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Companion coronaviruses

Knowledge about the many coronaviruses that infect pets and farm animals can inform our battle with covid-19, finds Anthony King

Reports of pet cats and dogs catching covid-19 from their owners are mounting. They come as no surprise to virologist Gary Whittaker. For the past year, he has surveyed cats brought to a veterinary hospital around the corner from New York Presbyterian hospital in Manhattan’s affluent Upper East Side, which was ground zero for covid-19 in the US last spring. His unpublished findings suggest that around 15 to 20 per cent of pet cats in the area have antibodies for SARS-CoV-2, the virus that causes covid-19. “Cats are easily exposed,” says Whittaker. Yet most of them are doing fine, as are infected dogs. “What’s puzzling is that cats are dealing with it pretty well, but they can’t cope with their own coronavirus.”

It is alarming to think that we might pass SARS-CoV-2 to our pets. But most people are unaware that cats have coronavirus of their own. And they aren’t alone: coronaviruses commonly infect a range of domestic animals, including dogs, pigs, cattle and chickens. Yet, while SARS-CoV-2 has become probably the most scrutinised virus ever, very little attention has been paid to these other coronaviruses. That is a missed opportunity because veterinary virologists have been studying them for decades. “Animal coronaviruses have lots to teach us about interspecies transmission, pathogenesis, immunity and vaccines,” says Linda Saif, an expert in coronaviruses of livestock at Ohio State University. This information could be extremely valuable as we try to work out where SARS-CoV-2 came from and where it might be headed, and vital in our efforts to learn how to live with this virus and try to avert new pandemics.

Coronaviruses are weird, promiscuous and flexible. They have the largest genome of any RNA viruses and a complex spike protein, which gives them a greater ability to evolve new forms and infect a wide variety of tissues and host species. They are also capable of rapid evolution because, while they mutate quite slowly—typically about 30 times a year—small changes in these viruses can have colossal effects.

“The mild feline virus transforms into a killer with just minor genetic tweaks”
Pet dogs are far less threatened by SARS-CoV-2 than by their own coronaviruses

Although coronaviruses use around a dozen proteins to evade their host’s immune system, it is the spike that makes them so adaptable. It consists of around 1300 amino acids, far more than is strictly necessary, and makes the essential manoeuvres to allow the virus to attach to and then fuse with a cell. “The thing about the spike is that it is very plastic,” says Whittaker, who is at Cornell University in New York. “It’s big and with that size comes power because it’s more able to adapt to situations and gain entry to cells.” This makes coronaviruses the master conjurors of the virus world.

Feline coronaviruses provide a perfect example. The most prevalent one is fairly harmless, causing a stomach illness that is usually mild or asymptomatic. Most street moggies have antibodies to it, signalling prior infection. A 10-year study of 26 pet cats found that they were all infected at least once, and up to three times. The virus can remain in a cat’s gut for weeks or months. During this period it is shed in their faeces, mirroring the persistent shedding of SARS-CoV-2 that surprised some clinicians, but which animal virologists say is part of this viral family’s bag of tricks.

However, this mild feline virus transforms into a killer with just minor genetic tweaks. “It starts with one mutation in the spike protein, and thereafter a few more mutations occur,” says veterinary virologist Peter Rottier at the University of Utrecht in the Netherlands. This ignites a devastating blitz, termed feline infectious peritonitis, which is nearly always fatal. The mutations happen in a hidden part of the spike protein, which springs out and fuses with the membrane of a host’s cell after the virus has latched on to it. It isn’t known why
“Viruses from different species can swap genetic material to form mash-ups”

For much of 2020, there was intense media speculation about whether it would be possible to create a vaccine against the SARS-CoV-2 coronavirus that causes covid-19. Veterinary pathologist Ian Tizard at Texas A&M University had no doubt. “I found myself shouting at the television,” he says. Of course, that didn’t work, so instead he wrote a review highlighting the fact that veterinarians have been administering coronavirus vaccines to livestock and pets for years.

In fact, the world’s most widely used vaccine is for a coronavirus – infectious bronchitis virus (IBV). In 1939, IBV was the first coronavirus discovered, and it remains a major pathogen of poultry. “ Virtually every commercial chicken is vaccinated against IBV, which, like SARS-CoV-2, is a respiratory virus,” says virologist Paul Britton, who recently retired from the Pirbright Institute in the UK. One-day-old birds are usually sprayed with vaccine formulations containing weakened virus, and birds are often given a second vaccine of a different strain a few weeks later. There are hundreds of variants of IBV, so chicken flocks are constantly monitored and repeatedly vaccinated. “ Vaccines often have to be made specifically for different ones,” says Britton.

As Tizard points out, animal coronavirus vaccines have some downsides: protection can be relatively short-lived and inactivated vaccines are less effective than live ones. Nevertheless, they are invariably cheap to make and lend themselves to mass vaccination programmes. All of which bodes well for our prospects of keeping covid-19 under control with vaccination.

Pigs are particularly prone to coronaviruses: they harbour half a dozen types and have regularly contracted new ones in recent decades. One of these causes a gut infection, which, until the 1980s, was a common and deadly disease of young pigs. Then, almost overnight, it disappeared. Scientists were left scratching their heads, but eventually discovered that pigs with a mild lung infection had another coronavirus that differed from the gut infection one by the removal of just one piece of spike protein. “ One tiny little tweak turned it from a virus that causes diarrhoea to one that exclusively replicates in the lung,” says virologist Benjamin Neuman at Texas A&M University. The new swine respiratory virus was very infectious and ran rampant, mostly unnoticed, which solved the gut infection problem. “ It spreads and thereby immunises the animals. The more virulent

Mutations here make the virus so deadly, but Whittaker suspects that they arise frequently and cats usually suppress them. They seem to take hold more easily in stressed cats, for example after surgery. Males are also more prone to the severe disease, another characteristic of coronaviruses that has been apparent with SARS-CoV-2, says Whittaker.

Feline coronavirus illustrates how small mutations in the spike protein can alter transmission too. Although the mutated virus is more deadly, it is unable to transmit from one cat to another. So far, several new variants of SARS-CoV-2 seem to do the opposite, magnifying their ability to spread from person to person. Increased transmissibility has proved problematic in our efforts to quash SARS-CoV-2, but it needn’t necessarily be, as the evolution of another coronavirus of domestic animals reveals.
virus was more or less kicked out,” says Rottier.

As we try to extinguish the covid-19 pandemic and prevent new ones arising, other insights from the coronaviruses of domestic animals are less encouraging. For a start, they clearly show that mutation isn’t the only means by which these pathogens can evolve. If different coronaviruses replicate in the same cell, and if certain critical genetic sequences match up, new types can emerge. This happened when the benign swine respiratory virus interacted with another coronavirus called porcine epidemic diarrhoea virus to form a chimera. We have also seen this in SARS-CoV-2, where recombination of different versions of the virus within individuals is thought to have resulted in new variants.

Such rejigging makes it particularly difficult to predict the evolutionary trajectory of coronaviruses. And they have another ability that confuses things further: viruses from different species can swap material to form mash-ups. One feline coronavirus, for example, arose when viruses hosted by cats and dogs exchanged some of their RNA sequences. Or take two coronaviruses that can infect a dog’s gut. Their RNA sequences are very similar, but they have strikingly different spike proteins: one looks like a feline virus and the other has clearly been exchanging genetic material with a pig coronavirus. Another example is canine respiratory coronavirus, which was first detected at a dog rehoming centre in the UK in 2003. It turned out to be almost identical to bovine coronavirus, which can also transmit to other animals, including pigs, horses and alpacas.

**Surprising sources**

The animals that live most closely with us don’t just mix up their coronaviruses, they can also acquire new ones from surprising sources. In 2012, a coronavirus turned up in pigs and a cat in Hong Kong. It turned out to come from a group of coronaviruses thought to be exclusive to birds: the main reservoir of these viruses in the wild. In 2017, a virulent disease called swine acute diarrhoea syndrome (SADS) struck down 25,000 piglets in southern China. It shared up to 98 per cent of its RNA code with a virus found in horseshoe bats. These bats also host a virus very similar to SARS-CoV-2 and have been identified as the source of SARS-CoV-1, which killed hundreds of people between 2002 and 2004. Worryingly, the instances of bat coronaviruses jumping into pigs seem to be increasing. What’s more, lab experiments have revealed that the SADS virus can infect human cells.

Each time a virus moves to a new host, it is pressured to adapt, and it may also recombine with a related coronavirus in the new animal. This revs up viral evolution, rendering these viruses more unpredictable. “We have to avoid that at all costs,” says Saif. She is particularly concerned by the recent detection in Haiti of a coronavirus that appears to have jumped from birds to pigs to humans. This is also a major reason virologists were so worried last November when mink contracted SARS-CoV-2 and transmitted it back to people, and to cats too. That outbreak was quickly dealt with. However, history offers a salutary lesson about what can happen if we aren’t alert to this danger: a modified version of the same bovine coronavirus that jumped into dogs in 2003 is also a prime suspect for the 1890 “Russian flu” pandemic, which killed an estimated 1 million people. The virus, called OC43, still regularly infects us, although it has evolved further so that now it usually causes nothing more than a common cold.

Based on their experience, animal coronavirus experts warn us not to underestimate these viruses, nor assume a predictable trajectory for SARS-CoV-2. “When I was doing my training, the dogma was that coronaviruses were not good at jumping from one species to another,” says Neuman. Now they are viewed as troublemakers and rule breakers. “Whenever I hear someone say, coronaviruses can’t do this because of what human coronaviruses do, that’s always a facepalm moment,” he says. “Don’t make assumptions about coronaviruses.”

**In covid-19 hotspots, up to 20 per cent of pet cats could be infected with SARS-CoV-2**