

Highly Pathogenic Avian Influenza A(H5N1) Virus Clade 2.3.4.4b Infections in Wild Terrestrial Mammals, United States, 2022

[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 Dr. Betsy Elsmo, an assistant professor of clinical diagnostic veterinary pathology at the Wisconsin Veterinary Diagnostic Laboratory and the University of Wisconsin School of Veterinary Medicine. We'll be discussing infections of H5N1 bird flu in wild mammals in the United States.

Welcome, Dr. Elsmo.

[Betsy Elsmo] Thanks so much, Sarah. I'm honored to be here today.

[Sarah Gregory] There has been a lot of reports regarding these H5N1 bird flu outbreaks here in the United States. How many have there been since 2020? While the COVID pandemic was going on, this flu was taking off, right?

[Betsy Elsmo] Yes, that is correct. The current global outbreak of highly pathogenic avian influenza with this current H5N1 strain did begin in 2020 in countries in Africa and Asia and Europe. And I like to think of it as sort of one large global outbreak that has been moving in waves. And it didn't make it to North America until the end of 2021 and was first detected in the US in 2022 in January. So yes, globally this outbreak did begin during the COVID pandemic and has been making its way throughout the globe since 2020.

[Sarah Gregory] What caused these outbreaks to begin with? Do we know?

[Betsy Elsmo] We do know. Avian influenza viruses evolve really rapidly, and so there have been sporadic avian influenza outbreaks throughout the globe for decades, and sometimes these new strains are better at transmitting between birds and replicating in birds, and so those strains that are better at infecting birds can become the dominant strains. And outbreaks of avian influenza happen occasionally locally within the world and sometimes those outbreaks then tend to spread globally and affect a large number of places like what we're seeing with this current outbreak, and that's because a lot of times these viruses become adapted to replicating in wild birds. And so they can spread across the globe during migration.

[Sarah Gregory] Is it a specific type of strain that's causing these recent outbreaks?

[Betsy Elsmo] So the current outbreak is due to a variant of the Goose/Guangdong lineage H5N1 clade 2.3.4.4b avian influenza virus.

[Sarah Gregory] Where did this goose clade originate?

[Betsy Elsmo] This H5N1 goose clade was first identified in a goose in southern China, and that's where it gets its name. And that happened back in 1996. And that strain caused poultry outbreaks and human illnesses in China, and then it sort of seemed to disappear for a while before it reemerged again in China in 2003. And since that time, the virus has diversified or evolved into different genetic groups that they call clades, and these H5 viruses that are mixing with other various low pathogenic and high pathogenicity avian influenza viruses and spreading throughout countries in Asia, Africa, Europe, and the Middle East. And so, a new H5N1 clade

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2.3.4.4b virus emerged as the predominant strain circulating in the Netherlands and in Europe at the end of 2020. And it's that Eurasian strain that has been the predominant strain detected globally since that time.

[Sarah Gregory] How does a bird flu spread from one bird to another?

[Betsy Elsmo] Avian influenza can spread in a number of different ways. The virus can be spread in respiratory secretions, through feces, and it can also survive in the environment and in contaminated farm equipment or even water sources. So there are a lot of different ways that the virus can be transmitted between birds. And then additionally, between farms or between locations.

[Sarah Gregory] And what are the symptoms of it in birds? I did a podcast last week on *Salmonella* killing songbirds. How is this virus different?

[Betsy Elsmo] Symptoms of avian influenza in birds vary by the type of bird. And so historically, avian influenza is primarily carried by waterfowl and wading birds, and they often have very few clinical signs, so they can be normal but carrying and shedding this virus. However, with this current strain, it seems that we're seeing a lot more infected waterfowl that do have symptoms. And in general, the signs are going to be mostly acute deaths—so a lot of birds dying acutely due to this virus infection without any symptoms. But in birds that do show symptoms, we can see nasal discharge, sometimes skin hemorrhages or edema in domestic poultry, and sometimes watery green diarrhea. And that is different than in raptors and in birds of prey, where neurological signs tend to be more common when they are infected. And so, that will be birds that are acting inappropriately, say they can't fly, or they seem disoriented.

In regard to the birds that have *Salmonella* infection, some of those signs do overlap. And so, ill birds tend to often have a lot of non-specific symptoms because they are really good at hiding illness. And so, some of the things that we see universally in sick birds are lethargy, sort of ruffled up feathers, and sometimes diarrhea, which I think are symptoms of *Salmonella* in those songbirds. So those are also things that we can see in birds that have avian influenza infection.

[Sarah Gregory] Do we know how many birds have been affected so far, both in the United States and globally?

[Betsy Elsmo] We do. So in the US, the USDA-APHIS maintains a lot of really great data on their website. And so, based on their website, since the beginning of this current outbreak in the United States, there have been 1,012 domestic poultry flocks that have been confirmed positive across 47 states in the United States, and they estimate that approximately 72.5 million domestic birds have been infected with avian influenza since the beginning of this outbreak. And so, that includes both production animals and backyard or hobby farms.

Globally, estimates are a little bit harder to come by, but in July of 2023, the World Health Organization and the World Organization for Animal Health reported that an estimated 81 countries have been affected by this current avian influenza outbreak, and they estimate 131 million domestic poultry have been lost either due to dying from avian influenza or being culled resulting from influenza infection on a farm. With wild birds, it's a lot harder to get a good estimate because there aren't great population level estimates of wild bird species in general, and disease surveillance is pretty sporadic in wild birds. So what we do know is that with this current strain of avian influenza, in contrast to previous outbreaks of avian influenza in the US and

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globally, there have been a lot more outbreaks in wild bird species, including some really highly endangered bird species such as the California condor, Eurasian cranes, and Peruvian pelican.

[Sarah Gregory] What have these outbreaks done to the poultry industry?

[Betsy Elsmo] Unfortunately, these outbreaks have caused a huge amount of loss in the poultry industry, both due to death of affected birds and culling in affected flocks in the poultry industry. And so, that does translate into large economic losses for poultry producers, loss of export value, and of course increased prices to the consumer. I think in the US we've all seen increased egg prices over the last several years, and similarly with poultry products in the market.

[Sarah Gregory] How did this particular bird flu evolve to become so deadly?

[Betsy Elsmo] That's a great question, and there are a lot of really smart people working on that question right now. I do have to give a disclaimer that I'm not a molecular virologist, so I may not be the best person to answer this question, but I sort of compare it to what we saw during the COVID pandemic. So some strains of COVID were better at infecting people, and eventually those strains that were really good at infecting people spread more and became the dominant strains that we were seeing, and those waves of viral strains develop and sometimes out-compete each other. So that's what's happening with avian influenza as well. Some of these strains that evolved are really good at replicating in birds or being transmitted between birds. And so, those strains eventually can become the dominant strain, and that's what we're seeing with avian influenza is that this current strain just appears to be really good at infecting wild birds and poultry, and it also appears to be causing more severe symptoms in birds than previous strains.

[Sarah Gregory] Are there particular geographic regions in the United States that it has been found and what are they and will it expand into other areas?

[Betsy Elsmo] Yeah. Initially, avian influenza infections during this outbreak were detected on the eastern coast, and these are often following large migratory pathways that birds take. And so, eventually avian influenza has spread to all of the migratory pathways that cross the United States, including branching out down into Central and Southern America as birds migrate and carry this influenza infection along this end. But at this point in the US, detections of avian influenza have occurred in 47 states, including Alaska, but not yet in Hawaii. And really there has been unprecedented global expansion of avian influenza virus during this outbreak. Typically, Central and South America did not get affected during the avian influenza outbreaks of the past. So this virus unfortunately has shown that it's probably going to continue to spread.

[Sarah Gregory] This is sort of the opposite of the usual bird flu migration patterns. Don't they usually come from China over the Pacific Rim and spread that way? And since this is a Eurasian one, we're getting the opposite effect, right?

[Betsy Elsmo] Yes, you're absolutely right. Yup, in the past, introductions tend to happen on the Pacific Flyway on the West Coast. And so, this was unusual in that outbreaks were happening more in Europe and seen across initially on the Eastern Coast of North America and sort of spread westward, which isn't the same that we've seen in the past. Additionally, in past outbreaks, a lot of the spread within a country was deemed to be due (likely due) to movement of contaminated equipment or birds across the country, whereas with this outbreak, what we've really seen is that most of the introductions onto farms are associated likely with wild bird

contact. So in this outbreak, it really seems that wild birds are playing a bigger role in moving this particular virus across the country and across the globe.

[Sarah Gregory] Let's talk about your study, which is about this H5N1 Eurasian strain we've been talking about spilling over into wild mammals in the United States. Is this something that has happened overseas already?

[Betsy Elsmo] Yes. In Europe, particularly the Netherlands, spillover of this particular strain of avian influenza had already been detected in the Netherlands in wild red foxes in May of 2021. And that happened following some outbreaks in wild birds in the Netherlands. And around that same time, there were also some reports in the UK of infections in a seal and in a fox from an animal shelter that had contracted avian influenza (this particular strain). So we have seen this happen in countries in Europe that were experiencing this outbreak earlier than we saw in North America.

[Sarah Gregory] You mentioned water and poop and that kind of thing before for the spread. Is that how it's spreading from birds to mammals? Is there some mutation in the virus that needs to occur for this to happen and how exactly are the mammals getting it?

[Betsy Elsmo] These are really great questions, and the answer isn't really clear quite yet. I think this is something that we still need some research on, and a lot of people are still investigating. From our study and from some other studies on historical outbreaks, there's a lot of evidence that suggests right now that mammals are getting infected after eating an infected bird or being in very close contact with an infected bird. So in our study, several of the infected foxes had evidence that they'd recently ingested a bird. And of course, right now with this outbreak, there are a lot of wild birds on the landscape that have died or are ill from highly pathogenic avian influenza. So there is a lot more opportunity for these animals to be scavenged or easily preyed upon from small carnivores. And we've seen in past outbreaks as well that direct feeding of infected birds through mammals can cause these infections to jump into mammals. So that's sort of the most clear-cut answer. It really seems like for a lot of these mammals, they need to eat an infected bird or have very close contact with it.

What's a little less clear is how marine mammals are getting infected. And so, there have been a fair number of marine mammal infections due to this outbreak, and it's a little less clear whether or not those mammals are ingesting birds, which might not be a typical component of their diet, or whether those mammals might be just getting exposed to a lot of this virus from species that are in the water sources that they are sharing. There is a lot of research going on right now about the types of mutations that we're seeing in these avian influenza viruses that might make these viruses better at infecting mammals or better at replicating in mammals, and potentially then better at transmitting between mammals.

And so, some of those genes that have been shown in experimental studies to make influenza viruses better at adapting to mammalian hosts have been found in these mammals. So for example, in our study, 20% of the mammals that we looked at did have known gene mutations that have been associated with or are concerning for mammalian adaptation. And in a similar study to ours from Canada, about 17% of the mammals that they tested had these concerning gene mutations as well. So there might be something about the genes of these particular avian influenza viruses that are making them more likely to infect mammalian hosts.

[Sarah Gregory] I just wanted to throw in here that earlier this year, I did do a podcast on H5N1 in harbor seals. So if listeners are interested, they can find that podcast also.

Tell us how you conducted your study.

[Betsy Elsmo] This study initially started as a local investigation in collaboration with a wildlife rehab center. And that wildlife rehabilitation clinic had noticed an uptick in sick wild fox kits that were being submitted, and a lot of those wild fox kits had neurologic signs—so they had seizures and ataxia, things like that. So we started investigating those cases and then leaning on work that had recently been published from the Netherlands about avian influenza in wild red foxes there. We decided to do some testing for that, and it turned out that a lot of those red fox kits were in fact positive for avian influenza. So that is how the study started as sort of a local collaboration doing diagnostic workups for these wild fox kits.

And it was quite convenient that around the same time that we were starting to disseminate some of that information, there was a conference in Madison, Wisconsin (where I'm located)—International Wildlife Disease Association Conference—that took place that summer. And so, fortunately we were able to network with a lot of state wildlife officials across the country who were seeing similar things in red foxes and in other wild mammal species. So through networking at that conference, we were able to gather a lot of collaborators, sort of collect all of that data about what we were seeing in these mammals infected with avian influenza across the US. And so, that's how the study grew into this sort of more national overview of what we were seeing.

[Sarah Gregory] You mentioned your local partners. Who were your partners in this study? What were the groups?

[Betsy Elsmo] Our initial local partners were the Dane County Humane Society's Wildlife Center, which is a fantastic group, and they also collaborate with the University of Wisconsin-Madison School of Veterinary Medicine, and they fantastic veterinary technicians and veterinarians that oversee the care of the wild animals there. And so, that was our initial partner, and that sort of grew locally then to collaborate with our Wisconsin Department of Natural Resources, who manages free-ranging wildlife in the state of Wisconsin. And through that work, we found a couple of additional cases in bobcats.

We also collaborated with pathologists at the National Wildlife Health Center, which also happens to be in Madison, Wisconsin, and they're a federal organization that does a lot of work with diagnostics and research in wildlife diseases. Of course we had a lot of local partners here, and then it expanded to a lot of veterinary diagnostic labs across the country, and then really importantly the National Veterinary Services Laboratory and the amazing staff there that did a lot of the molecular workup on these avian influenza viruses.

[Sarah Gregory] It's always so wonderful to see these partnerships and all the people that become involved in figuring these things out.

Were these sick animals found out in the woods or in urban environments, close to people?

[Betsy Elsmo] Most of the animals in this study were found ill, and they were predominantly in urban or semi-urban environments. And so, that's one of the inherent biases in this dataset, is that sick wild mammals in remote areas are often not encountered at all or investigated because no one is there to see it. So these animals were being picked up because they were in locations

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where humans were likely to run across them and to notice them. And so, what that means is that probably the caseload in this paper is just the tip of the iceberg as far as true numbers of infections of mammals during these outbreaks.

[Sarah Gregory] You mentioned the foxes and bobcats. Were there any other kinds of animals that were sickened with it?

[Betsy Elsmo] Yeah. In our paper, we have seen several other species. We have red foxes, bobcats, also a fair number of striped skunks, raccoons, Virginia opossums, and a single fisher, one coyote, and one gray fox. I will mention again that USDA-APHIS does maintain really great dashboards of this data nationally, and they have a great map of all of the mammalian infections that have been detected in the United States during this outbreak. And there also have been reports in harbor seals, as you mentioned, bear, and lots of other species as well.

[Sarah Gregory] It seems like there were more red foxes that were affected. Is there a reason for this?

[Betsy Elsmo] I think that this might have more to do with people than animals. People really seem to have an affinity for red foxes. They're cute, and people tend to like them much more than they do some of the other mesocarnivores that live in urban environments like raccoons, opossums, and coyotes. And so, because these red foxes tend to thrive in urban areas where people are and people like them, I think that they're...people are just more prone to submit a red fox when they notice it ill or dead to their local rehabilitation center. So I think some of that is just a bias of people really liking red foxes and red foxes being around people. But it is also possible that this species (the red fox) might be more susceptible to infection, or potentially they're more likely to prey on these sick or dead wild birds. Unfortunately, there's just not enough data to really sort out the cause of that just yet.

[Sarah Gregory] We talked about the symptoms in birds, but what are the symptoms in these mammals and were the symptoms different in the different mammal species?

[Betsy Elsmo] Most of the mammals in this study had neurological symptoms. So a lot of the time, they were presenting with seizures, tremors, ataxia or problems getting around, some of them were real lethargic. And a lot of times, they just didn't have an appropriate fear of humans. And so, those symptoms are somewhat similar to what we are seeing in birds of prey that have avian influenza infection as far as the neurological aspects of it. We did see not a huge difference in symptoms across mammal species, but again, we really had a big number of red foxes and much fewer of the other species, so it's a little bit hard to compare just based on those small numbers of the other species that we looked at.

[Sarah Gregory] Did any of the animals you looked at survive?

[Betsy Elsmo] In our study, two of the red foxes did survive, and only one of those foxes had neurological signs. The other fox was lethargic and thin when it was admitted to the rehabilitation center. And both of those foxes did have a really low positive result off of an oropharyngeal swab. So it's possible that those foxes might have had milder infections, and it's also possible that the supportive care that they receive helped them through those infections.

There are other studies out there that have looked for antibodies in red foxes specifically, and they have found a fair number of red foxes that had antibodies to these avian influenza viruses.

And so, that suggests then that there certainly is the capacity of mammals to survive these infections occasionally.

[Sarah Gregory] Anything else you found you want to tell us about?

[Betsy Elsmo] Yeah. One of the interesting findings from the study was that not all mammals respond to infection the same. So in particular, it seems like striped skunks are less prone to neurological disease or brain lesions, and they tended to have more severe lesions in their livers and lungs. And so, essentially that just shows us that this infection might look a little bit different based on the mammal species that's infected. So that was really interesting. And then lastly, we were surprised to find that 21% of the mammals evaluated in the study had at least one mutation within the avian influenza virus genome that had been previously associated with mammalian adaptation. And that finding was a bit concerning.

[Sarah Gregory] Well, clearly this is really bad. What would you like public health to do with your findings?

[Betsy Elsmo] It is concerning because each time this virus gets a chance to replicate within a mammal, there's a selective pressure and an opportunity for that virus to then get better at infecting and replicating within mammals. And of course the concern is, will this virus then become good at spreading between mammals, including humans? So in regard to public health, I think one of the things that I wish there was more funding to do on a bigger scale is surveillance in wild mammals for these avian influenza virus infections. And then of course, along with that, evaluation of those viral genomes for concerning mutations. I think that information would be really helpful to inform vaccine technology going forward, and that would be our best defense if this virus ever does become better at infecting mammals and transmitting between mammals.

[Sarah Gregory] Can pets get it and if so, what can people do to protect their pets? And I guess from what you've just said, there's no vaccine for them.

[Betsy Elsmo] Right. Unfortunately, there is no vaccine for pets at this point in time, but there is evidence that pets—primarily domestic cats and domestic dogs—can be infected. In recent months, there's been a fair number of detections in domestic cats, both in the United States and in Europe, and in most of those cases there has been evidence of ingested infected wild or domestic birds that were linked to those infections in cats. There have been much fewer reports in domestic dogs, although even historically in past avian influenza outbreaks, there are sporadic reports of dogs getting infected, and again, it's usually due to them ingesting or having really close direct contact with infected birds.

So it's certainly a possibility that pets can get infected with this virus, and the best way in general to protect your pets is to reduce any exposure or contact that they might have with wild and domestic birds. So this means keeping cats indoors so that they can't have the opportunity to prey on infected birds and keeping dogs (including hunting dogs) away from species of wild birds that might be carrying this virus. Unfortunately, there is not a vaccine for avian influenza that's labeled for use in mammals at this time. In dogs, there are commercial vaccines for canine influenza, and it's currently unclear if this vaccine has any cross protection against avian influenza. But of course, it could reduce the likelihood that a dog gets a co-infection with canine influenza and avian influenza. And as we know, influenza viruses from different species can mix within an animal, and that's one of the ways in which these viruses evolve to adapt to a broader

host range. So taking any steps to prevent that from happening within dogs would also be a good idea.

[Sarah Gregory] Are people getting it? Is there a vaccine for people?

[Betsy Elsmo] Since the start of this outbreak in 2020 or 2021, there have been only 11 reports globally of human infection with this current circulating strain of avian influenza. And some of those infections were mild with few symptoms and people recovered. But in some of those infections, they have been fatal. Unfortunately, there's not currently a vaccine for people.

[Sarah Gregory] What do you think is the future research that needs to be done?

[Betsy Elsmo] There is a ton of ongoing research right now to understand the transmission dynamics and evolution of this avian influenza virus. A lot of brilliant people are working on this topic right now. And I think one of the gaps in our knowledge that would be important to address is the ways in which mammals, especially wild mammals, are being infected and how the virus is responding and evolving to those selective pressures of spilling over into wild mammals. Ongoing surveillance for gene changes that might make this virus better at adapting to spread in mammals would be really important. And then, of course, vaccine technology that can provide prevention against influenza viruses in general is another huge area of research that needs to be done.

[Sarah Gregory] You mentioned that there was research, however. So what are these global measures—or are there, in particular, in the United States—aimed at stopping all of this?

[Betsy Elsmo] One of the most challenging things about this virus and this current outbreak is that it's being spread throughout the world in wild bird populations as they migrate. So of course, we can't quarantine or vaccinate or cull as options to sort of control the spread of the virus, and that makes it really hard to control globally. So really what we are doing nationally and globally is to take measures to protect domestic bird populations. And on that end, generally what is recommended is intense biosecurity measures and then culling of birds in affected flocks to prevent those viruses from further evolving and getting better at spreading within poultry. Again, there's also education measures that are happening globally to try to reduce the spread of this virus on small farms in between species as well. Some countries are using vaccination as a preventative strategy. In the US, that's really only being done in one specific population, and that is the California condor. And that's due to its highly endangered nature.

[Sarah Gregory] Tell us about your job and how you were involved in this study initially I think you mentioned the local investigation into the kits.

[Betsy Elsmo] My job is I'm a veterinary anatomic pathologist. And so, what I do day to day is investigate disease in pretty much all vertebrate mammals except for primates. And so, in Wisconsin we primarily serve the dairy industry, so I see a lot of cows and disease in a lot of cows. But I also see a lot of other species as well. And so, one of our clients that we serve is the local wildlife rehabilitation clinics. And that's how this study came about, was through an interest of mine in collaboration with the veterinarians and veterinary technicians at the wildlife rehabilitation clinic, and trying to dive deeper into this unusual fox kit mortality that they were experiencing.

And one of the problems for detecting these types of diseases in wildlife populations is that often the first folks who are encountering disease in wild animals are people in the wildlife

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rehabilitation community. And those folks have very limited funding in general, and so a lot of the time they're more likely to spend the limited funds that they do have available to keep animals alive that are currently alive, and there's less funding to do diagnostic work in deceased animals. So in this case, I was able to use some research funds that I had to sort of do a further workup than the clinic would have initially done because of funding constraints. So that collaboration really allowed us to dig deeper into this and to find some really interesting things out.

[Sarah Gregory] If you could eradicate just one infectious disease, which one would you choose?

[Betsy Elsmo] This is a really tough question. But I think given the topic today, I'm going to have to say that if I could eradicate influenza A viruses, that would be really fantastic. It certainly impacts human patients and a lot of animals globally, from wild animals to domestic poultry. Swine and lots of other animals get influenza A viruses. So if we could wipe those out from the globe, I think that would do a lot of good.

[Sarah Gregory] It does seem like it's spreading so rapidly and killing so many forms of life, that that's a good choice.

Well, thank you so much for taking the time to talk with me today, Dr. Elsmo.

[Betsy Elsmo] Thank you so much for having me. I really enjoyed it.

[Sarah Gregory] As did I.

And thanks for joining me out there. You can read the December 2023 article, Highly Pathogenic Avian Influenza A(H5N1) Virus Clade 2.3.4.4b Infections in Wild Terrestrial Mammals, United States, 2022, online at [cdc.gov/eid](https://www.cdc.gov/eid).

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