



What is the role in transmitting

How easily does the coronavirus jump from minks and other animals to humans? Researchers are working hard to figure out how the virus functions. Part of the answer lies in the ACE receptor. 'We suspect that that receptor in minks resembles the one in humans.'

TEXT NIENKE BEINTEMA PHOTO VIDIPHOTO / ANP INFOGRAPHIC STEFFIE PADMOS

of animals Covid-19?



Piles of animal carcasses on concrete floors, and people in protective clothing shovelling them into large bins... Such images remind us of the outbreaks of bird flu, swine fever, Q fever and foot-and-mouth disease that are still in our collective memory. This time it is minks that are being culled. This has happened on over half of all Dutch mink farms since April.

The animals have proven capable of transmitting the coronavirus SARS-CoV-2, both to each other and to humans. This makes them a public health risk.

'We already knew that mustelids (such as weasels, martens and minks) are susceptible to the virus,' says special professor Wim van der Poel, who researches Emerging and Zoonotic Viruses at Wageningen Bioveterinary Research (WBVR). 'When the virus turned up on mink farms, we went into action straightaway.'

Wageningen consulted its partner institutes and the Ministry of Agriculture, Nature and Food Quality (LNV) in a teleconference. 'We agreed that large-scale research was needed. How many animals are affected, how susceptible are they to the virus, and how easily can they pass it on to each other and to humans?'

THE VIRUS MUTATES

WBVR and several partners are now doing surveillance research at mink farms and re-

search on the virus's RNA. 'There are minor variations in the virus's RNA sequence,' says Van der Poel, 'because the virus mutates all the time. That enables us to see how the different virus strains in circulation are related. We could see, for instance, that an employee on a mink farm was infected with the same coronavirus variant that had been identified in the minks on that farm. A variant that we hadn't seen before in the human population.'

Meanwhile, several employees on mink farms have become infected with the mink strain. Yet the researchers did not find that strain among people living near the infected farms, so the mink variant did not seem to have spread beyond the farms yet. But to prevent that happening in future, the ministry announced that it would speed up the planned phasing out of the sector. All mink farms were already expected to close by 2024, because of public opposition to fur

'We know that the virus is not primarily spread via aerosols'

farms. That deadline has now been brought forward to 1 January 2021. Infected farms are being closed down immediately, while a scheme for closing down the remaining farms with financial compensation is being introduced.

HOW DANGEROUS?

'We are now studying whether there are differences in the genetic building blocks and biological traits between those mink variants and the variants we have identified so far in humans,' explains Van der Poel. 'On the basis of the genetic structure, we distinguish five clusters of virus variants on the mink farms. What causes these variants to spread very fast among minks on some farms, but without giving them many symptoms? And how dangerous are they for the human population compared with the other variants? How easily do they penetrate the cells of the host, and do they easily jump from one individual to another?'

Knowing this could help us come up with useful measures to stop the virus spreading, and to develop effective vaccines and drugs. Researchers still know relatively little about how the coronavirus functions biologically. What is known is that receptors on the outside of cells play a role in their susceptibility to the virus. A receptor is a protein of a particular shape that the virus is able to latch onto, like a key fitting into a slot.

A virus needs such a receptor to penetrate the host cell. 'Research has already shown that the ACE receptor is an important factor in infections with the new virus,' says Van der Poel. When the two meet, the cell membrane changes in a way that allows the virus to pass through it. >

ORIGINS OF SARS-COV-2 UNCERTAIN

The new coronavirus SARS-CoV-2 first appeared in China. It was thought to have jumped from a wild animal – possibly a horseshoe bat – to a person, perhaps through an interim host in which the virus could mutate into a strain that is infectious for humans. At first all the signs seemed to point at the market in the city of Wuhan, where a wide range of live wild animals are traded in pretty unhygienic conditions. But experts think that conclusion is premature: a direct causal link between the market and the virus has yet to be found. The new coronavirus has never been found in an animal that was for sale at that market. The market might just have served as a 'superspreader' event: a large gathering of people where the virus could spread like wildfire. In the case of SARS a direct link with a 'wet market' was proven, but only in 2018 – 15 years after that epidemic.

WHICH ANIMALS CAN SPREAD COVID-19?

There have been reports from several countries that the coronavirus SARS-CoV-2 can infect animals as well as humans. Scientists around the world are doing research on which animals could spread the coronavirus.

Bats

Coronaviruses are common among horseshoe bats. Scientists found a coronavirus that closely resembled SARS-CoV-2 in this species. The virus has not yet been found in other bat species. Wageningen is involved in a study of the droppings of Dutch bats.

Mustelids (including minks)

Chinese model studies suggest that the pattern of virus spreading among martens and bats closely resembles the pattern of SARS-CoV-2. The outbreaks on Dutch mink farms confirm that impression. Minks are very vulnerable to the new coronavirus. Wild mustelids such as stone martens and polecats often frequent farmyards and could pick up the virus on mink farms.

Raccoon dogs

Raccoon dogs are farmed in China for their fur. It has been proven that they can be infected with SARS-CoV-2 and can spread the virus. Infections have not yet been reported, however.

Armadillos

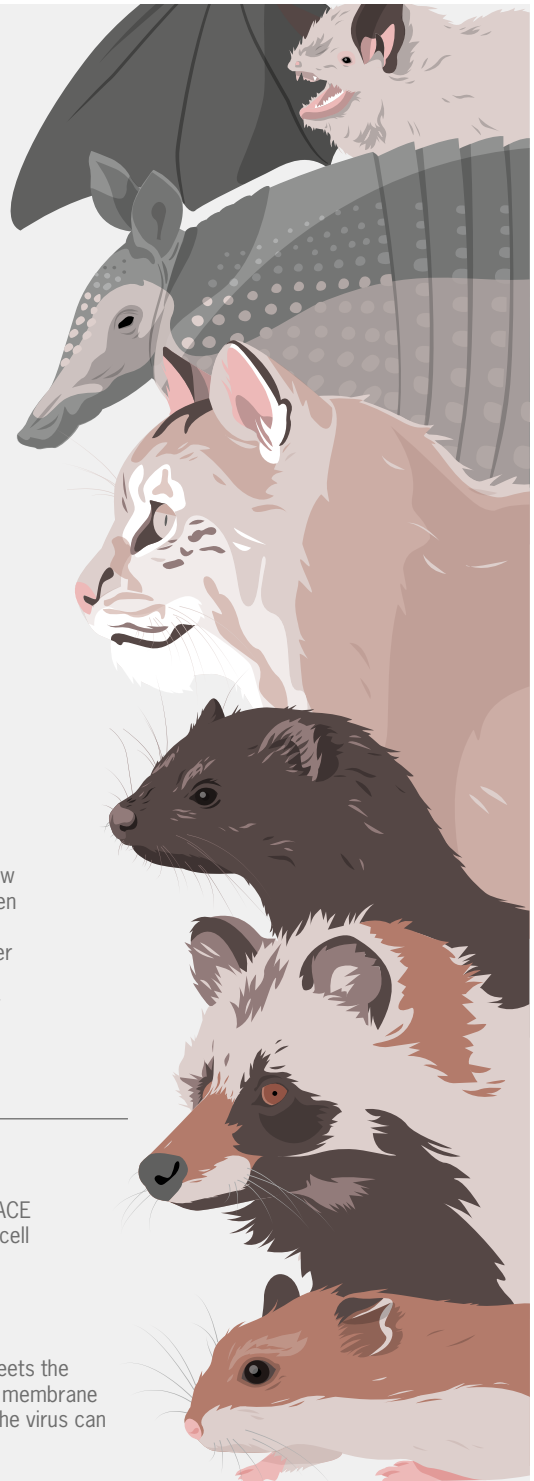
A virus strain similar to SARS-CoV-2 is found among armadillos, which are apparently often for sale at the market in Wuhan. But the coronavirus strain that infected the first Chinese patients has never been found in an armadillo.

The cat family

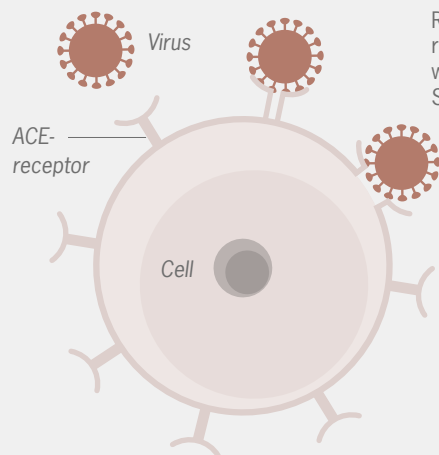
Domestic cats, feral cats and tigers in a zoo have been proven to be infected with the coronavirus. Scientists are studying how the virus gets passed on.

Rodents

The only rodents which we know can become infected – and even become sick – are hamsters. Research is ongoing on whether other rodents spread the coronavirus, on mink farms for instance.



THE ROLE OF THE ACE RECEPTOR



Research has proven that the ACE receptor on the outside of the cell wall is key to infections with SARS-CoV-2.

When the virus meets the receptor, the cell membrane changes so that the virus can pass through it.

It is thought that the ACE receptor in minks may resemble the one in humans. Pigs have a similar ACE receptor too, but are not susceptible to the virus.

‘We suspect that the ACE receptor in minks is very similar to that in humans,’ says Van der Poel. WUR is researching this now in another new project – ‘Covid-19 in animals’ – started by the Netherlands Centre for One Health (NCOH).

COUGHING TIGERS

It is already known that pigs have a comparable ACE receptor, but are nevertheless not susceptible to the virus. Monkeys do get infected by the virus, but do not display any symptoms – unlike minks – although they can spread the virus further. Cats and, to a lesser extent, dogs do not seem to get sick either, but infected tigers at the zoo in New York did suffer from a dry cough and loss of appetite. ‘We haven’t yet seen clear patterns in which animals show symptoms and which don’t, and which animals can play a role in spreading the virus,’ says Van der Poel. ‘That makes it difficult to do efficient tests on animals yet. The only animals of which we know for sure that they get really ill from the virus are hamsters. That offers potential for studies contributing to the development of vaccines.’

By this, Van der Poel is referring not just to fundamental research on the virus’s functional mechanisms, but also to trials of candidate vaccines being developed in the Netherlands and abroad. ‘We are trying to minimize animal testing of course, but candidate vaccines are still being tested on animals first. You can’t get around that. But when you do it, you must make sure you keep such testing as targeted and efficient as possible.’

CANDIDATE VACCINS

This research is being done in Wageningen and was commissioned by the Coalition of Epidemic Preparedness Innovations (CEPI), an international organization that seeks to get new vaccines on the market as soon as possible. CEPI gets financial support from many governments. Van der Poel is not free to disclose how far the research has got, exactly, or which candidate vaccines are being developed. ‘But there are certainly



Stray cat being fed in Indonesia.

‘Transmission between cats is probably just as effective as between humans’

two or three that are producing promising results.’

Mart de Jong, professor of Quantitative Veterinary Epidemiology at Wageningen, leads a team that models and quantifies the transmission of infectious diseases between different animals. ‘We are looking for the factors that influence that transmission,’ he says. ‘We are studying the underlying mechanisms of transmission with a combination of mathematical models, observations and experiments. Once we understand those mechanisms better, we can get better at predicting, measuring and extrapolating the effect of measures for preventing the spread of the virus.’

The group gained a lot of experience during

earlier national crises concerning the bird flu and swine fever. ‘From comparisons with other diseases, we know that SARS-CoV-2 is not primarily spread via aerosols. If that was the case, the reproduction factor (the R value) would be much higher than it is. My guess is that transmission on mink farms mainly occurs via mucus in the nose or dust particles from the cages.’

The main thrust in De Jong’s account of the state of play is that the details are not clear yet. For example, we still don’t know exactly how long the virus can remain infectious under different circumstance. Tests on cages which have housed infectious animals for some time could cast some light on this.

The fact that domestic pets can get infected means they too can play a role in spreading the virus. There is no evidence of this yet, but the researchers are highly alert to it. De Jong's group is using modelling and data analysis in a large-scale study of infections among the dogs and cats of coronavirus patients. A similar study has already been done in Italy, where about three to four per cent of the dogs and cats turned out to have antibodies to the coronavirus. As a rule, people who are infected with the virus are advised not to cuddle their pets, especially if the pet roams freely out of doors, and could therefore spread the virus further. So De Jong and his colleagues are also modelling the role of cats in the transmission of the virus. They combine the models with experiments and observations in households with the coronavirus, in collaboration with Utrecht University.

EFFECTIVE TRANSMISSION

'Transmission between cats is probably just as effective as it is between people, but they don't fall ill,' says the professor. 'So the question is whether they can pass it on to people just as easily. We don't know the answer to that yet. We are studying whether, from the epidemiological angle, you can see a cat as an extra member of the household with its own social network out-

side the home. Except of course that the cat doesn't go on holiday abroad.' Data from stray cats is being included in the research as well. The data are being collected by teams which were already at work catching and sterilizing stray cats in the countryside. 'They are doing that even more intensively now around mink farms,' says De Jong, 'to help prevent the virus from spreading. And to collect data. There haven't been many infections among stray cats up to now, but there have been some.'

VIRUS RESERVOIR

De Jong has been following the vaccine development closely. 'A lot will depend on which vaccine wins the race in the end,' he says. 'Will it only prevent you from having symptoms, or also from becoming infected? There is a difference between these two. If a vaccine doesn't prevent you from getting infected, the virus will go on multiplying and spreading. And then there is a reservoir of the virus present, which makes us much more vulnerable.' Wim van der Poel is also thinking about a reservoir of the virus that could hang around after we've got a working vaccine. 'Among people, but out in the wild too,' he says. 'Among cats, martens, bats... The truth is that we just don't know yet to what extent a reservoir could develop.'

The danger is that new variants will emerge in that reservoir that are more dangerous, or that more easily make the jump between different animal species, and between people. This is a familiar phenomenon in flu viruses: many strains of flu are mild, but now and then a strain crops up which is highly dangerous or infectious, like the Spanish flu. That unpredictability is the reason why vulnerable groups in the Netherlands are offered an annual flu vaccination. A new vaccine is offered every year, which provides protection against the cocktail of flu strains that are dominant at that point in time. 'There is a risk that we'll have to do something of the sort with a coronavirus vaccine,' says Van der Poel. 'In other words, that it won't provide protection for very long because the virus changes too fast. The question is what role is played by reservoirs in animals. Yes, this issue is going to keep us busy for a while.'

SWINE FLU

De Jong mentions a further concern: 'This is now a single virus that has the world in its grip. But we have seen before that it can happen with other animal diseases too, as is the case now with the West Nile virus, for instance,' he says. 'People blame this pandemic on China, but it could have happened here. If a dangerous strain of flu starts spreading among pigs here, and jumps to humans, it will spread around the world in no time and we won't be able to do much about it. Just as happened with the swine flu.'

The good news, De Jong notes, is that researchers are getting better and better at detecting and characterizing pathogens, and that doctors and nurses are getting better and better at treating infection diseases. But: 'This risk continues to exist because contact between humans and animals is simply part of our way of life. That underlines all the more the importance of good research to help us understand that transmission.' ■

www.wur.eu/covid19inanimals

CONSORTIA FOR CORONAVIRUS RESEARCH

When the coronavirus turned up on mink farms, several parties went into concerted action without delay. WNV joined forces with the Animal Health Service, Utrecht University and the Erasmus Medical Centre in Rotterdam to conduct an extensive survey of mink farms and research on virus variants and transmission, at the behest of the ministry of Agriculture, Nature and Food Quality (LNV). They are also researching the RNA of the virus strains to identify relationships between the different strains.

The Netherlands Centre for One Health, meanwhile, has started work on the 'Covid-19 in animals' project commissioned by the ministry of LNV. Utrecht University and Erasmus University Rotterdam are working with WUR on this project, which will look at the role of domestic cats and wild animals in spreading the coronavirus. The research makes use of modelling, experiments and observations.