Global Trends in Norovirus Among Children

[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. Jan Vinjé, a research microbiologist and the head of CDC's National Calicivirus Laboratory. We'll be discussing trends of norovirus in children around the world.

Welcome, Dr. Vinjé.

[Jan Vinjé] Yeah, glad to be here.

[Sarah Gregory] So to start, what is acute gastroenteritis, or AGE?

[Jan Vinjé] Acute gastroenteritis is usually shown as diarrhea and vomiting. And then usually for norovirus, if you look at the number of people that in more than 50% of those people show vomiting. Which is very typical, but usually is very sudden onset (we also call it explosive vomiting). The incubation time of norovirus is usually between the 18–24 hours. So, it's not very short but it's about a day. And then you find nonbloody diarrhea opposed to bacterial infections where you see often bloody diarrhea.

[Sarah Gregory] And how common is it?

[Jan Vinjé] Norovirus diarrhea is the leading cause of outbreaks of this syndrome, and you can find it in people of all ages (for example, long-term care facilities and hospital wards, but also schools), primarily where people are congregated together. Also, think about what is often in the news early in the year on cruise ships.

[Sarah Gregory] Yes, cruise ships. You do hear it a lot about cruise ships.

A lot of diseases are caused by a specific pathogen, for example, whooping cough is caused by a bacterium called *Bordetella pertussis*. But your article says that noroviruses are associated with approximately 20% of AGE cases around the world. Does this mean that many different viruses all cause AGE?

[Jan Vinjé] Yes. There are actually five well-known viruses, and the most important one for risk—there is currently is already a vaccine available, even here in the U.S.—is rotavirus. But in addition to rotavirus, there are also viruses lesser known primarily causing AGE (or acute gastroenteritis) in children called sapoviruses and astroviruses and enteric adenovirus. So in total with norovirus, together we have five viruses and four of them are primarily causing disease in young children, and then norovirus is the exception. Norovirus can cause this syndrome (this disease) throughout your lifetime.

[Sarah Gregory] So, there is an age-specific group that's most at risk for norovirus? You said children. What age children would that be?

[Jan Vinjé] Yeah, the young children. When we look at the age spectrum, then we see primarily children younger than five years of age. And you can actually narrow it further down to their first two years of life. But then also (and I just mentioned long-term care facilities), if you look at outbreaks, then you see the elderly and so, the older people probably with waning immunity that are more vulnerable for norovirus infections. So, it's the extremes of the age spectrum—the very young and the very old. And then also we have a group that we call the immunocompromised

(think about people that undergo cancer therapy). So their immune system is suppressed. So they are also of increased risk for infections with norovirus.

[Sarah Gregory] And is it seasonal, or does it just happen all year round?

[Jan Vinjé] Yeah, dependent where you are. But in the northern hemisphere (like in here in the States) it's winter seasonality. We usually say it starts around Thanksgiving (late November), and then that's until the end of April. But it doesn't mean that during the summer months, there's no norovirus activity. There are still outbreaks, but there are significantly less outbreaks than during the winter months.

[Sarah Gregory] That sort of follows along with cold and flu season. Why would that be?

[Jan Vinjé] Yeah, that's a good point, because there usually is the activity that needs to be done by the laboratorians in the laboratory. In the state health labs, for example, they have to deal with both with usually the same people that have to test for flu, as well as they also have to test norovirus outbreaks. And we think it has to do with the temperature in combination with humidity. For example, in the…and it's supported by some studies that show that in the more tropical countries you see that norovirus activity is higher in the drier season and not so much in the wet season. So, we think it's a combination…temperature and humidity. But many more viruses do have that seasonality.

[Sarah Gregory] Okay, thank you. You mentioned a vaccine for rotavirus. So there's no other vaccines for this?

[Jan Vinjé] Yeah, there are actually several vaccines in clinical trials against norovirus. And two of them have passed initial Phase I trials that basically looking at the appropriate dose and, of course, if they are safe. And at least one of those vaccines will soon move to Phase III trials. So, there is a vaccine in the pipeline and I'm always asked "well, how long will that take?" Well, we think maybe between three and five years from now. But who knows with the new technology as we have seen now for COVID, who knows that new technology can also increase the speed where these vaccines might be available.

[Sarah Gregory] And is this another children's vaccine? Or is this for all ages?

[Jan Vinjé] So, one of the trials has been done in the U.S. military. And so the expectation...and we also have the elderly. I think it is what we are thinking at CDC that probably some of those companies are trying to get FDA clearance for these vaccines for adults. And one of the key reasons is that it's challenging to add an additional vaccine in an already crowded vaccination schedule for the first year of life for most kids.

[Sarah Gregory] Okay. So your study used a dual-typing strategy. Tell us what that means.

[Jan Vinjé] We're basically typing two parts of the virus, or two parts (two genes) of the virus. And so it's basically to more precisely identify what kind of norovirus type we are dealing with. And you can compare it with, for example, with influenza, we're talking about H1N1 virus, that's also a dual-typing system. So, for norovirus we have a similar system to be more precisely identify what strain we're dealing with.

[Sarah Gregory] So as you said a little while ago, there's a lot of different types of noroviruses. Why is it important to keep track of all of them individually?

[Jan Vinjé] Yeah. Well, one of the cases…that is a very good question, and so one of the reasons is that we're not completely sure if infections with one type will give you protection against another norovirus type. And there are total, at least 30 different types that we are aware of. And if you have vaccines that are under development, then you would like to have those vaccines ideally protect against all these types. So, having at least starting with the baseline, that's what this study's intention was—these global trends in norovirus genotype distribution—is to try to get the baseline to which strains are circulating.

[Sarah Gregory] Your study used data from a platform called NoroSurv. Tell us about that.

[Jan Vinjé] Yeah. NoroSurv, the name refers to, obviously, to norovirus and Surv is surveillance. It is a global pediatric norovirus surveillance network. And it means we have identified collaborators globally on all continents that are willing to participate in this study, and they are using a standardized protocol in the laboratory to identify and to type noroviruses. And then that information is uploaded to a central database that is coordinated by us here at CDC.

[Sarah Gregory] So you analyzed data on norovirus sequences collected from young children around the world during September 2016–August 2020. What specifically were you looking for?

[Jan Vinjé] This network (this NoroSurv network) was basically try to establish a global network. This is the first time that we are able to get a glimpse of what kind of viruses are circulating on different continents, and we were very interested to, A) if to make it possible that everybody participating on the technical side of things to setting this up with the central database. But the data that we were interested in is trying to see are there changes over the years in different parts of the world.

[Sarah Gregory] And what did you find?

[Jan Vinjé] We found that more than half of all of those norovirus infections belong to a single genotype. So, that's an important one. But there are also other types that we found and so, for example, a handful of types causing the majority of all infections, although there are some differences.

[Sarah Gregory] Did the most common types vary from country to country? And if so, why would this happen?

[Jan Vinjé] Yeah. There was some variation. But for several countries, we could not draw a conclusion and that's primarily because the numbers of sequences that those countries (those laboratories) have been uploading were a little bit on the low end. So, but overall it is GII.4 viruses that are commonly...that we commonly seeing in all of the countries.

[Sarah Gregory] And were there any findings that surprised you?

[Jan Vinjé] Not really, because we were really wanting to have a baseline study. We knew that the GII.4 viruses were important in outbreaks, and we have seen some studies here in the U.S. in hospitalized children that these same types are also causing disease (the same disease) in young children. So, it was basically trying to see, is it true globally? So that was not a surprise, we were expecting it based on what has been published in the literature. But I think this study was for the first time that we using a standardized protocol. So, all these laboratories we were providing with a protocol, this is the way how you generate the typing information.

[Sarah Gregory] Your study included data up until August 2020. How did the COVID-19 pandemic affect your results? Or did it?

[Jan Vinjé] Yes, it did. And the numbers are lower, but not zero. In a lot of the laboratories, the participants have not been able to upload it because they worked on COVID for the past year. And next week, we will have some calls with all of the labs to ask them when they expect to upload the data from last year all the way up to date. Because we know there is information out there, but most of the laboratories don't have had the time to upload into NoroSurv. But it definitely had an effect, that's what we know.

[Sarah Gregory] Okay. As you said, your study focused on norovirus in young children. But in general, do young children get the same types of norovirus infection as older children or adults, and just more of them? Or are they actually prone to different infections?

[Jan Vinjé] Yeah, that's a very good question, and one of the areas that we're still trying to learn more. We know that children have a lot of infections during the first two years of life. That is not necessarily symptomatic infections. So, not all the norovirus infections in young infants are leading to this vomiting and diarrhea, which can be sometimes very severe. That's the reason why they are in the hospital with those symptoms, and make sure that they are properly treated. So, what we see is certain types are more seen in young children than in the adults. And again, in adults you see primarily the GII.4s, and in children see some other types are circulating. So, we're trying to find out if these young infections during the first, let's say, six months of life, what they exactly are and if they are able to generate protection. That information will be crucially important if a vaccine becomes available for the pediatric population. You don't exactly know which virus in those first six months when you typically vaccinate. You should prevent the most serious effects of this infection.

[Sarah Gregory] Does this data help predict where and when future norovirus strains might circulate?

[Jan Vinjé] Oh, we would love to. And I think we've taken...this is kind of the playbook for influenza (for flu), so the idea is that now we have a baseline—a global picture of these trends that we can use that for hopefully predicting if a new strain arises. And we know for norovirus that happens quite frequently, maybe not every year, but every couple of years we see new strains emerging and we hope that this network will help to be able to predict what those new strains are—and then obviously with a vaccine in the future—if that vaccine needs to be reformulated.

[Sarah Gregory] In your opinion, what's the biggest public health takeaway from this study?

[Jan Vinjé] Centralize, standardize, be able to have a global picture. So, not being in for surprises that new strains are emerging in other parts of the world, and we here in the U.S. are not looking at it. We are looking at it with a global vision. So, we see what happens in other parts of the world, and then we know if how we, for example, need to come up with an alarm that signals strain is emerging somewhere else that at some point will end up in the U.S. So we can then alarm hospitals, we can alarm the state health departments and the epidemiologists that usually are investigating outbreaks. So, I think having this system in place will help us a lot into the future, I think that's the biggest public health takeaway.

[Sarah Gregory] Tell us about our job at CDC, your career, and how did you become interested in this research? And as we've said, you're the head of CDC's National Calicivirus Laboratory. What does it do?

[Jan Vinjé] Yeah. Well, I've been in love with these viruses since my early days. I grew up in the Netherlands, I did my Ph.D. there on these viruses. And when I moved to the U.S. 21 years ago, I first went to academia for five years and tried that out and enjoyed it, but then I couldn't resist go back to my old love here at CDC in 2006. And I've been sticking around in this virus because there's so many different angles that we can work on this…started to develop a national system of an outbreak surveillance system (it's called CaliciNet). The virus cannot be grown in cell culture (that makes it very difficult to study), so we're working on that with very exciting new technologies. And now we are also moving towards more trying to get an international picture. So, there are different aspects that cover all kind of areas that norovirus is still not completely known. It's not a virus we know a lot about, for example, and polio that's already almost eradicated from the world. But this is a virus that is maybe less severe, but it still is associated with sickness and a good number of severe infections in primarily young children across the world. And I think I'm very excited about this type of work (the NoroSurv) to connect with all these people. Most of these people I know in these laboratories across the world, or most of them I've visited there in the local laboratory. And just setting up this surveillance network, that's really where my passion is. So, I'm very happy with finally the first product of this in the form of this paper in *Emerging Infectious Diseases*.

[Sarah Gregory] Well, it's always wonderful to have something that's not been studied that much come to light.

I have to ask you here, you said that the cells for calicivirus couldn't be grown in cells, studied from the cells? Is that what you said and why is that?

[Jan Vinjé] Yeah, I think most viruses there is traditionally a cell line that the viruses can be grown, and so you can measure infectivity. And once you can measure infectivity, then you can also test products (for example, hand sanitizers) and see if they're actually effective. So if the sanitizers are effective, then you can suggest that to as the best way how you can sanitize surfaces. Imagine a lot of children that are in a healthcare center and they are all starting with vomiting and diarrhea. So how do you sanitize these environments appropriately? So, having a laboratory method to measure infectivity, for which you need to have a cell culture system, you can infect those cells with the virus and then you can measure if, with apps of treatment if you see reduction of infectivity.

So, we've tried—we in the field (all the people that work on norovirus globally) have been working on that, trying to figure that out in the last 35–40 years since the virus was discovered and described first in 1968. And only recently there is a new system available that is based on adult stem cells. You can actually isolate stem cells from the gut and you put them in a petri dish, and these cells can grow as really as mini guts. They have all the cells that our gut (our small intestine) has. And that cell line is now able to do what we were looking for, that it's able to show replication of the virus so we can measure if it's infectious. And so now we can, for example, use chlorine and show that chlorine is actually able to kill the virus. So that is a totally new area, and is a very exciting field that it is not only for noroviruses in mini guts, but it's also for other viruses that, for example, cause neurological syndromes for which there was not really a system available to better study that but also these stem cell–related organoids is really something that's opened up a lot of opportunities to come up with better treatment measures for different viral infections.

[Sarah Gregory] Wow, that is astounding and wonderful, and after so long of studying it. That's great, and probably will be very helpful to cruise ships as we said early on.

[Jan Vinjé] Yeah. They are interested.

[Sarah Gregory] Has your life changed much during the last year? I mean, new hobbies, interests, that sort of thing?

[Jan Vinjé] Yes. I'm working from home most of the time, it's… you know, you adapt to it. I have not really had time for new hobbies because we have also been involved in trying to help out with the COVID response. So some of the methods that we were using in the laboratory for norovirus, we said, "well, there are some ideas here that we can do and use for COVID-based research." For example, we had developed an assay for testing for antibodies in saliva, and saliva is a noninvasive…you ask people to spit in a tube, and they are more than willing to do that compared to, you know, a blood draw. And so we just are finalizing a study to look into saliva, looking for antibodies after CDC vaccinees got their vaccine here at CDC. We enrolled 200 people and we asked them to self-collect saliva samples and keep them in their freezer, and now we're asking to bring them back to CDC. That's logistically pretty challenging, but I think we are pretty successful so far with 80% of the people being able to return it back to the campus in Clifton. And now we are going to test them, we are going to look for antibodies. And that laboratory assay, that was basically adapted from what we did for norovirus like five years ago. And so we had the subject matter expertise for dealing with testing saliva samples, and we were able now to convert that to looking for antibodies against coronavirus.

[Sarah Gregory] That's incredible. I actually get a lot of people asking me about antibodies and where they can get tested and what kind of tests exist and stuff. So, that's really good to know that there's something being tested. I didn't get my vaccine at CDC, I got it elsewhere. So, I'm not involved in that test, but…
Well, thank you so much for taking the time to talk with me today, Dr. Vinjé.

[Jan Vinjé] You're very welcome.

[Sarah Gregory] And thanks for joining me out there. You can read the May 2021 article, Global Trends in Norovirus Genotype Distribution among Children with Acute Gastroenteritis, 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.