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Transcript

[To think, you know, in 10 years time we would be having Strep A vaccines that are being manufactured and deployed is very exciting, very exciting.]

Andrew Pollard: Hello, my name is Andrew Pollard. I'm director of the Oxford Vaccine Group at the University of Oxford. Welcome to our podcast series, The Oxford Colloquy: Trust in Science, bringing you the stories, facts, and people behind the science.

In this episode, I'll be talking with Professor Andrew Steer, who's a world leading expert on the bacteria that cause strep sore throat, and many other serious complications of this organism. He'll also tell us about the terrible itching parasite scabies, which causes epidemics in many communities and affects countries everywhere.

[END INTRO]

Andrew Pollard: Professor Andrews Steer, Director of Infection, immunity and Global Health at the Murdoch Children's Research Institute and Pediatric Infectious Disease Specialist at Royal Melbourne Children's Hospital, welcome to the podcast.

Andrew Steer: Thank you, Andy. It's a pleasure to be with you.

Andrew Pollard: So Andrew, you've worked in Melbourne for most of your career, so can you just give us a little bit of an idea about your training and your experiences before you ended up as director at the Murdoch Children's Research Institute?

Andrew Steer: Yes, thanks Andy. You're right to say I've spent most of my time in Melbourne, but I think the experiences that sort of changed my career trajectory were actually in the Pacific.

So it was during my medical school days, I had a little bit of a crisis of confidence about my future career and took a year off and spent some time in Samoa in the Pacific. And during that time I fell in love with infectious diseases, public health, pediatrics, and the Pacific and their people. And that really directed my career from then onwards, I did my medical school, my pediatric training, interrupted my training to go live in Fiji for three years where I did my PhD, which was a great place to do a PhD, and then had some time in Vancouver doing an infectious disease, a pediatric infectious disease fellowship.

And not only did that time, you know, broadly guide my future, it also guided the areas that I was interested in as well, which were group A streptococcus, neglected tropical diseases and rheumatic heart disease.

Andrew Pollard: So you talked about your PhD in Fiji and what was the nature of the work there and how did that then sort of inspire your research career?

Andrew Steer: So I had colleagues who were working in Fiji and it was evident to them as clinicians and researchers that there's a large burden of rheumatic heart disease. And rheumatic heart disease is the most common acquired heart disease in the world. It is a chronic disease of the heart valves that leads to heart failure, frequently leads to death in the second or third decade of life. Affects women more than men. It occurs as a result of an aberrant immune response to group A strep - or strep A - infection.

Andrew Pollard: So strep A, this is the sore throat bug that we're all familiar with.

Andrew Steer: Yes that's right.

Andrew Pollard: It's something which we actually don't worry too much about. We just treat it with antibiotics, and yet you went to Fiji to study a complication of it?

Andrew Steer: That's, exactly right, yeah. And I think the other part of that travel to Fiji, was also a sense of the burden of disease. It might sound a little bit strange, but there's a large burden of disease amongst the indigenous population of Australia, and in fact, many of the disease entities that we see that lead to a gap in health outcomes in indigenous Australians occur in the Pacific as well.

So I mean, as I said that strep sore throat doesn't seem such a big deal, sitting here in the UK - and perhaps we'll talk about whether I'm right in saying that in a moment, but we don't see avalanches of children and young adults with rheumatic heart disease.

Andrew Pollard: So what's different about the experience that you described in Fiji and amongst indigenous Australians?

Andrew Steer: Yes, and there is a stark difference isn't there between what we see in the UK, Europe, the US, Australia with some exceptions, with some particular populations. But if we were to rewind the clock back to the thirties, forties and fifties in the UK, there was a lot of rheumatic fever and rheumatic heart disease in the UK. And certainly in Melbourne, we had a whole ward, in fact a whole hospital at one stage dedicated to patients with rheumatic fever and rheumatic heart disease.

So something has clearly happened in high income countries as social and economic development has occurred. And that is still a little poorly understood, I think. There's a couple of different factors. So one is access to antibiotics and treatment, and access to care to get those antibiotics and treatment. But clearly just economic development in itself has had an effect. And I think in my mind, a big part of it has been changes in crowding within homes. So clearly lots of strep exposure within homes is important, just that force of infection, in the development of rheumatic heart disease.

And you know, Andy sometimes, sitting here in Melbourne, I have these moments of thinking, "Why am I studying rheumatic heart disease?" We have a project site in Uganda and I was in Uganda a couple of months ago and visited the main hospital in Kampala, Mulago Hospital, and visited the cardiology, adult cardiology outpatient department. And more than half, probably 75% of adult cardiology patients in the main clinic have rheumatic heart disease. And it's those moments when you have a little light bulb thinking, yes, this is an important disease and we need to do something about it.

Andrew Pollard: I certainly remember as a junior doctor and I still looked after adults, there were many patients who came in during our general medical on call, who had valve problems that had originated in their childhood from strep infections. But as a pediatrician, I hardly ever see rheumatic fever, the condition that then eventually leads to damage to heart valves. So something switched in a relatively short period of time. Do we have any insight into what that is? You were suggesting it may be crowding, force of infection, in other words the exposure that children have.

Andrew Steer: Yes, I think they're the main things. There are a few other clues. I still see patients here in Melbourne with rheumatic fever and remarkably, many of the patients, or the majority of the patients that we see are Pacific Islanders. So there is this question about whether there may be some form of genetic susceptibility. There's been a series of genome wide association studies, in the Pacific in a couple of different countries and also in Africa as part of a large study. And there are a few clues around immune markers, but nothing definitive as yet.

So there's still an open question about why we've seen this big change which fascinates me no end.

Andrew Pollard: So we've talked about the adults who have damage to their heart valves that is the real long term problem. But the disease that you describe, rheumatic fever, that then eventually causes that damage, what do those children have that then damages their heart valves?

Andrew Steer: So after a strep A infection, there's an immune response and that helps eradicate the bacteria. But that immune response for some reason, and that's a bit of a holy grail of this area of research, leads to a cross reactive immune response and that attacks different parts of the body. So most frequently, it causes fever and joint pains and joint swelling or arthritis. It can also affect the brain, and that's a syndrome called Sydenham chorea, where you get writhing abnormal movements, which can be very distressing. It can also cause some skin manifestations, but the main one that we worry about is when it affects the heart, and so it causes leaky valves, particularly on the left side of the heart.

The joint symptoms will go away, but the heart changes to the valves remain, and that causes rheumatic heart disease. So the saying is that the rheumatic fever licks the joints, but bites the heart.

Andrew Pollard: Are there other complications of having strep infections, apart from rheumatic fever?

Andrew Steer: Yes so what makes it interesting as a clinician on the clinical side is the wide array of clinical syndromes from strep infection. This is strep A, so there's the, you know, the standard sore throat, which we've been discussing, which in some settings is treated in other settings is not. It can be complicated by development of more severe infections around the throat, and it's called quinsy. Strep A can infect the skin, so a common infection is impetigo of the skin, or skin sores, and that can be more complicated and cause a broader infection of the skin. And then it's also being called the flesh eating bacteria because it causes necrotising fasciitis.

Andrew Pollard: Yes, although, in the media here, you often see it described as the "flesh eating virus" which is incorrect since it's a bacterium, not a virus.

Andrew Steer: Yes. As a pedant around these issues, that's something that does drive a few of us a bit crazy, but yes, that's right.

And then there's this series of what we call immune sequelae - or immune responses. So there's rheumatic fever, rheumatic heart disease, and there is also kidney disease or post-streptococcal glomerulonephritis, which is quite poorly studied but is an important contributor to kidney disease around the world.

Andrew Pollard: So that's some sort of an inflammation in the kidney, which can lead to kidney failure or not?

Andrew Steer: So acutely that can lead to renal failure, although not frequently, but there is some emerging evidence that suggests that episodes of this kidney disease in childhood can contribute to later chronic kidney disease.

Andrew Pollard: So you mentioned that not everyone treats strep sore throat, but with that array of really worrying complications you've described, it seems crazy that we wouldn't treat all strep sore throats.

Andrew Steer: Yes and there are differing approaches, but I guess what we do know is that if you do get a sore throat, most cases of sore throat will be self-limited, and treatment does provide some symptom relief. But on the flip side of that is just the widespread use of antibiotics. Sore throat in itself is the second most common reason for prescription of antibiotics in general practice, at least in Australia, and I think it's similar in the UK, Europe, and elsewhere.

And so some guidelines will suggest: don't test, don't treat. Although in the US and Europe, there is a different approach, which is often: test and then treat. So I think all of those considerations, and the burden of sore throat, I think does speak to the need for better prevention of streptococcal disease.

Andrew Pollard: So if we look at children with sore throat and as you say, there's many of them go to their GP what proportion of those will be strep, which is potentially treatable and might prevent some of the complications versus other types of infection like viruses for which we really can't do anything at the moment.

Andrew Steer: So it varies by jurisdiction, but it's around 20 to 25%. And so you do need to test, I think if you're gonna treat, of course what frequently happens is there's no test, there's just a treatment given. So I think there's been, you know, over the last decade or so, some improved point of care tests where you can do a rapid test, like we've become very experienced with COVID testing, which can help, you know, make a rapid decision about providing treatment.

Andrew Pollard: So these strep sore throats, there's a lot of it about, if it's 25% of all sore throats, and there's these risk of complications. So why don't we just vaccinate and prevent strep?

Andrew Steer: That is a great question and we would love to be able to consider a vaccination strategy. But the problem is we don't have a vaccine. And so that is an area of our work that we've really focused on over the last couple of decades around what it's going to take to develop a vaccine for strep.

There's a long history of vaccine efforts for strep A going back to at least the first part of last century, but even before, and many of those studies were conducted in Europe and the US

when rheumatic fever was recognised as a major public health problem. I think that the impetus for vaccine development has diminished with reductions in rheumatic fever, rheumatic heart disease in high income countries. But as we've discussed, there's still a very large burden in lower and middle income countries. And there's a clear need for prevention of streptococcal disease across the full spectrum, whether that's sore throat, skin disease, invasive disease when the bacteria gets into the bloodstream, heart disease or kidney disease.

The second thing is that it is a tremendous amount of antibiotic prescribing, and you can imagine if we had a highly effective vaccine that then obviated the need for any antibiotic treatment of sore throat, that we would substantially reduce the amount of antibiotics that we're using across the globe. So I think there's a potential antibiotic resistance argument as well for strep A vaccines.

Andrew Pollard: So there are some strep A vaccines which are being developed at the moment, and assuming they're safe, the real question is do they work? And so given that strep sore throat is so common, and presumably if you prevent strep sore throat, it'd also prevent rheumatic fever, isn't it easy just to do a vaccine trial?

Andrew Steer: Yes, I think that there is a path for vaccine development and maybe just to take a little step back just in terms of the number of candidates that are sort of in preclinical or early clinical development. So it's a very different pipeline to the COVID pipeline, but I think we can say that there is increasing interest and investment and effort, over the last few years around these vaccines.

So there's about 10 vaccines that are in, I'd say late preclinical development, one that's currently in phase one and another handful that are going to be in phase one pretty soon, we hope.

Andrew Pollard: So phase one is the first studies in people.

Andrew Steer: Yes, sorry, the first studies in people. And there's a range of different approaches including an mRNA approach, which is, you know, exciting. The mRNA vaccines have been mostly used for viruses rather than bacteria, so that's an exciting time, I think.

But to come to sort of what the pathway will be towards testing and showing that these vaccines work. So I think that what we call the target product profile or the group of people of the population that we really wanna prevent infections in, it's really amongst young children as they enter into school, because we know that's when the largest burden of sore throat is, and that's also when rheumatic fever occurs.

And so, the vaccine clinical trials that are being planned and thought out at the moment, would need, you know, a few thousand children to be enrolled, for a strep A vaccine study. And that might sound like it's not too difficult, but any of these sorts of studies require quite substantial effort and investment and not necessarily going to be straightforward, but I think, can be achievable.

Andrew Pollard: Yes, I mean certainly a few thousand is fairly standard in clinical trials because even for safety, most regulators require 3 to 5,000. So it is the sort of numbers that certainly pharmaceutical companies should be used to.

But what I wanted to come on to is that there is an alternative approach, which you have been pioneering, which is using human challenge studies. So this is where you deliberately infect

people with these bacteria, group A strep bacteria - this is adults, not children - to cause infection and sore throat. So tell us about that and what progress you've made.

Andrew Steer: Yes, so I think this has been a really exciting area for the field. And our group here in Melbourne, with a number of collaborators, took inspiration from some human challenge studies in the 1970s, which were used as vaccine studies that did actually demonstrate efficacy of vaccines. So we thought in the modern era we had the opportunity to rejuvenate that approach.

So we carefully chose our strain, and tested that and produced that in lots that were acceptable to a regulator. And then we carefully consented adults aged 18 to 40, and we essentially did what we call a dose finding study. So what was the dose of the bacteria that we could paint on the back of consenting adults? And what dose would cause an infection rate above 70%...

Andrew Pollard: So you're putting the bacteria into the throat and seeing whether you can then recover them later to show there's an infection.

Andrew Steer: Yes, that's right. And we had a series of plans about how we would potentially increase the dose if we needed to, but as it turns out, our first dose level of the bacteria produced an infection in 17 out of 20 of our first lot of volunteers.

And we also thought, well, maybe we need a lower dose. So we then went down to a lower dose and painted the back of the throat of participants with that dose as well. And I think we got one out of five of those participants. So we feel like we've got the right dose of this particular strain of bacteria to be able to move forward to do some proof of concept, quite rapid assessment of vaccine efficacy.

Andrew Pollard: The great thing there is that you can test vaccines, work out which ones might have an effect so that you are not doing trials on 10 different vaccines in the community. You can choose the one that's likely to work, which would be great.

So given that there's vaccines being developed, there's the challenge model, there's the potential to do the studies in the field. Are you optimistic that we will have a strep A vaccine in the near future, in the next five years, let's say?

Andrew Steer: I'm more optimistic than ever at the moment.

I think that there are a number of key pieces coming together, and those key pieces are investment, which is really important, we saw that during COVID and with other vaccines. I think international efforts that are drawing together the community and tackling some of the key big questions. And then I think the science is changing, so different approaches and different groups coming into the field who are trying different things.

So of course, as you said before, the key thing I think for all of us is to see some early proof of concept and proof of efficacy. So I would hope over the next couple of years that we see that and that we do see some efficacy of these vaccines and that further stimulates investment and efforts as we move forward.

Andrew Pollard: So the future could be one where we no longer have strep sore throats in children, which is unpleasant and requires lots of contacts with GPs, perhaps a big reduction in antibiotic use if they're not coming to the GP with those sore throats and getting antibiotics, but also the more serious complications that we've talked about that we see here in the UK, the bloodstream infections, and the severe skin infections. But perhaps, particularly in the world

that you are working in, also that big impact on rheumatic fever in low middle income countries, if we did have strep vaccines. So it's a very exciting time.

Andrew Steer: That is the dream, yeah.

Andrew Pollard: So I'd like now to move on to just talk very briefly about scabies, which is another passion of yours.

Now I, as a pediatrician, looked after many children presenting with extreme itching, and it is usually a fairly straightforward diagnosis, when you've excluded eczema and other things to work out that it's scabies. And it's often other members of the family affected as well, and mostly relatively straightforward to treat, but that's not always the case, is it? Do you want to tell us what scabies is and about its treatment?

Andrew Steer: Yes, scabies is a tiny mite you can't see with the naked eye. And the female burrows under the skin, lays her eggs, and as you say, it causes this intense itch.

If we were sort of returning to our initial discussion about my time in the Pacific, I was doing echocardiography, so heart ultrasounds, looking for rheumatic heart disease. And every second child had terrible scabies. And it became apparent to me that scabies was a big public health problem, and I think it has been largely neglected.

And the other part of it was that that itching and scratching leads to a break in the skin, obviously, and the introduction of bacteria, particularly the strep A bacteria. And in those communities we see higher rates of the bloodstream infections, higher rates of the severe skin infections, and higher rates of rheumatic heart disease and kidney disease.

Andrew Pollard: So what can we do about scabies?

Andrew Steer: Probably the best treatment is permethrin cream. You need to put that on all over your skin because sometimes the mites may be there, but you can't actually appreciate that they're causing infection just yet, and you need to leave it on for a period of time, like hours. That's not the nicest thing and, I must admit, living in Fiji, if I had put on the cream and there was a nice beach to go and swim in, I'd probably go jump in the water and a wash off and maybe would not be effective. And then you need to apply it again in 7 to 14 days.

There is an alternate treatment, which is called ivermectin, which I think many people will be aware of. And what we do know about ivermectin is that number one, it's a very effective antiparasitic drug. The discoverers of ivermectin won the Nobel Prize for Medicine in 2015 because of its public health impact for two other tropical infections.

And as it turns out, ivermectin is highly effective against the scabies mite. So it's an oral treatment. You take it today and it kills the mite, and then you wait for the eggs to hatch, which happens within about seven days, and you take a second dose to kill the mites that are hatched.

And one of the issues with the treatment of scabies is that it's all very well to treat the individual, but if they then go back to their home or into the classroom where everybody else has scabies, the chances of reinfection is very high. So an important aspect of treating individuals is to treat their contacts. And for us, we have done some research where we've expanded that concept and taken the approach of treating all members of the community, with ivermectin, whether they have scabies or not. And we've had some success in a number of trials that range from trials in about 700 to 2,500 to 30,000 to 150,000 people.

Andrew Pollard: And the results of those trials is that scabies then disappears completely from the community, or does it come back again after a few weeks?

Andrew Steer: So our studies, we did community-wide treatment, and then came back at 12 months to assess the prevalence of scabies. So in our original studies in Fiji with our Fijian colleagues and a number of collaborators, actually in the islands that we were working, the prevalence of baseline was about 30 to 35%, which still blows my mind, I just can't imagine...

Andrew Pollard: So 35% of people had scabies when you visited?

Andrew Steer: Yes, over 50% of children had scabies, which as I say, I just think is, you know for me as a pediatrician and a infectious disease physician, is just a terrible situation and it's unacceptable.

So we treated, did the community-wide treatment then we came back at 12 months to assess the prevalence at that time, and the prevalence had come down to 1.9%. So a really remarkable reduction.

So all of this work has led us to receive some investment for the World Scabies Program. So we have demonstration sites running the first national mass drug administration campaigns, which is community-wide treatment across the entire population of Fiji and the Solomon Islands. And we're about to launch our second round of the Solomon Islands and some of our results are coming through. And we're hoping that number one, the approach is successful, and number two, that we learn a lot how to do this better in the future as a model for other countries and settings where scabies has this sort of similar high burden as a public health problem.

Andrew Pollard: The drug ivermectin, I just wanted to come back to that because the reason why people may have heard about it is that it was promoted as a treatment for COVID-19, which it doesn't provide any useful benefit.

Andrew Steer: Yes, that is correct.

As I often say, it's a terrible drug for COVID but a fantastic drug for parasites and particularly a great drug for scabies.

Andrew Pollard: And so you have to, in those big interventions, you have to do everyone in the community on day one and then do everyone again seven days later.

Andrew Steer: Yes, that's right. Ivermectin has been given to billions of people as part of the river blindness and lymphatic filariasis programs, and so we know it's safe.

But in those programs, it's a once off dose. It doesn't require a second visit, so that is certainly an issue, I think. And a couple of things there, it's an issue because it requires more of the drug, and it also requires more human resources to do the delivery.

We are working with an australian not-for-profit called Medicines Development for Global Health, who have a drug that's related to ivermectin called moxidectin that has a longer half life and there's some very encouraging data and evidence for some preclinical and clinical studies that suggest that moxidectin in one dose might be highly effective against scabies. So that's an area of research that we hope to pursue.

Andrew Pollard: So one of the big challenges in doing a new big population intervention like you are discussing is actually getting the community on board, and particularly in this post-COVID

world where there's a lot of suspicion of science. Has it been difficult to get communities involved? How do you get people to trust the science that you are promoting?

Andrew Steer: Yes and I think this is some of the key learnings, Andy, that we've had from the World Scabies Program. I think that the key principles are co-design of the program, and so in fact our program in Fiji and Solomon Island is run by Fijians and Solomon Islanders in the country.

So co-design, a lot of consultation and then a lot of community awareness. So TV and radio and increasingly obviously social media and watching social media quite closely.

I think with scabies as opposed to COVID or even river blindness or onchocerciasis, is that people see it in their community. They have friends and family who have it. And so the opportunity to access treatment is actually in our favour in getting high adherence. And also when the ivermectin is taken, and people within the community start to see the number of people with scabies coming down, I think that's also a motivating factor as well.

Andrew Pollard: And then coming back to the group A strep vaccines, do you think there's a risk there that the public perception of sore throat is that it's not very important, and it may be difficult to get engagement with that?

Andrew Steer: That is something I think that is an area of work that requires more research, I think, I don't think we understand that as well as we should.

A better understanding of the demand and market in high income countries in particular is going to be quite important. And how that is then communicated back as we move forward is also going to be very important.

Andrew Pollard: And the sort of implication of what you said then is that perhaps the driver for the pharmaceutical companies to actually produce these vaccines may well be the need for a high income market that would then benefit the rest of the world for the more serious complications.

Andrew Steer: That's right. There is the potential for a dual approach here, I think, with a high income country market around sore throat and invasive disease. And I think, you know, we can't underestimate how severe some of these invasive infections are, this is the bloodstream infections. I'm sure you, Andy, as a pediatrician have some quite severe cases that are etched in your mind, certainly in my mind and other colleagues I work with here. And then the second market for prevention of rheumatic heart disease. And both are important drivers and both could do great good.

Andrew Pollard: So looking to the future, what excites you most about the next 10 years? So things that you think will change the world in your sphere.

Andrew Steer: Well, I think the work over the next 10 years in the strep A vaccine field, I think is very exciting. I think there's this period of acceleration at the moment and if we can demonstrate some proof of concept efficacy, that would be very exciting. And I think things will accelerate even more quickly.

So that excites me tremendously and to think in 10 years time, we would be having strep A vaccines that are being manufactured and deployed is yes, very exciting. Very exciting.

And then in my other work in neglected tropical diseases, and I'm very excited to see where the scabies program goes, and that nexus between research as a researcher and implementation and how that implementation can be scaled up so that we reach communities in need. And I think also attached to that is the sort of potential role that moxidectin might take in there as well.

So there are a couple of things that, you know, you can think forward to 10 years and some pretty amazing things might happen,

Andrew Pollard: On that very optimistic note, thank you very much, professor Andrew Steer, for joining us on the podcast.

Andrew Steer: Thank you, Andy. It's an absolute pleasure.

Andrew Pollard: That was the Oxford Colloquy: Trust in Science, bringing you the stories, people, and facts behind the science. So you might be wondering, what is a colloquy? A colloquy is a discourse or conversation, and I hope you'll agree that's what we've been having.