effective for preventing disease symptoms developing. But there are subtle differences in the immune responses provoked by each approach, notes Griffin. Researchers might eventually find that one approach works better than another in certain groups of people, or that one is the best at limiting transmission.

Differences in costs and logistics will also shape which vaccine is best for which region. Shortly after the UK government announced the authorization of the Pfizer vaccine, officials acknowledged that getting the vaccine to residents in individual care homes would be a challenge, because it needs to be stored at extremely low temperatures (−70 °C). The other two vaccines do not need to be kept at such low temperatures, and the AstraZeneca immunization is likely to be the easiest and cheapest to store, says Head.

Comparisons between the effectiveness of the different vaccines are important and should be done, but until then, the path forward is clear, says Altmann. "Grab any vaccine that your government can buy," he says.

### Could the virus evolve to evade immunity given by vaccines?

Some viruses, such as the influenza virus, are notorious for mutating. The SARS-CoV-2 genome, however, seems to be fairly stable so far. Most of the vaccines being developed, including the three that lead the pack, target a molecule called the spike protein, which the virus needs to infect cells. And immune responses elicited by those vaccines will probably target multiple sites on that protein.

This gives researchers some reassurance that the virus might not evolve ways to evade immunity. But mass vaccination campaigns will, for the first time, put enormous pressure on SARS-CoV-2 to adapt, and will select for any strain of the virus that might be able to escape immune defences. "We've never seen a virus like this under selective pressure," says Griffin. "So we don't know how it's going to respond."

As a result, researchers will need to monitor samples of SARS-CoV-2 for signs of change, says Charlie Weller, head of vaccines at the biomedical research charity Wellcome in London. "Robust surveillance with ongoing sampling and sequencing will be key," she says.

### How will scientists monitor for long-term safety concerns?

The Pfizer vaccine has completed only a few months of the two-year clinical-trial period needed before it is approved to be sold freely on the market. As a result, people will be watching closely for as-yet unobserved signs of danger.

Clinical trials vet vaccines rigorously for potential side effects with a combination of self-reporting from participants and data collection by clinicians. Pfizer's trials revealed that some recipients experienced pain at the injection site, along with fever, fatigue, sore muscles and headaches — although these symptoms are generally not serious.

But after a vaccine is approved, whether fully or only for emergency use, clinicians are expected to continue reporting any adverse reactions. Many countries have some kind of programme, such as the US Vaccine Adverse Event Reporting System, that collects reports of serious symptoms after people receive a vaccine. US doctors are legally bound to report such symptoms. For COVID-19 drugs and vaccines, the United Kingdom has set up a specialized Coronavirus Yellow Card reporting site.

Such systems work, says Jerome Kim, director-general of the International Vaccine Institute in Seoul. "You still need strong surveillance. These rare events can be important," he says.

# CAN JOE BIDEN MAKE GOOD ON HIS AMBITIOUS CLIMATE AGENDA?

The US president-elect faces an uphill battle, but there are levers he can pull to curb global warming.

**By Jeff Tollefson**

When Joe Biden won the US presidency last month, it seemed like a huge opportunity to restore the country's position as a leader in the fight against climate change. But whether he'll be able to deliver on his aggressive climate agenda remains to be seen, especially because he will face a powerful Republican opposition in Congress.

Still, climate-policy experts say that there is a lot the former senator and vice-president to Barack Obama can do, including exerting his authority over federal agencies and leveraging his experience working with both parties in the Senate to push legislation in Congress.

"This is really the first time that a US president is leading with climate," says Vicki Arroyo, executive director of Georgetown University's Climate Center in Washington DC. That's exciting, she says, but suggests cautious optimism: global warming is still a partisan issue on Capitol Hill, and "that is going to limit what Biden can accomplish".

Biden's election comes at a crucial juncture. President Donald Trump pulled the United States out of the Paris climate agreement last month, but other players on the world stage, from China to the European Union, are preparing to present a new round of commitments at the United Nations climate conference in Glasgow, UK, next year.

Having the United States back on board will give an important boost to these negotiations, says Jean-Pascal van Ypersele, a climatologist at the Catholic University of Louvain in Louvain-la-Neuve, Belgium, and former vice-chair of the Intergovernmental Panel on Climate Change. "The stars are much better aligned for a successful outcome in Glasgow than they would have been if Trump had been re-elected."

Biden's first opportunity to advance his