provide such insights, the virus would have to share more than 97% of its genome with SARS-CoV-2, which is more than is shared by its closest known relative, say researchers.

But the new virus might be more distantly related, in which case, studying it will help scientists to learn more about the diversity in this virus family, says Etienne Simon-Loriere, a virologist at the Pasteur Institute in Paris, who plans to sequence the virus, after which it will be shared publicly.

That is the case with the other virus, called Rc-o319, identified in a little Japanese horseshoe bat (*Rhinolophus cornutus*) captured in 2013. That virus shares 81% of its genome with SARS-CoV-2, according to a paper[1] published on 2 November — which makes it too distant to provide insights into the pandemic's origin, says Edward Holmes, a virologist at the University of Sydney in Australia.

No matter what the Cambodian team finds, both discoveries are exciting because they confirm that viruses closely related to SARS-CoV-2 are relatively common in *Rhinolophus* bats, and even in bats found outside China, says Alice Latinne, an evolutionary biologist at the Wildlife Conservation Society Vietnam in Hanoi, who has seen some of the Cambodian team's analysis but was not involved in the investigation.

"This is what we were looking for, and we found it," says Duong. "It was exciting and surprising at the same time."

The findings suggest that other as-yet undiscovered SARS-CoV-2 relatives could be stored in lab freezers, says Aaron Irving, an infectious-diseases researcher at Zhejiang University in Haining, China, who also plans to test stored samples of bats and other mammals for antibodies against SARS-CoV-2.

"I did not expect to find a relative of SARS-CoV-2," says virologist Shin Murakami at the University of Tokyo, who was part of the team that decided to retest frozen animal samples for viruses in the wake of the pandemic.

Pandemic origins

Only a handful of known coronaviruses are closely related to SARS-CoV-2, including its closest known relative, RaTG13. That was discovered in intermediate horseshoe bats (*Rhinolophus affinis*) in the Chinese province of Yunnan in 2013, and was published[2] only earlier this year. There are also several other coronaviruses, found in other *Rhinolophus* bats and pangolins captured between 2015 and 2019, that scientists now know to be closely related to SARS-CoV-2.

"SARS-CoV-2 probably wasn't a brand new virus that popped up all of a sudden. Viruses in this group existed before we became aware of them in 2019," says Tracey Goldstein, associate director of the One Health Institute at the University of California, Davis, who is involved with the Cambodian team.

Latinne says the discoveries confirm that *Rhinolophus* bats are the reservoir of these viruses.

Duong's team captured the Shamel's horseshoe bats in Cambodia as part of the US-government-funded PREDICT project, which surveyed wildlife worldwide for viruses with pandemic potential for decades and ended earlier this year. In April, the US Agency for International Development gave the programme an extra US$3 million and a 6-month extension to look for evidence of SARS-CoV-2 in animal samples — mostly bats, as well as pangolins and other animals — that were sitting in lab freezers in Laos, Malaysia, Nepal, Thailand, Vietnam and Cambodia. A full report of these investigations is expected in the coming weeks.

Duong says preliminary genome sequencing of a short fragment of the new bat virus — 324 base pairs long — showed that it was similar to the same region in SARS-CoV-2 and RaTG13, suggesting that the three are closely related. That region is highly conserved in coronaviruses, says Latinne, and is often used to quickly identify whether a virus is new or already known. But it's not yet clear whether RaTG13 or the new virus is more closely related to SARS-CoV-2.

It's difficult to say with such a small fragment, says Vibol Hul, a virologist at the Pasteur Institute in Cambodia, who trapped the Shamel's horseshoe bats at the entrance to a cave in 2010. The genomes of most known coronaviruses contain about 30,000 base pairs.

In a separate analysis, the Cambodia team sequenced some 70% of the new virus's genome using the technology available locally, says Erik Karlsson, a virologist at the Pasteur Institute in Cambodia, who helped to analyse the bats. Missing from that sequence were the instructions for crucial parts of the virus, such as the genes that encode the spike protein that coronaviruses typically use to enter cells. Sequencing that section will indicate whether this virus can infect human cells, says Duong.

The new virus would have to be at least 99% similar to SARS-CoV-2 to be an immediate ancestor of the current pandemic virus, says Irving. The genomes of RaTG13 and SARS-CoV-2 differ by only 4%, but that represents 40–70 years of evolution since they shared a common ancestor. Although decades apart, the viruses are similar enough to use the same receptor to enter cells. Cell studies suggest that RaTG13 could infect people[3].

Of the known coronaviruses related to SARS-CoV-2, the newly discovered Rc-o319 seems to be the most distantly related, says Duong.

In cell studies, the Japan team found that the virus cannot bind to the receptor that SARS-CoV-2 uses to enter human cells, suggesting that it could not easily infect people.

Shin says his colleagues captured more bats in Japan earlier this year, and plan to test them for coronaviruses. And in October, Hul returned to the cave in northern Cambodia to catch more bats.

More SARS-CoV-2-related coronaviruses probably exist in *Rhinolophus* bat populations, which live across the region, says Holmes. "Hopefully, one or more of these will be so closely related to SARS-CoV-2 that we can regard it as the true ancestor."

1. Murakami, S. *et al. Emerg. Infect. Dis*. https://doi.org/10.3201/eid2612.203386 (2020).
2. Zhou, P. *Nature* **579**, 270–273 (2020).
3. Shang, J. *et al. Nature* **581**, 221–224 (2020).

OXFORD COVID VACCINE RESULTS PUZZLE SCIENTISTS

Preliminary data suggest that the immunization was more effective when given in a lower dose.

By Ewen Callaway

A highly anticipated COVID-19 vaccine has delivered some encouraging — but head-scratching — results. The vaccine developed by the University of Oxford, UK, and pharmaceutical giant AstraZeneca was found to be, on average, 70% effective in a preliminary analysis of phase III trial data, the developers announced in a press release on 23 November. The findings follow recent positive results from two other major COVID vaccine trials.

But the Oxford–AstraZeneca analysis found a striking difference in efficacy depending on the amount of vaccine delivered to a participant. A regimen consisting of 2 full doses given a month apart seemed to be just 62% effective. But, surprisingly, participants who received a lower amount of the vaccine in the first dose

and then the full amount in the second dose were 90% less likely to develop COVID-19 than were participants in the placebo arm.

Last month, drug companies Pfizer and BioNTech reported that their RNA-based vaccine was around 90% effective, and an interim analysis of an RNA vaccine by biotechnology firm Moderna showed it worked roughly as well (see page 18).

Researchers caution against making head-to-head comparisons of vaccines on the basis of incomplete data. The disparity in the latest results means there will be considerable uncertainty over precisely how well the Oxford vaccine protects against COVID-19 until ongoing efficacy trials report more data, say scientists. "We're slightly in danger of rushing to compare apples and oranges," says Daniel Altmann, an immunologist at Imperial College London. "There's a long, long way to go before these data settle down and get reported and published in full."

FELIX DLANGAMANDLA/BEELD/GALLO IMAGES/GETTY

The Oxford vaccine results are based on data collected in Brazil and the United Kingdom.

Viral vector

The Oxford–AstraZeneca vaccine is made from a cold-causing adenovirus that was isolated from the stool of chimpanzees and modified so that it no longer replicates in cells. When injected, the vaccine instructs human cells to produce the SARS-CoV-2 spike protein — the immune system's main target in coronaviruses. The vaccine entered phase III efficacy trials before other front runners, including Pfizer and Moderna, and trials are continuing in countries including the United States, South Africa, Japan and Russia. The 23 November analysis is based on 131 COVID-19 cases among more than 11,000 trial participants in the United Kingdom and Brazil, up to 4 November.

Overall, the developers found that the 2-dose vaccine had an efficacy of 70%, when measured 2 weeks after participants received their second dose. But that figure is an average of the 62% and 90% efficacy from the two dosing regimens. "90% is pretty good, but the 62% for the second tested regimen are not that impressive," said Florian Krammer, a virologist at Icahn School of Medicine at Mount Sinai in New York City, on Twitter.

A top priority for researchers is understanding why the vaccine seems to have performed so much better with a lower first dose. One explanation could lie in the data: the trial might not have been big enough to gauge the differences between the two regimens, in which case the differences might vanish once more cases of COVID-19 are detected, says Luk Vandenberghe, a virologist at the Massachusetts Eye and Ear institute and Harvard Medical School in Boston. The more effective 'half-dose, full dose' results were based on 2,741 trial participants, whereas the less efficacious arm included 8,895 volunteers. The press release did not specify in which group cases occurred.

On the basis of the data, Stephen Evans, a statistical epidemiologist at the London School of Hygiene & Tropical Medicine, estimates that the 'half-dose, full dose' regimen could have an efficacy as low as 66%.

Dosing theories

But, if the differences are real, researchers are eager to understand why. "I don't think it's an anomaly," says Katie Ewer, an immunologist at Oxford's Jenner Institute who is working on the vaccine. "I'm keen to get into the lab and start thinking about how we address that question." She has two leading theories for why a lower first dose might have led to better protection against COVID-19. It's possible that lower doses of vaccine do a better job at stimulating the subset of immune cells called T cells that support the production of antibodies, she says.

> **"It would be madness to use more vaccine than you needed to get less efficacy."**

Another potential explanation is the immune system's response to the chimpanzee virus. The vaccine triggers a reaction not only to the SARS-CoV-2 spike protein, but also to components of the viral vector. It's possible that the full first dose blunted this reaction, says Ewer. She plans to look at antibody responses to the chimpanzee virus to help address this question.

"This is a plausible explanation," says James Wilson, a virologist at the University of Pennsylvania in Philadelphia who pioneered the use of adenoviruses for vaccines in the 1990s. By giving a half-dose first, "it is possible that AstraZeneca threaded the needle with their dosing", he adds.

Hildegund Ertl, a viral immunologist at the Wistar Institute in Philadelphia, says the results make sense in the light of some of her work on adenovirus vaccines in mice. She, too, has found that for a two-dose vaccine, a low first dose can lead to better protection than a high first dose. She thinks this is because a lower first dose leads more quickly to the establishment of 'memory' immune cells that are triggered by a second-dose boost. Waiting longer between the two doses could achieve the same effect.

AstraZeneca hopes to gather more data on the dosing regimen. The company has so far given the vaccine to around 10,000 participants in a US arm of the efficacy trial, which was paused for more than a month starting in September, while researchers investigated a neurological condition in a UK trial participant.

The company plans to ask regulators whether it can modify the trial to include the more efficacious dosing regimen, said Mene Pangalos, vice-president of biopharmaceuticals research at AstraZeneca, which is based in Cambridge, UK, at a press briefing.

"It would be madness to use more vaccine than you needed to get less efficacy," says Ewer. "I think we will see a move towards roll-out of the 'low dose, standard dose' regime."

Hints of optimism

While Oxford and AstraZeneca make sense of their trial data and gather more, there is reason for optimism in other facets of the vaccine's performance, say scientists. No participants who received the vaccine were hospitalized or developed severe COVID-19, suggesting the vaccine might do a good job at preventing severe disease.

There were also hints that the vaccine might

prevent infected people from transmitting the virus, even if they aren't showing symptoms. In the trial's UK arm, some participants routinely swabbed themselves for SARS-CoV-2 testing, even if they weren't showing symptoms. Differences in infection rates between people who received the placebo and those who got the Oxford vaccine suggest the vaccine blocks transmission, says Ewer. (The Pfizer and Moderna trials tested only people who showed symptoms.)

Even with a question mark hanging over its efficacy, the Oxford–AstraZeneca vaccine could see wider roll-out than some other COVID-19 immunizations. The vaccine is stable at refrigerator temperatures, in contrast to the Pfizer and BioNTech vaccine, which must be stored at −70 °C until hours before vaccination.

And more of the vaccine could be available sooner, relative to other jabs. AstraZeneca estimates that it will have 200 million doses ready worldwide by the end of 2020, and the capacity to produce 100 million to 200 million doses per month once production is ramped up, according to Pam Cheng, vice-president for operations and information technology at AstraZeneca.

"The battle really between all these vaccines is going to be really a logistical one," says Vandenberghe.

WHY EMERGENCY COVID VACCINE APPROVALS COULD POSE A DILEMMA

If approval comes before clinical trials end, this could complicate the study of vaccines' long-term effects.

By David Cyranoski

After a flurry of positive results from clinical trials of COVID-19 vaccines, developers are now seeking 'emergency use' approvals, which could see these immunizations deployed in potentially tens of millions of people. But scientists are concerned that this kind of early deployment could compromise the ongoing clinical trials that seek to show conclusively how well the vaccines work.

Following the release of early data from phase III trials on 9 November, vaccine makers Pfizer and BioNTech have sought regulatory permission to deploy their vaccine under emergency-use rules in the United States. The developer of another leading vaccine, Moderna, sought similar approvals for its jab in the United States and in Europe this week.

People wait to take part in a trial of a Chinese vaccine in Abu Dhabi, United Arab Emirates.

KHUSHNUM BHANDARI/REUTERS

Once a vaccine is granted emergency approval, there is pressure on developers to offer the immunization to trial participants who received a placebo. But if too many people cross over to the vaccine group, the companies might not have enough data to establish long-term outcomes, such as safety, how long vaccine protection lasts and whether the jab prevents infection or just the disease.

"It's a real vaccine-development dilemma," says Klaus Stöhr, who formerly headed vaccine design at the pharmaceutical company Novartis in Cambridge, Massachusetts, and is now retired. Still, Stöhr thinks that the vaccine should be granted emergency-use authorization, because its effectiveness has been established and there is a dire need.

Such competition between a clinical trial for a vaccine and emergency use of it is new for vaccine development. Only this month, the World Health Organization approved the first-ever emergency use for an immunization still being tested, against a type of poliovirus that is spreading in the Southern Hemisphere. But phase III trials for that jab have not yet begun.

Pfizer, based in New York City, and BioNTech, based in Mainz, Germany, submitted an application on 20 November for an Emergency Use Authorization (EUA) from the US Food and Drug Administration (FDA). On 30 November, Moderna also applied for an EUA in the United States, and for conditional marketing authorization from the European Medicines Agency. Under the FDA's rules for COVID-19 vaccines, companies can apply for an EUA when half of the trial participants (half of 43,000 people in Pfizer's case and half of 30,000 participants in Moderna's) have been followed for two months after their last dose.

The FDA's vaccine advisory committee will meet on 10 December to consider Pfizer's application, and a week later to discuss Moderna's. The committee will assess the companies' data and decide whether the vaccines are safe and effective enough for restricted use.

Vaccine conundrum

Many researchers expect that the EUAs will be granted. Once a vaccine is authorized, a committee of the US Centers for Disease Control and Prevention in Atlanta, Georgia, will determine which groups should be the first in line for vaccination. The panel is considering high-risk groups, such as elderly people, those with diseases such as diabetes that make them more susceptible to COVID-19, and health-care workers.

Early use of the vaccines in high-risk groups will almost certainly save lives, says Jerome Kim, director-general of the International Vaccine Institute in Seoul. The vaccines have been tested for only a couple months, however, so it is too early to know how long they will be effective for, he says.

Trial participants are typically 'blinded' as