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## On a quiet mission in the jungle

Rabies, Ebola or the new coronavirus: Viruses from the animal kingdom can be dangerous to humans. A possible counter-strategy: Vaccinate wild animals with vaccines that, just like viruses, spread independently in a population. The idea sounds good, but it's not without its pitfalls.

By *Claudia Doyle*

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*Vaccinate instead of killing? Vampire bats are rabies carriers ( Kevin Bakker )*

Viral diseases that leap from animals to humans are a real threat. We have been living with Sars-Cov-2 for months, we have neither vaccine nor medication against it and are at the mercy of the virus because it takes time to develop medication or vaccine. Maybe the animals should be vaccinated. In time. Running through the jungle with syringes and immunizing thousands of animals is not practical, however. Scientists are therefore researching vaccines that - just like a disease - spread all by themselves. What is the potential of the idea? And: how safe is the whole thing?

My research on self-spreading vaccines begins long before the new corona virus rules our lives in Germany. At the end of 2019, I will write the first interview requests to scientists who are concerned with how to vaccinate wild animals and prevent zoonoses. At that time, the first newspapers were already reporting on a new lung disease in China. But nobody in Europe thinks that we could get a problem with that. Then everything turns out differently. I can no longer take my research trips in spring 2020, the flights have been canceled. But the topic is all the more explosive.

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Fight against zoonoses  
[[https://b2bwe2pf34wu4izdiis23ztz74-ac4c6men2g7xr2a-deutschlandfunk-de.translate.google/kampf-gegen-zoonosen-wenn-tiere-den-menschen-anstecken.724.de.html?dram:article\\_id=414993](https://b2bwe2pf34wu4izdiis23ztz74-ac4c6men2g7xr2a-deutschlandfunk-de.translate.google/kampf-gegen-zoonosen-wenn-tiere-den-menschen-anstecken.724.de.html?dram:article_id=414993)] When animals infect humans

## Small bloodsuckers as carriers of rabies

"Everyone thinks vampire bats are huge bloodsuckers, but they are quite small."

Daniel Streicker researches the spread of infectious diseases at the University of Glasgow. He is particularly familiar with the vampire bat:

"They only weigh 40 to 50 grams, and when they put their wings on, they easily fit on one hand. Their wingspan is between 25 and 30 centimeters. The color of the fur is very different. Some are brown, others orange-red, some have an almost white breast. They are also very agile. Many other bats just sit around on the ground, but the vampire bats hop and jump and gallop. "

The bats owe their name to their razor-sharp canine teeth, with which they bite animals or, in rare cases, humans in order to suck blood from them. They also transmit diseases in the process. Streicker has been conducting field research in Peru for more than 13 years. Vampire bat rabies is a particular problem there.

"That affects smallholders more than anyone else. If they lose an animal or two, it means that there is no more money for repairs or that the children can no longer go to school. It is a devastating disease for people who already live in neglected communities. "

Better to vaccinate than poison?

So far, the local people have only known one strategy against vampire bat rabies:

"For the past forty to fifty years people have tried to solve the problem by killing the bats. They usually do this by catching some bats, applying a poisonous paste to their fur, and then licking the poison off the other bats. But this method is not very efficient. It kills bats, but it doesn't stop rabies from spreading. So we asked ourselves whether we could not use this practice as well. But instead of a poison, we would use a vaccine. "

Because then they would be protected from rabies and could no longer carry the disease into the villages. At the time, nobody knew how well a substance applied to the fur would spread in the bat colony. So the biologist flew once again to Peru, the capital Lima. From there it was just under an hour by car until he and his team arrived at large sewer tunnels where vampire bats lived. Easy prey for the scientists:

"We just had to put nets in front of the tunnels and we could easily catch all the bats."

Lick dissemination strategy not too effective

About one hundred and fifty vampire bats live together in such a colony, a third of which the scientists captured. Then they smeared a gel containing the dye rhodamine B on their fur. If a bat ingests this dye, it will show up in its fur. When viewed under a fluorescence microscope, the hair follicles glow bright orange.

"We drove to the sewer tunnels again and again over a period of several weeks and caught vampire bats. We took a hair sample and could see how many of them had licked the gel off another bat. That showed us how well a vaccine would spread. Or how well the poison that is being used spreads. "



After measuring and marking with the dye, the bats are released again ( [Kevin Bakker \[https://translate.google.com/website?sl=de&tl=en&ajax=1&u=https://news.umich.edu/scientists-make-vampire-bats-glow-to-simulate-vaccine-spread/\]](https://translate.google.com/website?sl=de&tl=en&ajax=1&u=https://news.umich.edu/scientists-make-vampire-bats-glow-to-simulate-vaccine-spread/) )

Each bat apparently passed the dye on to one or two other bats

[\[https://translate.google.com/website?](https://translate.google.com/website?sl=de&tl=en&ajax=1&u=https://news.umich.edu/scientists-make-vampire-bats-glow-to-simulate-vaccine-spread/)

[sl=de&tl=en&ajax=1&u=https://news.umich.edu/scientists-make-vampire-bats-glow-to-simulate-vaccine-spread/\]](https://news.umich.edu/scientists-make-vampire-bats-glow-to-simulate-vaccine-spread/). That doesn't sound like much at first. But it would double or even triple the rate of vaccinated bats and further reduce rabies. Of course, it would be even better if a vaccine spread independently of grooming. If it were to jump from animal to animal, that is, if it spread like viruses do: via body fluids or droplets that get into the surrounding air when they shout and breathe. Viruses would be ideal vehicles for vaccine distribution. This is exactly what Daniel Streicker and other researchers are already working on.

## Viruses as a vehicle for vaccines

I have an appointment to call Michael Jarvis. The virologist works at the University of Plymouth in the UK and has long had the idea of self-spreading vaccines:

"We started in 2008, mainly with Ebola and other highly pathogenic agents such as the Lassavirus. If animals could be vaccinated against it, it would stop the viruses from spreading to humans. And it would also be of use for the animals themselves. Ebola is a huge problem for great apes in Africa, these animals die as often or even more often than humans. So that would also have a positive effect on species conservation. "

Jarvis developed an Ebola vaccine in his laboratory, which he first tested on mice.

"We started by vaccinating mice directly with a cytomegalovirus that contains Ebola antigens. We wanted to know if that could protect against Ebola. That was in 2011. In 2015, I think we demonstrated that it was possible. You get a long-lasting immunity that lasts almost the entire life of a mouse - after a single vaccination. That's pretty impressive. "

"Oral vaccination" with feeding bait

2015 was also the year of the largest Ebola outbreak in West Africa to date, with over 11,000 deaths. Once again, the Ebola virus had managed to pass from animals to humans. Jarvis would have liked to prevent such recurring outbreaks with his vaccine - but he wasn't that far back then.

Having a vaccine is one thing. How best to bring it to the various animal species also depends on their dietary preferences.

"In North America and Europe, rabies was helped by dropping vaccinated bait from airplanes. If raccoons eat this bait, they are vaccinated. "



*Raccoons are cute - but also often carriers of rabies (Arco Images GmbH)*

Says Scott Nuismer from the University of Idaho, a collaborative partner of Michael Jarvis. But not every vaccination works as an oral vaccination. And not every animal eats laid bait. This method can only be transferred to other diseases and animal species to a limited extent.

"Vaccine baits are the only option until you have self-spreading vaccination. Because you couldn't catch all rodents, that would be hopeless. But I think we could easily catch 20 animals, vaccinate them and release them again. A self-propagating vaccine would be scalable. "

A harmless virus as the "backbone" of the vaccine

The vaccinated animals touch others, eat the same carcass with them, breathe the same air. A vaccine could also migrate through the population. Developing such a vaccine is not easy. And the scientists consciously distance themselves from the idea of using the disease-causing virus in a weakened form as a vaccine. Nuismer:

"Vaccines have long been based on a weakened form of the pathogen. The virus is allowed to grow for a long time under unnatural conditions, for example at low temperatures or in alien cells, so that it becomes less dangerous. The problem is that such a weakened form can turn back into the dangerous virus. This is exactly what happened with an older variant of the polio vaccine. "

Instead, Scott Nuismer and Michael Jarvis rely on so-called recombinant vector vaccines.

"You need a harmless virus that spreads well in the population you want to vaccinate. The DNA of this harmless virus is the backbone of the vaccine, so you copy a gene from the dangerous virus into it, which can trigger an immune response. "

Cytomegalovirus is "ideal" spread vehicle

Recombinant vaccines are already being tested in clinical studies, for example against HIV. This technology is also used in the development of a vaccine against the new corona virus. What is new is that the vaccines should spread by themselves. The harmless virus, whose DNA is supposed to serve as the backbone, has to be highly infectious at the same time, explains Michael Jarvis:

"Evolution has created a virus for us that is ideal for a self-spreading vaccine. The CMV, i.e. cytomegalovirus, spreads very well within a population. In the blood it is firmly attached to the blood cells. In breast milk, however, it is decoupled from the cells and released into breast milk so that it is passed on to the next generation. "

CMV can also be transmitted through saliva, urine or semen. And as well as cytomegaloviruses can spread within one species, they are just as bad at spreading to other species.

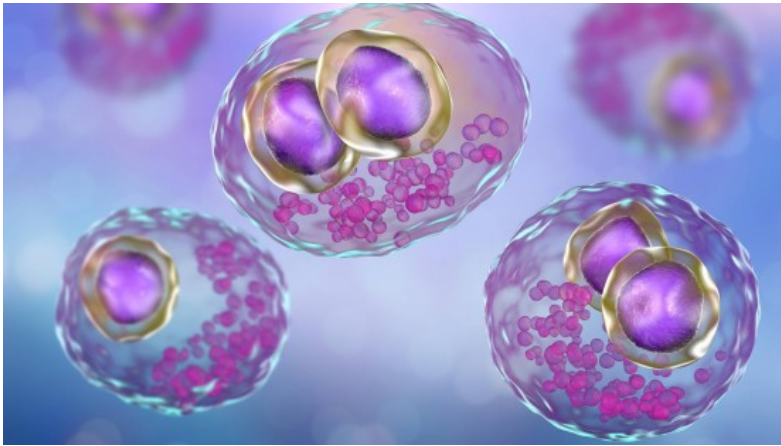
Benign, species-specific and always infectious

"The virus has evolved with its host for probably 80 million years. It is therefore very species-specific. There are animal experiments where attempts have been made to infect closely related species with the same virus, but it cannot cross the species barrier. "

For example, a cytomegalovirus that specializes in chimpanzees cannot spread to gorillas. Or, to put it with the necessary scientific inaccuracy: such an event is so far unknown and also extremely unlikely. In addition, the cytomegalovirus is benign; damage to the fetus can only occur in very rare cases in mammals such as humans, but these do not pose an additional risk due to the wide spread of CMV due to the vaccination viruses. In animals with normal immune systems, it hardly causes any symptoms of disease. And there is another quality that makes the virus special. It can infect a host again and again.

"A previous immunization does not prevent re-infection with the same CMV. That's extraordinary. Even if you already have a good immune response against CMV, that does not protect you from re-infection. "





*Cytomegalo viruses could be the ideal transport vehicle for wild animal vaccination (imago stock & people)*

This property is important because cytomegaloviruses are widespread. If all animals were immunized after a single contact with a naturally occurring CMV, then the herd immunity would stop the spread. So cytomegaloviruses were the perfect vector for the Ebola self-spreading vaccine from Plymouth.

Laboratory transport virus has gotten too tame

After the vaccination in mice had been so successful, Michael Jarvis took the next step. Because Ebola is not naturally transmitted from mice to humans, but most likely from bats or monkeys.

"We then did the gold standard experiment, that is, on non-human primates. Here, too, the question was whether a direct vaccination with CMV Ebola vaccine protects against Ebola and that was also successful, we published that in 2016.

[[https://translate.google.com/website?](https://translate.google.com/website?sl=de&tl=en&ajax=1&u=https://www.plymouth.ac.uk/news/new-study-highlights-effectiveness-of-a-herpesvirus-cytomegalovirus-based-vaccine-against-ebola-virus)

[sl=de&tl=en&ajax=1&u=https://www.plymouth.ac.uk/news/new-study-highlights-effectiveness-of-a-herpesvirus-cytomegalovirus-based-vaccine-against-ebola-virus](https://www.plymouth.ac.uk/news/new-study-highlights-effectiveness-of-a-herpesvirus-cytomegalovirus-based-vaccine-against-ebola-virus)]."

Jarvis is now working with his team to make the CMV from the laboratory fit again for real life. Because the long time in the Petri dish has made the virus too tame.

"In the laboratory, viruses are grown in glass dishes. When you do that, you don't ask the virus to do anything other than keep the genes that are important for growth in glass dishes. Genes that are needed to infect epithelial cells are gradually sorted out by the virus. However, these genes are the key to ensuring that the virus can spread well. "

## Infection genes need to be repaired

When compared with wild cytomegaloviruses, Michael Jarvis found a total of 12 locations in the genome. He now wants to repair these mutations.

"We are currently working on restoring the CMV's ability to infect cells and spread from the laboratory. No one has yet shown that a recombinant Rhesus monkey CMV can spread from one animal to the next. We think of course that it can, in nature it happens all the time. But so far we haven't demonstrated it in the laboratory. If we have the proof, then of course you think: That was clear. But until then it's a big step. "

Around a dozen groups around the world are now working on self-spreading vaccines. Almost all of them cooperate with each other. They include, for example, Brian Bird from UC Davis in California, who searches the forests for as yet unknown viruses that could pose a threat to humans.

Michael Jarvis has now even set up his own company to further develop his self-spreading vaccines for animals. Other researchers were working on this topic twenty years ago. Jarvis:

"A couple of scientific papers came out in the early 2000s describing their attempts to immunize wild rabbits in Spain against two diseases with self-spreading vaccines. They even carried out field tests, but didn't push it any further. "



*Myxomatosis is the most dangerous disease for wild rabbits (imago stock & people)*

Rabbit hunter as client for virologists



I also stumbled upon this work from the early 2000s during my research. And got in touch with one of the scientists from back then.

Juan Bárcena is a virologist and now works at a research institute in Madrid that deals with animal health. Almost twenty years ago, his sponsor was not the Spanish government or any other official authority, but: the Spanish Hunting Association.

"The hunters wanted a vaccination that would protect rabbits. So they paid us and we did it. "

The thing is a bit bizarre: the hunters wanted to protect the rabbits from death from disease so that they could continue to hunt rabbits successfully.

"I don't think it's a problem if hunters can't shoot rabbits - but well, they paid me. And the dwindling rabbit population is also causing problems for predators such as the Spanish imperial eagle or the Iberian lynx, for which wild rabbits are the basic food source. So I think we tried to do something good for the environment. "

Early experiments on "recombinant vector vaccines"

Wild rabbits in Spain are threatened by two viral diseases: the myxoma virus and the RHD virus. The self-transmitted vaccine should immunize against both. So Juan Bárcena put together a recombinant vector vaccine: myxoma backbone with a little RHD genome. Unlike Jarvis and Nuismer, Juan Bárcena tried to use a weakened form of the disease-causing myxoma virus as a backbone.

"At the beginning of our research project, it was clear to us that this virus from the laboratory would probably no longer be able to spread in the wild. So the first challenge was to find a naturally weakened myxoma virus in nature. The concept was: if you find it outside with the rabbits, then it should also be able to spread on its own. "

The ideal virus would still spread, but no longer cause symptoms of the disease.

"So the hunters helped find a rabbit that had myxoma symptoms but was still alive. They collected samples all over Spain. I wasn't involved in the tests, but I know that 90 percent of the myxoma viruses found were extremely fatal in our tests. Five out of five rabbits died from it, which is normal for this virus. We couldn't use them. But of all the samples, there was one that didn't kill a rabbit. All that remained was a small scar at the puncture site, the animals survived and recovered. "

## Field trials on an uninhabited Mediterranean island

Juan Bárcena had a virus that could serve as the backbone for his vaccine. He copied a gene from the RHD virus into it. Then the field tests started. First on a small uninhabited island in the Mediterranean [[https://translate.google.com/website?sl=de&tl=en&ajax=1&u=https://www.academia.edu/15389387/First\\_field\\_trial\\_of\\_a\\_transmissible\\_recombinant\\_vaccine\\_against\\_myx](https://translate.google.com/website?sl=de&tl=en&ajax=1&u=https://www.academia.edu/15389387/First_field_trial_of_a_transmissible_recombinant_vaccine_against_myx)]:

"The experiment was mainly about biosecurity. We wanted to show that nothing unusual happens when you release this virus into the world. That the rabbits don't die and the other wild animals don't suffer either. But of course we also wanted to see whether the virus spread. "

About 300 rabbits lived on the island. The scientists vaccinated about a quarter of them. Another quarter was also caught and was officially considered a "contact" for the vaccinated wild animals. After a few weeks, they returned to the island, recaptured it, and checked blood samples for antibodies. The result: about half of the unvaccinated rabbits had developed antibodies against both viral diseases. It looked promising.



*Site of the rabbit field trial: Isla del Aire (imago stock & people)*

Vaccine virus was not "particularly successful"

But Juan Bárcena remained cautious.

"The rabbit population on the island is artificial. The hunters bring the rabbits there so that they can hunt them. Or they just die of an illness. But there are no predators there, for example. What I want to say: The situation was not comparable to the mainland. "

The next experiment took place on the mainland, in a kind of giant rabbit farm that tried to recreate natural conditions. But the results of this experiment were disheartening. The vaccine myxoma virus was not able to spread well in the population. The hunting association turned off the tap, the experiments were stopped.

"We noticed right from the start that our virus was not particularly successful in spreading. I believe that under the optimal conditions for the virus, if we had released it in the right place at the right time, it might have spread better. But it would never have become a virus that could have spread across the entire country or the entire continent. "

Competing vaccine viruses with the opposite purpose

What Juan Bárcena did not know at the time: Scientists in Australia had also developed a recombinant vector vaccine based on the myxoma virus. However, with the exact opposite goal. Because after rabbits were introduced to the Australian continent, the fauna there suffered. The Australian virus should not protect the rabbits, but make them sterile and exterminate them.

"What we didn't consider back then is what would happen if our virus, which makes sense in Spain, if it spread to Australia. Or the other way around, if the Australian virus found its way to Europe. I think there should be international regulations about these things. "

It seems a bit strange that a private donor can pay molecular biologists to create a genetically engineered virus to save wild rabbits. In any case, Bárcena no longer thinks too much of the idea.

Animal vaccines can be developed faster

But Michael Jarvis and Scott Nuismer are not interested in rabbits in their project. It's about protecting humanity from deadly viruses at best. Scott Nuismer:

"The focus is clearly on pathogens that pose a threat to humans and for which we do not yet have human vaccines. And we can't vaccinate animals using conventional methods because it's just impossible to go out and vaccinate 5000 small rodents. I really see the great potential here. "

Vaccines for animals can be developed much faster than those for humans, explains

Michael Jarvis:

"Instead of waiting for a virus to make its way into the human population, you can use the time and vaccinate the animals. It usually takes fifteen to twenty years to develop a human vaccine. For animals, it's more like two to five years. This is simply because animals do not live that long and, among other things, the safety requirements for new vaccines are much lower. "



*In search of Ebola host animals: taking blood from a bat (imago stock & people)*

Ebola isn't the only zoonotic problem

And Michael Jarvis is not only thinking about the containment of Ebola in his project, but also about all possible zoonoses:

"All of these emerging pathogens were unknown before they first appeared in humans. We've talked a lot about Ebola now, but there is more. The Marburg virus, a relative of Ebola, has spread to humans several times. MERS, SARS, Nipah, Hendra, all of these viruses were unknown before they appeared in humans. And you don't know what's next. We therefore want to develop vaccination vectors into which a new antigen can be introduced very quickly as required. Because you only know which virus is coming next when it has already occurred in humans. "

Unlike the new Sars-CoV2 coronavirus, many viruses that pass from animals to humans cannot jump from person to person. Vaccination of the animals would therefore prevent people from becoming infected with these diseases again and again, as happens with the Nipah virus in Bangladesh, the MERS virus in countries in the Middle East or worldwide with the hantavirus. Scott Nuismer:

"Maybe a little off the topic, but you also have to keep in mind that the alternative is often to kill the animals en masse. They do that in Latin America with vampire bats. And that was done in Europe with badgers that transmitted tuberculosis. For me, a communicable vaccine is a much more attractive idea. Instead of killing all the animals, you could vaccinate them and eradicate the virus. Then the animal communities remained intact. "



*Badgers are vaccinated in England and Ireland to stop the spread of bovine tuberculosis ( [Seth Jackson](https://translate.google.com/website?sl=de&tl=en&ajax=1&u=https://www.eurekalert.org/pub_releases/2019-10/zsol-bbi100319.php) [[https://translate.google.com/website?sl=de&tl=en&ajax=1&u=https://www.eurekalert.org/pub\\_releases/2019-10/zsol-bbi100319.php](https://translate.google.com/website?sl=de&tl=en&ajax=1&u=https://www.eurekalert.org/pub_releases/2019-10/zsol-bbi100319.php)]*)

Self-spreading vaccines remain controversial

But not all scientists are as euphoric as Scott Nuismer and the bat researcher Daniel Streicker. Juan Bárcena warns that there is an urgent need for a debate about this technology. Because there are currently no regulations for the production or release of such self-spreading vaccines.

"All of this shouldn't be in the hands of molecular biologists, because their specialty is just molecular biology. I am of the opinion that we need an international set of rules for these activities. "

However, there are certainly similarities to other methods of containing pathogens, which are already controversially discussed. For example, there is the "gene drive", an accelerated inheritance of a genetic change. With its help, disease-transmitting mosquito populations should be eradicated or the spread of pathogens prevented. Or the targeted infection of mosquitoes with the Wolbachia bacterium, which is also supposed to stop the spread of dengue fever, zika, chikungunya or yellow fever. But what risks would a vaccine virus pose at all?

## Risk assessment by the scientists

I asked all of my interviewees that too.

"I thought about this question for a long time. We take a virus that is already circulating in the animal population as the backbone and incorporate a gene from another virus. It is really difficult for me to imagine how a Frankenstein virus could develop from this that would take over the world and destroy everything. "

... says Scott Nuismer. Probably the additional gene would not stay in the population at all, as the bat researcher Daniel Streicker explains:

"If the virus replicates, it will probably just lose the newly inserted gene at some point, because it offers it no evolutionary advantage. It doesn't depend on it to survive, so it won't cling to it. "

Nevertheless, the scientists want to install additional security mechanisms in order to be able to "switch off" the vaccine virus if necessary. Scott Nuismer:

"We are working on ways to keep the virus at bay. The newly inserted immunogenic gene is supposed to be deliberately removed from the virus. It's not exactly a self-destruct mechanism, but the idea is that you put the gene in, it does its job, and then over time it breaks down again. "

And Michael Jarvis's assessment:

"I don't see how inserting an antigen into a harmless cytomegaly virus would make it any more dangerous, but it's nice to have some kind of safety switch. Then you have control of the virus after it has been released into the world. "

Research on self-propagating vaccines is still in its infancy. The social discussion about it is still pending. The current corona crisis makes it clear what danger new viruses pose to mankind and that new ways may be needed to counter this danger. Daniel Streicker:

"I think maybe there were just too great concerns about releasing a genetically modified virus. Many people have reservations about this. We scientists now have to show that this technology can work and that it is safe. I hope that if we can do that, we



can use these apparently ideal tools. "

*Editor's note: The research for this article was supported by a grant from the European Journalism Center (EJC) as part of the [Global Health Journalism Grant Program for Germany](https://translate.google.com/website?sl=de&tl=en&ajax=1&u=http://healthde.journalismgrants.org) [<https://translate.google.com/website?sl=de&tl=en&ajax=1&u=http://healthde.journalismgrants.org>]*

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