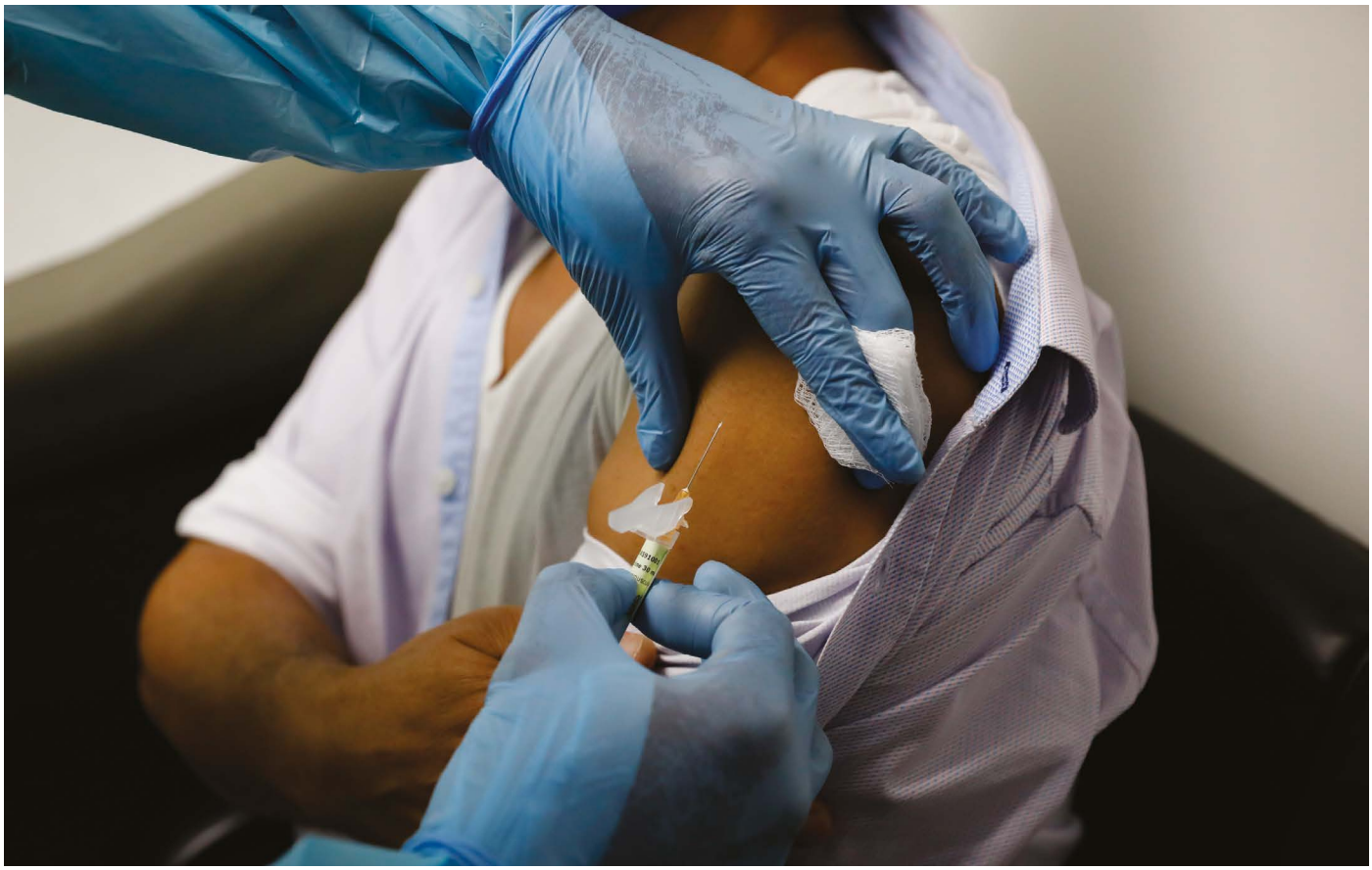
News in focus



EVA MARIE UZCATEGUI/BLOOMBERG VIA GETTY

COVID-19 vaccines are being tested in tens of thousands of people around the world.

WHAT LANDMARK COVID VACCINE RESULTS MEAN FOR THE PANDEMIC

Scientists welcome the first compelling evidence that vaccines can prevent COVID-19 – but questions remain about how much protection they offer, and for how long.

By Ewen Callaway

Scientists have greeted with cautious optimism a slew of positive preliminary results from phase III trials of COVID-19 vaccines – the final round of human testing for these experimental immunizations. In the past week, three major efforts – led by drug firm Pfizer, biotech company Moderna and Russian developers – reported early data from phase III trials. Each said that its vaccine is more than 90% effective at preventing coronavirus infection. The results offer the first compelling evidence that vaccines can prevent COVID-19 – but the data do not answer key questions that will show whether the vaccines can block transmission of COVID-19, and how well they work in different groups of people.

"We need to see the data in the end, but that still doesn't dampen my enthusiasm. This is fantastic," says Florian Krammer, a virologist at Icahn School of Medicine at Mount Sinai in New York City, of results from Pfizer's trial, which was the first to report early data, on 9 November.

In phase III trials, candidate vaccines are given to a large number of people who are followed for weeks or months to see whether they become infected and symptomatic. These results are compared with those for a group of participants who are given a placebo.

Pfizer, a New York City-based drug company that is developing a vaccine with German biotech firm BioNTech, revealed in a press release that its vaccine is more than 90% effective. The two-dose vaccine consists of molecular instructions – in the form of messenger RNA – for human cells to make the coronavirus spike protein, the immune system's key target for this type of virus. The effectiveness was based on 94 cases of COVID-19 among 43,538 trial

participants, when measured a week after participants received their second vaccine dose. The trial, which started on 27 July, will continue until 164 COVID-19 cases are detected, so initial estimates of the vaccine's effectiveness could change.

Pfizer's news was followed on 11 November by a press release from a Russian vaccine trial dubbed Sputnik V, which said that its candidate seems to be similarly effective.

The Gamaleya National Center of Epidemiology and Microbiology in Moscow and the Russian Direct Investment Fund said that an interim analysis of 20 COVID-19 cases identified among trial participants has found that the vaccine was 92% effective. The vaccine is composed of two different adenoviruses that produce the coronavirus spike protein, administered three weeks apart. The analysis looked at more than 16,000 volunteers — who received either the vaccine or a placebo — 3 weeks after they had taken the first dose. The trial has enrolled a total of 40,000 participants, the release said.

Some scientists criticized the scant data on which the analysis was based. It is difficult to interpret the clinical-trial results without more information, says Shane Crotty, a vaccine immunologist at the La Jolla Institute for Immunology in California. "I would not conclude anything from 20 events."

The Sputnik V trial's protocol has not been made public, in contrast to those of Pfizer and some other leading candidates in phase III trials, so it is unclear whether an interim analysis after just 20 COVID-19 cases was in the works all along.

"I worry that these data have been rushed out on the back of the Pfizer/BioNTech announcement," Eleanor Riley, an immunologist at the University of Edinburgh, UK, told the Science Media Centre in London. "This is not a competition. We need all trials to be carried out to the highest possible standards and it is particularly important that the pre-set criteria for unblinding the trial data are adhered to avoid cherry picking the data."

Moderna makes three

Then, on 16 November, biotech company Moderna in Cambridge, Massachusetts, reported that its RNA-based vaccine is more than 94% effective at preventing COVID-19, on the basis of an analysis of 95 cases in its ongoing phase III efficacy trial.

Scientists say that these press-released results share a few more details than do the announcements from Pfizer and BioNTech, and the Russian developers. Moderna released figures suggesting that its vaccine is likely to prevent severe COVID-19 infections, something that was not clear from the other developers' announcements.

"The results of this trial are truly striking," says Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, which is co-developing the vaccine. Fauci says he told reporters several months ago that he would be satisfied with a vaccine that was 70% or 75% effective, and that one that prevented 95% of cases would be "aspirational". "Well, our aspirations have been met and that is very good news," he adds.

Cold supply chain

The company began a phase III trial of its vaccine on 27 July, and has enrolled roughly 30,000 people. That study continues, but an analysis conducted on 15 November by an independent data committee found that 95 participants had developed COVID-19. Of these, 90 were in the group that received a placebo injection and 5 had received the vaccine, which equates to an efficacy of 94.5%.

Researchers were also buoyed by Moderna's announcement that its vaccine remains stable in conventional refrigerators for a month and in ordinary freezers for six months; Pfizer's vaccine must be stored at −70°C before delivery, which means it could be difficult to distribute in parts of the world that do not have the infrastructure to keep it that cold.

Easier storage is "a really big plus", says Daniel Altmann, an immunologist at Imperial College London. "We've always said that we need a number of vaccines ready and that the devil will be in the detail."

Once the trials are completed and all the data have been analysed, the final calculations of the vaccines' efficacies could be lower. Researchers say it is likely that the Pfizer and Moderna vaccines' effectiveness will stay well above 50%, the threshold that the US Food and Drug Administration (FDA) says is required for a coronavirus vaccine to be approved for emergency use. "Both the Pfizer vaccine and the Moderna vaccine have notably more efficacy than most scientists would have expected," says Stephen Evans, a statistical epidemiologist at the London School of Hygiene & Tropical Medicine.

> **"Our aspirations have been met and that is very good news."**

But the low number of cases reported in the Sputnik V trial means there is less certainty that the interim results of more than 90% efficacy are close to the true figure, says Evans. "Follow-up is needed because the results are compatible with a much lower efficacy — 60% — based on these data."

Sarah Gilbert, a vaccinologist at the University of Oxford, UK, agrees that the Sputnik V results should be interpreted cautiously because of the small number of cases. But she is encouraged, because the vaccine her team is developing with pharmaceutical company AstraZeneca also uses an adenovirus to expose the immune system to the coronavirus spike protein. "Seeing the Russian results, albeit from a small number of endpoints, does indicate that we would expect to see high efficacy, but we have to wait and see," she says.

Missing information

Key questions about all three vaccines remain. Pfizer and the Russian group have not released details about the nature of the infections their vaccines can protect against — whether they are mostly mild cases of COVID-19 or also include significant numbers of moderate and severe cases, say researchers. "I want to know the spectrum of disease that the vaccine prevents," says Paul Offit, a vaccine scientist at the Children's Hospital of Philadelphia in Pennsylvania who sits on an FDA advisory committee that is set to evaluate the Pfizer vaccine next month. "You'd like to see at least a handful of cases of severe disease in the placebo group," he adds, because fewer such cases in the vaccine group would suggest that the vaccine has the potential to prevent such cases.

Moderna presented some evidence that its vaccine protects against severe cases of COVID-19. Its analysis found 11 severe cases in the trial's placebo arm, and none in the vaccine arm. That's a good sign, says Evans, but hardly surprising, given the vaccine's high effectiveness. "If a vaccine starts to get to that kind of efficacy, then there isn't a lot of room for severe cases in there," he says.

But it is not yet clear whether the vaccines can block people from transmitting the virus; whether they work equally well in higher-risk groups such as older adults; and how long their protective effects last.

"To me, the main question is what about six months later, or even three months later," says Rafi Ahmed, an immunologist at Emory University in Atlanta, Georgia. There will be a chance to answer that question if trials continue for several more months, says Ahmed. And although little is known about the vaccines' long-term effectiveness, that is unlikely to hold up use, he adds. "I don't think we should say, 'Well, I'll only take a vaccine that protects me for five years.'"

One thing about the Pfizer and Moderna vaccines is certain: regulators will soon decide whether they are ready for roll-out. Both companies said they would seek emergency-use authorization from the FDA in the coming weeks, when half of the participants have been followed for two months — an FDA safety requirement for COVID-19 vaccines.

And although researchers want to see the data behind the vaccine results, they are prepared to accept caveats that come with them. "Right now, we need a vaccine that works," says Krammer, even if it works for only a few months or doesn't stop transmission. "That's what we need in order to get halfway back to normal."