An ambulance crosses a deserted bridge in Wuhan, China, which has been cordoned off from the outside world.

PHOTO: AP PHOTO/CHINATOPIX

INFECTIOUS DISEASES

New coronavirus threat galvanizes scientists

As China outbreak spreads worldwide, researchers probe its origins and how to fight it

By **Jon Cohen**

Barely 1 month after Chinese health authorities reported the first cases of a mysterious new pneumonia in the city of Wuhan, the world may be on the cusp of a new pandemic. As *Science* went to press, the number of confirmed cases of the novel coronavirus, dubbed 2019-nCoV, had shot up to more than 4500, most of them in mainland China but more than 80 in 17 other countries and territories. China has quarantined 35 million people in Wuhan and several other cities in a desperate attempt to slow the spread of the virus. But as the case numbers keep soaring, the realization has set in that it may be too late to have much impact.

Even seasoned epidemiologists are astonished at the virus's dizzying spread. Early estimates of the number of infected people—thought to far exceed the number of confirmed cases—became obsolete overnight. "Our original results are NO LONGER VALID," University of Hong Kong epidemiologist Gabriel Leung tweeted on 22 January, 1 day after his group had posted its first mathematical model of the epidemic. Leung is now estimating that Wuhan alone had 43,590 infections by 25 January—and that the number is doubling every 6 days. "How widespread does this go?" asks Marion Koopmans, a virologist at Erasmus Medical Center. "This deserves our full attention."

Early this week, the World Health Organization (WHO) had not yet declared the outbreak a Public Health Emergency of International Concern (PHEIC), the loudest alarm the agency can sound. In meetings on 22 and 23 January, a special WHO committee that includes Koopmans was divided on whether a PHEIC was warranted, in part because there was no evidence the disease was spreading between people outside of China. But by 28 January, several countries had reported local human-to-human transmission, which may change the equation.

So far 2019-nCoV appears to be milder than its cousin, severe acute respiratory syndrome (SARS), which had a mortality rate of 10%. Only 106 deaths have been recorded to date. But hundreds more people are seriously ill, and their fate is unclear. And countless other questions remain. Scientists don't know how long the incubation period lasts or whether infected people who show no symptoms can transmit the virus. China's state-run news agency Xinhua reported on 26 January that a seemingly healthy man appeared to have infected "a few colleagues." If asymptomatic people frequently infect others, it could vastly complicate efforts to contain 2019-nCoV.

The virus's explosive spread has been met by an unprecedented rush by scientists to uncover its origins, find treatments, and develop vaccines that could save millions of lives if the world really does face a pandemic. Here are some of the ways researchers are attempting to better understand 2019-nCoV and reduce its harm.

WHERE DID THE VIRUS COME FROM?

Almost certainly from animals, but when and how are mysteries. Genetic analyses are starting to yield some clues. Chinese researchers first shared a genomic sequence of 2019-nCoV on 11 January. Labs in China and abroad have since announced nearly three dozen additional sequences of the virus—"a stellar job," Koopmans says.

A team led by Shi Zheng-Li of the Wuhan Institute of Virology reported on 23 January that 2019-nCoV's sequence was 96.2% identical to that of a bat coronavirus and 79.5% identical to the SARS coronavirus. That doesn't mean 2019-nCoV jumped directly from bats to humans, says evolutionary biologist Kristian Andersen of Scripps Research. SARS, for example, probably moved from bats to civets—sold as a delicacy in many markets—to humans.

From the start, the Huanan Seafood Wholesale Market in Wuhan—which sold mammals as well as fish—was considered a likely source of the outbreak because most of the early patients had visited it. On 27 January, Xinhua reported that researchers have found evidence of the new coronavirus in 33 of 585 environmental samples

taken at the market on 1 January—the day it was closed—and on 12 January. They all came from the western end, which had a concentration of booths selling wildlife.

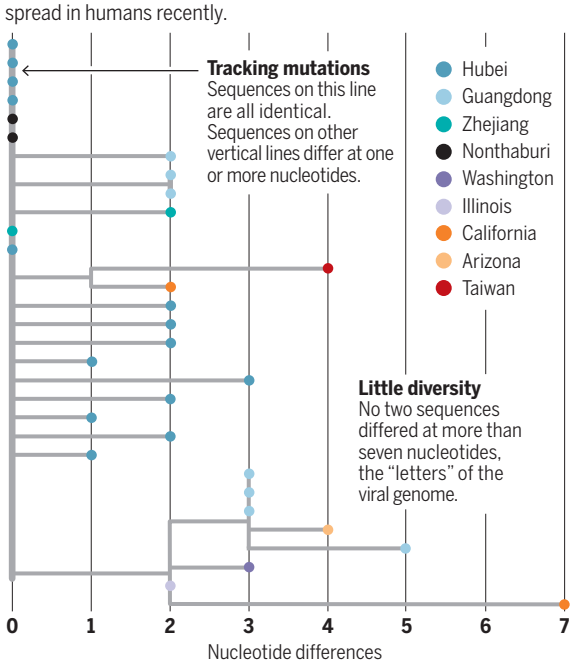
That indicates the market played a role in spreading the virus, says Daniel Lucey, an infectious disease specialist at Georgetown University—but he says other data suggest it wasn't the origin. The first known patient became ill on 1 December 2019 and had no links to the market, according to a paper published by Chinese researchers in *The Lancet* on 24 January that offered details about the first 41 patients in Wuhan. In that group, 12 others also had no links to the market. Lucey contends the virus was already circulating silently among humans before it contaminated the seafood market, possibly by infected animals, humans, or both.

The genomic data cannot pinpoint the origin, but they do show that the jump from animals to humans happened recently, Koopmans says. An analysis of the first 30 publicly posted sequences shows they differ from each other by no more than seven nucleotides (see graphic, right). Using these differences and presumed mutation rates, several groups have calculated that the virus began to spread around mid-November 2019—which supports the thesis that spread may have occurred before any of the cases linked to the market. One group put the origin of the outbreak as early as 18 September 2019.

Bin Cao, a pulmonary specialist at Capital Medical University in Beijing and the corresponding author of *The Lancet* article, agrees the story is more complicated than many thought. "Now it seems clear that [the] seafood market is not the only origin of the virus," he wrote in an email to *Science*. "But to be honest, we still do not know where the virus came from now."

Genomes offer clues about virus's past

A phylogenetic tree of viral sequences from dozens of patients shows very few differences between them, indicating the new virus began to spread in humans recently.



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COULD EXISTING DRUGS WORK?

It may take years to develop treatments specifically designed for 2019-nCoV, but researchers hope existing drugs can help. Wuhan's Jin Yintan Hospital has already launched a randomized, controlled trial of the anti-HIV drug combination of lopinavir and ritonavir, according to the report in *The Lancet*. The duo targets the protease enzyme used by HIV to copy itself, and it might thwart the coronavirus's protease as well. There's a precedent from the SARS outbreak: In a nonrandomized trial published in 2004, researchers saw an "apparent improved outcome" from the same two protease inhibitors, combined with a third drug, ribavirin, in SARS patients.

Saudi Arabia is now conducting a trial with the same protease inhibitors, combined with interferon beta-1b, against Middle East respiratory syndrome (MERS), a coronavirus distantly related to SARS and 2019-nCoV that is occasionally spread by camels. But in a recent mouse study by Ralph Baric of the University of North Carolina, Chapel Hill, this cocktail had lackluster results against MERS.

The same study showed better outcomes for remdesivir, an experimental drug made by Gilead and previously tested against Ebola that interferes with the viral polymerase enzyme. Remdesivir combined with interferon slowed viral replication in MERS-infected mice, and their lung function improved. "Remdesivir has had activity against every coronavirus we've tested, and I'd be surprised if it didn't have activity against" 2019-nCoV, says co-author Mark Denison, a virologist at Vanderbilt University.

Development of entirely new treatments has started as well. U.S. biotech Regeneron is trying to identify monoclonal antibodies effective against 2019-nCoV, as it did previously for MERS and Ebola. The ideal treatment for 2019-nCoV may well be a drug like remdesivir plus monoclonal antibodies, Denison says. "The idea of using those in combination would have profoundly good prospects."

CAN VACCINES BE DEVELOPED IN TIME?

In the stock pandemic movie, scientists develop a vaccine just in time to save the world. In real life, new vaccines have never been developed fast enough to have a significant impact on an emerging virus. But in the case of 2019-nCoV, scientists are trying to work at Hollywood speed.

The Coalition for Epidemic Preparedness Innovations (CEPI), a nonprofit formed in 2016 to fund and shepherd the development of new vaccines against emerging infectious diseases, has already given two companies and an academic group a total of $12.5 million to develop 2019-nCoV vaccines. The efforts began hours after Chinese researchers first published a viral sequence 3 weeks ago.

One is a collaboration between the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and U.S. biotech Moderna, which makes vaccines by converting viral sequences into messenger RNA (mRNA). (When injected into the body, mRNA causes the body to produce a viral protein, which triggers immune responses.) Moderna and NIAID have worked on a vaccine against MERS that consists of mRNA coding for a protein on the viral surface called the spike; in theory, all the team needs to do now is swap in the genetic sequence for 2019-nCoV's spike.

CEPI funded a second company, Inovio, to produce vaccines that work in a similar way but are made of DNA. It, too, has a template for a 2019-nCoV vaccine: another candidate MERS vaccine that relies on the spike protein. CEPI's third grant went to researchers at the University of Queensland who are developing a vaccine made of viral proteins produced in cell cultures. Vaccine projects are also underway in mainland China, Hong Kong, Belgium, and Germany. Once candidate vaccines are available, researchers will test them in animals, then seek approval for phase I human trials. "We're building the airplane as we're flying," says Inovio CEO Joseph Kim.

NIAID Director Anthony Fauci says the first clinical trial of the Moderna vaccine could start within 3 months. In the best-case scenario, Barney Graham, who leads the project for NIAID, says the Moderna vaccine could be ready for larger, real-world efficacy tests in humans by summer. Even if it works, mass-producing it or any other vaccine quickly would present a huge challenge.

With luck, however, the outbreak will fade by summer, and with it the urgency of having a vaccine at the ready. "Nobody knows what's going to happen," says Stéphane Bancel, Moderna's CEO. "We're all hoping we'll never need this vaccine." ■

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