ON 21 MARCH 2012, A 25-YEAR-OLD STUDENT in Jordan started coughing. A few days later, he developed fever and shortness of breath. He was admitted to a hospital, where he ended up in intensive care. By the time he died on 25 April, several nurses and doctors had developed similar symptoms. One of them died, too. Then the mystery disease disappeared again.

Two years later, it’s clear that the outbreak was the prelude to a protracted struggle against what is now known as the Middle East respiratory syndrome (MERS) virus. And although scientists still have lots of unanswered questions, evidence is mounting that camels play a key role in spreading the new pathogen. The camel-borne threat may extend far beyond the Middle East. Last month, a team led by Malik Peiris, an infectious disease researcher at the University of Hong Kong, showed that almost all camels in four Egyptian abattoirs had MERS antibodies in their blood; most had been imported from Ethiopia and Sudan, suggesting the virus may reside in large parts of Africa.

As a result, scientists are shifting their focus from human cases to camels. “It is becoming ever clearer that MERS is a classic zoonosis,” says virologist Christian Drosten of the University of Bonn in Germany. “We need to concentrate more on the animals.”

One idea gaining traction is to vaccinate camels. “Protecting camels right now may be the single most important thing we can do to protect humans,” says Michael Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, Twin Cities.

But vaccines against coronaviruses, the group to which MERS belongs, are difficult to make, and researchers face hurdles ranging from money problems to the lack of a suitable animal model. Neither veterinarians nor health officials in the Middle East have risen to the challenge. To make matters worse, there are very few labs capable of safely studying deadly viruses in animals as big and unruly as camels.

The evidence mounts
After it was identified in June 2012, MERS quickly made its way to the top of the global public health agenda. The virus is related to severe acute respiratory syndrome (SARS), a deadly pathogen that emerged in China in late 2002, killed 800 people around the world, and nearly caused a pandemic. The World Health Organization (WHO) still worries that MERS could be the sequel to that frightening episode. But while the disease has sickened at least 199 people and killed 84, it has largely been confined to the Middle East (see map, p. 1423).

The first clue that camels might be involved came from a patient from Abu Dhabi who died in a German hospital in March 2013. He owned racing camels and reported having had close contact with a sick camel before falling ill. Then in August, a team including Marion Koopmans, now at Erasmus MC in Rotterdam, the Netherlands, reported that 50 retired racing camels from Oman all had antibodies against MERS in their blood, which is evidence of a past or current infection. None of the cows, goats, and sheep they tested had such antibodies.

Some scientists were skeptical. Other coronaviruses known to infect domestic animals could have caused the positive tests, they argued. “We don’t think camels have anything to do with it,” said Ziad Memish,
Beyond borders. A recent study found MERS in camels in Egypt, including animals imported from Sudan and Ethiopia.

an infectious disease specialist and Saudi Arabia’s deputy health minister, at the time. “It just seemed so weird,” says Peter Daszak, a veterinary epidemiologist at the EcoHealth Alliance in New York City. Genetically, “the virus looks like a bat virus.” But later, MERS antibodies were reported in camels in Jordan, Egypt, the United Arab Emirates, and Saudi Arabia. And scientists investigating an outbreak on a farm in Qatar found snippets of the genome of the MERS virus in nasal swabs from three camels, suggesting that these animals were actually infected at the time.

Last month, a team led by Columbia University virologist Ian Lipkin reported evidence of a MERS infection in three-quarters of more than 200 Saudi Arabian camels tested; they also recovered MERS viral sequences that proved an exact match to viruses found in humans. Because the researchers rarely found the virus in camel feces, Lipkin believes fine droplets from the animals’ noses transmit it. Some of the positive samples dated back to 1992, suggesting that isolated, unrecognized human MERS cases may have happened for decades, he says. And just last week, scientists from Saudi Arabia and Europe reported about a MERS patient who fell ill after caring for sick camels; they managed to sequence snippets of the genome of the MERS virus in nasal swabs from three camels, suggesting that these animals were actually infected at the time.

No one is suggesting that contact with camels is the only way humans can become infected. Infected people can also spread MERS, as clusters of infection—such as the one in Jordan—indicate. Memish now accepts that camels seem to transmit MERS, but he says that some so-called index cases—patients who did not contract the disease from another patient—say they had no contact with the animals. It’s unclear how they got infected.

Some may have been exposed indirectly, says Anthony Mounts, WHO’s point person on MERS. In one recent instance, a man who worked with camels remained healthy, while his wife developed MERS. “The husband could have brought the virus home on his clothing,” Mounts says, though he adds, “this is not proven at all.” Contaminated food could be another route. But to identify all possible routes, local knowledge is crucial, Mounts says. He recently learned that drinking camel urine and applying it to the skin is used as a natural remedy for a variety of ailments in the region. The practice is probably not the primary route of transmission, he says, but it’s something that should be studied.

Other animals may still be involved. Bats seem to be MERS hosts, too; a fragment of viral RNA recovered from the feces of an Egyptian tomb bat living close to the first known Saudi MERS patient’s house was identical to the patient’s virus, so perhaps contact with bats can explain some cases. “It is important to remain open-minded about all potential sources of exposure for human and animal cases,” a representative for the World Organisation for Animal Health writes in an e-mail.

If camels are MERS’s main conduit, however, that puts the spotlight on countries far beyond the Middle East. Only about 260,000 of the world’s 27 million camels live in Saudi Arabia. Africa has far more: 7 million camels in Somalia alone, 3 million in Kenya, and 1.5 million in Chad.

The virus probably circulates in these herds as well, Peiris says. His 27 February paper in Emerging Infectious Diseases presented some early evidence. The scientists tested 52 camel blood samples from four abattoirs around Egypt and found antibodies against MERS in 48 of them, mostly from camels imported from Sudan and Ethiopia. They also took nose swabs from 110 camels and found MERS RNA in four imported animals. It’s very likely that infection has gone unnoticed in Africa, both in animals and humans, Peiris says. “Health authorities really need to test patients with severe pneumonia all across Africa for MERS.”

Beauty parades
For now, the MERS outbreak is generating a steady trickle of new cases: WHO reported four in January and four in February. But other zoonotic diseases have smoldered for years before they exploded, and no one knows whether MERS could also hold a nasty surprise. The fact that it didn’t spread around the world after the Hajj, the massive pilgrimage to Mecca, in 2012 and 2013, has put some minds at ease. But Drosten says that may have been a lucky break. “Camels all give birth around the same time in the winter months,” he says. They may contract MERS shortly after birth and be at their most infectious in spring. The Hajj is now in autumn, but because the Islamic year is shorter than the calendar year, it will eventually occur in the spring, Drosten says, “and that may change everything.”

If camels are the problem, vaccinating them might be the solution. A camel vaccine would be far cheaper to make than a human one, because testing in animals is faster and easier. Keeping the animals healthy would also make economic sense because camels are valuable, Daszak says: “They’re eaten; they’re raced; there are beauty parades. The Saudi government is going to have to act on this.” Breeding facilities would be the place to deploy a vaccine, says microbiologist Matthew Frieman of the University of Maryland School of Medicine in Baltimore. “We have an opportunity to vaccinate all newborn camels to block infection from older camels, which seems like it’s what’s happening,” he says.
But it’s not that simple. Camel breeders don’t see MERS as a problem because it does not seem to make camels very sick, and perhaps not at all, says Juan Lubroth, chief veterinary officer of the Food and Agriculture Organization of the United Nations in Rome. Nor have veterinarians and animal health officials shown great interest. “I have not been very successful in engaging my peers at the national or regional level,” Lubroth says. Most countries don’t see MERS as an immediate threat, and the U.S. National Institutes of Health has not yet awarded any grants for vaccine studies. Microbiologist Shibo Jiang of the New York Blood Center in New York City says he could not stir up any interest among companies either, “because of the unpredictable market in the future.”

Nor does anyone know how to make a MERS vaccine. Jiang believes the best target may be the virus’s spike, a protein sitting on the surface that it uses to attach to cells. He and his colleagues fused a 212- to 214-amino acid piece of the spike to the stem of a human antibody. This vaccine caused mice to produce antibodies that protected cells in a petri dish from infection.

But coronavirus vaccines pose special challenges. One worrisome example is feline infectious peritonitis, a fatal cat disease. Cats carrying antibodies against this coronavirus are known to get sicker, instead of being protected. Fears that this might happen in humans, too, have plagued attempts to develop a SARS vaccine based on a whole, killed virus. The exact mechanism isn’t quite clear, but Jiang found that with SARS, using just the part of the spike protein that binds to the cell receptor avoided the problem. He hopes the same will hold true for MERS.

But the receptor-binding area can change rapidly as the virus evolves, Frieman says, which might limit the protection offered by a vaccine. He has tried another approach: In collaboration with a company called Novavax, Frieman produced insect cells engineered to express the whole MERS spike protein. He harvests the protein as nanoparticles, small clumps of molecules sticking together. When these were injected into mice, the animals produced antibodies against MERS, Frieman reports in an as-yet unpublished paper.

A third strategy comes from Gerd Sutter of the Ludwig Maximilians University in Munich, Germany, who engineered a small-pox vaccine strain called MVA to carry the genetic information for the spike. The vaccine might kill two birds with one stone: It would act as a MERS vaccine in the animals but should also protect them against camelpox, making it more interesting to camel owners.

Testing vaccine candidates is the next hurdle. A good animal model for MERS has been hard to develop; the spike protein binds to a protein called DPP4 on the surface of human lung cells, but the murine version of DPP4 is so different that MERS does not infect mice. Rhesus macaques seem to become infected but show hardly any symptoms: “Without a CT scan it’s hard to tell that these animals are ill,” says Lisa Hensley of the National Institute of Allergy and Infectious Diseases’ lab in Frederick, Maryland. Marmosets get sicker, but they are hard to come by. Other groups have tried mice, ferrets, hamsters, and guinea pigs; none of them worked very well.

So microbiologist Stanley Perlman of the University of Iowa has engineered an animal model: He packaged the human form of DPP4 into an adenovirus and then infected mice with it, coaxing them into expressing the protein on their cells’ surfaces. The animals could then be infected with MERS, Perlman reported in a paper this month. How closely such a model mirrors what happens in camels or humans is unclear, however.

In fact, scientists still know disappointingly little about what MERS does in camels, says virologist Bart Haagmans of Erasmus MC. It’s still unclear whether infected camels get sick, and at what stage they are most infectious to other animals or to humans. “There are a lot of questions that need to be answered in camel experiments,” Peiris says. Haagmans says he would love to do those studies, but Erasmus MC doesn’t have facilities to house the animals. Few labs around the world do.

Politics instead of science
Many other important questions about MERS remain unanswered, and scientists say that’s in part because the affected countries have been uncooperative from the start. Are many people infected without showing symptoms? Are some people more susceptible to the disease than others? “The only people who can really answer those questions are people in Saudi Arabia, where that information resides,” Lipkin says.

Mounts has long tried to set up a so-called case-control study in the affected countries to understand what patients have in common. “We need to agree on a series of questions about animal exposure, environmental exposure, and compare the answers with controls of a similar age and the same sex,” he says. But the idea has been met with resistance in the region; an early March meeting with scientists and government officials in Riyadh didn’t help. “Public health is rarely about the science. It’s usually the politics that stand in the way,” Mounts says.

Memish, the Saudi deputy health minister, disputes that his country is dragging its feet. He says he’s interested in working with any scientist, provided they don’t have financial or business interests in MERS. One problem is that the disease has a stigma attached to it, Memish writes in an e-mail: “Nobody wants to take part in anything related to MERS,” making it “difficult to get a 6-page, very detailed questionnaire filled by a grieving family member.” Some patients’ families even moved away to avoid media attention and health officials’ questions, Memish writes; questioning enough index cases could take “some years,” he adds.

Still, not a single lung section of a MERS patient has ever been published, Frieman notes. “No one has any idea what this thing does in humans,” he says. “It blows my mind.”

The lack of progress may matter only to a handful of patients and scientists, if MERS continues to remain largely confined to its camel hosts. But SARS, too, lurked in the shadows for years, until it picked up the ability to transmit more easily from one human to the next—and threatened the world with a pandemic. If that happens with MERS, Osterholm says, “we’ll all look at ourselves and say ‘Why didn’t we do more?’”

-KAI KUPFERSCHMIDT
The Camel Connection
Kai Kupferschmidt

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