GENES & CELLS

MERS outbreak picks up pace

In recent weeks, virus infected hundreds, including two U.S. cases

BY TINA HESMAN SAEY

More than two years after it first appeared, the Middle East Respiratory Syndrome virus has suddenly exploded, with more than 200 new cases in April. As doctors struggle to treat patients, scientists are rushing to answer some basic questions about the virus's biology, whose answers could stop the outbreak from becoming a pandemic.

As far as anyone knows, the first human victims of MERS were a university student and a nurse who got sick and died in Jordan in the spring of 2012. In the two years between then and March 2014, public health officials recorded a total of 207 cases. Of those cases, 93 people died, making the mortality rate about 45 percent.

"If you do the math on the mortality rate of the virus and the number of people on the planet, it's scary," says Ralph Baric, a virologist at the University of North Carolina at Chapel Hill, who has long studied coronaviruses, including MERS and its cousin SARS.

The situation has rapidly worsened. In April 2014, the MERS virus infected at least 261 people — more than in the previous two years combined — and killed 38, mostly in Saudi Arabia and the United Arab Emirates. Those countries have been focal points of the disease since early in the outbreak. The first two documented cases in the United States were announced on May 2 and May 12; the patients are both health care workers who recently traveled from Saudi Arabia (*SN Online*: 5/2/14, 5/5/14, 5/12/14). By mid-May, the world's case total was 538, according to the U.S. Centers for Disease Control and Prevention.

The World Health Organization has

a team in Saudi Arabia attempting to determine why MERS has begun to spread so rapidly, says WHO spokesperson Tarik Jasarevic. Scientists have already ruled out one possibility: "There is absolutely no evidence that the virus has changed," he says.

Part of the mystery is that no one is certain how people become infected, Jasarevic says. Camels and bats have been found to carry related viruses, with camels regarded as the most likely source for human infections.

Now, researchers have discovered that dromedary camels carry live MERS viruses in their noses that can infect primate cells. Thomas Briebe, a virologist at Columbia University, and his colleagues report the finding April 29 in *mBio*. Previous studies had hinted that the dromedaries could carry MERS (*SN*: 4/5/14, p. 8), but fell short of demonstrating that the animals have live viruses that can transmit to humans.

Camels can't be blamed for all MERS cases. Many people who have fallen ill were city dwellers who had no contact

with camels, Briebe says. And if the animals were the primary source, he says, one might expect camel handlers or people who work at slaughterhouses or otherwise have intense contact with camels and their bodily fluids to be the people who get MERS most often. But that's not the case, Briebe says.

Instead, the virus most often attacks the old and already sick. Scientists are trying to determine what makes some people susceptible. Also unclear is exactly how the virus makes the leap from camel to human. Briebe and his colleagues are testing camel meat, milk and urine as possible sources of the virus.

The method of transmission is just one of the fundamental questions that scientists have yet to answer about MERS. Researchers have learned that the virus uses a protein on its surface, known as the spike protein, to pick a particular molecular lock and gain access to human cells. The lock is a protein

The MERS virus (yellow) was unknown two years ago. Now it has infected at least 538 people in 16 countries.

known as dipeptidyl peptidase 4, or DPP4, that sits on the surfaces of cells (*SN Online*: 3/13/13). Many species make a version of DPP4; the MERS virus can crack a limited number of those, including the versions made by humans, camels and bats. It can't get past the DPP4 locks on the surfaces of cells from mice, rats or ferrets, says Vincent Munster, a virologist at the National Institutes of Health's Rocky Mountain Laboratories in Hamilton, Mont.

That's a problem, because it means those laboratory favorites can't be experimentally infected with MERS. Munster and his colleagues discovered that the coronavirus can infect rhesus monkeys. But the monkeys don't completely mimic the human infection, Munster says, and "not that many labs can handle nonhuman primates."

The problem of finding a useful animal MERS model may be partially solved thanks to a team led by Stanley Perlman, a virologist at the University of Iowa in Iowa City. Perlman and his colleagues devised a way to get mice to temporarily produce the human version of DPP4 in their respiratory tracts, the researchers reported in the April 1 *Proceedings of the National Academy of Sciences*.

Mice with human DPP4 can be infected with MERS, enabling the researchers to learn how the immune system handles the virus. Perlman's group is now genetically engineering mice to permanently replace their DPP4 protein with the human version.

Other potentially good news surfaced when two groups of researchers reported April 28 in the *Proceedings of the National Academy of Sciences* and in the April 30 *Science Translational Medicine* that they had isolated human antibodies that could prevent the MERS virus from latching on to its target.

The discovery raises the possibility that the antibodies could treat MERS infections or protect health care workers or close contacts of MERS patients from infection, says Wayne Marasco, an immunologist at Harvard Medical School and a coauthor of one of the reports.

The study also suggests that healthy

A moving target The MERS outbreak has centered on the Middle East, but travelers have carried the respiratory virus to many other countries. The numbers represent cases documented through May 6 in each country, with the exception of the United States, which saw its second case later in May. SOURCE: EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

human immune systems can keep the MERS virus in check, Marasco says. During the course of the experiments, the virus sometimes developed mutations in its spike protein, allowing MERS to evade the antibodies. "In cases where viruses could escape, they did so at the expense of their own fitness," says Marasco. The mutated viruses either had a harder time grasping cells, which would make infection harder, or they grew less well in primate cells. Weakened viruses may be easy pickings for a strong immune system.

Unfortunately, many people who have contracted MERS already had other illnesses that may have damaged their ability to fight the virus. Each infected person is like a test tube where the virus can mutate; having more test tubes means an ever-increasing chance that the virus could become better at growing in humans. "A weakened immune system is clearly consistent with an environment where adaptation can occur," says Marasco.

Many of the new cases in Saudi Arabia and the United Arab Emirates have been spread from a sick person to a health care worker, family member, hospital patient or another contact. People who caught the virus from someone else tend to have mild illnesses or no symptoms at

all, Jasarevic says, and the virus rarely transmits beyond the second person infected.

That's an assertion that Trish Perl, an epidemiologist at Johns Hopkins University, challenges. Perl traveled to Saudi Arabia last year to investigate a large MERS outbreak at hospitals. Her team found evidence for long chains of person-to-person transmission of the virus, especially among dialysis patients (*SN Online*: 6/19/13). "It's clear that there is a lot going on in the health care environment," Perl says.

In recent weeks, health officials have reported a growing number of milder cases and cases with no symptoms. Some may have been detected thanks to better surveillance; mild cases may have been missed earlier. The growing number of milder cases has also lowered the virus's overall mortality rate to somewhere around 30 percent. That's still a frightening number, Perlman says, but "it's not as scary as it could be."

He sees MERS as primarily a camel cold virus that sometimes leaps into susceptible people; proper precautions, he says, may make it disappear. "If you have good infection control measures and people stop getting so close to sick camels, there's a good chance it will die out." ■