CORONAVIRUS VACCINES PASS SAFETY TRIALS BUT NO LEADER EMERGES

Scientists caution against comparing results and say there might be multiple paths to an effective vaccine.

By Ewen Callaway

Scientists working at feverish pace to develop vaccines against the coronavirus have released a flood of data from their first human trials.

The results come from phase I and II trials of four promising vaccine candidates. Because the trials were focused on safety and dosing, the data cannot say whether the vaccines will prevent disease or infection — large-scale efficacy trials are needed for this. But they suggest that the candidate vaccines are broadly safe, and offer the first hints that vaccines can summon immune responses similar to those in people who have been infected with the virus. Crucially, researchers say the data look good enough to merit testing the vaccines in efficacy trials, in which volunteers receive a vaccine or placebo and rates of COVID-19 disease are compared.

"I'm really happy that there are quite diverse vaccine strategies going beyond phase I trials," says Shane Crotty, a vaccine immunologist at the La Jolla Institute for Immunology in California.

But scientists caution against over-interpreting the results, and say the data shouldn't be used to compare the vaccines. Eventually, such comparisons will be key to identifying how the vaccines work, or why they fail, and which should be speeded through development. But none of this is possible yet, because researchers don't know the precise nature of the immune responses that protect against COVID-19 — and there are likely to be multiple ways to fend off infection.

Viral vectors

All four developers said that their vaccines elicited some kind of immune response, broadly similar to the responses seen in people who have recovered from COVID-19. None had serious side effects.

Two teams — one at the University of Oxford, UK, in collaboration with drug company AstraZeneca, and one at CanSino Biologics in Tianjin, China — are developing 'viral vector' vaccines. Both groups published[1,2] their results on 20 July in *The Lancet*.

"The vaccine is inducing the kind of immune responses that we think are inducing protection against coronavirus," said Sarah Gilbert, a vaccinologist co-leading the Oxford effort, in a press briefing. That vaccine harnesses a virus that causes colds in chimpanzees, but that has been genetically modified so that it can't grow in humans, and expresses the 'spike' protein that the coronavirus uses to infect human cells. CanSino's vaccine uses a similarly modified human virus.

A third group, BioNTech in Mainz, Germany, is developing an RNA-based vaccine with drug company Pfizer. On 20 July, the team released detailed immune data from people who had received a vaccine containing RNA instructions for the 'receptor binding domain' portion of the spike protein[3]. This followed long-awaited clinical-trial results published on 14 July[4] by Moderna, a biotech company in Cambridge, Massachusetts, that has developed a competing RNA vaccine using the entire spike protein, in collaboration with the US National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland.

Immune response

The latest data offer the best insight yet into the nature of the immune responses prompted by the vaccines — the only indication, short of an efficacy trial, that the jabs are likely to work.

Vaccines expose the immune system to components of a virus — the coronavirus spike protein, in the case of most COVID-19 vaccines — in the hope of teaching it how to react against a real infection in the future. The trials looked at two broad types of immune response: production of antibody molecules that can recognize and, in some cases, inactivate viral particles; and production of T cells that can kill infected cells and promote other immune responses, including antibody production.

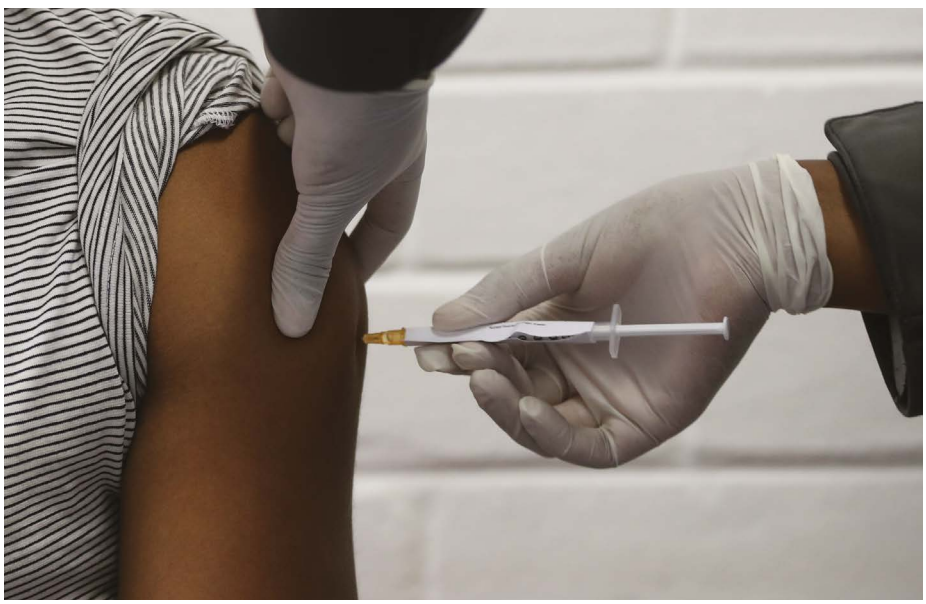
So far, most focus has been on 'neutralizing antibodies' circulating in the blood, which can render viral particles non-infectious. "All of these [vaccines] are inducing some antibodies that neutralize, which is better than no neutralizing," says Rafi Ahmed, an immunologist at Emory University in Atlanta, Georgia. That's a decent sign, he says.

T-cell responses have received less attention from vaccine developers. That's partly because they are more difficult to measure, especially as the number of trial participants pushes into the thousands. But emerging data suggest that T cells might have an important role in controlling the coronavirus, says Crotty.

If a vaccine can elicit a combination of neutralizing antibodies and both kinds of T cell, it could bode well for protecting against disease, says Crotty. "It's definitely plausible that there's more than one way to protect against this virus."

The nature of the immune response that protects — or fails to protect — against COVID-19 will become clearer when efficacy trials deliver their first results. Oxford's vaccine is being tested for efficacy in the United Kingdom, Brazil and South Africa; the Moderna–NIAID vaccine is set to begin its phase III trial in the United States this month.

Such data — known as a correlate of protection — could make it easier to interpret



SIPHIWE SIBEKO/AFP VIA GETTY

The University of Oxford's COVID-19 vaccine is being tested in South Africa.

early-stage trial results such as those released this week. But comparisons can be thwarted by the fickle nature of the tests researchers use to measure neutralizing-antibody and T-cell responses. The same test can return widely different values when performed in different laboratories, or even on different days.

"It's hard for us to compare our vaccine results to other people's," said vaccinologist Adrian Hill, a co-leader of the Oxford effort, in the briefing. "We would really like to see different vaccines being tested in the same lab by the same people."

Most of the front-runner vaccines "could do the trick", says Daniel Altmann, an immunologist at Imperial College London. But he worries that there is not enough emphasis on identifying candidates being developed by companies that are capable of making enough vaccine for much of the world. That could depend on myriad issues, such as sourcing glass vials and maintaining temperature-controlled supply chains. "That's like organizing a Moon landing or a world-war invasion," says Altmann. "Whichever candidates we pick, we want them to be the ones that can most optimize that."

1. Folegatti, P. M. *et al. Lancet* https://doi.org/10.1016/S0140-6736(20)31604-4 (2020).
2. Zhu, F-C. *et al. Lancet* https://doi.org/10.1016/S0140-6736(20)31605-6 (2020).
3. Sahin, U. *et al*. Preprint at MedRxiv https://doi.org/10.1101/2020.07.17.20140533 (2020).
4. Jackson, L. A. *et al. N. Engl. J. Med.* https://doi.org/10.1056/NEJMoa2022483 (2020).

WHEN DID PEOPLE REACH THE AMERICAS? CAVE TOOLS STOKE DEBATE

Stone artefacts point to occupation more than 30,000 years ago – but not everyone is convinced.

By Colin Barras

Archaeologists excavating a cave in the mountains of central Mexico have unearthed evidence that people occupied the area more than 30,000 years ago – suggesting that humans arrived in North America at least 15,000 years earlier than thought.

The discovery, which includes hundreds of ancient stone tools, is backed up by a statistical analysis that incorporates data from other sites. But the conclusion has stirred controversy among some researchers.

The first humans in the Americas came from East Asia, but when they began to arrive is hotly debated. Some researchers think that it could have been as early as 130,000 years ago, although most of the archaeological evidence supporting this theory is disputed. For instance, some of the stone artefacts are so simple that sceptics say they were probably produced by natural geological processes rather than by people. The mainstream view is that the peopling of the Americas began about 15,000 or 16,000 years ago – based on genetic evidence and artefacts found at sites including the 14,000-year-old Monte Verde II in Chile.

The latest discoveries (C. F. Ardelean *et al. Nature* http://doi.org/d4wz; 2020) question that consensus. Since 2012, a team led by Ciprian Ardelean at the Autonomous University of Zacatecas in Mexico has been excavating Chiquihuite Cave, which is 2,740 metres above sea level in the country's Astillero Mountains. The researchers found almost 2,000 stone tools, 239 of which were embedded in layers of gravel that have been carbon dated to between 25,000 and 32,000 years ago.

Ardelean thinks the site might have been used as a refuge during particularly severe winters. At the height of the last ice age, 26,000 years ago, North America would have been a dangerous place. "There must have been horrible storms, hail, snow," he says, and the cave could have provided shelter to any humans who were around to witness the blizzards.

MADS THOMSEN

Excavations in Chiquihuite Cave, Mexico.

The team makes a good case for ancient human occupation, says François Lanoë, an archaeologist and anthropologist at the University of Arizona in Tucson. But he adds that data from caves are "notoriously troublesome" to interpret. Stone tools might have been shifted into deeper layers by geological or biological activity – perhaps moved by burrowing animals – making them seem older than they really are.

That's assuming they really are stone tools. "If an artefact is a stone tool, you see numerous chips removed from the edge," says Kurt Rademaker, an archaeologist at Michigan State University in East Lansing. He sees no clear evidence of this in the images in the paper.

Ardelean admits that some of the tools might have shifted into lower layers, although he says the 239 oldest ones lie beneath an impenetrable layer of mud formed during the last ice age, so they must be at least that old. He insists they are tools – in fact, he thinks some have telltale marks suggesting that they were made by novices learning from experts.

Aside from the stone tools, the team found relatively little evidence of humans at the site. Geneticists led by Eske Willerslev at the University of Copenhagen searched for ancient human DNA in the cave dirt, but with no luck.

Early settlers

In a second study (L. Becerra-Valdivia and T. Higham *Nature* http://doi.org/gg5s5f; 2020) two of Ardelean's co-authors – archaeologists Thomas Higham and Lorena Becerra-Valdivia at the University of Oxford, UK – combined the Chiquihuite Cave evidence with data from 41 other sites in North America and a region of eastern Siberia and western Alaska called Beringia, and built a statistical model of early human settlement. They concluded that people were present across North America much earlier than the accepted date of 15,000–16,000 years ago.

Some archaeologists think that it is time to take these ideas seriously. "The growing body of evidence for people in Beringia before 15,000 years ago renders their appearance in places like Mexico 20,000 or 30,000 years ago less surprising," says John Hoffecker, an archaeologist at the University of Colorado Boulder.

Others disagree. Collins says Becerra-Valdivia and Higham assume that early sites such as Chiquihuite Cave offer unambiguous evidence of human activity. "This is far from the case," he says.

Becerra-Valdivia accepts that evidence from most sites – except Monte Verde II – is disputed, but says that the analysis purposely omitted information from the most controversial sites, to make its case stronger.