clinical-trial holds in future. The transparency bar should be set much higher than this latest example, says Kieny. "When, ultimately, a vaccine will be made available, public trust will be paramount to ensure public-health impact. And trust needs transparency."

Leading vaccine

The vaccine, AZD1222, is one of the leading candidates being developed to protect against the virus that causes COVID-19, and one of a handful of immunizations in the final stages of clinical testing. The pause in global trials sent a shudder around the world.

Such a quick resumption of the trials was the most likely outcome, says Paul Griffin, an infectious-diseases researcher at the University of Queensland in Brisbane, Australia. In large trials, adverse medical events in volunteers are common, and trial holds are designed to ensure that such events are investigated and volunteers are protected, he says. But, most often, it is later decided that the event was probably not related to participation in the trial and does not pose a safety concern to the rest of the volunteers, says Griffin. That seems to be what has occurred in this case, he says.

It can be difficult to pin down the cause of adverse events, says Jonathan Kimmelman, a bioethicist who studies clinical trials at McGill University in Montreal, Canada. "Often, the best you can do is say that there is a possible link, and then proceed with collecting more data and monitoring outcomes," he says.

The University of Oxford said in a press release on 12 September that the pause, which applied to all trials of the vaccine, was necessary "to allow the review of safety data by an independent safety review committee, and the national regulators".

"The independent review process has concluded and following the recommendations of both the independent safety review committee and the UK regulator, the MHRA [Medicines and Healthcare products Regulatory Agency], the trials will recommence in the UK," the statement reads. The university also said that it cannot disclose medical information about the participant's illness for reasons of confidentiality.

It's appropriate not to disclose information, for patient confidentiality and to ensure valid interpretation of the trial results, says Kristine Macartney, the director of Australia's National Centre for Immunisation Research and Surveillance in Sydney.

Lack of details

But Paul Komesaroff, a physician and bioethicist at Monash University in Melbourne, Australia, questions the university's claim that it could not release information about the adverse event on the basis of confidentiality. It is possible to provide information in a manner that avoids identifying a particular individual, but still provides a summary of the clinical issues that arose, and the conclusions the committee reached about the implications for the study, he says. "It is of concern that they sought to avoid doing so," says Komesaroff.

The University of Oxford and AstraZeneca have not yet responded to requests for comment on this criticism.

Although the university and AstraZeneca have not released information about the adverse event to the public, Pascal Soriot, AstraZeneca's chief executive, reportedly told investors on a telephone call last week that a person in the UK trials had developed symptoms of transverse myelitis, according to health-news website STAT. This condition involves inflammation of the spinal cord, which can be triggered by viruses.

But other scientists say there is a good reason why the company hasn't released more details. If information about the trials is released prematurely, it could present a bias to the clinicians involved in them, says Griffin. The integrity of the trials is on the line, he adds. Griffin expects the pause to have little impact on the UK trials' overall timeline.

But it has not been reported when trials of the vaccine in the United States and South Africa will restart. A spokesperson for AstraZeneca told *Nature* that the company "will be guided by health authorities across the globe as to when other clinical trials of the vaccine can resume".

So far, some 18,000 people globally have received the vaccine. Phase III efficacy trials in the United Kingdom, which began in June, aim to recruit 10,000 people, and a phase III trial in Brazil hopes to recruit 5,000 participants. The US trial, which started in August, is aiming to recruit 30,000 participants. A phase I/II safety and efficacy trial in South Africa wants to recruit 2,000 volunteers.

THE UNDERDOG COVID-19 VACCINES THAT THE WORLD MIGHT NEED

Small developers struggle to get their candidates noticed, but they'll be crucial if front runners stumble.

By Ewen Callaway

When it comes to developing vaccines, Peter Palese is no slouch. A virologist at Icahn School of Medicine at Mount Sinai in New York City, he pioneered genetics techniques that are used to make some of the billions of influenza vaccine doses produced annually, and his team has won millions of dollars to develop a universal flu jab.

Palese is developing a COVID-19 vaccine, too. It consists of a bird virus that has been genetically modified to make a protein found on the surface of SARS-CoV-2. The vaccine fully protects mice from an experimental model of COVID-19, according to a preprint[1] (the research has not yet been peer reviewed). It also grows in chicken eggs, like most flu vaccines, so manufacturing could be ramped up using tried-and-tested technology.

Despite its potential, Palese's vaccine has struggled to gain the attention and funding needed to progress to human trials. "We thought this would be the best thing after sliced bread, and people would break down our doors to get it. That's not the case. We are very disappointed," he says.

As leading drug and biotechnology companies rush their COVID-19 vaccines through clinical trials and eye up fast-track regulatory authorization, dozens of underdog vaccines such as Palese's have stalled, or are advancing along a slower, more conventional path.

Scientists acknowledge that it would be a waste of resources to take every candidate to clinical trials. But they argue that it's essential to have a diverse selection of COVID-19 vaccines in development. Early favourites could fail, confer only partial protection or work poorly in certain age groups; high costs and other barriers might make some of the front runners unsuitable for wide-scale deployment in lower-income countries.

"Everyone is rooting for them to succeed beyond anyone's expectation, but it's prudent to think about what happens if they don't," says Dave O'Connor, a virologist at the University of Wisconsin–Madison. "We need to make sure we have back-up plans — and back-up plans to those back-up plans."

Dozens of candidates

There are more than 320 COVID-19 vaccines in development, according to a tally by the Coalition for Epidemic Preparedness Innovation (CEPI) in Oslo, a fund created to finance

EVA MARIE UZCATEGUI/BLOOMBERG VIA GETTY

Dozens of coronavirus vaccine candidates are in clinical trials.

and coordinate vaccines for outbreaks. Most of these are in the early stages of preclinical development; several dozen are in clinical trials, and only a handful have begun final-phase tests for efficacy. "Everybody and their mother has a vaccine. My dogs have two vaccines," says one scientist working on a leading candidate. Although on the face of it this is good news, it also presents challenges. One is determining which candidates should move forward to costly clinical trials: running even a small study to test safety and dosing is beyond the reach of most academic groups, and smaller teams face an uphill struggle to get their candidates noticed.

In some cases, the breakneck pace of COVID-19 vaccine efforts has created openings for academic groups. One of the leading candidates is being developed by the University of Oxford, UK, and drug company AstraZeneca (see page 331). The vaccine is based on a kind of chimpanzee cold virus, called an adenovirus, that has been used to make experimental vaccines against Ebola, malaria and other diseases, allowing Oxford vaccinologists to quickly adapt the platform to a COVID-19 vaccine. Another technology comprises RNA instructions for a coronavirus protein, and two front-runner vaccines are being developed by firms with expertise in that platform.

But neither technology has yet produced licensed vaccines, and there is no guarantee that the candidates will generate strong immunity against the coronavirus, says Michael Diamond, a viral immunologist at Washington University in St. Louis, Missouri, who is working on two early-stage vaccines. One[2] is based on a weakened livestock virus. The other[3] is based on a chimpanzee adenovirus, like the Oxford–AstraZeneca effort.

Diamond's adenovirus vaccine, unlike any of the leading candidates, is designed to be administered through the nose. A team led by Diamond and Washington University cancer biologist David Curiel found[3] that mice given a single dose of the intranasal vaccine were fully protected from SARS-CoV-2, with almost no sign of virus in their upper or lower airways. Mice that received an injection of the same vaccine were only partially protected, echoing animal data from some leading candidates. This was because the intranasal vaccine summoned potent 'mucosal' immune responses that can block the virus at the site of infection in the upper airways, the team says.

"We don't have a billion dollars, but we are moving the programme forward and making sure we don't lose time."

On the basis of such results, Diamond feels that his team has "a mission" to push its vaccines into human trials, to "see if they're going to be one of the last ones standing — even if they're not the first ones out there". His university has completed a deal to license the intranasal vaccine to a manufacturer, but Diamond hasn't yet found anyone to advance his team's livestock-virus vaccine. Pharmaceutical company Merck is developing its own vaccine based on the same virus, which is also the backbone of the Merck Ebola vaccine that was approved in the United States and the European Union last year. Many companies "just don't have the bandwidth, money, the wherewithal or desire to actually pick up additional platforms", says Diamond. "The challenge has been to find partners."

Many of the vaccines gunning for the first approvals won early funding from CEPI, which has so far spent nearly US$900 million on nine COVID-19 candidates. US government agencies including the Biomedical Advanced Research and Development Authority (BARDA) have spent billions of dollars supporting a handful of candidates as part of Operation Warp Speed. But other funders, with their own priorities, are stepping in to help academics turn their experimental vaccines into products.

Global coverage

With many wealthy countries snapping up early supplies of the leading COVID-19 vaccine candidates, some of these teams have set their sights on developing vaccines for the rest of the world.

Neil King, a biochemist at the University of Washington in Seattle, and his team are readying a nanoparticle vaccine for clinical trials, with support from the Bill & Melinda Gates Foundation in Seattle. The effort, which King is leading with University of Washington structural biologist David Veesler, has produced a vaccine consisting of a self-assembling virus-like particle that is dotted with 60 copies of the receptor-binding domain of the spike protein that SARS-CoV-2 uses to enter human cells. In a preprint, the team reported that tiny doses of the vaccine led to whopping immune responses in mice[4].

The jab could be supplied to low- and middle-income countries, says King. It comprises 'recombinant' proteins made using DNA from multiple sources — which are already used as medical products, including insulin, so there is huge global manufacturing capacity for them. 'Virus-like particle' vaccines that self-assemble from these proteins also have a strong track record: existing vaccines against human papillomavirus, a cause of cervical cancer, and hepatitis B are based on the technology. Clinical trials of the nanoparticle vaccine are set to begin in December. "We don't have a billion dollars from BARDA, but we are moving the programme forward and making sure we don't lose time," says King.

Researchers say that funders need to step in to provide guidance and financial support for COVID-19 vaccines. But as much as underdog developers would like to see their vaccines help bring the pandemic to an end, they are still rooting for their better-funded competitors to succeed. "As a human being, my hope is that none of the candidates fail," says King.

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