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#309: Viral diary: The global rise and near demise of polio

VOICEOVER
This is Up Close, the research talk show from the University of Melbourne, Australia.

DYANI LEWIS
Hi. I'm Dyani Lewis. Thanks for joining us. For most places in the world the sight of children in leg callipers has been relegated to the pages of history, the paralysing effects of poliovirus having become a thing of the past. The advent of the polio vaccine in the 1960s has seen polio progressively extinguished in well off regions like North America, Australia and Europe, as well as in many poorer parts of the world. Gradually and with the dogged determination of co-ordinated vaccination teams, efforts to eradicate the disease have restricted its occurrence to just a handful of war-torn nations. But as we await that final declaration that polio is no more it's perhaps a good time to reflect on how well we actually understand this mortal enemy. How does poliovirus infect us? Why is it so debilitating and will we in fact ever be able to rid the world of polio forever?
I'm joined on Up Close today by a virologist who's investigated the intricacies of poliovirus infection and is well versed in all things polio. Vincent Racaniello is Professor of Microbiology at Columbia University Medical Centre. Vincent is also the creator of a number of science podcasts well worth checking out and which we will have links to on our website. They include This Week in Virology, This Week in Microbiology and This Week in Parasitology. Welcome to Up Close Vincent.

VINCENT RACANIELLO
Thanks Dyani, great to be here.

DYANI LEWIS
Vincent, viruses are very much a fact of life for most of us. We catch a cold every now and then. We get immunised or vaccinated to make sure that we never catch some particular viruses and yet when you look at the typical tree of life you've got the bacteria, the archaea, plants, animals, fungi, protozoans, but there are no viruses in that tree. How is it that viruses don't belong in the tree of life?

VINCENT RACANIELLO
Well they probably do, but it's been difficult to put them in the tree. The traditional

trees of life, before we were able to determine DNA sequences of organisms, were based on morphological features for the most part. So we could order a set of mammals for example on a tree based on what they looked like, the length of their bones and so forth. Then we got more sophisticated and we began determining genome sequences and then it became very easy to make trees of life, but the viruses don't fit in when you put the genome sequences together. I do think they belong somewhere there because my personal view is that viruses were before all life and we are all probably indebted to viruses for being here. There's a lot of debate about this, whether they should be on the tree and I suspect it's going to take a long time to change that, because scientists are very slow to change their ways.

DYANI LEWIS
You said there was debate about whether they should be on the tree of life. This is around a debate actually whether they are indeed alive or not.

VINCENT RACANIELLO
That's right, so there is a debate and I think I can settle that here but not everyone will believe me. The way I look at it is a virus is an organism with two phases; there is the particle that goes from person to person and that infects you. This cannot be considered living at all. It's a particle of a nucleic acid and some protein and maybe a little lipid. But when that particle infects a cell it takes over the entire cell. It directs all processes, it reproduces itself, it evolves. Certainly the infected cell is living, so the virus particle is not but the infected cell; together they're a living organism.

DYANI LEWIS
And like plants and animals, viruses can be grouped into these families and smaller divisions based on how similar or different they are to each other. And your particular interest has been in picornaviruses, so what distinguishes this particular group of viruses from other viruses?

VINCENT RACANIELLO
So before we were able to sequence the genetic information of viruses all we could do was look at them and watch them infect cells, or infect animals and classify them in that way. So just on that basis along it was easy to put viruses into different categories or different families as the picornavirus family is. So this family has a number of features in common. The viruses are all quite small. They're made up only of proteins; there's no lipid in the virus particle at all. The nucleic acid inside is RNA, Ribonucleic acid, as opposed to DNA which makes our genome. This RNA is what we call plus or positive-stranded. Now that has nothing to do with electricity, but it refers to the fact that it can be translated or produced directly into protein, so these features are some of the ones that place the picornaviruses by themselves.

DYANI LEWIS
How widespread are they? Are they something that only infects humans?

VINCENT RACANIELLO
Picornaviruses are probably infecting many, many different kinds of animals out

there. As we have been getting better and better at virus discovery, we've been able to find not just picornaviruses but all viruses everywhere. So at one point you might have said picornas are largely human and maybe a few animals. Now we realise they're not only in people but many different kinds of animals, probably even fish and maybe plants as well.

DYANI LEWIS
Now perhaps the most well-known of the picornaviruses is poliovirus, the virus responsible for polio. Many of us would have no firsthand experience of polio today, so could you give us an idea of what the disease is, poliomyelitis and what it involves?

VINCENT RACANIELLO
So poliovirus was actually among the first viruses discovered at the beginning of the 1900s and it was discovered because there was a paralytic disease that was becoming more and more frequent after the early 1900s. And eventually it was determined to be caused by a virus which was called first poliomyelitis virus, then that was shortened to poliovirus. The way that you acquire the disease is you ingest the virus in contaminated food, or through touching, contaminated hands. The virus passes through your stomach and then it goes into your intestines. It lodges into the wall of the intestine and it enters the cells there and begins to reproduce. Billions and billions of new polioviruses are shed into the intestine. They exit your body in the faeces. It's very efficient at going from person to person. Now this multiplication in the intestine does not cause any disease. It doesn't cause diarrhoea, it doesn't cause gastroenteritis. In most cases it's silent.
It silently goes from one person to another without causing any harm, but in one out of a 100 infections the virus gets into your brain and spinal cord and it kills the cells in there called neurons and that's what makes you get paralysed. I think it's an accident that the virus gets into the brain and spinal cord, because if you think of it, the goal of a virus, if we can ascribe goals to viruses at all, is to be transmitted to a new host. Getting into your brain doesn't achieve that, it's a dead end. So I think it's an accident that the virus gets there. Most of the time it's growing very well in the intestine and passing from person to person.

DYANI LEWIS
The paralysis that results from polio infection, is that just damage to the neurons during that replication process?

VINCENT RACANIELLO
Yeah, the current idea is that the virus kills the neuron as it's replicating in it and if you destroy enough neurons that innervate a particular muscle, but the number is 5000 or something like that, then the muscle gets paralysed. So I think it's rather straight forward damage of neurons in paralysis.

DYANI LEWIS
You mentioned that the disease was becoming more and more common in the beginning of the 20th Century. Why hadn't it been as common previously?

VINCENT RACANIELLO
That's a great question and we know exactly why. Probably polio has been in humans for thousands and thousands of years, because we have very old records and it occurred as a sporadic disease. There would be a case here and a case there, nothing that anyone would ever recognise and certainly no kinds of epidemics. This is because the virus circulated quite freely. We didn't have good sanitation right; we used to throw our sewage right out onto the streets and it passed readily from person to person. When you were born you immediately got infected with the virus, so within your first few years of age you got infected. But if you were infected as a baby you were protected by the antibodies that you got from your mother, so you didn't get polio. As we got past the early 1900s we began to learn about good sanitation. We developed sewers and we didn't get infected any longer as a baby.

We delayed infection a few years, to the point where we no longer had protective antibodies from our mother; hence we got outbreaks of polio.
DYANI LEWIS

This is Up Close. I'm Dyani Lewis and in this episode we're talking about poliovirus with virologist and science podcaster Vincent Racaniello. Vincent, why is it that only that one per cent of people end up getting a disease that causes paralysis, whereas everyone else gets away unscathed?
VINCENT RACANIELLO
That's a really good question and I'm afraid we don't have an answer to that, but I do have an idea. I think that the virus probably doesn't grow the same way in different people. You know we're genetically not the same, humans, we're all quite different and so it's possible that in some people the virus grows a lot better. In that case it can enter your brain and spinal cord. I think probably if we looked at those one in 100 people who get poliomyelitis, who get paralysed, if we sequenced their genome I'll bet we would find mutations in their immune system that are allowing poliovirus to get into the central nervous system.

DYANI LEWIS
Now you've looked at how the poliovirus gains entry into cells. What do we know about how it does this?

VINCENT RACANIELLO
So like all viruses that infect animals the cell is a nice barrier to things getting inside and usually you have to get in by specific mechanisms. Viruses have to bind to molecules that are on the surface of the cell. We call them receptors and then they get taken into the cell. So there's a pathway in the cell that exists to take in molecules for nutrition and viruses latch onto that. They bind receptors, they get taken into cells and then their nucleic acids go inside the cell.

DYANI LEWIS
You mentioned that the very first stage of infection is in the intestine, so where are the first cells that are being infected located in the gastrointestinal tract?

VINCENT RACANIELLO
Right, so in the small and large intestines as you know, the intestine is composed of a layer of cells called the mucosal epithelium and this is the barrier between in the inside of the intestine and the rest of you, because below that there's the circulatory system. The virus enters those epithelial cells lining the intestinal tract, so it grows there and as it grows it is shed into the intestine as well. But the virus can also cross these cells and get into the underlying tissues. We call those the subepithelial tissues and eventually get into your bloodstream. In fact most people who get infected with polio, there's virus circulating in your blood but this is of no consequence - unless there's accidental invasion into your brain and spinal cord.

DYANI LEWIS
The process of entry into the cells that happens in the intestine, is that the same as what happens when it enters the neurons?

VINCENT RACANIELLO
Good question. We don't know. I think it's probably dangerous to say anything is the same in biology, so we study the virus getting into cultures of cells in the laboratory and whether that is the same as what's going on in our intestine or in our central nervous system isn't clear. I think what we can say is that the same receptor is involved, because we know that receptor is present in all of the cells. And if it's not there the cells won't be infected.

DYANI LEWIS
So if that receptor is present in all cells I guess that also begs the question of why then is it causing a neurological condition as opposed to say infecting heart cells once it gets into the bloodstream?

VINCENT RACANIELLO
You should be a virologist Dyani, you're asking all the right questions. So this is actually something that we work on. In humans the receptor is on many, many different cells in different tissues, but the virus never replicates in any of them. It just replicates in the intestine and sometimes in the spinal cord. It looks like most of our tissues, heart, lungs, liver et cetera which have polio receptors; they're protected by part of our immune system. It's the very early stages of our immunity. It's called the innate immune system, which is based on a rapid response to infection. And we know this because in our mice that we've developed as a model for infection, if we take away this innate immune system the virus will replicate everywhere in the mouse. So most organs are protected by this innate immune system. Why isn't the brain and spinal cord? This is something that we're trying to figure out in my laboratory.
And so far the data hint at the innate immune response being dampened in the brain, because it is damaging so when you get an influenza infection you get these so-called flu-like symptoms: fever, aches and pains, malaise. These are all caused by the interferons that your cells are making in response to virus infection. So even though these interferons are good - in the long run they dampen the virus infection - they do cause symptoms. And we think that your brain and spinal cord does not want

to make these interferons, because it would be damaging to cells that are not renewable like neurons.

DYANI LEWIS
You mentioned that you do some work on mice. How is it that you can work on a mouse when poliovirus, I assume like many viruses, would be very specific in the host that it chooses?

VINCENT RACANIELLO
Mm-hm, so polio in fact is only known to infect people in nature. We can artificially infect some primates and monkeys but they are not natural hosts, only humans. Mice cannot be infected with poliovirus and the reason is they don't have the right receptor on the cell surface, so in the 1980s in my laboratory one of my students identified the cell receptor for polio. She cloned the gene encoding this receptor and then a second student of mine took that gene - it's a human gene - and made a transgenic mouse with it. That mouse now produces the human polio receptor and you can infect it with the virus and they will become paralysed, so that's how we created a model to study the disease.

DYANI LEWIS
That would have been no mean feat in the 1980s I imagine?

VINCENT RACANIELLO
Science has changed considerably and things that were hard back then are very easy now. Yes, it was at the cutting edge of what we could do. In fact I look back at the early days and I often tell my audiences when I speak to them, that how long it took to do something that you can do in a few minutes.

DYANI LEWIS
And in terms of being able to watch the disease process, I presume having an animal model would be far more informative than just being able to look at tissue culture cells in a Petri dish for example.

VINCENT RACANIELLO
Absolutely. You can't really study disease in a cultured dish of cells. A mouse is much better. It is a living organism. It's a mammal. It certainly doesn't tell you everything that's going on in people, but you can breed them easily. You can have large numbers. They're rather inexpensive, so you can learn a lot about how the virus gets in, how it spreads and how it damages neurons, for example.

DYANI LEWIS
So what are the limitations though in translating that knowledge from mice to humans?

VINCENT RACANIELLO
Well the problem is that physiologically any animal is very different from us. And so the way a virus gets into the animal and moves about and kills cells can be different,

but we have to still use animal models otherwise we don't get any information at all. But you can sometimes take what you learn in an animal and ask is the same thing happening in people? Now you can't do experiments in people but you can make observations in people, so for example if you found in the mouse that a certain gene was important for paralytic disease, you could then ask in people who get paralysis does that gene have the same mutation for example. So you try and extend your findings in animals by doing certain kinds of observational experiments in people.

DYANI LEWIS
I'm Dyani Lewis and my guest today is virologist and science podcaster Vincent Racaniello. We're talking about polio here on Up Close. Vincent, you work on mutant polioviruses as well to try and understand the different structures of the virus, particularly the viral capsid or the outer coating of the virus and how those are involved in the infection process. I was wondering whether this carries any particular risk of creating a more virulent or infectious form of polio?

VINCENT RACANIELLO
It's interesting that you ask and I suspect that when we started our work 30 years ago no one would have asked such a question. It was a time in virology - maybe it was because the public wasn't as engaged as they are now - that no one asked such questions. There had never really been any serious consequences of working with viruses in the laboratory. I mean there certainly had been infections from time to time, but nothing happened as a result of genetic manipulation of viruses. When we change viral sequences by mutation we're always making guesses about what to do. We're not thinking as nature would think, to make the virus that's best for the current situation. So inevitably we typically disable the viruses when we do whatever manipulation we do and so I have little concern that altering poliovirus or influenza virus, or any other virus by mutation, is going to create a problem. Nature is far better at that than we are in the lab.

DYANI LEWIS
When you do consider other viruses like HIV or influenza, there are huge efforts to understand the virus in order to develop antiretroviral treatments, or to develop vaccines. Now polio already has a vaccine which has been very effective, so where is the interest in still studying polio further?

VINCENT RACANIELLO
There are many answers to that question. Even though there are two good vaccines that we're using to eradicate polio, it's going to be a problem to use them to get complete eradication. So we have Sabin's vaccine and we have Salk's vaccine; the Sabin is an infectious vaccine which you drink. It goes into your intestine and it immunises you without causing paralysis. Salk vaccine is injected. It gives antibodies in your blood. Now the Salk vaccine does not protect your intestine against polio infection. Right now we are down to 200 to 400 cases a year of paralytic polio globally and these are in three countries - Afghanistan, Pakistan and Nigeria - where they've never gotten rid of the wild virus. That wild virus periodically jumps to other countries and infects people who haven't been vaccinated. The World Health

Organisation has been using the Sabin vaccine because it interrupts transmission by immunising your gut.
They have recommended that we switch to the inactivated vaccine, the Salk vaccine, very quickly. But the Salk vaccine doesn't eliminate intestinal replication and this is really illustrated beautifully by the recent isolation in Israel for the past year of wild polioviruses in the sewage. Now these have come from Pakistan. There have been no cases of polio in Israel because the population has been immunised with the inactivated vaccine, but clearly their intestines are still susceptible. So what do we do? Do we go back to the Sabin vaccine in Israel? Well if we do that then that virus ends up in the sewage. If we keep using the inactivated vaccine we'll never get rid of the circulating virus, so this is a real conundrum. Because of this the Gates Foundation has called for new research on new kinds of vaccines that might take care of this.
So even though we have two great vaccines I think we're going to have to have another one, or another approach to really get rid of infection.

DYANI LEWIS
The Salk vaccine that is injected, usually when we are vaccinated with such a vaccine I would have assumed that we would get complete protection in all of our cells. How come it doesn't protect us in our intestine?

VINCENT RACANIELLO
So the ability to protect the intestine depends on a very specific kind of antibody. It's called IgA and it's only produced in the intestine in response to a virus or a bacterium present there in the intestinal tract. So if you inject a virus into the muscle it cannot reach the gut, so you're not going to get good what we call gut immunity, so that's why the injectable vaccine doesn't protect your intestine.

DYANI LEWIS
So what sort of vaccine would give total protection then?

VINCENT RACANIELLO
Okay, so the problem with the Sabin vaccine, you drink it, it replicates in your intestine, it gives you immunity and then it's shed in your faeces. But what's shed is now no longer a vaccine. It actually can cause paralysis and that can spread in the population, so we don't want that kind of a vaccine. We need to develop a vaccine that similarly immunises your intestine, but does not get shed in a form that can cause polio and there are lots of candidates out there for such a vaccine. That's a good reason why we need to keep working on the virus.

DYANI LEWIS
So I guess you're not necessarily optimistic about eradicating in the immediate future then?

VINCENT RACANIELLO
I have been for many years but the situation in Israel has really made it clear that we're not going to be able to get rid of the virus in the near future. We may be able to

get rid of all the polio, the cases of paralytic disease, using the Sabin vaccine. It's not easy because in the countries where it remains armed conflict has been preventing the immunisers from doing their jobs, but let's assume we can take care of that which is a big assumption. I think we can get rid of the paralytic disease, but then how do we stop using the vaccine because there's still going to be circulating virus and the day we stop immunising, kids are going to get polio again. So this is a conundrum that we've never had to deal with before and I think we can work it out, but it's not going to be straight forward. We're really going to have to depend on philanthropy of the sort that Bill Gates is doing, to pay for the immunisation.

DYANI LEWIS
So a better vaccine is certainly something that would be on the cards with this extra research, but what about other reasons for studying polio?

VINCENT RACANIELLO
A few viruses have the ability to go from our circulation into the central nervous system, like West Nile viruses, herpes viruses and a number of others. We really don't understand how this happens, how the virus gets from the blood into a nerve cell and eventually replicates in there. For polio we have great ways to study it. The virus is relatively easy to work with. We can grow it in large quantities. We have a mouse model. So it's a resource to be a model for understanding in general how viruses get into the nervous system.

DYANI LEWIS
Do you think the scientific community will ever retain stores of poliovirus beyond eradication, assuming that we eventually do get to that point?

VINCENT RACANIELLO
Well you may know that we still have stocks of smallpox in two locations and there has been huge debate over whether to destroy those or not. When the time comes there will be similar debate for poliovirus. I have a freezer full of stocks of the virus and they're a resource for future study if anyone ever wanted to study it. But of course in a post-eradication era they're a threat, so they should either be destroyed or put in a safe place. Personally I don't see why these viruses that have been eradicated couldn't be stored in a secure location, kept indefinitely. You never know when you're going to need them again. That said, if we have the genome sequence of any virus we can make it. We can synthesise the DNA and put it in cells and we can recover a virus, so in some way it's a moot question because even if no stocks are left, as long as the sequence is on a computer somewhere we can make the virus.

DYANI LEWIS
Vincent, thank you for being our guest today on Up Close.

VINCENT RACANIELLO
My pleasure, always love to talk about viruses.

DYANI LEWIS
Vincent Racaniello is Professor of Microbiology at Columbia University Medical Centre. He's also the man behind Virology Blog and the creator of the podcast This Week in Virology. If you would like more information or a transcript of this episode, or to find links to Vincent's podcasts, head to the Up Close website. Up Close is a production of the University of Melbourne, Australia, created by Eric van Bemmel and Kelvin Param. This episode was recorded on 7 July 2014. Producers were Eric van Bemmel, Kelvin Param and myself, Doctor Dyani Lewis; audio engineering by Gavin Nebauer. Until next time, goodbye.

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