



Medics check on people with COVID-19 in Jinyintan Hospital in Wuhan, China.

## SLEW OF TRIALS LAUNCH TO TEST CORONAVIRUS TREATMENTS IN CHINA

HIV drugs, stem cells and traditional Chinese medicines are vying to prove their worth.

By Amy Maxmen

**C**hina has more than 80 running or pending clinical trials on potential treatments for COVID-19, the illness caused by a coronavirus that has so far killed more than 1,800 people and infected more than 70,000 across the country, and for which there is currently no cure.

New drugs are listed beside thousand-year-old traditional therapies and existing treatments for other diseases in a public registry of China's clinical trials that is growing every day. But scientists caution that only carefully conducted trials will show which measures work.

Soumya Swaminathan, chief scientist at the World Health Organization (WHO), says that the agency is drawing up a plan for a clinical-trial protocol that researchers around the world could use, and working with scientists to help set standards for the trials in China, which include as many as 600 people each.

For example, a person's stages of recovery or decline should be measured in the same way, regardless of the treatment being tested, says Swaminathan. "We can hopefully bring some sort of structure into the whole thing."

The WHO's clinical-trial protocol will compare two or three therapies, including

an HIV-drug combination (lopinavir and ritonavir) and an experimental antiviral called remdesivir.

Researchers in China have begun testing these drugs in clinical trials, according to the Chinese Clinical Trial Registry, and there is already some evidence to suggest they have potential to fight the coronavirus. "Getting the clinical trials straight is a priority, since if we get information on what is working and not working, we can benefit patients now," Swaminathan says.

### Animal results

The two HIV drugs block enzymes that viruses need to replicate. In animal studies, they have reduced levels of the coronaviruses that cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)<sup>1</sup>. Remdesivir, a nucleotide analogue made by the biotechnology company Gilead in Foster City, California, has also had some success against coronaviruses in animals<sup>2</sup>. And in January, researchers reported that one person in the United States had survived a COVID-19 infection after being treated with remdesivir<sup>3</sup>.

In the first week of February, two placebo-controlled trials of remdesivir, set to include a total of 760 people with COVID-19,

began in China. Those studies should be completed by the end of April, and remdesivir could be approved by Chinese authorities as early as May, says Shibo Jiang, a virologist at Fudan University in Shanghai. "But the epidemic might be gone by then," he says.

Researchers in China have also launched a few trials that test chloroquine, a malaria drug that killed off the new coronavirus (recently named SARS-CoV-2) in cell culture<sup>4</sup>. And scientists are studying whether steroids diminish inflammation in people with severe COVID-19, or cause harm. "It will be interesting to see these results," says Yazdan Yazdanpanah, an epidemiologist with France's national health agency, INSERM, in Paris. Research clinicians around the world will need this information if the outbreak continues to spread, he adds.

Another study – a 300-person controlled trial – will test serum from COVID-19 survivors. The same basic idea – that the antibodies one person steadily builds up to fight a virus can help someone freshly infected to fight it off rapidly – has had modest success when used to treat other viruses in the past<sup>5</sup>.

Two stem-cell trials are also listed in China's registry. In one, a team at the First Affiliated Hospital of Zhejiang University will infuse 28 people with stem cells derived from menstrual blood, and compare results with those from people who did not receive the infusions. So far, there is minimal evidence indicating that stem cells clear coronavirus infections. Swaminathan says that the WHO cannot control what researchers do, but that the agency published guidance on the ethics of running trials amid outbreaks in 2016. And it will be posting a more accessible brief report on the issue soon.

About 15 trials listed in China's registry expect to enrol a total of more than 2,000 people in studies on a variety of traditional Chinese medicines. One of the largest assesses shuanghuanglian, a Chinese herbal medicine that contains extracts from the dried fruit *lianqiao* (*Forsythia fructus*), which is purported to have been used to treat infections for more than 2,000 years. The trial has 400 participants, including a control group given standard care but not a placebo therapy.

The WHO is working with Chinese scientists to standardize the design of all the studies, including those on traditional medicines. That reflects a controversial move last year, in which the organization recognized traditional Chinese medicine in its compendium of diseases. Critics argued that the WHO's recognition amounted to endorsement, but Swaminathan disagrees. She says that the move helps to codify medical terminology so that herbal remedies can be evaluated with the rigour expected of pharmaceutical testing. "We want a scientific approach to testing traditional medicine," she says.

With many therapeutic possibilities and limited time, Jiang says the WHO should provide advice about which treatments to move forward, and which to ditch, as trials progress. And he hopes that research on better, broader therapies will be continued after the outbreak ends. “I worry this will be the same situation as during SARS,” he says,

“where the work starts, then stops.”

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# SCIENTISTS FEAR CORONAVIRUS SPREAD IN VULNERABLE NATIONS

## Concerns are rising about the virus’s potential to circulate undetected in Africa and Asia.

By Smriti Mallapaty

Infections with the new coronavirus have now been detected in 25 countries outside China. But researchers warn that cases might be going undetected in some nations that are considered to be at high risk of an outbreak but are reporting fewer cases than expected, or none at all.

The possibility of unreported cases of the disease, known as COVID-19, is particularly concerning in countries with weaker health-care systems, such as some in southeast Asia and Africa, which could quickly be overwhelmed by a local outbreak, experts say. So far, only one case has been reported in Africa – in a person in Egypt – but some countries there, such as Nigeria, are at particular risk because of their strong business ties to China.

Researchers have been using flight data to create models of the possible spread of the virus around the world. One model identified 30 countries or regions at risk of importing the virus on the basis of the large number of flights from Wuhan, the outbreak’s epicentre, and from other cities in China with many travellers from Wuhan.

Thailand is the country most exposed, according to the study, which was published on 5 February and used flight data from February 2018 (S. Lai *et al.* Preprint at medRxiv <http://doi.org/dmr4>; 2020). Thirty-five people with the infection have been reported there so far, of whom 23 had been in China. But study co-author Shengjie Lai, an epidemiologist at the University of Southampton, UK, says the model estimates that Thailand probably imported 207 cases in the 2 weeks before travel into and out of Wuhan was restricted in late January.

Indonesia has not reported a single case so far, and yet the country is a popular destination

for Chinese tourists. Lai says it might have imported as many as 29 cases. Several other countries, including Malaysia, Vietnam, Cambodia and Australia, have also reported fewer cases than the model predicts, he says.

Although it’s possible that there have truly been no cases in Indonesia, infected people might have recovered before they were detected, says epidemiologist Andrew Tatem, a co-author of the study also at the University of Southampton. Undetected cases might also be spreading under the radar, he says.

Despite the predictions, Amin Soebandrio, an infectious-disease scientist and chair of the Eijkman Institute for Molecular Biology in Jakarta, says Indonesia has the capacity to detect the virus in people if it arrives.

But some countries in southeast Asia have limited numbers of health-care workers,

hospital beds, support staff and ventilators, and would struggle to respond to a surge in cases of the virus, says Richard Coker, a retired physician based in Bangkok.

Tedros Adhanom Ghebreyesus, director-general of the World Health Organization (WHO), said the agency’s decision to declare the outbreak a global health emergency was mainly due to concerns that the virus could spread in countries with weaker health-care systems.

## What about Africa?

For that reason, infectious-disease researchers are also worried about the virus spreading among people in Africa. A large number of Chinese labourers work in Africa, and their travel between China and Africa is a possible route for transmission, says Marc Lipsitch, an epidemiologist at the Harvard T.H. Chan School of Public Health in Boston, Massachusetts.

Another model found that Egypt, Algeria and South Africa are the countries in Africa that are most at risk of the virus spreading. The analysis, published on 7 February, examined flights to Africa from Chinese cities that had reported infections, but excluded cities in Hubei province, where Wuhan is located, because of the lockdown that has restricted travel from many cities there since late January (M. Gilbert *et al.* Preprint at medRxiv <http://doi.org/dmr5>; 2020).

But these three countries also have the capacity to respond effectively to an outbreak, says Vittoria Colizza, who models infectious diseases at the Pierre Louis Institute of Epidemiology and Public Health in Paris and is a co-author of the Africa study.

Colizza is most concerned about seven African nations that have a moderate risk of importing the virus, but whose weak health-care systems, low economic status or unstable political situation make them highly vulnerable. These are Nigeria, Ethiopia, Sudan, Angola, Tanzania, Ghana and Kenya.

Until two weeks ago, many African nations did not have laboratories that could diagnose COVID-19, and samples had to be tested abroad. But the situation is changing rapidly, says Colizza. Africa has gone from having only two labs with the capacity to confirm the virus to having at least eight, according to the WHO.

Three of the newly added labs are in Nigeria, says Chikwe Ihekweazu, director-general of the Nigeria Centre for Disease Control in Abuja.

Ihekweazu says Nigeria’s size, the volume of travellers it receives and its vibrant economy already make it vulnerable to importing an infectious disease, and that the country’s strong business ties with China pose a further risk.

Nigeria has ramped up screening of travellers from China. Ihekweazu says the worst-case scenario for the country would be if an infected person goes undetected and begins to infect others. “That is really what keeps me up at night,” he says.



The coronavirus responsible for COVID-19.