43,000 people – most of whom were followed for a median of 2 months after their second shot of the vaccine. An analysis of the first 170 cases of COVID-19 in the group indicated that the vaccine is 95% effective at preventing symptomatic SARS-CoV-2 infections. The results from the trial were published on 10 December in *The New England Journal of Medicine* (F. P. Polack *et al. N. Engl. J. Med.* https://doi.org/ghn625; 2020).

Reported side effects

The vaccine also seems to be safe, the trial found: the most common side effects included fatigue, headache and fever. There were four cases of Bell's palsy – a condition that temporarily weakens some muscles in the face – among those who received the vaccine, compared with none among those who received the placebo. But the FDA could not definitively link the condition to the vaccine, agency medical officer Susan Wollersheim told the committee: this frequency of Bell's palsy is not unusual in the general population, and one of the study participants affected by it had a history of the condition.

Nevertheless, on the first day of administering Pfizer's vaccine to older adults in care homes and to front-line health-care workers, the United Kingdom uncovered another possible safety concern: two recipients with a history of severe allergic reactions, called anaphylaxis, experienced an episode after getting the vaccine.

That serves as a good example of the side effects that can emerge when a vaccine is moved out of carefully controlled clinical trials, says Todd.

Still, the FDA advisers were not dissuaded by the reports: "The vaccinator should be able to handle anaphylactic reaction," said Cody Meissner, a paediatrician at the Tufts University School of Medicine in Boston, Massachusetts. "That's recommended for any vaccine."

But paediatrician Paul Offit at the Children's Hospital of Philadelphia in Pennsylvania expressed concerns that anyone with a history of strong allergies could be deterred from receiving the vaccine. He recommended that a small study be done of people with common allergies, for example to eggs or peanuts, to confirm safety in that population. "This issue is not going to die until we have better data," he told the committee. "I think we need to offer people some solace that this is not going to be a problem for them."

Long-term monitoring

Most reactions to vaccines become apparent within six weeks of receiving the jab, but longer tracking is useful for picking up any adverse events that might appear later, and could also help to rule out connections to medical events that are falsely attributed to vaccines, FDA vaccinologist Philip Krause said. "Safety follow-up can play a big role in helping us determine what the vaccine doesn't cause," he said.

At the advisory meeting, the US Centers for Disease Control and Prevention (CDC) laid out complex plans for monitoring Pfizer's vaccine if it is approved for rollout across the country. The plans included pre-existing programmes, such as the FDA and CDC Vaccine Adverse Event Reporting System, which collects reports of safety concerns. The CDC also intends to roll out a new programme called v-Safe, which will send text messages to health-care workers who receive the vaccine, to ask about any possible adverse events. Meanwhile, researchers at Brown University in Providence, Rhode Island, are designing a system to monitor residents of long-term care homes.

"It is not until you see these vaccines implemented at scale that you'll start to see unusual events."

Researchers will trawl through reports of adverse events in search of those that might have some connection to vaccination. That link is usually established through a combination of factors: the number of people who experienced the event, the length of time that elapsed between vaccination and the potential side effect, and a possible biological link.

The more time elapses between the jab and the event, the more cases are needed to suggest causality, says Robert Heyderman, an infectious-disease researcher at University College London who chairs the data and safety monitoring boards for a COVID-19 vaccine developed by the University of Oxford, UK, and AstraZeneca in Cambridge, UK. "It is not until you see these vaccines implemented at scale that you'll start to see unusual events and try to work out whether there's a link to the vaccine," says Heyderman.

As the vaccine rollout continues, it will be important to communicate information about any potential vaccine side effects to the public – while conveying the relative size of those risks. A person would probably be more at risk from crossing a road than from receiving a vaccine, says Heyderman.

Clear communication is particularly important in the era of social media and vaccine hesitancy, when anecdotal reports of a medical event after vaccination can be amplified on the Internet and can feed into existing fears about vaccines. "As soon as you get mistrust around a vaccine, you won't get the vaccine uptake that you need in order to control the pandemic," says Heyderman.

OXFORD COVID-VACCINE PAPER HIGHLIGHTS LINGERING UNKNOWNS

Oxford–AstraZeneca partnership is the first major developer to publish detailed phase III trial data.

By Heidi Ledford

The first formally published results from a large clinical trial of a COVID-19 vaccine – which scientists hope could be among the cheapest and easiest to distribute around the world – suggest that the vaccine is safe and effective. But the data also highlight a number of lingering unknowns, including questions about the most effective dosing regimen and how well it works in older adults.

The vaccine, developed by the University of Oxford, UK, and the pharmaceutical firm AstraZeneca in Cambridge, UK, has been closely watched, in part because it is likely to be simpler to distribute than the two RNA-based vaccines from companies Pfizer and BioNTech (see page 377) and Moderna, which need to be stored at low temperatures. The Oxford team is also now the first of these three leading COVID-vaccine developers to publish results from its phase III trials in a peer-reviewed journal – so far, the findings have been disseminated only through press releases.

Researchers have been eager to delve into the details of Oxford's results, which were published in *The Lancet* on 8 December (M. Voysey *et al. Lancet* https://doi.org/fmq2; 2020), after preliminary results released last month showed an unexpected increase in efficacy among a subset of study participants who, owing to a measurement error, received less of the vaccine in the first of their two doses. Some statisticians also raised concerns

JUAN MABROMATA/AFP/GETTY

The results suggest that the Oxford–AstraZeneca vaccine is safe and effective.

that the results pool data from different trials, rather than drawing from a single study.

When data from the various dosing regimens were combined, the study found that the vaccine was 70% effective at preventing symptomatic coronavirus infections. The standard regimen — two doses of the same strength administered a month apart — had an efficacy of 62%, whereas the regimen with a lower initial dose yielded an efficacy of 90%. "The efficacy and the safety are fine," says virologist Stephen Griffin at the University of Leeds, UK. "Overall, what you can say is that it does work."

Dosing puzzle

At a press briefing on 8 December, study investigators said that the data were pooled in agreement with guidance from regulators. However, researchers have struggled to explain how a higher efficacy could be achieved from a lower initial dose, and trial investigators have said that a separate trial is needed to follow up on the finding. Furthermore, the low-dose arm of the trial did not include anyone over the age of 55, raising concerns that the higher efficacy was merely a by-product of excluding an age group that is particularly vulnerable to COVID-19.

But reviewers of the *Lancet* paper asked the team to break down its data by age, which revealed that even in adults under the age of 55, efficacy was still higher in the low-dose group than among those who received the standard dose, says Andrew Pollard, director of the Oxford Vaccine Group at the University of Oxford and a co-author of the paper.

Overall, it remains unclear how much the over-55 age group will benefit from even the standard dose of the vaccine: only 12% of those in the group evaluated for vaccine efficacy were over 55. Earlier studies of the vaccine showed that immune responses in people over 55 were comparable to those in younger study participants, suggesting that the vaccine will work well in older adults (M. N. Ramasamy *et al. Lancet* https://doi.org/ghk7t7; 2020). But the larger clinical trial has few data from older adults so far, because they were recruited to the study later, says Pollard. The published results are interim data from more than 11,000 of the roughly 24,000 participants enrolled, and researchers might learn more about the vaccine in older adults as more data come in.

"This is the only study that's given us data on how vaccines might affect spread. And it's a bit troubling."

Another lingering question is whether the vaccine is capable of fighting asymptomatic infections; an immunization that could do that could be key to shaping the course of the pandemic. The Oxford–AstraZeneca team is the only one of the three leading vaccine developers that monitored for asymptomatic infections, by collecting weekly swabs from some participants to determine whether they had the coronavirus but did not become ill. The data show that the low-dose vaccine regimen was about 60% effective at reducing asymptomatic infections, but it is unclear whether the standard dose significantly reduced them at all.

Researchers are concerned about asymptomatic infections because people who have them might unknowingly continue to transmit the virus to others, despite being vaccinated. Although asymptomatic infections are not a direct measure of disease transmission, researchers have looked to these data as an indication of how much vaccines might affect the spread of COVID-19. "For now, this is the only study that's given us data on that," says Griffin. "And it's a bit troubling."

Trials of the two leading RNA vaccines have not gathered data on asymptomatic infections, but the vaccines have been more than 90% effective in preventing symptoms of COVID-19. And even if the efficacy of the Oxford vaccine proves to be lower than those of the other two, it is still likely to be beneficial, says Griffin. The lower efficacy has to be balanced against the practicalities of vaccinating everyone who needs it, he adds. "It's going to come down to a cost–benefit analysis."

Oxford and AstraZeneca have agreed to provide the vaccine to buyers for US$2–3 per dose. And the vaccine is made of DNA encoding a coronavirus protein that is shuttled into cells in a harmless virus, a product that will be cheaper and easier to make in bulk than the RNA vaccines from Pfizer and Moderna, says Griffin. It also does not need to be stored at temperatures as low as the RNA vaccines, one of which must be kept at −70°C until shortly before it is administered.

More than one

And the scale of the pandemic means that it will be crucial to have more than one COVID-19 vaccine, said AstraZeneca chief executive Pascal Soriot at a press briefing. Even combined, the planned number of doses from Moderna, Pfizer and AstraZeneca would still not be enough to vaccinate everyone in the world. "It is really important to have several vaccines," he said.

Oxford's data came on the day that the United Kingdom began administering the Pfizer and BioNTech vaccine outside trials, less than a week after UK regulators became the first to grant an emergency-use authorization to one of the major vaccines.

The Oxford data have now been submitted to regulators around the world, said Mene Pangalos, AstraZeneca's executive vice-president of biopharmaceuticals research and development at a press briefing.

In the United States, a panel of advisers to the Food and Drug Administration (FDA) met on 10 December to discuss the Pfizer–BioNTech vaccine, and the agency issued an emergency-use authorization the following day. Moderna, which is based in Cambridge, Massachusetts, also announced positive clinical-trial results last month for its vaccine, which FDA advisers are set to discuss on 17 December.