Iceland as Stepping Stone for Spread of Highly Pathogenic Avian Influenza Virus between Europe and North America

[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. Martin Beer, a professor and head of the Institute of Diagnostic Virology at the Friedrich-Loeffler-Institute in Germany. We'll be discussing Iceland as a stepping stone for highly pathogenic avian influenza virus between Europe and North America.

Welcome, Dr. Beer.

[Martin Beer] Thank you. Welcome, and I'm happy to be together with you talking about this interesting field.

[Sarah Gregory] So let's start. Your article is about HPAI flu viruses in birds. What are they and how are they different from, say, other bird flu viruses?

[Martin Beer] So bird flu viruses can be divided into the large group of the low path viruses. So they are everywhere. All birds more or less have it, but especially any waterfowl. And normally they make these birds not sick. And we have 16 hemagglutinin types and nine neuraminidase types (so, H1-H16 to N1 and 9). But there is a special type, and this is more an accident...though the hemagglutinin type 5 and type 7, if they come into chicken and turkey, they can change to a higher pathogenic type. And this is only for these two H-types (or H5, H7). Then, they are killing these birds. And the only change (or the main change) is the cleavage site within the hematogene. And normally, this is an accident which happens from time to time. If a low path virus is transmitted to a chicken farm, the virus is replicating and changing. And this is the normal story, which later changed when the H5N1 Asia came up.

[Sarah Gregory] Okay. So we're specifically talking about H5N1 today. How did it develop and when and where did it start circulating?

[Martin Beer] There were H5N1 viruses before other low path, and everything always starts with these low path viruses. And in 1996, there was a virus coming up which is called the goose Guangdong virus in China, and this is a high path H5N1 virus (which we often call the H5N1 Asia). And all H5 high path viruses which are relevant at the moment, and we are talking now then 30 years, are related to this virus. And this is changing over the time until today, we have this special clade 2.3.4.4b.

[Sarah Gregory] And, as you said, it's now highly pathogenic. So that's pretty devastating. Tell us about that.

[Martin Beer] So these viruses, if they come into birds like chicken or turkey, they normally kill these birds. So we have mortality rates of up to 100%. If you look in a farm, it could be that all animals are dead until you come there. This is...can happen within 48–72 hours. And to stop the circulation normally, these bird farms are culled. But what we also saw is that these high path viruses can also kill water birds. It depends on the species, it depends on the type of strain. And

especially the H5N1 strains and the related ones in the last years, especially from 2016 on, they were all so devastating to wild birds, and we saw mass die-offs in the last years depending on the bird species or the type of strain. But if I look at Germany, for example, red knots...we had more than 20,000 red knots dying of an H5N3 (this was a reassortment of this virus), and we saw many, many of this reassortment. So we have to be careful talking about one type of virus. It's related viruses, but many, many different genotypes or even subtypes.

[Sarah Gregory] How actually do these new strains come about? I mean, what genetically happens here?

[Martin Beer] So genetically we have to go back again to the geese Guangdong strain (this original H5N1), which was spreading in a kind of ping pong system in Asia. So there were farms infected, farms infected wild birds again. And the virus has years to adapt more and more to this situation, and it's adapted also more and more to wild birds. The next step was infecting migratory wild birds, and then the virus could travel from Asia to other countries. And if you look today, it's more or less everywhere. Only Australia we don't find this type of virus, and the very south of South America, but it's on the way there.

So over the years, the virus got better and better, and it was reassorting mainly with the low path viruses in the same environment. So we have a high path virus, which is getting more and more efficient in wild birds, and it's coming together with low path viruses. It's a segmented RNA virus, okay? They can exchange segments. And this was leading in the last years to more and more reassortments, which again allowed the virus to improve. So what we see there is in the last years, a virus getting fitter and fitter for spread in wild birds with some spillover events to other species.

[Sarah Gregory] Let's get to the heart of your article here. Bird flus usually come from Asia across the Bering Strait, landing on the West Coast first. Now why has that always been the case?

[Martin Beer] So for the first time where these viruses reached the US (this was the 2014 cases), and they came the other way around (so mainly with migratory birds going this route) and the story started then more in Asia. This time, we had virus spreading for months all over Europe (also in the north of Europe). And for the first time, it was staying over summer, infecting, for example colony breeding birds, and especially also in the UK. And obviously, this virus then was at a time present where birds are traveling in the other direction—so, going to Iceland, and from Iceland to other parts on the American continent. And therefore, this change in the epidemiology—staying in summer, staying in the north of Europe a longer time infecting more birds which are also migrating—then allows the virus to take this way. And genetic analysis shows that this probably did not happen only once, this happened several times.

[Sarah Gregory] Okay, so this is pretty unusual for it to come to Iceland using Europe as a stepping stone. What path exactly did it take? Do we know (to get to Iceland)?

[Martin Beer] From the genetic analysis, and if you look at the Iceland story, this was really by accident that we found one of the earlier introductions. And as we see in other countries, the predator birds (like the white-tailed eagle, in this case), they are eating the dead birds (the infected birds) and get also infected. And these are birds which are observed and highly

controlled. So we received samples for other reasons of the white-tailed eagles in Iceland, and one of these birds was positive (we sequenced it from October '21) and this was exactly the virus which was matching the North American type. And it's also matching the type which we could see in UK and the Netherlands.

So there are several theories we had before in another paper where we said, "Okay, the virus could take the way via Greenland; it could go directly via pelagic seabirds, or it could use Iceland as a stepping stone". And with this positive bird, and then the people were doing more surveillance in Iceland and then we had more positive birds, we could see, yes, for the first time this high path virus was introduced to Iceland, there's a new possibility the virus is able to do this and jump further to the North American continent. So I think the overall situation that the virus gets fitter in wild birds, is longer present in more bird populations, and is moving with these bird populations, makes it more mobile and therefore we see the situation that we have today.

[Sarah Gregory] So this flu was pretty terrible in the British Isles before it got to Iceland, isn't that correct?

[Martin Beer] That's correct, but it's not only on the British Isles. It was also in other parts of Europe, where especially the colony breeding birds like cormorants, gannets, and other birds were really, really hit hard (so, a high rate of dead birds). The breeding success looks very, very awful, and at the moment, we don't know how this is impacting also these wild bird populations. So this is something where people are really worried, and we have to see this year how it develops, how many birds will come back. But it also shows—because this happened not before in this number of birds and cases—that the virus and the situation is different. And this explains why we see it now everywhere.

[Sarah Gregory] Is it affecting particular types of birds in Iceland, or just all wild birds?

[Martin Beer] So we know that it's not only a particular type. It's always difficult to say if it's all of them because some have (by accident) some immunity, others are not so susceptible. But it is a broad range also in Iceland (so, a broad range of birds is infected). So when the surveillance went up and people looked closer, there were several types of birds infected, and the predator birds are normally the ones which you see pretty early as well as large birds. This is seen by citizens also. They tell the official vets and then they are tested. And there were also poultry outbreaks in Iceland, which they did not had seen before. So it was really clear this virus was introduced to Iceland, and it was spreading there to all parts of Iceland.

[Sarah Gregory] As you said a minute ago, then this flu is pretty disastrous, potentially, for the Icelandic bird populations, and bird populations everywhere, yes?

[Martin Beer] Yes, this is right. But it's different...in some areas, large bird populations were unaffected, so the virus was not introduced. In others, more than 50% of colony breeding birds were dying. So it's always when the density of the birds is pretty high and it's a species which was not effective before—so there's a lot of naïve birds, maybe even a nestling and non-adult birds—then we see the highest impact. And it will be interesting how this will be in the next years.

[Sarah Gregory] And I understand that this flu gets into poultry populations, I think you just mentioned that. How does that happen? And how bad does it get? I mean, the poultry aren't eating wild birds. What's going on here?

[Martin Beer] So there is several ways. One is a direct introduction by a wild bird having contact to poultry. So there is sometimes outdoor poultry. Not every stable is completely tight, so the biosafety/biosecurity of these stables is one factor. Then indirectly, people are...they have rubber boots contaminated with feces of an infected bird. You go into a turkey holding, and there you might introduce the virus. So hygienic measures is one of the key issues.

The next is then, if you have an infected farm, is a farm-to-farm spread what we call not a single spillover event into a farm from a wild bird to a poultry farm. The next step—and this is one of the more dangerous, because it can induce large chains of outbreaks—is the secondary contact (so, from one farm to another). And you can imagine, if this virus is spreading in a farm, a lot of birds are infected. A lot of virus is involved, so you have to be careful with everything what you do. You have to be as fast as possible in killing birds on this farm to reduce the amount of virus. And if you ask how bad it can be, it can be really, really bad. If you look in France, for example, hundreds of duck farms were affected. If you look in the US, there is millions and millions of birds which died of the infection or had to be killed. So we are talking overall in the last 18 months, more than 130 million poultry which were infected and died or had to be killed.

[Sarah Gregory] Which is devastating for the economics of the poultry industry, correct?

[Martin Beer] That's, on one hand, really devastating for the industry. It's really bad for the animal (for animal welfare). And it has consequences for what is the future of holding these animals, talking about identity of farms, and so on (the owner, the farm management), if you have these kind of viruses around.

[Sarah Gregory] Going back to this spread. So what exactly does this mean for North America and the United States?

[Martin Beer] It means that now for the second time, this type of virus was introduced, and it was a lot of outbreaks inducing. This time, it was very, very fast spreading all over North America, Canada, and now it's going south. So it means that it could be that this kind of virus will be present for a longer time. So we cannot predict exactly, but for Europe, we predict that we probably have an endemic situation, and we have to see if this also will be the case. And if this is the case, then we have a completely new epidemiology because it means a high path virus is not a seasonal or a temporary event; it's always present in wild birds and is always a risk for being introduced and also spill over infection to other species.

[Sarah Gregory] Going back to the investigation, what was going on that alerted people that you wanted to investigate this in Iceland?

[Martin Beer] So when we analyzed the birds in Iceland, this was in our overall surveillance in Europe and also to understand how is the virus behaving, spreading? Because the good thing with the new technology is we can do the whole genomes of these viruses. We can compare it in databases, and we can do phylogenetics. So I call it genetic fingerprinting. So we can say where probably does it come from, what is the most related virus? And we were first analyzing the introduction into Newfoundland.

So this happened first, and then there was a lot of discussion how the virus came there. And then we had this eagle, which we checked. So we could find the virus, and it was matching from the genetics. So it's a story where the virus first went into North America and afterwards was sent from Iceland. Because the first reports from Iceland were no infections. And obviously, the level of the outbreak in Iceland in the beginning was too low, so they were not detecting it (not enough dead birds). Then this eagle was collected, we tested it, and then it was clear Iceland was first and the North American continent was second.

[Sarah Gregory] And what kind of surveillance was done in Iceland after the first bird was detected?

[Martin Beer] So then it was clear that first you...it's mainly a passive surveillance, so you look for dead birds. And that's for the high path virus something we recommend. So a low path virus, you will normally have to do active surveillance. So you have to test feces samples of live birds or catch live birds, or if there's a hunting activity, you can take samples. Passive surveillance is good for these deadly viruses because a lot of birds might die, and the first we always say is the predator birds like goshawks or falcons or buzzards and the eagles. And if you find that, they have to be sampled and tested. And this was done in Iceland. Then also active surveillance...so we had a lot of contact to the veterinary authorities in Iceland. We were transferring protocols, because this was for the first time that they had to deal with this. So there was also a transfer of knowledge how to do this, and they did really very, very well and within days, they were sampling. Some samples went to us, some to the EU Reference Lab in Italy, and then they were starting their own diagnostics on high path virus.

[Sarah Gregory] And was there anything surprising that you found from all of this? From your surveillance?

[Martin Beer] So at the end, it was as predicted. The only thing what was really surprising is that we could not say that this bird or this bird colony will be hit harder than another one. So it's still a random story where we really have to do the passive surveillance to see where the virus is. If you do active surveillance—we were doing this in other countries, also in Germany and the Netherlands it's done a lot—you really have to sample thousands of birds and feces to finally get a positive detection. So at the end, the virus behaved as we expected and some colonies were more affected, some birds had a higher death rate. And this is always difficult to predict because there's so many factors influencing this.

[Sarah Gregory] I think you mentioned that this is pretty much everywhere now, except maybe Australia. Do you want to go back over what geographic locations H5N1 has been found, again?

[Martin Beer] So the region of H5N1—so, we are talking about this 2.3.4.4b clade (this is now the one which is the most important one)—so we find it in Asia and Europe and Africa. We find it in North America, Iceland, Greenland has reports. And we find it now in Central and South America. And this is, again, an area where this type of virus was never seen before. So there is now bird colonies affected which have never seen this kind of virus. So again, hundreds and thousands of birds are dying. It's going more south, so we are really afraid of what's happening in the Antarctic, happening with penguins and so on. So this is a completely new situation. And we have contact there, there will be sampling. So we try to be ahead of the race. And there is

questions from Ecuador, for example, from Chile and other countries. And they are pretty afraid, especially also Brazil, because these are large poultry producers. So we are talking about one of the largest poultry producers globally. And now this kind of virus is reaching for the first time this continent also. So it is a worrying situation.

[Sarah Gregory] This is a terrible outbreak, and it was happening at the same time as the COVID pandemic. How difficult was it for scientists to juggle those constraints? What were the challenges?

[Martin Beer] There was also a good part, because we were not as before disturbed by any questions from journalists, from newspapers. So nobody was worrying about bird flu. So if you have a pandemic, nobody is talking about a panzootic. So this was a good thing so we could concentrate on work. But we were also hit by constraints because we had to organize work here (all the restrictions due to the pandemic) and we also worked with SARS-CoV-2 in animal models, so we had to decide what to use our BSL-3 facilities for—so, doing experiments with SARS-CoV-2 or doing experiments on birds and ferrets with the further spreading strains and H5N1/H5N8 strains. And we tried to find a balance. So we were still doing a lot of research for the bird flu together with research on SARS-CoV-2. So at the end, I think it's good that we now have more time to concentrate on the H5N1 story.

[Sarah Gregory] As you're talking, it has occurred to me (and I guess you sort of explained it just now) how the media hasn't picked this up at all. You read no popular articles. No New York Times or Washington Post or CNN is talking about this. It's just sort of mind boggling, considering the extent that you've mentioned here.

[Martin Beer] Yeah, I think it changed now. So the interest in the pandemic goes down, and if I look at the last days, we have every day three, four, five questions from journalists to avian flu, and it's going up. And if you look at the newest development with spread in a mink farm in Spain with exactly this type of H5N1 virus, people now recognize there is a panzootic and this virus is spreading also, in some cases, to mammals and there might be even some zoonotic risk.

[Sarah Gregory] Yes, which leads me to my next question. So we're talking about spillover, here. And I think the world is more aware since COVID of what spillover means and the ramifications of it. So alright, spreading to mammals. Tell us about the spillover possibilities here to humans.

[Martin Beer] So if you look at the original H5N1 Asia, which was a virus which was not so much changing but had a high zoonotic potential. So there were several hundred people infected, so it was jumping to humans and more than 400 died. And then the virus adapted to this more and more and better and better spreading virus type. So in 2016, then we had this 2.3.4.4b and H5N8, which is now more an H5N1. And we got more and more infected birds. So the pressure to get spillover infections was very high, but the number of spillovers was not so high. So there were seals and there were some other carnivores in North America, for example, some black bears, grizzlies. So... but it was all single spillover events. So it happens, but all the analyses we did up to now showed it has not the same potential as we saw with the original H5N1.

So this adaptation, this probable adaptation to wild birds, made the virus less zoonotic. The problem now is it's everywhere. It's still spreading, it's still reassorting. So we have for this H5N1...this is not a single virus. Although in Europe, we have around 30 genotypes. So these

eight segments are not all the same. So this virus has further changed, adapted. And it's doing from time to time, spillover, especially to carnivores—foxes (a lot of foxes) in their affected countries, and we have a handful (a little bit more than a handful) of mild to moderate (and a very few severe) spillover infections in humans. And the newest one is a mink farm in Spain, where the animals got sick. It was spreading—and this is different to the single spillovers—so, it was spread from mink to mink. And therefore, it's the correct decision to kill these animals and now start the analysis, "How has the virus further adapted?".

[Sarah Gregory] There are a whole lot of public health implications from this virus. You want to list them in order of what you think are the most worrisome?

[Martin Beer] So I think the most critical is that it's so widespread—so, that it's a panzootic globally spreading; a lot of birds, a lot of contact, therefore—and that the virus is not genetically stable. We have this reassortment, we have this further adaptation. And the good thing is that it's still at a low risk zoonotic level, but the more we have these spillovers, there is the risk of adaptation. So I think the main public health implications is to really try to reduce the number of outbreaks (especially in poultry), the number of animal-human contacts (so, don't allow the virus to try out this chance), and also the spillovers to farmed fur animals, for example, and follow all the spillovers. So exactly if there is an animal...mammal, especially, mammal to mammal spread, because this would mean that the virus has further adapted. And this is something we have really to follow very precisely to find out if there's any adaptive change of the virus. Because at the moment, it's still a bird virus. It's a devastating, perfectly adapted, spreading bird virus with very few spillovers to mammals. But if this is changing, then we are in the next level, and this we should avoid and detect as early as possible.

[Sarah Gregory] And it’s obviously important to know about these events, but do you think there's actually anything that's going to be able to stop it or at least slow it? And the million-dollar question here...if not, what happens?

[Martin Beer] So on one hand, in wild birds it is difficult. So you cannot control wild birds, and this is a lot of protected species, and so on. So the spread in wild birds will go on, and we have to accept this and hope that especially protected species will survive those spread. In poultry, we need these hygienic measures to avoid introduction. We need early detection (so, detected as early as possible). We need an early detection program in all these countries, and we have to talk like it is done in Asia and other parts of the world (Egypt, for example). We have to think about vaccination now.

So even in the EU, which does not allow vaccination against high path influenza, we are now talking about could we use vaccination to protect poultry and to reduce the virus load in those farms or the spread from farm to farm? So there is a change now, because endemic pressure means maybe it will not be possible to control everything by culling measures. So therefore, vaccination might be an option, but this is in an early phase of the discussion at the moment. And first pilot studies in France, for example, have started to vaccinate poultry, especially ducks, for example. If we don't stop it, it's something we only can observe, and I hope that the virus will not adapt to mammals and will not adapt to humans. So I think we therefore should be careful, follow it, so the awareness should be high.

[Sarah Gregory] Tell us about your job, what you do, and how you are involved in this study.

[Martin Beer] So I'm the head of the Institute of Diagnostic Virology of the Friedrich-Loeffler-Institute. So we are an institute like the USDA Institute in Ames, Iowa, or the Plum Island Institute. So we are the government institute of the agricultural ministry, and here is the reference laboratory. So my institute is, for example, the ref lab...the national one but also international one for avian influenza and animal influenza. But we are also working with foot and mouth disease, Peste des petits ruminants, also with monkeypox virus, especially other zoonotic viruses. So my job is, on one hand, to have the diagnostics on the top level, support the local labs in the country, and do research on these viruses. And I myself also concentrated in the last 15 years very much on the avian flu.

So when Germany was first hit in 2006 by H5N1 Asia, I was working on the pathogenesis, diagnostics, of these viruses. And I was involved in this study having contact to the people, and a PhD student of mine was doing the PCR of the white-tailed eagle and was sequencing it. So we were really directly involved together with the other colleagues which are mentioned on the paper. So this was really a team effort. So there were several people here at the FLI involved, also the reference lab people, but also people from our EU consortia—so, one is DELTA-FLU, one is EU, and this is a consortia where we exactly do research on these viruses and emerging viruses, and avian flu is one of the focuses there.

[Sarah Gregory] Well, thank you so much for taking the time to talk with me today, Dr. Beer.

[Martin Beer] Thank you very much, you are welcome. I'm happy that we could talk about this.

[Sarah Gregory] And thanks for joining me out there. You can read the December 2022 article, Iceland as a Stepping Stone for Spread of Highly Pathogenic Avian Influenza Virus between Europe and North America, online at cdc.gov/eid.

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

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