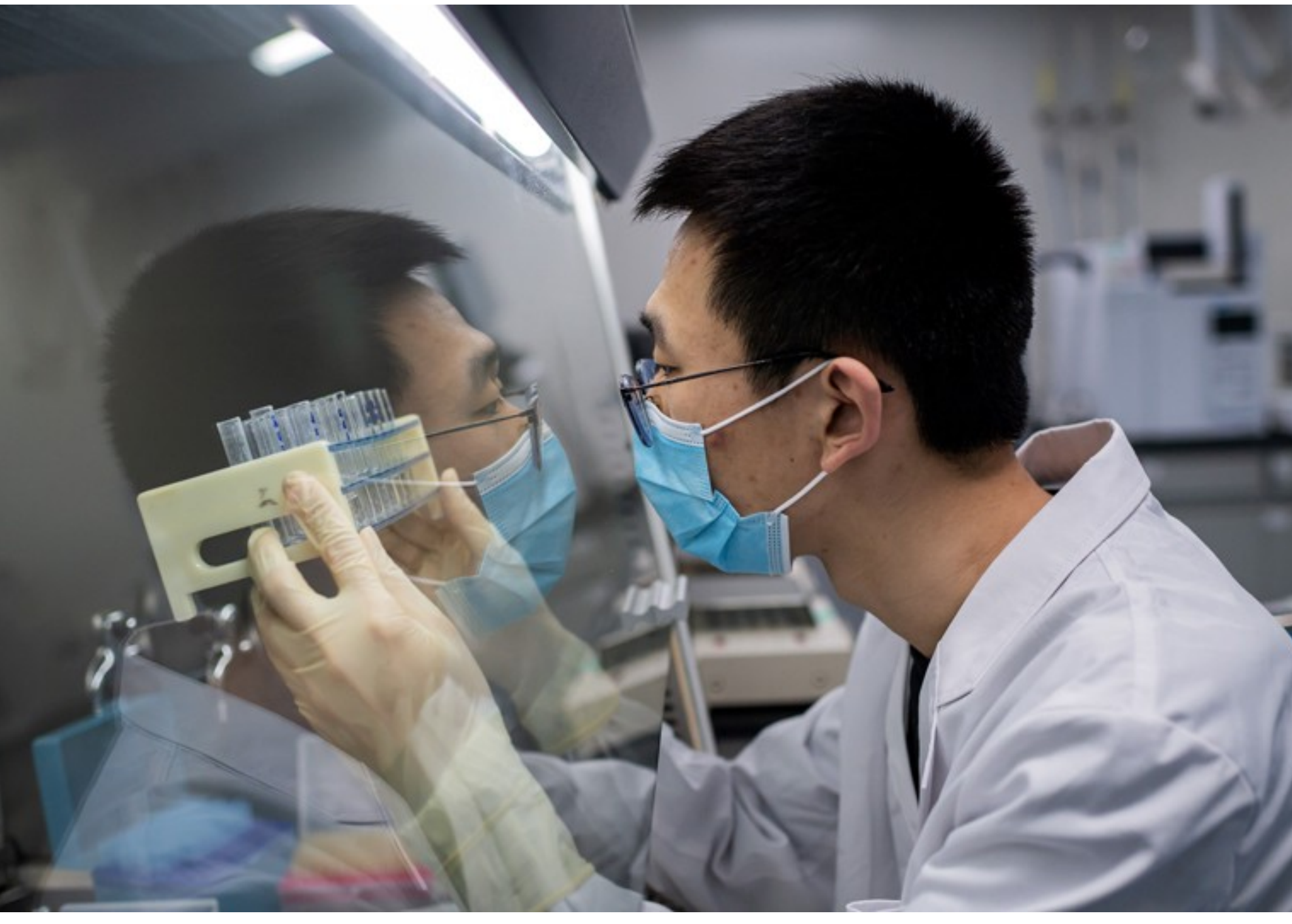
David Cyranoski



Chinese companies have made several vaccines that are currently being trialled. Credit: Nicolas Asfouri/AFP/Getty

Chinese companies are at the forefront of global efforts to create a vaccine for the coronavirus, with more than half a dozen candidates in clinical development. Last week, Tianjin-based CanSino Biologics published results[1] from an early-stage clinical trial showing that its vaccine is safe and can trigger an immune response.

Yet the companies could face difficulty as they try to push vaccines through phase III trials, a crucial stage of testing that is needed to prove efficacy and secure approval from regulators. These trials usually require tens of thousands of participants, and with the outbreak in China largely under control, companies are having to test their vaccines elsewhere. But researchers say they might still struggle to enrol so many participants and employ enough health-care professionals to collect data.

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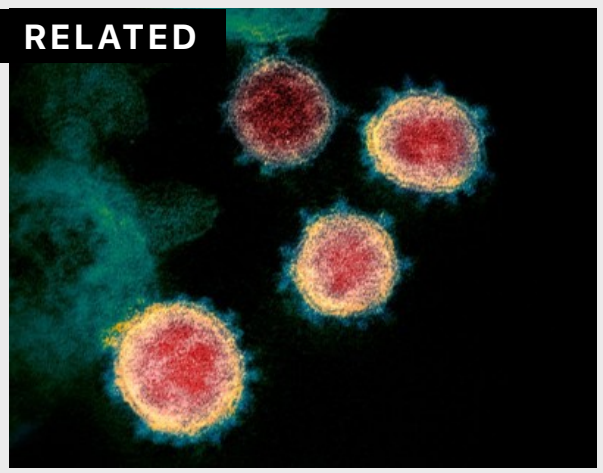

Coronavirus and COVID-19: Keep up to date

"The Chinese companies will need to step outside of China," says Jerome Kim, director-general of the International Vaccine Institute in Seoul. "The race is on," he says, "and it's really about who can set up in a high-risk area most quickly."

Chinese vaccine-makers will face other challenges, too. Vaccines will probably face extra scrutiny, given the country's opaque regulatory system and previous vaccine scandals, say scientists. In 2018, hundreds of thousands of children reportedly received defective diptheria, tetanus and whooping cough vaccines.

Quick to act

As the country where the coronavirus outbreak began, China was fast out of the gate in developing vaccines. CanSino's offering is made from a common-cold virus, tweaked to mimic the coronavirus. Sinopharm, a state-owned pharmaceutical company in Beijing, is developing two vaccines made using particles of the coronavirus that have been inactivated so that they can no longer cause disease. The company said in press releases in June that both vaccines had produced antibodies in all participants in preliminary phase I and II trials. And Beijing-based company Sinovac has announced similarly promising results for its own inactivated-virus vaccine.

This month, Sinovac launched a phase III trial of its vaccine in Brazil. Sinopharm will be testing its inactivated vaccines in the United Arab Emirates (UAE). Only three other coronavirus vaccines have entered phase III trials: one produced by biotech company Moderna in Cambridge, Massachusetts; one by the University of Oxford and drug maker AstraZeneca, based in Cambridge, UK; and one by biotech company BioNTech of Mainz, Germany, in collaboration with New York City-based drug firm Pfizer.

CanSino is also poised to launch a phase III trial. But the Chinese government has already said that its vaccine can be used by the military — making CanSino the first company to have a vaccine for COVID-19 approved for limited use in people. China has worked hard "to generate an efficient vaccine as soon as possible and to be transparent" when doing so, says Stéphane Paul, a vaccine researcher at the University of Lyon in France.

The speed with which Chinese vaccine-makers are moving has raised hopes around the world. Sinopharm has even promised to have a vaccine ready to distribute by the end of the year.

Inactivated vaccines are widely used vaccine types, so it makes sense for Chinese companies to focus on them, says Paul. "As a first line of vaccine, it is immunogenic, quick to develop and low-cost," he says.

But some viruses become more potent when they infect organisms previously treated with inactivated vaccines, in a poorly understood phenomenon known as antibody-dependent enhancement (ADE). This was reported[2] last year in monkeys given a vaccine for the coronavirus that causes severe acute respiratory syndrome (SARS). Sinovac says its COVID-19 vaccine did not trigger ADE in monkeys, but the risk will be closely monitored in all the inactivated-vaccine phase III trials, says Paul.

Hurdles ahead

Some observers also question whether companies will be able to work at the promised speed, and with the precision that such trials require. And the fact that China was willing to approve CanSino's vaccine for use in the military before phase III trials were complete raised eyebrows. "The decision is political, and not scientific in nature. It doesn't demonstrate anything on the potential efficacy of this vaccine," says Marie-Paule Kieny, a vaccine researcher at INSERM, the

French national health-research institute, in Paris.

Phase III trials present challenges for vaccine-makers around the world, such as the need to recruit enough participants and qualified health staff. Demonstrating that vaccines provoke an immune response and protect people from the virus requires data on 20,000–40,000 people who have been split into control and test groups and then followed closely for several months or even years, scientists say. To reach the numbers required, the trials might need to combine results from dozens of hospitals, each supplying data from hundreds of patients. “All of these things have to be done, and done correctly,” says Kim. “The number of sites that can do this and handle the volume is limited,” he adds. “Even the best sites will have difficulty.”

Many Chinese companies are at a disadvantage because they don’t have established networks of hospitals around the globe, says Kim. AstraZeneca, which published[3] promising early trial results for its vaccine — based on a chimpanzee cold virus — the same day as CanSino, is carrying out phase III studies in the United Kingdom, Brazil and South Africa. Moderna has launched a trial of its vaccine, which elicits an immune response with synthesized RNA that mimics the RNA that the coronavirus uses to replicate, in 30,000 people across the United States, a country with a lot of experienced clinical researchers to carry out trials, and a large coronavirus outbreak.

US President Donald Trump said last week that he was willing to work with any country that can deliver an effective vaccine, but Chinese companies had previously been ruled out of receiving funding from the US government’s Operation Warp Speed, which aims to speed vaccine development. The possibility of a US–China collaboration was also damaged on 21 July, when the US Department of Justice made public allegations that two Chinese hackers had tried to steal COVID-19 vaccine designs from a US company.

Still, Kieny points out that Sinopharm has partnered with the UAE’s government and Group 42 Healthcare, a local artificial-intelligence company, for its phase III trial, and Sinovac has partnered with the Butantan Institute in São Paulo, Brazil. “So far, Chinese companies seems to have been successful in finding partners,” she says.

Sufficient data?

But some researchers question whether the trials in the UAE and Brazil will gather enough data

to convince regulatory agencies that the vaccines work. In the UAE, where Sinopharm plans to enrol 15,000 participants to study its two vaccines, relatively few people are infected with COVID-19.

And although Brazil has a large coronavirus outbreak, the Butantan Institute plans to test Sinovac's vaccine among health-care professionals because it is assumed they will face greater exposure to the virus than will non-health-care professional. Because of this, the trial will enrol only 9,000 people to test whether it works, says Ricardo Palacios, a clinical researcher at the institute who is leading the trial. "We designed a trial in order to obtain answers in a more efficient way," says Palacios.

Kim notes that in countries where health-care workers wear proper personal protective equipment, they might not face greater exposure to the virus, which would undermine the justification for a smaller trial.

The most important thing is that trials collect data that adhere to international standards expected by drug regulators and by bodies such as the World Health Organization, says Kim. "If you can't do that, you're in trouble," he says.

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