

Single-Dose Vaccine to Protect against Nipah Virus Disease

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

[Sarah Gregory] Hi, everyone. I'm Sarah Gregory, and today I'm talking to Dr. Thomas Geisbert in Galveston, Texas. He's a professor in the Department of Microbiology and Immunology at the University of Texas Medical Branch. We'll be discussing his article about a vaccine to protect against Nipah virus disease. Welcome, Dr. Geisbert.

[Thomas Geisbert] Good afternoon.

[Sarah Gregory] The World Health Organization considers Nipah virus to be a priority pathogen. What does this designation actually mean?

[Thomas Geisbert] Okay, so the World Health Organization has basically developed criteria for, you know, determining which pathogens, which diseases that they should prioritize for research and development, particularly for public health emergency situations, so, you know, in other words, kind of help direct resources worldwide and where people should put an emphasis on, again, research and development, you know, particularly, again, for those diseases that pose, you know, a public health risk and have epidemic potential. And this is really important for particular pathogens for which there are no medical countermeasures—so, no vaccines or treatments.

[Sarah Gregory] Okay, and what is Nipah virus?

[Thomas Geisbert] Okay, so Nipah virus, it's a paramyxovirus. It was discovered initially in 1998 and 1999 during a large outbreak. This occurred in pig farmers and people that had close contacts with pigs that were infected in Malaysia and Singapore, pretty much concurrently. So, what Nipah virus does when it infects a person or a susceptible animal is it causes an acute respiratory illness and, then, also can also can cause fatal encephalitis. The case fatality rates during human outbreaks have typically ranged from around 40 percent to greater than 90 percent, and that depends on the strain of Nipah virus. There are two particular types of Nipah virus, what we call strains or variants, that are genetically distinct. One is called the Bangladesh strain and one is called the Malaysia strain. The Bangladesh strain has been associated with the higher case fatality rates, you know, probably more in the 75+ percent range.

[Sarah Gregory] Backing up just a second. Right at the beginning, you said that Nipah virus was a certain virus class. What was that?

[Thomas Geisbert] Yeah, it's a paramyxovirus.

[Sarah Gregory] Which is what?

[Thomas Geisbert] Paramyxovirus is a family of viruses, and it includes a number of different genera. One is the paramyxoviruses, like parainfluenza virus in mumps. And another is pneumovirus, which includes, you know, like respiratory, syncytial virus, things like that.

[Sarah Gregory] So, tell us about the recent outbreaks.

[Thomas Geisbert] And again, you know, it's the one strain, the Malaysia strain was first identified in the concurrent outbreaks in 1998 and '99 in Malaysia and Singapore. But the

Bangladesh strain, which is the more pathogenic strain, has caused repeated outbreaks in both Bangladesh and Northeastern India that have occurred almost on a yearly basis from 2001 to 2015. And then, it started to get some media attention last year. There was a deadly outbreak that had a very high case fatality rate of almost 90 percent. And this occurred in Southwestern India it started in the spring of 2018 and it occurred in an area where Nipah virus had previously not been reported. And then, again, in that same area, there's been a single case so far this year.

[Sarah Gregory] So the virus affects both humans and animals, so it's a zoonotic disease. How is it spread between species?

[Thomas Geisbert] Well, so, there is strong evidence that suggests that bats, these large bats, Pteropic bats, they call them—very large bats—are the reservoir host of Nipah virus in nature. So, Nipah gets into these bats, it doesn't cause disease in the bats, but the bats can then transmit Nipah to humans or pigs or other animals. So, basically, humans become infected with Nipah through close contact with either infected bats or infected pigs or actually from people that were infected with Nipah. I think one of the big concerns with Nipah, particularly the Bangladesh strain, is that you have person-to-person transmission that's actually been documented in Bangladesh and in India. This would mostly occur, you know, between, like, family members or primary care providers or things like that. One of the other frequent examples of Nipah transmission occurs because of human consumption of date palm sap in that part of the world. So, you know, people, they collect sap from date palm trees, these palm trees, and what happens, you know, the bats are up there and they get infected and the excreta of the feces, the urine, things like that, from the bats get into the date palm sap and contaminate it, and then people ingest that and they contract Nipah that way.

[Sarah Gregory] I'd just like to interject right here for listeners that we actually have a podcast on that date palm infection scenario. So, if you want to look for that, you can find it in our list of podcasts.

Are there any current vaccines that protect against this virus?

[Thomas Geisbert] There are currently no licensed vaccines for human use. There have been at least eight different candidate vaccines that have been tested in preclinical models, you know, in animals, in biosafety level 4 laboratories. One of...Nipah virus is a biosafety level 4 agent, so all the work that is done with Nipah has to be done in a biosafety level 4 lab. And that's a lab where you basically—you've seen the movie *E.T.*—you have to wear a spacesuit. And there's only a few labs here in the United States where...and even in the world...where you can work with Nipah. One is obviously at CDC in Atlanta, one is in Galveston, and there's a few others across the country. So, that's kind of hindered some of the research and development on Nipah—but, but, so basically, you know, again, no licensed vaccines for human use. There's been some vaccines that have been tested in preclinical animal models. Most of that work, believe it or not, was done against the less pathogenic Malaysia strain, that was initially...of Nipah...that was initially discovered during the original outbreak. And so, it's only recently that work has started to be done on the more pathogenic Bangladesh strain.

[Sarah Gregory] So, okay, well tell us about your study then.

[Thomas Geisbert] Our study was designed basically to test the protective efficacy of some vaccines that we recently developed against Nipah virus in the African Green monkey model.

Now the African Green monkey model is the animal model that most accurately represents...or reflects the human condition. So, you know, if you're going to test any medical countermeasure, whether it's a vaccine or a treatment, to see if it works or not, you want to use an animal model that...you know, because we have an animal... something called the FDA animal rule, here in the United States, that, in order to license a vaccine, if you're not going to test it in people, you have to show, in addition to being safe, you have to show that it works in a relevant animal model. And the most relevant animal model was the African Green monkey, it currently has, so we used that model to test our newly developed vaccines.

[Sarah Gregory] So, this study tested to see if recombinant vesicular stomatitis viruses, also known as rVSVs, could be used as a vaccine for this virus. What is this virus and why would it protect against Nipah?

[Thomas Geisbert] VSV is actually a rhabdovirus, so...a rhabdovirus is a virus like rabies virus. But VSV can cause mild illness and lesions in hooved animals, but it does not cause any significant disease in humans. So, a number of years ago, a researcher named Jack Rose really pioneered the use of VSV, vesicular stomatitis virus, as a vaccine vector system. So, you know, using a...an attenuated nonvirulent virus as a delivery tool, to deliver antigens against a particular pathogen, in this case, Nipah. So, basically, what you're doing is you're trying to trick the immune system, right? You, you...what you have is a bullet-shaped virus that looks like a rabies virus. And what we do is...it's basically like a protein exchange vector. So, these, these VSV vectors would be coated on the surface with a, what we call a glycoprotein, and that's how the virus would attach to a host cell. Well, basically, we take out the gene that encodes that virus or that surface glycoprotein and we put in a glycoprotein of interest, like Nipah or Ebola, or any kind of a particular agent that we're interested in. And so, what you end up with is this...you know, envision like this little cartoon of a bullet-shaped virus, and instead of having a VSV coat on the surface, it now has a Nipah coat or a Ebola coat, for example. So, when you inject this into an animal or a human, it doesn't behave like Nipah or Ebola, but it makes your body think you're seeing Nipah or Ebola, so you develop... so you develop an immune response against it. I would say that probably, you know, your audience may be very familiar with what we call the VSV Ebola vaccine that was used in the Ebola outbreak in 2013 to '16 in West Africa. It's currently being used in the Ebola outbreak in the Congo. Merck took over the licensure of that vaccine and is manufacturing it. But this is basically the exact same system where, instead of, you know, having an Ebola glycoprotein, we have a Nipah glycoprotein.

[Sarah Gregory] I may be misremembering, but these are kind of short-lived vaccines, right?

[Thomas Geisbert] Yeah, you get a very...they're replication-competent vaccines, so, you know, you have situations where some vaccines are killed vaccines, some vaccines are live vaccines. Yellow fever is a great example of a live vaccine, where it's, you know, basically a crippled virus that, you know, replicates, but doesn't really cause any harm, and you generate a long-lived immune response. So, what we're trying to mimic here, we wanted to have a vector that was a replication-competent...or, let's just say, maybe it's not fully replication-competent, but it's...it's single-cycle, so it goes through as, you know, one replication cycle, so it's like you get a transient infection—I'm trying to say this in layman's terms as best I can—but you don't have a fully replication-competent...so, it's not like the virus is going to keep replicating and cause damage to the animal or the human that you...that you give it to.

[Sarah Gregory] Okay, so how effective is this vaccine now, for Nipah?

[Thomas Geisbert] Yeah, it works great. All of the nonhuman primates that were in...were given a single injection of this vaccine, when we came back 28 days later and we challenged them with a really large, high dose of Nipah virus, they were all completely protected.

[Sarah Gregory] Oh, okay. How would this be administered?

[Thomas Geisbert] It's given by a single intramuscular injection in the arm or leg or any muscle, like you would give any other vaccine. Well, I say any other vaccine—most other vaccines, because there are oral vaccines.

[Sarah Gregory] Right, like polio.

[Thomas Geisbert] Right.

[Sarah Gregory] So, this would move on from primate testing, theoretically, to being used to protect humans that are in the path of this virus?

[Thomas Geisbert] Correct, correct. There's, there's been a lot of interest, not just from the World Health Organization, but the...I don't know the...the acronym is CEPI, C-E-P-I, basically it's a philanthropic agency that's funded by Wellcome Trust and a lot of other partners, and Nipah and Lassa are two of the viruses that they picked to move forward for vaccine development. And, so, I'm not...I don't know what the status will be for this particular Nipah vaccine, but there certainly appears to be some interest now in developing vaccines for some of these neglected pathogens, like Nipah.

[Sarah Gregory] And why did you do this study?

[Thomas Geisbert] I have always been interested in high-consequence pathogens. I started my career working for the Army at USAMRIID in Fort Detrick, Maryland, back in the late 1980s, and was associated with a story called *The Hot Zone* that Richard Preston made famous.

[Sarah Gregory] Um-hum. A different rVSV vaccine has also made headlines. Are these vaccines related? Is this the Ebola one you were talking about?

[Thomas Geisbert] Yeah, yeah—I think you're referring to the VSV Ebola vaccine that was successfully used in West Africa during the 2013 to '16 Ebola epidemic. It was shown to be effective, so it did work, it protected people. It's currently being used in the Congo during the current Ebola outbreak. And so, what we call "the backbone," or the vector system, that's used to make the Nipah vaccine that we have in the current paper, is the same backbone that was used to make the Merck Ebola vaccine that's being used in Africa.

[Sarah Gregory] What was the most challenging part of this study for you?

[Thomas Geisbert] I would, by far, say having to do these studies in biosafety level 4 containment. Everything takes two to three times as long or more to do when you're wearing the spacesuit and you're hooked to an air hose. You know, there's, there's a lot of challenges in working in that environment.

[Sarah Gregory] Why don't you give us a little rundown of some of those. I think listeners would be really interested in that. And I just want to say, you mentioned there was one at CDC, which there is, and these are deep, deep, deep down into the ground.

[Thomas Geisbert] Well, they're not...they're actually just, they're high security. So, you...we actually...ours...most of them are built above ground. But they're basically what I would say is a box within a box within a box. So, they're in the very center of the facility, you know. They're, you know, the labs are under negative pressure and there's multiple layers of security and built-in safety designs, so that the agents cannot get out.

[Sarah Gregory] So, when you go into one, you kind of, you put on...

[Thomas Geisbert] Yeah, so basically, there's multiple layers of security that you go through with either, you know, a badge or a fingerprint...a combination of a badge and a fingerprint and a pin code. And you eventually end up in a change room. And it's just like any other change room, you know, and you strip down to your birthday suit and you put on scrubs. And then you go, you walk, you don't take a personal shower, but you walk through, just like a regular shower, water shower, and you walk into this larger room where all the spacesuits are hanging, and then you put your spacesuit on. And then every lab maybe has a little bit of a unique system. Some of them have iris scans for your eyes, some of them have pin codes, but you'll go through a pin code and you'll walk through what we call a "disinfectant shower." And again, you're not taking a shower, but that's what you'll do on the way out. So, you walk in—and it's designed so that both doors cannot be opened at the same time—and so, when you get into the hot side, where we work with the viruses, when you close that side of the shower door, then it automatically triggers the disinfectant shower to go off. So, then, you know, you're going to be in your spacesuit, and you're doing whatever you would do in any other laboratory. So, you know, there's cell culture areas where you would work with the viruses, and then there's animal areas where we have the animals, and you know, you do the studies with the animals. When you're done and you clean up, you know, you obviously spray any areas where you would have virus, and you clean your boots off, and that kind of thing. You go down and you would take your boots off, and you would get back...you would go into the disinfectant shower. And that's like being in a car wash, right, it's like, you know, it's like just...that's the best way that I can describe it is a car wash. So, you're going to be in there and you're going to get like 30 seconds of water, and then you're going to get like 7 to 8 minutes of a...it's called microcaman naphal chloride solution that kills viruses and things like that. And you're just going to be in there, and it's this big, heavy fog-mist, and not a place for claustrophobic people to be, right? And then you're going to get another 30 seconds of water. And then there's a mechanism that will release the door, and then you go into the area where you take off your spacesuit. And then you go into a little, small change room where you take off your scrubs, and then you have to take a personal shower. And then you're back in the area where you put your street clothes back on.

[Sarah Gregory] Um. Okay.

[Thomas Geisbert] So, you know, just the process of leaving the BL-4 lab and taking...you know, going through the disinfectant shower, taking your spacesuit off, you know, taking your scrubs off, going through a personal shower, and putting your street clothes back on—you're looking at, you know, 25, 30 minutes, just for that.

[Sarah Gregory] Right. Okay. Your article highlights the fact that this is a single-dose vaccine. Why do we need a single-dose vaccine?

[Thomas Geisbert] Good question. So, in the context if there's an outbreak of some kind, or there's even some kind of a, you know, deliberate misuse of the virus, there's some kind of

bioterrorist incident, you're not going to have time to have a vaccine that takes a long time to work, and you want a vaccine that works rapidly. So, you know, let's say there's an outbreak in some part of the world, and the World Health Organization, or some humanitarian aid organization, like Médecins Sans Frontières, or some other country, you know, our country, CDC helps out with these outbreaks frequently. You know, if you send a team of people in there to help combat the outbreak, you're looking at multiple strategies of how to protect people. You want to protect the first responders because, in a lot of these outbreaks, particularly Ebola outbreaks, it's the first responders that are at the highest risk and often get infected. You know, and then you have situations where...the way that the VSV Ebola vaccine was so effectively used in West Africa a few years ago, is that it was used in a ring vaccination strategy. So, what that means is you identify people that have Ebola, and then you...it's very important, your epidemiologists are usually important, because you go out and find all the people that contacted those people, and then the contacts of those contacts. And then you basically create a ring around that, which is why it's called a ring vaccination strategy. And by vaccinating all those people and through that process, you can really stop an outbreak, and it really helps control, and helps control and manage an outbreak. So, that would be really, really hard to do if the vaccine required multiple injections and took a long time to work. So, ideally, you want a single-injection vaccine that works really quickly so that you can control an outbreak.

[Sarah Gregory] Okay, so, what are the next steps for this potential vaccine?

[Thomas Geisbert] You know, there's not a large global market for vaccines that are targeted for some of these exotic pathogens, you know, like Ebola or Lassa or Nipah. So, I think it really requires sponsorship or support from government agencies, not just the U.S. government, but other governments, philanthropists, and, as I'd mentioned earlier, CEPI and Wellcome Trust have gotten involved, I think AIDS Foundation has historically been involved, not necessarily Nipah, but things like this. So, I think really, for this or any other Nipah vaccine to really go forward for advanced development in human use, it's going to require that type of support.

[Sarah Gregory] You talked some about what you do, your high-consequence pathogen job, which I think is absolutely so fascinating, what a great job! You want to tell us a little bit more about it?

[Thomas Geisbert] I work with any virus that requires BL-4 containment, so, you know, Ebola, Marburg, Lassa, Nipah are some of the ones that we focus a lot on. I am a professor—UTMB is an academic institution, so we have students. That's, I think, one of the really important functions of my job, which I enjoy tremendously, you know, is the interaction and teaching other people how to work in a high-containment lab and, you know, set...you know, kind of how to work in that type of environment, which, you know, does take a lot of time. We've really focused on pathogenesis, again, trying to understand how a virus causes disease in a host. And, so not necessarily always a vaccine, but, you know, if we understand, you know, some critical pathway that the virus uses or, you know, can that help us develop interventions and, you know, stop the virus. So, that's kind of been, historically, the interest of my lab.

[Sarah Gregory] And finally, are you optimistic about the future of vaccines, in general?

[Thomas Geisbert] Yeah, yeah I am. Because, I think when you look historically, vaccines are the best way to prevent or control outbreaks or epidemics of infectious diseases. I mean, you know, I think there's so many examples of that through history, with, you know, pox virus or,

you know, smallpox or yellow fever; there's just been so many examples. You know, currently, I mean, you know, the flu vaccines, and certainly that's a challenge every year to get that right, but I think, you know, historically, they've...vaccines have really proven to be the best way to combat infectious diseases.

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

[Thomas Geisbert] Thank you.

[Sarah Gregory] And thanks for joining me out there. You can read the June 2019 article, Use of Single-Injection Recombinant Vesicular Stomatitis Virus Vaccine to Protect Nonhuman Primates Against Lethal Nipah Virus Disease, online at [cdc.gov/eid](https://www.cdc.gov/eid).

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

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