

Comprehensive Review of Emergence and Virology of Tickborne Bourbon Virus in the United States

[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. Christopher Stobart, a microbiologist and associate professor at Butler University in Indianapolis, Indiana. We'll be discussing the emergence and virology of tickborne Bourbon virus in the United States.

Welcome, Dr. Stobart.

[Christopher Stobart] Oh, thank you for having me.

[Sarah Gregory] What is Bourbon virus?

[Christopher Stobart] Well, Bourbon virus is a tickborne virus that we know infects a variety of animals and recently has been discovered infecting humans.

[Sarah Gregory] And when and how was this first discovered?

[Christopher Stobart] In 2014, there was a man in Bourbon County, Kansas—which is one of those counties right on the border between Kansas and Missouri (about two hours south of Kansas City)—who had been bit by a tick and started having fever, joint pain, diarrhea (the things you would associate with common tickborne infections), went to the clinic and was put on a broad spectrum antibiotic, thinking it might be Lyme disease. However, he didn't respond to that treatment, and regrettably, he wound up dying from that infection. All the tests that performed with known tickborne diseases tested negative, and so samples were sent to CDC, and it was the CDC that actually discovered this was a new virus, now known as Bourbon virus.

[Sarah Gregory] And how is it different from other tickborne viruses?

[Christopher Stobart] That is a really hard question to answer, because there aren't a lot of known tickborne viruses, and far less than there are tickborne bacterial infections. Four of the known tickborne viruses that we have some information about, let's say, for instance Heartland virus (which is another common tickborne virus that people will talk about) in the United States, it seems to have very similar symptoms, it seems to have a similar type of genome, and the host range—the range where we find the virus based on the organisms that carry it (in this case, ticks)—seems to be increasing for all of these. So I can't really answer that directly, because we just don't have enough information for a lot of these viruses to know the specifics on what they are and how they act.

[Sarah Gregory] So just for the audience, let's clarify here once again between virus and bacteria. Viruses cannot be treated with antibiotics, correct?

[Christopher Stobart] That is correct. Treating a viral infection specifically with antibiotics would not be effective. What we will often see is people will get infected with viruses, and then there will be a second infection of bacteria that will hop on, and then sometimes doctors will prescribe antibiotics to treat that bacteria. But treating the viral infection with antibiotics is not going to be effective.

[Sarah Gregory] Okay, I see. So how is it spread to people? Just by this tick bite?

[Christopher Stobart] Yes. So all the known cases to date seem to be associated with tick bites. There has not been any evidence of it spreading to people from other people or from any other animal.

[Sarah Gregory] Is there a particular species of tick that we now know carries it?

[Christopher Stobart] Well, up until recently, the only known tick in North America to harbor the virus and transmit it was the lone star tick, which we find throughout the eastern half of North America. It's a very common tick. However, recently... and this is in the last year, it was also found in an invasive species (Asian longhorned ticks) as well. So this suggests that it could be carried by other ticks, but the main one to date that we know of is the lone star tick.

[Sarah Gregory] Can ticks carry, like, multiple bacteria and diseases and viruses? I mean, if I got bit by a lone star tick, could I get three different things?

[Christopher Stobart] It's certainly possible. We know that these ticks as well as other types of insect vectors (such as mosquitoes) can harbor multiple different pathogens. This virus (Bourbon virus) we know is relatively rare, at least based on the cases we've seen to date in humans, but it is certainly possible that someone could get a coinfection from a tick bite with some other kind of pathogen, whether it be bacterial or viral.

[Sarah Gregory] You know, I've done so many tick podcasts and this is the first time I've thought about that. This is very disturbing.

I think you mentioned the symptoms of Bourbon virus, but could you go back over them, and can it be fatal?

[Christopher Stobart] Sure. Yeah, so Bourbon virus infections look very similar to other infections transmitted by ticks, both bacterial and viral. Usually it starts with a fever, fatigue, joint pain, often nausea and diarrhea. So that's not something you can just nail down initially and say, "Oh, I've got a Bourbon virus infection". Unfortunately, there's a lot of things that cause those. And so I don't want people to be alarmed hearing, oh it causes these diseases and be thinking "Oh, I've got Bourbon virus". But where it differs is that the virus seems to, during the later stages of disease, move to infecting multiple organs, and people will often have shock to the system, heart issues. And that's why this virus is associated with a very high mortality rate, and most of the cases to date seem to have resulted in death.

[Sarah Gregory] It's a virus, so it's not actually treatable, is that correct? I mean, doxycycline, as we said, won't work on it. It doesn't sound like much works, then. Or is it because people don't know what it is initially?

[Christopher Stobart] It's a combination of a few things. The big one is, as you said, we just don't know a lot about this virus. We just discovered it in 2014. So what I can tell you from laboratory studies, it seems that there might be some possible treatment options. Whether increasing our immune system's response with different types of chemical agents or even trying to block the virus and its replication, all those seem to be dependent upon early treatment. However, none of those have really been proven clinically because we just haven't had enough cases to try out and develop a regimen of treatment for Bourbon virus infections.

[Sarah Gregory] And is there now a specific test for it?

[Christopher Stobart] Well, there isn't. You know, with the current pandemic, you know you can go to the store (your local shop), and you can pick up a kit to test for COVID and see if SARS-

CoV-2 virus is there. Unfortunately with this virus, we don't have a commercially available test. All the testing that has been done to date really has taken one of two different forms, both done in a laboratory setting. One is testing blood to see if your body carries antibodies that suggest that you've actually seen the pathogen before. And the other way is to test using PCR. Now, those should sound familiar, because those are very similar types of tests that have been done early on for the coronavirus pandemic. But again, both of those have to be done in laboratories. There isn't a commercially available test for Bourbon virus, or regrettably for any of the other tickborne viruses that impact individuals here in North America.

[Sarah Gregory] So you would have to go to the doctor, and the doctor would have to order specific tests for specific things?

[Christopher Stobart] Exactly. Your local doctor or healthcare professional would have to go and order those tests, send some samples to the lab, and hopefully that laboratory would be screening... if they believe it's a tickborne pathogen, be screening for those known tickborne pathogens. And I can tell you that there's a lot more laboratories now that are including... as they are doing screens, they are including screens looking for Bourbon virus specifically.

[Sarah Gregory] Okay. So since this is a relatively newer tickborne disease, do doctors even know or to think of it when they send it off? Or is it just because, like you said, the labs know about Bourbon virus, so they would just do a panel that included all these things?

[Christopher Stobart] Most of the time, we're talking about panels. The doctor says, "Oh, I believe this is a tickborne pathogen. It's a bacteria or virus. We're not sure what it is, but we know that there was a tick bite. We know that the symptoms seem to cover the same array of diseases that we associate with tickborne pathogens". So they will send it to the labs, and those laboratories and their panels—whether it be screening using serological tests or screening with, commonly now, with PCR-based tests—they're going to be looking for in that panel these common pathogens. And Bourbon virus has likely been something added to several of these panels, and hopefully will pick up more incidence of this if, in fact, it occurs in people.

[Sarah Gregory] Do we yet know how rapidly it's spreading?

[Christopher Stobart] Sadly, the answer to that is no. Basically, we don't know exactly where it is other than where we've seen cases and positivity to date. We know that there's been several human cases in one part of the country, and there's also been a few serological evidence in animals somewhere else. So our best guess is that it seems to mimic where the ticks are and where the ticks are expanding to, but we don't know whether there's more virus out there today versus yesterday. We really don't have that information. And that's what is of key concern to ecologists, is where is this at and who's carrying it? What animals, what organisms are carrying it and where's the potential to jump into humans?

[Sarah Gregory] Okay. So in your article, you discuss Bourbon virus belonging to the genus *Thogotovirus*. What are thogotoviruses and where are they typically found?

[Christopher Stobart] *Thogotovirus* is a... it's a group of viruses that are distantly related to influenza—so they have a similar type of genome but not necessarily the same type of disease—and they are found almost exclusively in ticks. It is possible for other arthropods or other insects to carry them, but ticks are the main vector that carries these viruses. And before the discovery of Bourbon virus, there hadn't really been any human thogotoviruses found in North America. However, we now know that they are found worldwide. They've been identified in all six of the

colonized continents, we know they are present in a variety of different types of ticks. And so, they seem to be a common group of pathogens that are out there, and... well, we're just learning more each year. It seems like we're discovering another one of these in a new part of the world and a new population of ticks.

[Sarah Gregory] So based on what we know now, do we think that all thogotoviruses cause disease in humans?

[Christopher Stobart] I don't think so. Most of the data suggests that they carry mammalian or avian hosts (so, mammals or birds), and we think humans are probably just caught in the crossfire. The odds are we know ticks will bite humans, so we think that where's this... there's been, over time, there's these interactions between humans and ticks, and some of these viruses have just hitched on that ride and then jumped into humans and adapted to become human pathogens. But a lot of these likely have no impact on humans directly. They probably stay within some animal host that they regularly circulate through.

[Sarah Gregory] And as you said, there have been very few cases of Bourbon virus. But do you know specifically where each one was found?

[Christopher Stobart] Yes. All the human cases to date have been found in Missouri, Kansas, or Oklahoma—so, in the middle of the Midwestern part of the United States. And largely in and around Missouri is where we're finding a regular positivity in ticks, and we've seen cases in humans. However, recently there has also been some tests done in ticks over on the East Coast of North America. So in Virginia and North Carolina, we've found serological evidence (so, blood-associated evidence) that the viruses are at least being transmitted in animals in those parts of the country. So while there hasn't been a human case confirmed over on the East Coast, we at least know that the virus could be detected there as well. So those are the two main pockets of where we have found positive cases of the virus being present. Again, the tick itself... its range is far more vast. It covers all the way up into Canada and the Eastern half of North America. So it has got a quite wide range of potential locations where it could be.

[Sarah Gregory] How did this virus end up in the United States? Do we have any clue? Was it imported, did it mutate? What happened here? Why did it just spring up in 2014?

[Christopher Stobart] It's very likely that something that's Bourbon virus-like has been present in the United States and North America all along. And as we talked about with the thogotoviruses, we're discovering a lot of these viruses. It's not that they recently emerged, it's that we're just discovering they're there. And it's very likely that a virus like Bourbon virus has been present for potentially hundreds if not thousands of years and has only recently either been identified or has jumped from an animal into humans and adapted to humans to cause some kind of apparent disease. So it's very likely this pathogen... it didn't come from abroad, it didn't come from another continent per say, but it likely started here and just adapted into humans. Or we just simply didn't know it was there. As technology has advanced, we're far better today of detecting things, sequencing things, doing surveillance, and we might have just picked it up in the noise that has been in the past undetectable.

[Sarah Gregory] Since there's so few cases of it, has there been any surveillance established to track it?

[Christopher Stobart] So right now, there isn't a direct effort to do surveillance for Bourbon virus or really for any of the tickborne viruses. However, there are several groups that do ecological

studies in concert often with local fish and wildlife to just see, well, what is out there? And several laboratories have dedicated their work to looking at the ecological footprint created by these pathogens and what is being carried by both ticks as well as other animals. And it's through that effort that we're largely getting a snapshot of what is out there in terms of Bourbon virus, as well as these other tickborne viruses. So to date it has been mostly driven by the scientific community. The CDC (Centers for Disease Control and Prevention) has been very important in also confirming when there have been human cases, confirming that those are, in fact, cases of Bourbon virus. And so, this effort largely has been stemming from the health community as well as the scientific community through ecological studies and looking at clinical cases that have occurred to date.

[Sarah Gregory] And did we say yet how many cases there have been?

[Christopher Stobart] So there's been at least five confirmed cases. I say "at least" because there was a study that was from 2017 in Oklahoma that showed an individual had blood sera... so, their blood had antibodies against the virus, which suggested that they had recovered from a prior infection. But it wasn't a clinical case because we don't know when that happened, we don't know the specifics. So there likely have been a lot of undiagnosed cases that may have occurred elsewhere, but we know of at least five confirmed cases of Bourbon virus since 2014.

[Sarah Gregory] And let's go back to the emergence here for a second. What role do we think animals have played in this, potentially?

[Christopher Stobart] With ticks... we call ticks "vectors" because they move things from one host to another. And we know that with Bourbon virus, these studies done ecologically, we know that it's carried by a whole bunch of different animals (or at least we can find evidence of it... a lot of different animals). That includes racoons and deer, which were the two most commonly identified mammals in North America that were seropositive or showed positivity for having had an infection or exposure to Bourbon in the past. And with those animals... I mean, deer and racoons are everywhere. You can't drive through North America without running across one of those somewhere on your path. So they are very common mammals.

And when we're thinking about the viruses spreading, the goal of a virus (if you want to give it a goal) is it wants to replicate. And so, it's going to move from host to host and it's going to try to adapt and try to change its genome and evolve to best infect and replicate in that host. Now, when it comes to mammals and humans, if the virus is in mammals and is being carried by these mammals and there's continued exposures with humans, that gives the probability of a potential mutation or evolutionary change favoring movement towards humans an uptick, right? We have a higher chance of having those events occur. And this is why it's possible that this virus may have been carried in those mammals for a while, and it only recently jumped into humans because of the right opportunity and exposure from a tick to the virus.

So the mammals harbor the virus, they may help it amplify or grow and replicate, and they also may help with spread. And while I mentioned that the virus has only been found in these ticks, it's possible that the deer and racoons could take this pathogen elsewhere, because their ranges exceed that of the lone star tick. And so, it's possible they could expand the range and carry it to ticks in other parts of the country or expose it to other animals through contact.

[Sarah Gregory] How does your comprehensive review of Bourbon virus contribute to public health, generally?

[Christopher Stobart] Bourbon virus... we have several of these independent studies, but we really hadn't had a comprehensive review of what Bourbon virus is. And what we were trying to figure out about this virus and learn about its nature, it was hard to understand what exactly it is. And this is an issue for not just Bourbon virus but for a lot of these tickborne viruses, the literature is limited. So the goal for this review and what we hope this review will do is provide in one place an overview of what this virus is, what we know about it, where it is, and also hopefully give some direction to scientists who are trying to figure out what do we need to study? What do we need to know about this pathogen? And that's where the true benefit for this review is. And for clinicians, being aware that this virus is out there. Again, it's a low probability event, but you never know what you're going to have come through the door or the clinic. And keeping in mind, tickborne pathogens may continue to increase in prevalence certainly as we see changes in climate here in North America.

[Sarah Gregory] What further research do you personally think is needed, then?

[Christopher Stobart] Well, I think there's two main things that we need to do. One of them starts ecologically. As we mentioned, we don't really know where the virus actually is. What we do know is where we've found confirmation of its presence, but that doesn't give you a geographic footprint of exactly where it is. Like I said, it's mostly to date been driven by where the tick is—we know it could be here because the tick is here. But doing more ecological surveys, sampling ticks, and testing for Bourbon virus in parts of the tick range that we haven't really looked at. So again, we have these two pockets in North America. We see lots of presence of it in the Kansas, Missouri, and Oklahoma part of the United States; we see presence of it in Virginia and North Carolina. But is it the Great Lakes region? Is it in the South? We know the tick's there, and we know there's a lot of those ticks in the South and the Great Lakes, but are they harboring the pathogen? So that's one element... is where is this actually at?

And the second side of it is from a scientific perspective. We need to look more closely at the genome of the virus and try to understand if there have been any changes, and how quickly this virus is adapting or evolving. As we've seen with the coronavirus pandemic, we keep seeing these variants and these changes that occur in the virus that cause it to change its ability to infect and spread. Well, as you might imagine, that same principle is really important for Bourbon virus. Is it adapting? Is it changing? And if so, what are those changes doing to the virus and its ability to adapt and spread? So there needs to be more genetic analysis of the virus as well.

[Sarah Gregory] Now that winter is here in the United States, should people still be watching out for ticks?

[Christopher Stobart] Well, everyone seems to think that ticks can't bite you if it gets cold outside. And the reality is, is as long as it's not frozen, as long as it's at least 40 to 45 degrees (like round temp), ticks can potentially still bite. So there is still a potential to get tick bites. And people should still be vigilant, especially when they're walking through tall grass or walking where there's low-hanging trees, where there's a high probability of coming in contact with ticks. So while certainly, the prevalence of ticks is declined with winter, that doesn't mean the ticks are not there. And certainly in the parts of this country that are still about 40 to 45 degrees, you can definitely still get tick infections. You can still get tick bites.

[Sarah Gregory] What should people be doing to protect themselves against tick bites? Are there any new repellents on the market or in research?

[Christopher Stobart] Regarding protecting themselves against tick bites, it's the same old things you would have done in the past, right? You want to put a barrier between you and the tick. So wearing long pants, wearing long sleeve shirts when you're in tick territory. And while ticks can technically be anywhere outside, you're most likely to come in contact with ticks when you're brushing up against tall grasses or you're brushing up against low-hanging tree limbs because we're going to find them attached to those surfaces, waiting to latch on to a new host. So if you know you're going to be in the woods, if you know you're going to be in tall grasses, wearing long sleeves, wearing long pants, that's one key thing.

The other side of it is, of course, repellents are very effective. And you asked about are there any new repellents on the market or any research, there's always new research going on. But the market, as it is, the repellents that are there are actually quite effective as they are to date. The key is making sure you wear them. So I know that in a lot of clothing, you can have permethrin added to it, which is a good defensive molecule that's incorporated. You can spray it on the clothes as a good barrier, so the ticks don't want to attach. So thinking about this is two levels of the fence. One is physical barriers—having clothes, having clothing that can block. And the other side of this is the chemical defense—having some kind of a repellent or inhibitor that's attached to your clothing to block the ticks themselves. So just being vigilant, being careful, knowing "Hey, I'm going to be around ticks" is a key part.

And then lastly, of course, if you are around an area where there's ticks, checking yourself immediately after exposure. So checking over your body, making sure you don't have any attached ticks. We know in some of those cases of Bourbon virus that people had ticks on them for a long period of time, and the longer the tick is attached, the higher probability there is for transmission of whatever that tick might be carrying to that person. So just making sure that we're vigilant as we're out there.

[Sarah Gregory] Tell us about your job and how you came to be working on tickborne diseases.

[Christopher Stobart] As an associate professor at Butler University, my day job is working with undergraduates here at the university. So I teach several courses a semester, I run research with undergraduates in my lab, and we don't directly work on tick viruses in my lab right now. We started doing some studies to look for viruses in ticks like Bourbon virus here in Indiana, which there has not been any cases to date, or any prevalence shown to date of Bourbon virus in Indiana. But we do study other viruses that are RNA viruses like Bourbon virus. We study RSV, which is obviously right now in the news because of cases of disease with the pneumonia in babies and the elderly. And then the coronaviruses, we have a mouse coronavirus model.

And this study looking at Bourbon virus actually came from a course that I was teaching at Butler looking at emerging infectious diseases. And we stumbled upon Bourbon virus as a class, and several students were interested in learning more about it, and that's what led to us going and combing the literature and putting together this review. And that's why if you look at the list of authors for this review, most of them are undergraduates or recent graduates who were a part of that course (as a senior-level course) and had that opportunity to explore this virus and learn more about it. And we're excited to share it with the rest of the country and hopefully put more of a spotlight on this virus as well as related tickborne viruses.

[Sarah Gregory] And what a wonderful opportunity for the students.

Well, thank you for taking the time to talk with me today, Dr. Stobart. This was very interesting.

[Christopher Stobart] It was great. Thank you for the opportunity to speak.

[Sarah Gregory] And thanks for joining me out there. You can read the January 2023 article, Comprehensive Review of Emergence and Virology of Tickborne Bourbon Virus in the United States, online at cdc.gov/eid.

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

[Announcer] For the most accurate health information, visit cdc.gov or call 1-800-CDC-INFO.