

Rabies Virus Variant of Probable Bat Origin in 2 Gray Foxes, New Mexico

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Rene Edgar Condori, a microbiologist at CDC in Atlanta. We'll be discussing the detection of a rabies virus variant in two gray foxes in New Mexico.

Welcome, Edgar.

[Rene Edgar Condori] Hi, Sarah. Thanks for asking me to talk today about our study.

[Sarah Gregory] So tell us about the rabies virus. How long has it been around? And do we know its origins?

[Rene Edgar Condori] Yes. The rabies virus is part of the group of viruses named RNA viruses, because of the type on their nucleic acid. How long has it been around? Rabies actually is an ancient disease. Some historical records from the ancient Greek suggest that rabies may have been around 2300 BC, because they use the word "Lyssa" to describe the change of behavior in animals. Currently, the rabies virus belongs to the lyssavirus genus. This genus has around 17 species, and rabies virus is one of them. Regarding the origins of the rabies is still unknown, but we have two major groups of rabies that was identified analyzing the rabies genome. One group is related to the bats and the other is related to the dogs.

[Sarah Gregory] And how dangerous is it?

[Rene Edgar Condori] Rabies is a zoonotic disease that is transmitted through a bite. Commonly, rabies is maintained in animals but occasionally can affect humans. The rabies disease is actually very dangerous once the symptoms show up, it is almost always incurable but it's a preventable disease if a vaccine is given on time.

In the animals, the rabies virus is spread and is present in the saliva. When an infected animal bites another animal, it will inoculate the virus into the body. After that, the virus will travel through the nervous system to the brain. When the virus has reached the brain, the first few symptoms will appear. At this point, the disease almost always fatal. This is why it is important for the people to seek medical care as soon as possible.

[Sarah Gregory] And how many people die from rabies infections annually globally and in the US?

[Rene Edgar Condori] Some studies have estimated that at least 59,000 humans die around the world every year. In the United States, human cases are very rare. We have only between one to three cases per year. But the impact of rabies virus are measurable. Rabies causes an estimated 10 billion dollars in economic losses, primarily due to loss of life, the use of vaccine in persons exposed to rabies, and the vaccination of dogs. That demands a lot of economic resources.

In the US, the economic burden of rabies is over \$500 million per year. While the deaths are low, every year over 100,000 animals are tested for rabies. More than 60,000 Americans get Post Exposure Prophylaxis, and you can imagine that is a lot of investment.

[Sarah Gregory] And globally, where do most people get rabies from? What kind of animal?

[Rene Edgar Condori] This is a good question. From an estimated side, 59,000 human cases annually. Most of the human cases are related to a dog bite in Africa and Asia. In our continent, most human cases are associated to bats and other wildlife species.

[Sarah Gregory] Since rabies in dogs has pretty much been eliminated in the United States, where do people get it from here? Did you say mostly bats?

[Rene Edgar Condori] Yes, you're right. Dog-mediated rabies was formally eliminated in the United States in 2007. Currently, people get rabies from wildlife species (mainly bats). But we also have rabies in other species like raccoons, skunks, foxes, and in Puerto Rico we have rabies in mongoose. In our country, we have over 40 different bat species. And many people did not consider actually bats as a source of rabies. This lack of knowledge obviously increases the risk of being infected.

Here I'm going to give you some examples: one person could be in contact with a sick bat, another person can catch a bat in their house. In both cases, if they release the bat before testing, they are in the high risk to be infected. Bats can cause a scratch. A minor scratch, even, is a serious threat. It's important to recognize after the contact with a bat, if you have any mark or any bite (especially the bite of bats) could be...it's not a visible mark. This is the reason it's important to seek medical advice. Also there's some group of people that just refuse to be vaccinated.

[Sarah Gregory] And how do vaccines work in relation to rabies?

[Rene Edgar Condori] Yeah. I think that rabies is a preventable disease if the vaccine is given on time. When a person is bitten, first it's necessary to consider the point of inoculation and the incubation time. The incubation time refers to the time since the virus was introduced into the body until the first symptoms appear. Usually, the incubation period is usually between three weeks to three months in the majority of the cases. But in some cases, the incubation period can be shortened, for example, if a person is bitten in the head. In this situation, the point of inoculation is closer to the brain and the symptoms can appear as fast as 14 days. However, the vaccine inoculation is an inactivated rabies virus. The current vaccine is safe, and to prepare the vaccine, the virus is cultivated in cells and inactivated. And before to be released to the market, the vaccine passes strict controls. The commercial vaccine, for example, needs to be approved by the FDA. And the rabies vaccine....the rabies vaccine helps the body's immune system by producing antibodies against the rabies virus. These antibodies will recognize the virus as a threat and will neutralize them in the body.

I would like to mention that people can be vaccinated before and after the exposure. The pre-exposure prophylaxis is recommended only for people that are potentially at risk to be exposed to rabies as a result of their job or when they travel to rabies endemic regions. The typical dose...dosage consists of three doses and booster when is needed. But the post exposure prophylaxis consists of five doses and usually is given together with the rabies immunoglobulin when, for example, one person was bitten....is bitten by a wild animal.

[Sarah Gregory] Is there any other treatment for someone who has gotten rabies? Besides this vaccine?

[Rene Edgar Condori] That is a good question. As I mentioned earlier, rabies is a highly lethal disease but is preventable if the post exposure prophylaxis is given on time. I would like to highlight this. Once the virus reaches the brain, the symptoms will show up. There is no effective treatment at this point. For people, if someone had been exposed to rabies, it's better to go to the

closest healthcare provider. They will assess your risk and will provide the best recommendations.

[Sarah Gregory] Your article says, and now I'm quoting, "In the Western Hemisphere, bat-associated rabies viruses have established independent transmission cycles in multiple mammal hosts, forming genetically distant lineages." What does that mean?

[Rene Edgar Condori] Yes. At the beginning, I mentioned that there are two groups of rabies. In the Western hemisphere or the Americas we have both groups. The dog-related is known as the Cosmopolitan lineage and the bat rabies-related is known as the New World. The cosmopolitan lineage, as I mentioned earlier, is already eliminated in the US. And the New World lineage was established in bat species tens of thousands of years ago, and over time has undergone host-shift events.

When a host-shift event is successful, the virus is able to spread in the New World species. The New World lineage has multiple reservoirs, and there are multiple rabies variants. The only way to determine the rabies lineage in mammals is by using molecular tools and genetic analysis. And in our study, we conducted a phylogenetic analysis, and the phylogenetic analysis helps us control phylogenetic trees. And this can help us to determine if the viruses are closely related or not. For example, during the European colonization, dog rabies was introduced to the Americas and the Caribbean. Over time, this dog lineage has jumped to other wildlife species like fox, skunk, and mongoose. While dog rabies has been already eliminated in the US, currently, their relatives successfully established transmission cycles in foxes and skunks in the continental US, and in Puerto Rico we have rabies in mongoose.

How we can find if these species are related or not, we construct the phylogenetic tree. And in that way, we can observe if these viruses are each related or not. And going back to the New World lineage, as I mentioned, that group and many different bats with different bat variants in the Americas. As I said, bat variant is...we call bat variants because these bats have a specific variant and a specific and independent cycle of transmission.

Similar to the cosmopolitan lineage, the bat rabies jumped to skunks and raccoons. For example, the skunk rabies variant in the southwestern states diverged from the bats. And the raccoon rabies variant that we have in the Eastern states from Florida to Maine also diverged from bats. In 2019, the surveillance of the United States detected over 1,300 rabid bats, around half or less it was identified 23 different bat species. But we don't know how many of the other half are positive. We do not know which species of this have, because they didn't contain the bat identification. So it's likely that many more rabid bat species are collected every year and they are not indicated in our data because of lack of identification.

In the United States, up to today there are at least 17 different rabies variants that have been identified. Each variant is adapted to a specific host, and these form an independent cycle of transmission. As I mentioned, when using the molecular tools and the genetic analysis, you can accurately identify their reservoir host.

[Sarah Gregory] Your study is about a rabies variant in bats in New Mexico. What are the usual hosts there? Bats, again, as opposed to foxes or skunks or something?

[Rene Edgar Condori] Yeah. New Mexico has one of the lowest human population densities in the United States. This is important because our rabies surveillance system is primarily a passive public health surveillance method. This means that we test and sequence samples from animals

that have bitten or exposed to people. If there are very people....if there are very few people in an environment, it creates a gap in our surveillance system, and these gaps can be home to unique rabies variants. Also, New Mexico borders another country. All states that border other countries have for us a unique interest, because we don't always know which variants are circulating in neighboring countries. And the previous reports of the rabies surveillance in the United States have identified three different rabies reservoirs that are not only present in New Mexico but also in neighboring states. As was mentioned, the skunks for example formed an independent cycle of transmission known as south-central skunk. Foxes also formed an independent cycle of transmission, but the variant detected in New Mexico is similar to those found in Arizona and is named Arizona gray fox rabies variant. And finally, the bats formed their own cycle of transmission with at least seven different rabies variants. And as I mentioned, each variant is associated to a specific species. And recently we found a new rabies variant in two gray foxes.

[Sarah Gregory] And where specifically was this new variant found? I mean, I know in gray foxes, but like how did you find it? In a cave? Or where were they?

[Rene Edgar Condori] This new rabies variant was found in Lincoln County in New Mexico. This county, geographically, is located in the central part of the state and this county has the lowest human population densities of all counties in New Mexico. The cases....most cases were related to the exposure to humans. One was in 2015, and the other was in 2019.

[Sarah Gregory] Is this variant actually a new one, do you think? Or a previously undiscovered lineage?

[Rene Edgar Condori] Actually, this variant...it was previously undiscovered but is genetically different to other bat rabies variants. This novel variant has likely been circulating in New Mexico probably for many years. And to understand more about this new one, we need to find more cases and further conduct additional genetic analysis. For example, in our study the phylogenetic analysis showed that this new variant is most closely related to the silver-haired bat. The silver-haired bats are migratory bats (also known as tree bats). As of today, we don't know which wild species is the host. It could be a bat or a fox, but most likely is a bat based on the genetic analysis. It's often easier to imagine that a virus would be harder to find in a bat population, if you compare this population to a carnivore population. Because bats...some bats can migrate thousands of miles every season. Therefore, detecting this new variant in these two gray foxes is most likely as a result of cross-species transmission.

[Sarah Gregory] Tell us about cross-species transmission, how it works and how it's applicable to rabies.

[Rene Edgar Condori] The terminology cross-species transmission is also called spillover, host jump, or interspecies transmission. The cross-species event happens when an infectious pathogen (such as a virus) spill over a different species which is not the reservoir host. Normally for a cross-species transmission to happen, there should be a combination of different factors (ecological factors, efficient contact between species, frequency of contact, and the density of the population). For example, a rabies variant that commonly circulates in raccoons can jump to foxes or some domestic animals. Another example is bat rabies variants can jump to other bat species or terrestrial mammals. In our country, many cross-species transmission events occur every year, and the only way to detect this event is by using molecular tools and conducting genetic analysis.

[Sarah Gregory] You mentioned 2015 and 2019. Are those the time periods you looked at? And tell us again why?

[Rene Edgar Condori] First, I would like to mention that this new variant first was detected in 2015, as I said, in a gray fox in Lincoln County. The initial analysis showed that this strain was a bit different to others in New Mexico but was closely related to the variants circulating in migratory tree bats. We don't have more data about rabies in New Mexico. We requested archived samples from the New Mexico Department of Health to determine if this new variant was previously tested but not determined the rabies variant. At the same time, New Mexico implemented an active rabies surveillance.

The New Mexico Department of Health provided us some positive samples that were collected between 2004 and 2015. And the rabies surveillance system in New Mexico continues to collect more samples, and they sequence the partial nucleoprotein gene of the samples that they collected between 2016 to 2019.

In 2019, another gray fox in Lincoln County was in contact with a person. The sequence of the 2019 gray fox sample from Lincoln County we found was very similar to the 2015 strain that was in the same county. We conducted a genetic analysis using the partial and complete nucleoprotein gene. We looked for in the public database (specifically in GenBank) for any sequence similar that can help us to determine the reservoir of this new variant. To date, we didn't find any identical strain (we didn't find any identical sequence)—a reason why we concluded that this is a new rabies variant.

[Sarah Gregory] Why did you do this study?

[Rene Edgar Condori] That's a good question. As I mentioned, rabies is a zoonotic disease and circulates mainly in animals. For this new variant, we did not know much about it. Determining the reservoir, for us is very important because the surveillance system uses this information to implement an efficient rabies control in case, if in the future plans, we can have on any object.

We also didn't know much about the epidemiological implications that may arise, if some similar strains are detected in other species (it could be domestic or wild). And genetically, we want to identify which species is the potential reservoir host and its relationship with other rabies variants, and the risk that this variant may represent for public health. Now our study provides additional data that increase the number of rabies variants already identified in the United States.

[Sarah Gregory] Is there anything else you want to tell us about your study?

[Rene Edgar Condori] This study is really important because this is the first time that we identified a new rabies variant in New Mexico and it's the first newly described variant in the US since 2008. In New Mexico, the samples given during 2000 and 2020, at least 275 rabies cases were detected by the rabies surveillance system. The majority of the samples were from wild animals; 14 from these...14 additional samples were from domestic animals. In New Mexico, it's where we know the Arizona gray fox variant circulates in New Mexico and the south-central skunk variant was detected in wild animal species. But there is limited information about the genetic diversity of rabies across the state and the distribution of variants, particularly in bats.

And as I mentioned, in 2015 and 2019, we had two people exposed to rabies through a rabid gray fox. And that time, both people received the post exposure prophylaxis on time. As I mentioned, the gray foxes involved in both cases were identified as a new variant.

[Sarah Gregory] Were there any other findings you want to mention here?

[Rene Edgar Condori] Yeah. Besides to a new variant, when we sequenced samples from New Mexico, we also found other spillover events from bats to terrestrial mammals. Example: It's the rabies virus that is commonly found in big brown bats, and we detected this variant in gray foxes and skunks. Another important finding was detecting a rabies variant in a big free-tailed bat that jumped to a dog and a skunk, and this rabies variant is closely related to a rabies variant detected in Brazil. But we found only in the database partial sequence that helped us to determine that already this variant was circulating in the US. Also, we found a rabid bobcat that was infected with the Arizona gray fox rabies variant from foxes that were infected with the south-central skunk variant. All this information you can see in our data, that foxes in New Mexico were infected with different rabies variants.

[Sarah Gregory] What surveillance systems—you mentioned surveillance, earlier—what surveillance systems are in place to track rabies in the United States?

[Rene Edgar Condori] In the United States, the rabies surveillance system is established in every state. The system collects samples for rabies testing, and they take the samples in each state and conduct the antigenic characterization. The antigenic characterization is useful to identify the rabies variants but has limitations to identify new rabies variants because the new variants are antigenically different. Across the country, only a few states have implemented the genetic characterization of rabies. The genetic characterization actually helps to track the rabies virus and determine which variants are often detected and where those are detected. For example, if there is an outbreak, we can identify the source. Also in recent years, we identified rabies in imported dogs from different countries, and that's the reason I mention is the phylogenetic analysis is one tool that we can use to identify other types of rabies virus in the United States.

[Sarah Gregory] And are there gaps in this system? What are these gaps?

[Rene Edgar Condori] As I mentioned, every year we have thousands of rabies cases detected across the country. For example, in 2019 more than 25,000 bats were tested for rabies. From that amount, at least 5.5% tested positive; half of those positive cases did not have a bat identification. We are missing a lot of information every year because of the lack of bat identification. The vast majority of rabies that contain bat identification came from big brown bats and Mexican free-tailed bats and something we'd like to look at again.

In the country, we have more than 40 species of bats, some of them were never tested or they were tested a few times. To fill this gap, we should improve the bat identification and the genetic characterization. If we do that, we can find (probably) new rabies variants. And the other part is we should invest more in our state health departments to improve our knowledge about rabies in the United States.

And the other challenge of the surveillance system is sequencing the positive samples at the state level. Some states have the capacity to sequence their sample, but other states don't have the same capabilities. This is the reason why it is important to invest at the state level.

And finally, in last three years our branch at the CDC has been pushing to implement the rabies testing using the real time RT-PCR. This method was recently developed, and many states are currently implementing. One advantage of this technique is we can sequence the product of this technique and determine the rabies reservoir quickly.

[Sarah Gregory] Do you have any recommendations personally in your article on how these gaps might be filled?

[Rene Edgar Condori] Yes. So from the thousands of samples that is collected across the country every year, as I mentioned, mainly in bats, many of them don't have the bat identification and the rabies variant characterization. If we implement mechanisms (different mechanisms) to improve the bat identification, we will reinforce our surveillance system. I think that's going to be our recommendation.

[Sarah Gregory] Recapping here, what are the most important public health implications of your study?

[Rene Edgar Condori] Yeah. I mentioned earlier in the United States, we have two rabies variants that successfully jumped from bats and established in a terrestrial mammal—the raccoon rabies variant and south-central skunk rabies variant. In our study, we are reporting a new rabies variant that is closely related to the rabies in bats, but we don't know which species is the host, of course. If we continue finding more rabies viruses similar to this new variant (not only in foxes, but also in other species), this may represent an additional public health concern. In the coming years, if we keep finding more cases in foxes, we can be in front of a new host shift from bats to foxes. The host shift event in the United States actually hasn't happened in a long time.

[Sarah Gregory] Let's go back to vaccines for a minute, here. In the United States, rabies in dogs are under control, as you mentioned, and I know there's some programs that vaccinate raccoons for rabies. Is there a practical way to vaccinate bats?

[Rene Edgar Condori] You're right. In the United States, the oral rabies vaccination is used to control rabies in raccoons. This method of vaccination remains effective because the raccoon rabies variant has been contained in the Eastern states of the country. Implementing the vaccination of bats against rabies may be very difficult. It's not like the terrestrial animals that they will eat the vaccine. Bats usually feed on insects, fruits, or other small animals. One way to vaccinate bats may be using a topical vaccine. This consists of a vaccine in gel form or paste and put directly on the bat. That bat will ingest the vaccine when they are grooming themselves. But this approach is still challenging, because a vaccine needs to be tasteful to bats, and it could be logistically challenging to apply a topical vaccine to enough bats to actually impact the transmission rates of rabies. I think the main way to prevent bat rabies in people is through education on avoiding direct contact with bats and what to do when an exposure does occur.

[Sarah Gregory] Why aren't people vaccinated for rabies generally, like tetanus shots? Is there a time when someone should be vaccinated, even if they haven't been exposed to rabies?

[Rene Edgar Condori] Yeah. There are many studies that have been conducted to determine the cost and benefit of vaccination against rabies in an entire population. While rabies is a horrific disease, the general human population does not warrant yet the pre-exposure vaccinations. There are recommendations for pre-exposure vaccination in populations with certain risk factors like persons working in rabies diagnostic laboratories, persons working with susceptible wildlife, and those traveling to international destinations where rabies transmission is common.

So when should...someone should be vaccinated? The pre-exposure prophylaxis of rabies vaccine is currently recommended for people at high risk of being infected (veterinarians, animal handlers, rabies laboratory workers, people that are constantly exploring caves and people that work producing the vaccine). All these people, despite if they are vaccinated, if there is an

exposure to the virus, they still need a booster shot. Other recommendations include people traveling to rabies endemic areas. They should consider being vaccinated against rabies before they have been exposed to rabies. For example, people traveling to any country of Asia and Africa may consider to be vaccinated. If a rabid dog bit them they will be already protected, but they will still need a booster. Another example could be people traveling to the Amazon. If they rest in open areas, they are exposed to be bitten by a vampire bat. In Latin America, the vampire bats are the main source of rabies in Latin America.

[Sarah Gregory] Tell us about your job at CDC and how you are involved in this study.

[Rene Edgar Condori] Well, I am a microbiologist and a contractor at CDC. I started working at CDC since 2011 in the pox and rabies branch. I usually conduct the phylogenetic analysis of rabies cases. But also, I collaborated with a colleague in Dominican Republic, Argentina, Bolivia, Chile, and Peru. In this study, I analyzed all the samples that New Mexico sent us, conducted the phylogenetic analysis of all the samples sequenced at CDC.

[Sarah Gregory] And on a personal note, what do you like to do in your free time?

[Rene Edgar Condori] Well, like many others I have two dogs. I try to spend some time with them because they like to run. And in the summertime, I like to go camping with my family, stay close to a lake.

[Sarah Gregory] Well, thank you for taking the time to talk with me today, Edgar.

[Rene Edgar Condori] Thank you very much.

[Sarah Gregory] And thanks for joining me out there. You can read the June 2022 article, Divergent Rabies Virus Variant of Probable Bat Origin in 2 Gray Foxes, New Mexico, USA, online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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