Veterinarian Gets Flu Virus from Cats

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

[Sarah Gregory] With me today, I have Dr. Todd Davis, a research biologist at CDC. We'll be talking about the spread of flu virus from cats. Welcome Dr. Davis.

[Todd Davis] Thanks.

[Sarah Gregory] This is an unusual zoonotic event. Would you explain about zoonoses and how it relates to your study?

[Todd Davis] Sure. Within the influenza division, we have a branch, and it's focused on surveillance for all influenza viruses, and that includes both human seasonal strains, as well as influenza viruses that circulate in animal hosts. And I'm the team lead of a laboratory that focuses only on the zoonotic influenza viruses, or those strains that are typically found only in animals, but occasionally can infect humans. We know that there is a lot of different infectious diseases that are caused by viruses, parasites, bacteria that are typically found in animal hosts, but when humans get infected, they can cause disease, and influenza's no exception. And so we do quite a bit of surveillance in birds, in pigs, and even some pets, like dogs and cats, and other companion animals, like horses, and all of those animals have their own variety of influenza species. Most of the time those influenza viruses don't infect people, but when they do, we're especially concerned because humans don't have immunity to the viruses that typically circulate in those other animals that I mentioned. And so, when they do get infected, they don't have any antibodies at all to protect them from infection, and sometimes, even severe or fatal disease.

[Sarah Gregory] Your study was about a veterinarian who got infected from cats. What did you find?

[Todd Davis] So, I have to go back in history a little bit to explain what we know about influenza virus circulation in birds, and even a little bit in cats. Cats usually don't get infected by influenza viruses, but there have been a couple of sporadic cases that we know of. Sometimes cats can get infected with avian viruses because they're eating infected bird meat, where they might be exposed to feces or even water that might be contaminated with feces from birds. But cats typically aren't expected to get influenza viruses from birds.

But in the United States, and especially in the Northeastern United States, back in the late 1990s and early 2000s, there were quite a bit of these avian influenza viruses, known as the H7N2 subtype. And those subtypes circulate in other parts of the world, but especially in the Northeastern U.S. There are live bird markets where people can go and buy things like ducks and turkeys, chickens, and even things like quail, and have them slaughtered on site and then take them home to prepare meals. And there were quite a bit of these H7N2 viruses circulating in those live bird markets, back again in the late 1990s and early 2000s. They typically didn't do much, they didn't cause any other outbreaks in birds, but there are a couple of cases where there have been poultry outbreaks documented in places like Virginia in 2002, North Carolina in 2002. And during some of those larger poultry outbreaks, there have been other human infections with

H7N2 viruses. So, there was a human infection back in 2002 in Virginia, and then another human case that was detected in New York in a person that visited these live poultry markets.

So, where do we make the connection with cats? Well, in many of these shelters, where people are either dropping off animals that they find as strays, or there may be a city sanitation group that collects stray dogs, stray cats, and even some cases, stray birds. We know that those animals sometimes end up being sheltered together. And so, in this case, there was a veterinarian that was attending to a group of sick cats that were collected as strays and then maintained at this animal shelter in New York City. And the veterinarian started to experience influenza-like illness, really after doing quite a bit of work with these sick cats, and even doing an autopsy on a cat that had died. So this veterinarian had had prolonged exposure and very close contact with these sick and one dead cat. And so the specimen was sent to the New York City Department of Health and the New York City Department of Health was able to determine that it was influenza A positive. But they couldn't use any of their other detection methods to subtype the virus, so it looked like it wasn't a typical seasonal strain. And when that happens, usually the cases are escalated and the specimens are sent to state laboratories that have some advanced strategies to do things like real-time RT-PCR testing or even sequence analysis of the genetic material in the clinical specimen. And in this case, the New York State Department was able to demonstrate that the clinical specimen from the veterinarian was infected with an avian H7N2 virus, and then the sample was sent to CDC for some confirmatory testing. And then we're able to do some additional studies on those types of specimens, such as virus isolation. We're also able to do some additional genetic characterization to confirm the test results from the state laboratory.

[Sarah Gregory] Have there been other studies done at CDC about flu and cats?

[Todd Davis] So, at the same time that CDC was receiving this sample and confirming the result from both the city and state laboratories, several specimens were also collected from the sick and fatal infection in the cats in the shelter in New York City. And those samples were sent to the University of Wisconsin–Madison, where they have some expertise in detecting and diagnosing viral infections in cats. And then those samples were also sent on to the National Veterinary Services Laboratory, which is a USDA laboratory in Ames, Iowa. And concurrently those laboratories were able to also confirm that the cats were infected with an H7N2 avian influenza virus. And so, in parallel, CDC began to sequence the genome of the virus. We shared the sequence data with the University of Wisconsin and also with the USDA, and then they shared the results that they obtained from their studies with us, and we were able to determine that, in fact, the veterinarian was infected with the virus that was nearly 100 percent identical to the viruses that were detected in the sick and the one dead cat. We do phylogenetic analysis of the genetic material. We can build what's called a phylogenetic tree, which is—basically allows us to look at the similarities of different virus strains to one another, and we were able to show again that these viruses were nearly identical, and so close that it looked like the veterinarian has most certainly picked up the infection from the cat or cats that they had been exposed to in the shelter.

So, CDC then went on, in my laboratory, to isolate the virus. We use embryonated chicken eggs as a substrate to isolate these viruses, and by isolating the virus, we can take that clinical

specimen and actually grow, or propagate, virus so that we have more material to conduct additional studies. And those additional studies then allow us to do quite a bit of additional work, not just within my laboratory, but within the laboratories of other principal investigators here at CDC.

[Sarah Gregory] Tell us about LSTb glycan—what is it and what's the unusual role it seems to be playing in this event?

[Todd Davis] LSTb glycan is a unique glycan in that it's expressed on some mammalian cells, and it expresses a receptor that influenza viruses can bind to. And because this was a virus that we had seen before in these live bird markets, again in the 1990s and 2000s, we knew a little bit about how those viruses bound to human receptors. And after we had finished sequencing the virus that was isolated from the veterinarian, we realized that, in fact, it was also very similar to those strains that had been detected in live bird markets in the Northeast in the late 1990s and 2000s. And one of the hallmark features of those viruses is that they have a big deletion, a part of the protein, known as the hemagglutinin protein, was missing from those H7N2 viruses. And the same portion of the protein was also missing from this virus isolated from the veterinarian. And we knew from some previous studies that, when that part of the protein is missing, the receptor binding specificity, or the ability of the virus to bind to cells, can change. And typically, these avian viruses have a specificity for avian cells. But without this portion of the protein, they can also gain the ability to bind to human cells.

And so, by having that isolate, we were able to do the in vitro studies that allowed us to demonstrate that, in fact, this virus that had been isolated from the veterinarian, did, in fact, bind to what we call our alpha2,6 receptors. The LSTb glycan also has alpha2,6 receptor reactivity and once we saw that that portion of the protein was missing, we were able to do some additional in vitro characterization studies to show that, in fact, the virus that had been isolated from the veterinarian did have binding to mammalian host cell receptor glycans. And this is something that is of concern to us because typically the avian viruses do not bind to human cell-like receptors. And so we see that, in some of the viruses that have been known to infect humans, like the Asian lineage H5N1 viruses that we've read about in the media, and more recently, the H7N9 viruses that circulate in China and have caused more than 700 human infections, just in 2017. And so, it's of a concern to us, and so that then encouraged us to do additional studies to assess the potential risk of this virus being able to transmit in humans. And so, one of the things that we can do, within the Influenza Division, are transmission and pathogenesis studies using mice and ferrets. Ferrets, especially, are a useful animal model because the replication of the virus and the transmission of viruses typically mimics that of humans, and so we use that as a surrogate for studies to learn more about how these viruses might replicate and transmit between humans. And other groups within the influenza division were able to take the isolate that we had made and do those studies in ferrets to show that, in fact, this virus did transmit via direct contact from ferret to ferret. They were able to show that the virus also replicated well in human bronchial epithelial cells. And that presents some particular concern because it looks like this is a virus that could, in fact, infect humans and potentially transmit among humans that might have direct contact either with cats that are infected or other humans that might be infected.

[Sarah Gregory] Should people be concerned about getting flu from their cats?

[Todd Davis] So, there's always been some concern about companion animals and influenza, in particular because we know that dogs often carry a specific influenza A subtype and that virus tends to circulate readily among dog populations in the United States. Although the same has not been found in cats, we are concerned after this that there may be some additional vigilance needed and some additional surveillance to understand how many of these influenza strains can infect cats and whether there are any strains that actually are maintaining consistent circulation in cats. So, there's some additional work now being done, in part with the New York City Department of Health and also USDA, to try to understand the feline connection with these circulating influenza viruses.

[Sarah Gregory] What conclusions did you draw in your study?

[Todd Davis] I think the big take-home from this study is that this really documented the first known case of direct transmission of an influenza virus from a cat to a human. So, even though we've seen cats infected with influenza before, this is the first time we've been able to document a transmission event directly from a cat to a person. So again, it does give us some concern about companion animals and the prolonged exposure to companion animals that might harbor some of these influenza strains that can cause disease and even death occasionally in humans. This also has taught us a bit of a lesson about surveillance and the need to continue surveillance from year to year, so that we know what types of avian influenza viruses or other influenza viruses are circulating in animal reservoirs. We don't know from this study exactly where the cats picked up this low-path avian H7N2 influenza virus and that's going to be one of the mysteries that I'm afraid will go unsolved because we just don't have the data or the specimens to go back retrospectively to look at where the cats may have picked up this strain of influenza. But it does tell us that these H7N2 strains that were detected again in the Northeast in the late 1990s and 2000s appear to be still circulating in some animal reservoir. And obviously the cats may have been an indirect reservoir host, but were capable of transmitting the virus among those groups of cats that were sheltered together, and that humans that had close contact were also able to be infected with those viruses. So, I think there's going to be some enhanced surveillance that comes out as a response to this human case and, especially, the cats that were also infected, and we'll begin to follow those H7N2 viruses more closely, I think, as a result of this.

[Sarah Gregory] So, how is this information useful?

[Todd Davis] Well, one of the other things that it will help us to do is to understand how vaccines that are developed to prevent influenza infection disease can be proactively made to prepare for what we consider to be viruses of pandemic risk. So, many of the listeners may know that the World Health Organization hosts a twice annual meeting to select which influenza vaccines will be made to prevent seasonal influenza. But, as part of that vaccine strain selection process, myself and a number of other laboratories that conduct zoonotic influenza virus research also participate in the vaccine strain selection meeting. And we bring data to the World Health Organization to make decisions about which vaccines should be made as so-called prepandemic candidate vaccine viruses. And these prepandemic vaccine viruses may never actually be

manufactured as vaccines that go into humans and even if they are manufactured, they may never be used in humans. But we're able to create the seed strain, or the virus that's used to make the vaccine, by doing these types of studies.

And so, previously we've produced H7N2 vaccine strains that targeted viruses from 2002 and 2003. And we're able to take those candidate vaccine viruses and produce antibodies, and we typically produce those antibodies in ferrets. We can collect blood from the ferret and then we can test the antibodies in that blood to see whether those antibodies are able to react or cross-react with new strains. And in the case of this human infection with the H7N2 virus, we were able to demonstrate that these previously developed candidate vaccine viruses do, in fact, cover or cross-react with this new virus. And so that gives us some comfort in knowing that we've already got vaccines that have been produced and could be deployed if this virus were to take off and become transmissible human-to-human in the human population, either in the United States or in other parts of the world. And so again, it's a very useful discovery for us, because it not only tells us that the work that we've done in the past helps us to design vaccines that could be useful in the future, but also helps us to expand some of the surveillance work that we're doing and gives us a lot more knowledge about how influenza viruses are able to maintain circulation in different animal hosts, and then the ability for some of these viruses to make the leap into humans, as well.

[Sarah Gregory] Dr. Davis, you already told us a little bit about your job at CDC and your particular areas of interest. Is there anything else you'd like to tell us?

[Todd Davis] Well, the study that we've been talking about, you know, really focused on just one single human infection, and that was interesting enough because of the novelty of that human infection, but a lot of the work that we do focuses on influenza subtypes that circulate in, specifically, birds and pigs, because there are several hundreds of human infections each year with those types of strains. And so, we spend a lot of time trying to understand how viruses that circulate in poultry and swine, where people have a lot of exposure to those types of species, can actually infect humans and cause disease. These are viruses also that humans have very little immunity to and so, when they do infect people, there can be severe infection and sometimes death. Most recently, there have been more than 700 cases of an avian H7N9 virus circulating in China, so we're very concerned about that virus and what it's done in the Chinese population. And we've taken precautions to develop vaccines against those H7N9 viruses in the event that it became transmissible human-to-human. And we also spend a lot of time studying swine influenza viruses, both in the United States and internationally, to understand which types of viruses circulate in swine. And very recently, especially in the summer of 2017, there were a number of human infections, especially among young children that visited agricultural fairs in certain parts of the United States where there's a high density of swine being exhibited in these agricultural fairs. And we follow those human infections with swine influenza viruses very closely because, especially when they infect humans, they can become transmissible very quickly, and when they infect children, they can also lead to fairly severe infections. And so we follow those avian and swine viruses quite closely and also develop a lot of pre-pandemic

vaccine candidates, just in case there were a virus that became transmissible in the human population, we'd be prepared and ready to develop vaccines quickly against those strains.

[Sarah Gregory] Thank you Dr. Davis for taking the time to talk with us today. Listeners can read the December 2017 article, Avian Influenza A (H7N2) Virus in Human Exposed to Sick Cats, New York, USA, 2016, online at cdc.gov/eid.

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

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