

# Next Generation Research podcast

## Episode 5: Why my child? Understanding life-threatening infection

**GILES:** [00:00:00] Did you know that our genes can impact how we respond to infections? Most of us can live our lives without even knowing we've been exposed to certain diseases. For some, however, that same disease could be life-threatening. Why is that?

**Vanessa:** infectious disease can be due to a genetic defect, which most people don't notice. People think of genetic defects as [00:00:30] developmental big changes, but it can just alter your response to one pathogen.

**GILES:** Welcome to Next Generation Research, a podcast which brings you to the heart of the most important and exciting research being done in the UK. Right now. I'm Professor Giles Yeo, a scientist at the University of Cambridge.

**GILES:** And in each episode, I have the pleasure of introducing you to one of the best researchers working in the UK right now. Each of them are part [00:01:00] of the Future Leaders Fellowship. It provides longer term support to enable their work solving problems and improving our lives as we know them. This episode is about why some people, children in particular, respond so extremely to infections, which the rest of us don't even know we've been exposed to.

**GILES:** And it's actually not so far away from my own field in that we're talking about genes as a refresher. A gene is a small section of DNA that codes [00:01:30] for a particular protein. We need these proteins to perform all the things our body can do, and some of these proteins are connected to how our immune system works and how we fight infections.

**GILES:** We're going to be diving into Vanessa Sancho-Shimizu's research. You heard her voice just now. Vanessa is a senior lecturer in the Department of Infectious Diseases at Imperial College London, where she runs a research lab. Her Future Leaders project is about understanding the [00:02:00] genetic influence on life-threatening infections with a particular focus on children.

**GILES:** A genome is the collective noun for all D N A and all living things have a genome. The human genome is formed of 3 billion DNA base pairs. In fact, if you stretched it out completely, there would be around one metre of DNA in each of our cells. That is a whole lot, but only around 2% of our genome or around 60 million base pairs is coding.[00:02:30]

**GILES:** A gene is a unit for the genome that codes for a specific protein, and humans have 20 to 30,000 different genes. A mutation is a change in our DNA. Now, most of the time these changes have no measurable effect. Sometimes, however, you might have a small change that causes a gene to be completely non-functional.

**GILES:** Now, if that gene happens to code for a protein, which helps our immune response, then [00:03:00] we might be at risk of contracting viruses or infections. Vanessa and her colleagues study patients who come to hospital with life-threatening infections, and they try to work out what went wrong. Why was this particular patient not able to fight the infection?

**GILES:** They wanna work out if their body's response is down to one of these small changes in their genes. They have the mammoth task of trying to find one change in 3 billion base pairs, which is relevant to this [00:03:30] particular disease,

**Vanessa:** to set the stage basically when. All of us are born into this world. We are born into an environment full of bacteria and viruses that we will encounter in our lifetime. And we focus on children specifically because a child will go through and meet all the different bugs they will meet in their lifetime during childhood. And if they have a problem with any one of those bugs, it will appear during [00:04:00] childhood when they meet them for the first time.

**GILES:** So what do genetics mean in the context of disease?

**Vanessa:** I'd say probably most people would not think an infectious disease is caused by any sort of genetic change. We know that actually infectious disease is caused by a bug, whether it's the bacteria or the virus, that's absolutely necessary for the infection to take place. But the infection doesn't necessarily mean you're gonna get the disease.

**Vanessa:** Many people [00:04:30] get the infection and don't manifest any sign of disease, meaning that it's a silent infection, they're asymptomatic, and in some cases you will get disease, whether it's a little fever or a little cough. That's a disease, and then you can get various severity of that. So life-threatening infection where you're admitted to hospital, you have meningitis or encephalitis or sepsis, or you can have a disease where it's self-limiting and you [00:05:00] recover after two, three days.

**Vanessa:** We are particularly interested in immune genes, so genes that control the immune response. What we found is in a very small subset of our patients who present with these life-threatening infections, they carry small changes in their genes.

**GILES:** So why bother researching this if it only affects a few people?

**Vanessa:** We focus on the rare patients because, studying what went wrong in these patients [00:05:30] really helps us understand what's essentially protective for all of us. This is the only way we can find out. You know, it's like in engineering, you only know about how important the keystone in a bridge is because if the keystone falls out, everything crumbles.

**Vanessa:** So we really go to the most extreme to understand what is absolutely critical for protection and survival, basically. And the only way to do that is to study those patients. So this is why we're doing this, and we're proposing looking at their genes to understand [00:06:00] what is essentially protective in children and in human infection. I've had a longstanding interest in genetics. My PhD was working on understanding mouse genetics in a mouse model of infection, which was fascinating and amazing. Beautiful work animal models has contributed so much to our understanding of infection and immunity. But while I was doing my PhD, I had my future postdoctoral supervisor come to give a talk at [00:06:30] our university and.

**Vanessa:** He was doing the same sort of research I was doing with patients, so he had patients who were very susceptible to certain infections and he was able to identify the genes involved, and it was just so inspiring to see that he was able to actually treat them differently. Because of the genetic finding.

**Vanessa:** And that was exactly what I wanted to do. So this was the inspiration for me to move into human genetics of infectious diseases. And as soon as I finished my [00:07:00] PhD, I went to go work with him in Paris,

**GILES:** Vanessa and her colleagues can't study all infections. So they focus on one group of diseases at a time. Her lab had to pause their research on meningococcal disease to help research severe reactions to covid 19. Her team also researches a disease called viral encephalitis, which is inflammation of the brain caused by a virus.

**Vanessa:** All along, I've had a longstanding [00:07:30] interest in this viral encephalitis caused by herpes viruses, the herpes virus, herpes simplex virus, one, which 80% of adults are seropositive, meaning that we've been exposed to it and most of us will not recall ever having been infected.

**Vanessa:** And the herpes virus people associate them with cold sores. So some people may. Be able to identify that they do get cold sores, which means you were infected as a child. They stay [00:08:00] dormant with you and they will continue to recur during our life cycle. But obviously that's not life-threatening and in the majority of the population, for example, I know I've been infected with herpes

virus. I don't ever remember having it. I don't get cold sores, so in most cases people are like me. We can't even recall having that infection. And then in one in a million cases per year, you would have a child who has a grandma who has the cold sore, gets exposed to it for the first time and comes down with [00:08:30] debilitating brain infection, really life-threatening infection, and we don't know why. We didn't know why 15, 20 years ago, this was a complete unknown.

**GILES:** Herpes encephalitis is treatable, but it can cause lasting damage in the brain

**Vanessa:** when the child presents to hospital with a life-threatening infection or with signs of a brain infection. The main thing would be to identify that it is this particular [00:09:00] virus that is in the fluid that surrounds your brain. That would be the definitive diagnosis, that this is herpes encephalitis and, and most cases the treatment options are very clear. We have. Acyclovir, which is a very effective antiviral, which will get rid of the virus.

**Vanessa:** I think the problem associated with herpes encephalitis is really that even if we can give them acyclovir and get rid of the virus, there's still a lot of inflammation in the brain caused by that initial infection, and you can get a lot of side effects from the fact [00:09:30] that you've had a brain infection and it's very destructive. In most cases a child who ends up in hospital in the I C U with a very severe infection they can look at and know right away if there is an underlying known immune deficiency, which means that they're lacking something. And what we do is we don't focus on those patients because they will have pathway through the NHS to be treated and taken care of.

**Vanessa:** The children we focus on are children [00:10:00] who won't necessarily be followed up in the NHS just because these are very rare. One-off cases. Most cases these children are fine, but sometimes they may carry a change that would cause them to have recurrent infections or be susceptible to other things. So we focus on those children and take some patient samples into the lab to try and understand if their response to infection is normal and we carry out a full genetic analysis. And then we. [00:10:30] Are able to report back to them any of the results or findings that we have.

**GILES:** This research is impossible without recruiting patients. And Vanessa's lab is directly connected to the paediatrics department at St. Mary's Hospital in London, where she partners with Dr. Jethro Herberg. Jethro is a reader in paediatric infectious diseases at Imperial College London and is also a consultant in paediatric infectious diseases. [00:11:00]

**Jethro:** What really is exciting is when you work with someone who comes from a slightly different discipline to the one that you work in, because you both bring

your own knowledge and ideas. One of the things I'm very excited about in my day-to-day work is that we've set up a service that sees NHS patients who are children or even young adults who've had severe or unusual infections.

**Jethro:** And the clinic we're running together with looking at the [00:11:30] genetics of these children, was born out of an earlier study that we were both involved with, and we realised from this early data from a study called EUCLIDS that we should be doing something. That isn't just an abstract research question, but actually taking this information, taking this approach, and putting it into a clinical context where it can make a real difference to patients.

**Jethro:** And I think the approach we're taking is in part validated by the fact that this is something that is creeping into routine NHS work. There's a more and more of an [00:12:00] effort to try and bring genetics into routine clinical diagnostics, and I feel that's something we've been in the vanguard of for the last few years.

**Jethro:** And so it's exciting to see. Other people doing this now as well.

**GILES:** Vanessa's FLF grant is part of what allows Jethro and her to continue this research. So how does it work?

**Jethro:** What we do, we take the child and both parents and then we can look at the genetic information in the child and the genetic information in both parents.

**Jethro:** And we take the family's history of [00:12:30] disease, particularly in relation to infections. And we try and understand if there are any of the genes that are involved in the immune system have got changes that might explain why this child got so ill. That's really difficult, but it's actually the easy bit because if you do find something that's changed occasionally you're lucky.

**Jethro:** You say, aha, bingo, we've got an explanation. Someone else has published on this. We know what this is. We can be confident. That's rare. More often we get a really interesting new finding that no one else has described. [00:13:00] Then you are scratching your head and saying, Can we be sure that what we found here is an explanation for why this child got so sick?

**Jethro:** And that's where you need Vanessa leading an army of scientists to take this on and say, okay, we're gonna do some carefully planned experiments to look at this, to try and prove that this genetic change equals a change in the function of the immune system. And that can be a whole project in itself. So one important thing to think about when you bring [00:13:30] patients into research is that they have realistic expectations of what might come out of it.

**Jethro:** This is really difficult. A lot of the time we are not gonna be able to find anything. Sometimes we'll find a finding that we are interested in and we won't be sure and we'll have to do more. And very occasionally we get a clear finding that might be helpful.

**Jethro:** This is a really important area of research that Vanessa's involved with looking at children who've had. Encephalitis. Sometimes they have a encephalitis caused clearly [00:14:00] by a particular virus, say, and one of the interesting things that's come out of work over the last decade is that some of these patients have an encephalitis caused by an inflammatory problem, and they're actually got antibodies that are getting into their brain and causing their brain to get inflamed. So this is an autoimmune condition. And it's very difficult to treat these patients. I think this is exactly the sort of area where having of research [00:14:30] collaboration to really try and get to the bottom of things is really important, and also we hope will give the families, we are dealing with some comfort to know that people are taking it seriously and really trying to understand things.

**Jethro:** In other cases, it may be an encephalitis of unknown origin. But we're trying to understand if there are genetic reasons why some children are more likely to have these types of illness than others.

**GILES:** Vanessa's team are in charge of proving that the gene they have identified is definitely the cause of the [00:15:00] disease response in the child.

**Vanessa:** Yeah. I don't know if you can see, but basically each one of these things are the organoids. They're really tiny. Can you see the little specks? Yeah.

**Dillis:** So I'm Dillis. I'm a PhD student in Vanessa's lab. We found that there are some sort of changes in patients like in their genes, and we wanna see if this is what causes the disease that they have. So we test that in the lab. We try and recreate that, and if [00:15:30] the gene no longer works, then obviously I think that's probably what's caused the disease. But sometimes the gene can just work normally. In that case, it's probably not the cause of why they're so ill.

**Vanessa:** So that's our first snapshot of, oh, is the patient cells actually working like they should. At the same time, we're sending then the DNA off to be sequenced and we get the sequences back from the facility. And we actually look to see if we can find any major [00:16:00] genetic changes in their dna. And we tend to look at specific pathways that we know are involved in that response to infection.

**Vanessa:** And in some cases we also ask for a little skin biopsy, then we can grow skin cells from the patients. There's just an easier cell type to study, and in some cases we can actually now take patient cells and we do some reprogramming,

which basically means we take a blood cell and we're able to change them [00:16:30] back to a pluripotent stem cell state, which means that this blood cell, all of a sudden now, is back to an embryonic stem cell state.

**Vanessa:** And with that, that cell can be turned into any other cell type of the body. And because we are interested in what happens in the brain and we can't very easily biopsy brain samples from our patients, we then take these stem cells and we can derive them into neuronal cell types, so in brain cells, and [00:17:00] also even create sort of cerebral organoids.

**Vanessa:** So these 3D. Balls of brain cells. Basically, it's like a mini brain derived from the patient, and we are able to actually study the effect of the virus compared to healthy controls. This gives us a totally different way of modelling the disease to understand how that genetic change affects the brain in response to infection.

**Vanessa:** This fridge carries. [00:17:30] All the essential reagents to culture, our organoids, it's very well kept by my research assistant, and we have all our fixed organoid samples ready to be imaged. And yeah, this is sort of the future of our research right here. What's absolutely amazing is this herpes virus, we know in children when you take an MRI, it really destroys the brain, whereas it's very hard to see that.

**Vanessa:** [00:18:00] On a single cell layer, you can't really see. You can see cells dying, but in these infected organoids, they disappear. So after 24 hours, we go to look and it's gone. The organoid that was there was gone because the virus is so destructive, it destroys all the cells. It's really remarkable to see. It gives us insight into what happens in a 3D environment and the structure of this organoid during infection.[00:18:30]

**Vanessa:** So for me it's been quite impactful. I just didn't expect that the whole organoid would disappear. I would've thought we would see it, but only under the microscope. You just see the profound impact of how well adapted this virus is to us. It's just so tangible. You just suddenly think, where did they all go? Did you drop them? Was there a problem? Like they just disappeared. It's amazing.

**GILES:** Once Vanessa and her team have collected their findings, the children's families are of course informed [00:19:00] through Jethro and his clinic.

**Jethro:** We carry out the gene sequencing on these patients, and that takes a long time actually to send these samples off, get the data back, do the analysis, double check the analysis, discuss all the findings at a multidisciplinary team meeting where we've got scientists, geneticists, clinicians like me, nurses who are involved in recruitment, we put all our heads together thinking about the

symptoms the patients had and the genetic findings and what they might mean and try to marry up together.[00:19:30]

**Jethro:** And sometimes we'll get a finding which says, okay, we've identified a significant primary immunodeficiency. For instance, we have patients who've had nasty pneumonias, so. We find fundamental changes in their immune system, which may only be a single base pair change in their dna, but we know with that information we refer them to our colleagues at Great Ormond Street immunology team and they sometimes these patients are listed, for instance, for bone marrow transplant, so their whole immune [00:20:00] system will be replaced with a donor's immune system who doesn't have that fault.

**Jethro:** First of all, I think a lot of families actually want to understand. What's happened and what's going on. Secondly, they want to know, could this happen again? Could it affect my other children? And finally, really importantly, they might want to know, and we would also want to know, can we do anything if this is possibly gonna happen again to stop it happening again?

**Jethro:** For instance, if you find in your workup, you [00:20:30] find a genetic change and you manage to show that this is important, does this mean this this child is going to be vulnerable to more infections like this, and should we do something to stop that? Could we, for instance, give them some extra vaccinations? Could we just have some system of letting them know they have to take certain symptoms very seriously and come to hospital quickly?

**Jethro:** So I think there are sometimes practical advantages for the family.

**GILES:** Even if they don't find a genetic cause in the patient, it doesn't mean they [00:21:00] never will.

**Vanessa:** In most cases, we will not find any obvious genetic change. Doesn't mean that there isn't. It just means that based on the knowledge that we know now, we didn't find anything.

**Vanessa:** It could be that they harbour genetic changes in other pathways that we have no idea is involved. This is part of research, right? It's always evolving and in some cases we will find changes in genes already known and described before in [00:21:30] this condition, or we'll find other known immune deficiencies, so established diseases, but those are quite rare. These are extremely rare conditions.

**Vanessa:** It's like we're trying to identify the zebra fish with polka dots, and these patients may be faced with the idea that they [00:22:30] carry a new genetic disease that have never been described before. We try to support them through that, through genetic counselling, but also that there's a lot of unknowns that



come with it, but hopefully it brings them some sense of knowing that there was a reason for what happened. My hopes for. This research is that it becomes more mainstream, and I think it is. There's a move towards [00:25:00] sort of genomic medicine being part of normal workup in hospitals and the acceptance of genetics in the healthcare system. And really my sort of personal hope is we have this wonderful clinic that we've set up with my colleague and is to really to be able to increase the diagnoses of those patients and just bring more understanding to these understudied areas.

**Vanessa:** And secondary to that is that those findings will lead to understanding those diseases better, but also come up with different treatment and management strategies.

**GILES:** So why study rare conditions? I mean, in Vanessa's case, rare conditions of how children react really quite badly to infections. I study rare causes of childhood obesity and you might think, well, isn't it like butterfly collecting? Why do we care about rare people? Aside from being human beings, I think there are common pathways that keep us in health and they keep us alive.

**GILES:** And what these rare genetic diseases, conditions tell us is what happens when they go wrong. And so the more we understand about how something goes wrong, The better we actually understand the pathway, and so therefore we can then create better drugs, modulate the pathway better, and at the end of the day, make people's lives better.

**GILES:** And so the study of rare diseases is important because they give us rare insight into pathways that influence all human beings.

Thank you so much to Vanessa and also to Jethro and Dillis for their contribution to the episode. If you wanna find out more about their work, you can visit their website, which will be linked in the episode description.

**GILES:** In the next episode, we are going to be learning about who and what influences government policies in the UK and its implications for our health.

**Oliver:** One of the big challenges when we're looking at policies is we can't follow such a linear perfect pathway. We can't do randomised control trials. We can't give half the country a sugar tax and half the country, not a sugar tax.

**GILES:** Thank you for listening to this episode of Next Generation Research, and please do share this episode with someone who might find it interesting and we'd certainly love for you to give us a rating or review wherever you're listening to this. This podcast is supported by the Future Leaders Fellows Development Network.

**GILES:** You can find out more about the Future Leaders Fellowship by following @FLFDevNetwork on Twitter, and we will link to their website in our episode description. I'm Giles Yeo, and you can follow me on Twitter and Instagram @GilesYeo. The producer is Hester Cant. The executive producer is Freya Hellier, the sound engineer is Morgan Roberts. And thanks to Oliver Myttonn and Laura Carter for their additional support.