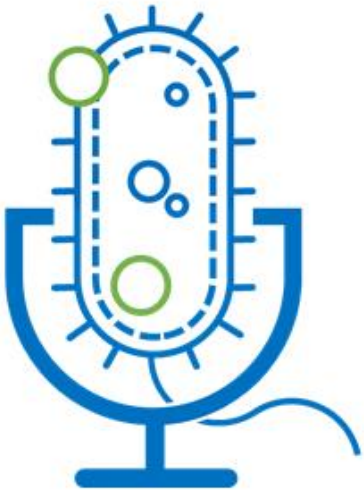

Innovating Alternatives

a podcast about AMR in food-animal production and the researchers around the globe who are working to reduce it.

Episode: *Streptococcus Suis*, have you tidied your bedroom?

Featuring: Professor Mariela Segura, Professor Todd Lowary, Dr. Egan, Dr. Blanchard, Dr. Nguyen Thi Bich Thuy and Dr Nguyen Xuan Huyen

Evelyn Baraké (EB) – Welcome to the last stop on our grand tour around the world of cutting-edge alternatives to antibiotics for food animal production. Can you believe this is our last episode?

Justin Kemp (JK) – Barely! It's been a pretty varied journey… from a crash course in antimicrobial resistance, AMR 101 so to speak, to phage-based alternatives for poultry farming and in our last episode, the many alternatives being developed for aquaculture.

EB – And yeah, we hung out in some galaxies not too far, far away from Sci-Fi territory:

Prof Sylvain Moineau

Bacteriophages are specific viruses that would attack only bacteria. they will inject their genetic materials inside of the bacteria. And at that point, they essentially take control of that bacteria. And the bacteria becomes like a factory of new viruses.

Prof Sophie St. Hilaire

A nanobubble is a very, very small bubble less than 100 nanometers in diameter. They have special physical characteristics that macrobubbles or larger sized bubbles don't have.

Prof Brian Dixon

Simply put, PACAP is a naturally occurring protein in animals, including aquaculture animals. It binds directly to the membrane on the outside of the bacteria and punches holes in it.

Dr Natrah Iksan

The idea is by quenching the signal molecules, all this behavior that somehow led to the pathogenicity of that bacterial pathogen can somehow be inhibited.[1]

JK - I'm Justin Kemp

EB – And I'm Evelyn Baraké and this is Innovating Alternatives – a podcast about AMR and the researchers around the globe who are working to reduce it. In this episode we meet researchers working to find solutions to a major bacterial pathogen facing pig farmers - *Streptococcus suis*.

[Theme Music]

EB – So there is one type of promising alternative to antibiotics that we haven't touched upon yet, one that will probably be much more familiar to everyone listening. It's a technology that's been around for hundreds of years. It's also in the news quite a bit these days.

JK – Are we talking about vaccines?

EB – Yep! Vaccines are a very powerful potential alternative to antibiotics. A we know, antibiotics are often used in food animal production as a preventative measure against infection. In medical terms, this is referred to as prophylactic use. The word prophylactic comes from Greek for "an advanced guard"

JK – And what better advanced guard against disease than a vaccine?

EB – Right, it's the single-most effective way we human beings have developed to guard ourselves and the animals we live in close contact with against dangerous and deadly pathogens.

JK – If you, as a producer, are able to effectively vaccinate an animal against a disease, you won't need to use antibiotics to treat outbreaks of that disease anymore, and you will no longer have the incentive to use antibiotics as a preventative measure.

EB – Exactly. But there are so many pathogens to guard against, and vaccines, contrarily to antibiotics, have to be quite targeted.

JK – That issue sounds vaguely familiar. Where have we heard that before?

Prof Sylvain Moineau

You will have phages that are specific for Salmonella*, you will have phages specific for* E. coli. *So there's really a specificity issue.*[2]

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[1] For full quotes and context, listen to Episodes 2 "Phages: My enemy's enemy is my friend" and 3, "The Curious Case of Aquaculture"

[2] See Episode 2 "Phages: My enemy's enemy is my friend".

EB – Very familiar! Do you remember how phage researchers explained how they picked their targets?

JK – Of course, they focus on finding phages for bacteria that drive the biggest volumes of antibiotic use.

EB – Yeah, so researchers, research funders and agenda-setters working on the issue of antimicrobial resistance use the same impact-maximizing approach to pick their targets for vaccine development. Today, we'll be zooming into efforts to develop a vaccine against one such pathogen that the international community has marked with a big red X on its back.

> Dr. Sharon Egan
> *I guess the first thing is that the world organization for Animal Health (OIE) has identified strep suis as being one of the priority areas for vaccine discovery because of the massive amount of antibiotics that are used for treatment. The big thing is that if we can generate a vaccine, we can then hopefully reduce the amount of antibiotics that are used both for treatment but also prophylactically, because some countries do still allow prophylactic treatment and antibiotics to be placed in animal feeds. So if we've got a clear-cut vaccine that is useful, we can not only reduce the need for those prophylactic antibiotics, but also the need for those pre-treatment.*

EB – That was Dr. Sharon Egan from the University of Nottingham. We'll be formally introduced later on in the episode, but first, let's get to know our pathogen:

JK - *Streptococcus suis*

EB – It's quite a mouthful, so throughout the episode it may be interchangeably referred to as *s. suis*, *strep suis* or by its full name.

JK – Only when it's in trouble I'm guessing. *Streptocccocus suis*, have you tidied your bedroom?

EB – Right. I'm going to admit that my mouth hasn't really settled on a pronunciation yet. Is it "strep swiss"? Strep "sue-iss", or "strep swees"? Anyway, let me introduce an expert on the subject to help with some of the explaining.

> Prof Mariela Segura
> *My name is Mariela Segura. I'm professor at the University of Montreal, and I'm the team leader of the IDRC*[3] *project on* streptococcus suis *vaccine development, to fight against antimicrobial resistance. First of all, I have been working on this pathogen,*

[3] International Development Research Centre

streptococcus suis *for 20 years now and it's the major focus of my research here in Canada.*

JK – So what animal are we talking about with strep suis?

EB -Well it's in the name… if you speak latin. *Streptococcus suis* is a bacterium that is found in pigs. It's a major cause of mortality in the pig industry worldwide, and it's especially deadly to piglets.

JK – Oh yeah, *Streptococcus*. So *S. suis* belongs to the same genus of bacteria that gives us sore throats, that's why it's called strep throat. But, how does it attack its swine host?

EB – I'll let Mariela explain this one.

Prof Mariela Segura
Septic shock means that the inflammatory response induced during blood dissemination of the bacteria is so severe and so high that the host, either animal or human, will die of their own inflammatory response. I guess it's something that we discuss a lot in the context of COVID, also. And the second problem clinical problem is meningitis. Once the bacteria will disseminate in the blood, they will reach the brain. And once in the brain, they will induce an inflammation in the brain which is called meningitis, and most of the time that will be fatal.

JK – Wow, that definitely doesn't fit into the minor infection category.

EB - And it's not just the pigs who should be concerned.

Prof Mariela Segura
Globally it is a major problem at two levels. The first level is animals of course, and pig farming, because it's an important disease. Bacteria cause an infection, which is very severe and may kill the animals, or the morbidity level will be very high. And the second reason why this is an important disease is because it's a zoonotic agent, which means it is transmitted from pigs to humans, and the rate of zoonosis is very high.

If the contact is by doing slaughtering or meat processing, or just handling the animals or taking care of the animals, the way of entry will be through small cuts in the skin and injuries in the skin. So if you are not using gloves, not washing your hands or taking all the biosecurity measures required to avoid direct contact between the contaminated meat and the hands, then you may have the pathogen entering through the skin cuts. Then it goes through the blood streams, and then once in the bloodstream, it will disseminate and cause disease. That's one way. The second way which is very common in some of Southeast Asian countries, like Thailand, is the consumption of raw meat. You eat the raw pork, the bacteria will get into the intestine, and once in the intestine, it will breach the intestinal barrier and disseminate in the blood and cause disease.

JK - So it's especially dangerous to pig producers who are in close contact with the animals or those who do the slaughtering and meat processing.

EB - Exactly, and its also dangerous to consumers of raw pork products, which is fairly common in Thailand and Vietnam, the two countries where the two project teams we're speaking with today are working. Human can get pretty sick from a strep suis infection. In Thailand, it's the second most common cause of adult meningitis. Infected people can also suffer other severe health outcomes like sepsis and loss of hearing!

JK –It's by all indications not a very friendly bacterium.

EB – Not to pile on, but there are also gender impacts to think about. In Thailand, women are often the ones to take care of the animals in small backyard production systems, which puts them at higher risk.

> Prof Mariela Segura
> *In the local backyard farms, women take care of the animals and are the one which are exposed, which means they are at the highest risk of zoonosis and they take care of meat processing. And sometimes they will even process sick animals for food. So the economic consequential consequences are also a public health problem because they are forced to also take sick animals for food, which is not good*

JK – Ok, so health issues aside, from the sounds of it, strep suis must also have major economic consequences for pork producers.

EB – Absolutely, and those are especially damaging for small-scale backyard producers, women included. In Southeast Asia, backyard pig rearing operations are very common, which creates some challenges for disease control. Some pig production areas may lack disease control resources, such as vets, and there may not be tracing and inspection systems in place that can identify and control an outbreak early.

JK – And what options do small-scale producers have when there is an outbreak?

> Prof Mariela Segura
> *The number of animals that these small backyard farms have is very small, so when they have an outbreak of streptococcus suis, local authorities will arrive and will eliminate all the animals. The economic impact is very high. To reduce the risk of outbreaks and reduce the number of animals which are sick, the farmers will use a huge amount of antibiotics to prevent disease. If we are trying to reduce the use of antibiotics, we will have more cases of* streptococcus suis. *As a consequence, the farmer will lose the animals and will lose income.*

JK – I'm guessing if you only have a few pigs, calling the authorities to cull all your animals would be something you would shy away from, and if it did happen, pretty devastating to your livelihood.

EB – And that brings us to the link with antimicrobial resistance and antibiotic use. Since antibiotics are cheap, easy to access and they prevent infections – at least for now – there is a major incentive for producers to use them liberally.

JK – Ok, so hence the need for a vaccine. But taking a step back here for a second, let me ask the obvious question: we live in a world where vaccines for a new coronavirus were developed, tested and approved in less than one year since the emergence of this new virus. Strep suis has been around for longer, and if it is such a priority for addressing antimicrobial resistance, what's keeping us from developing a vaccine against it?

EB – Well, there are a few major challenges to overcome, starting with the technical side of things

> Prof Mariela Segura
> *With this type of bacteria, meaning* streptococcus suis *in particular, we have two challenges: the first challenge is because of the capsule. We need to find a way to develop a vaccine to overcome the protective effect of the capsule. These kinds of pathogen that are covered by a capsule, which are called encapsulated, are very amazing pathogens. They cause severe infections and they once they enter into the host, it could be an animal or human, they invade, they persist in the bloodstream and they can resist the attack of the immune system that tries to eliminate the pathogen. And because of this capsule, which is kind of a sugar cover, the pathogen can escape the attack of the immune system and can survive and cause disease. So, it is very interesting to see how this strategy is so good, not for us, not for the animals, but very good for the pathogen to be able to cause disease*.

JK – Interesting. So, this is a stealth bacteria, because it's sugar cover lets it sneak into the body and hide from the immune system.

EB – Yeah, you could say that it's a pretty sweet disguise!

JK – Wow, we must have peaked on the comedy front in an earlier episode.

EB – Sorry, couldn't resist!

JK – Ok so that was technical problem number one. And the second?

> Prof Mariela Segura
> *The second challenge with this kind of pathogen, and particularly with* streptococcus suis, *is that the strains that encode the disease are highly variable. So, it is very difficult to find a unique protein or what is normally called sub-unit vaccine. A unique protein is*

part of the body of the bacteria that will be enough to confer protection against multiple and very diversified strains of streptococcus suis.

EB – It turns out that there are 35 different identified strains of strep suis, which means that an outbreak in one area might be due to a completely different strain than an outbreak a few villages over. So while there are some locally used vaccines out there against strep suis, they are only partially effective because they only protect against bacteria of the same strain. Every researcher I spoke to on both these projects mentioned this as the main reason there isn't yet a commercially available vaccine.

JK – It's kind of like the different strains of COVID-19 that are causing concern.

EB – Exactly.

JK – So how are Mariela and her team hoping to overcome these obstacles?

Prof Mariela Segura

Before starting this project, our team worked on the development of a first prototype of this kind of vaccine that targeted the sugar of the capsule using an old technology which is extremely expensive. But this allowed us to prove that there is potential for this type of vaccine to work. So now, we are working on a more sophisticated approach, which is the chemical synthesis of the antigen, and this will reduce the cost. Basically, we are using a new technology. My colleague in University of Alberta, he's the one who is doing the conception of the vaccine, may will explain in a better way.

EB – So of course, I had to speak to the expert in the chemical synthesis of carbohydrate antigens himself. And yes, we'll talk about antigens in a second.

Prof. Todd Lowary

My name is Todd Lowary. I'm a professor of chemistry at the University of Alberta. I'm an organic chemist by training. And my group spends most of their time making carbohydrate molecules that can be used as probes or tools to understand biology of carbohydrates. We're particularly interested in bacterial and other types of microbial diseases. And my role in this project is to synthesize or make carbohydrate structures that are then basically the raw materials of the vaccines that we're trying to generate.

EB – Alright, so let's go into the approach this team is using.

Prof. Todd Lowary

Mariela and Marcelo have spent a lot of their time, a lot of their career, trying to define what would be good antigens. And so they identified this polysaccharide as a good antigen for vaccine. And then basically, we've been trying to synthesize small fragments of that polysaccharide to then generate it and then test them to see how they are in terms of their ability to protect against the infection.

JK – Ok, so they've identified a particular polysaccharide as promising antigen, and now they're focused on synthesizing fragments of the polysaccharide to recreate it and see how well it can protect pigs against *strep suis*. Sounds pretty straightforward.

EB – I can't quite tell if you're kidding… But for those of us less fluent in organic chemistry, let's talk vocab for a second. First up: antigen. Care to take a crack at a definition?

JK – Sure. It's a substance that triggers an immune response in the body.

EB – Too easy! Ok next one: polysaccharide.

JK – Well, saccharide has to do with sugar, and poly means multiple. So a many-sugared molecule I guess.

EB – Yep. Or in other words, carbs! So in the context of strep suis, the sugar capsule Mariela told us about earlier is made up of polysaccharides. This capsule cloaks antigenic proteins, meaning the proteins that would tell your immune system to produce a bunch of antibodies to defend against this intruder.

JK – But Todd mentioned that they found a polysaccharide that they're hoping to use as an antigen for a vaccine. Which means they hope to use it to trigger an immune response. How does that work, if polysaccharides are what make the bacteria undetectable and actually prevent the immune response from being triggered?

EB – So the sugar capsule only protects against T-cell responses, but not against B-cells which control immune responses in body fluids, like blood, in which bacteria travel around the body.

JK – OK

EB – So with a vaccine, you can train these B-cells to react to the polysaccharide. But that being said, it may not create a strong enough immune system response to make for an effective vaccine. So to get around this, you can increase the body's immune response to a vaccine through a process called *conjugation*, where instead of just a polysaccharide, the vaccine is made up of a polysaccharide that is linked to a protein that will activate a T-cell response on top of the B-cell response. Their team is working on developing this type of vaccine, which is called a glycoconjugate vaccine.

JK – What stage is the project team at in this process of finding the perfect antigen?

> Prof. Todd Lowary
> *We're still fishing for what might be the best antigen. The best situation would be that we identify a fragment of this large polysaccharide that's protective. There's a lot of evidence in the literature to suggest that it's going to be possible, not specifically on s. suis, but certainly for other microbial diseases, this approach has been successful. So if*

you've identified a smaller piece of this, then then you can develop a perhaps an optimized synthesis to it. And then and then by doing that, we'll lower the cost.

JK – Ah yes, the question of cost. New innovations often face the challenge of ensuring cost-effectiveness.

EB – And that's the other big obstacle to why there isn't yet a commercially available strep suis vaccine.

JK – Makes sense. Vaccine producers need to make it sufficiently low-cost for enough pig farmers to be able to afford to use it to recoup their R&D costs.

EB – And vaccine R&D can be pretty expensive!

Prof. Todd Lowary
So I think there's been, relatively speaking, a fairly small amount of research that's been done on it. In general, animal vaccines have not been investigated as widely, simply because the market seems to be small. One of the challenges in developing an animal vaccine is the cost.

EB – But it's also a matter of priorities.

Prof. Todd Lowary
There's just not been enough incentives, and this is a place where governments really could probably step in and invest a lot of money in terms of developing new strategies and new molecules, new vaccines, etc., for preventing and treating infectious disease

JK - Anything's possible when governments, industry and global leaders put their heads and wallets together on an issue. Exhibit A – Covid vaccine development.

EB – Add that to the list of things we learnt in 2020… So, ready to officially meet our second team of researchers working on this issue?

JK – Let's go for it.

Dr. Sharon Egan
My name is Dr. Sharon Egan. I'm an associate professor of molecular microbiology at the University of Nottingham. And I'm their current PI[4] *on a project looking at strep suis vaccination strategies to develop better vaccines for pigs in Vietnam.*

EB – While this team is working on the same pathogen, strep suis, they're taking a slightly different approach.

JK – How so?

[4] Principal Investigator

EB – At the top of the episode I mentioned that strep suis is especially dangerous to piglets, right. This team's focus is on protecting these vulnerable piglets in the early stages of their development.

> Dr. Sharon Egan
> *The highest risk is for those weaning piglets. And that's when the piglets immune system is at this sort of critical point. They've lost all their maternal protection from their mothers, colostrum and milk, and they're starting to sense the environment and turn on their own immune systems, but they're not quite there yet. So we haven't got something that tells us what the trigger is for causing the disease in these animals. And we also often can't tell whether or not it was that disease that actually killed the piglets. The farmers are not necessarily going to go and send the carcass off for analysis by a vet, because it's just more money that they just they don't have to waste. So if we go on the loss of Piglet numbers, we know that it's the main cause of Piglet death in animals between three to twelve weeks of age. But we just don't know the exact numbers because it's really hard to capture that information.*
>
> *Instead of vaccinating adult pigs that are already pretty resilient and robust to these infections, maybe we're better off looking at the sow or the mother pig and providing a vaccine for her. You supercharge her immune system, so she provides more antibodies in her colostrum and milk. As the pig piglets suckle, that antibody is going to be going through their mouths and their throat. So hopefully that will be providing some additional protection against the disease.*

JK – Right, so they're tackling the cost problem head-on, since each vaccine administered will protect a whole brood of piglets.

EB – That's exactly it.

> Dr. Sharon Egan
> *If you could vaccinate the pregnant sow, it means that you have one vaccine for the mother, rather than twelve vaccines for the piglets, which helps for cost effective approach. I think that any farmer would be happier to pay for one vaccine for their precious sow, rather than having to pay for individual vaccines for all of the piglets*

JK – Still, this team has to contend with the same set of technological challenges that we talked about earlier – the multiple strains, the sugar capsule, etcetera. So what is their approach to finding that elusive antigen to make an effective vaccine?

EB – Well, a key aspect of this team's approach is the use of big data to find a needle in a haystack.

JK – Aaah, big data – you hear that term a lot these days, but what exactly does it mean in this context?

EB – It turns out that the strep suis bacteria normally lives in pigs, so it's around all the time. And sometimes, it is triggered and it causes disease in piglets, but researchers don't know why that is and what the trigger may be.

JK – Ok, and where does the big data come into this?

EB – I'll let the expert explain.

> Dr. Adam Blanchard
> *I'm Dr. Adam Blanchard I'm an assistant professor in computational biology at the University of Nottingham. And I'm the bioinformatics support for the* streptococcus suis *project out to the University of Nottingham.*
>
> *We're looking at identifying genes within* streptococcus suis, *that are necessary for the bacterium to grow in certain conditions, or certain environmental niches, like the pig, or in blood, or other kind of competitive niches that they may come under light from the immune response*
>
> *The lab side of the protocol is growing the bacteria within the lab in these environmental conditions. Then we sequence the bacteria that we get back from the experiment. And then, using the computational approach, we look for the genes that are identified as being essential for the bacterium to grow from that condition. And then that generates a list of putative targets that we look at. And then that goes into the downstream analysis process to identify genes that are potential vaccine targets or of interest for therapeutics.*

JK – Got it, so in essence, genetic information from sequencing the bacteria goes in, and a list of potential genes candidates comes out.

EB – Basically. And this approach enables you to see suspicious genes that had been flying under the radar.

> Dr. Sharon Egan
> *Those ones that we don't know about, we call them hypothetical proteins. And these are ones that nobody else knows much about. But we've already found a few of those that seem to be really important in early infection. So a lot of people haven't investigated these genes and proteins fully, because there's just no idea what they do or whether they're important or not. But we're able to find proteins that actually do look like they're important. Okay, we still don't know what they are and what they do, but it points us in the right direction to the sorts of proteins and genes that maybe have been overlooked in the past.*

JK – The hypothetical proteins… another great band name.

EB – They'd be the perfect opening act for Age of Phage! OK. So moving along swiftly.

JK – Yeah – so back to the topic at hand. This approach sounds like it has the advantage of speed and volume, basically they're harnessing the power and speed of modern computing to find the perfect antigen

EB – Definitely. And there's other benefits too. One of the objectives of this project team is to transfer technological capabilities across borders, starting with a transfer from the UK to Vietnam. What that also helps with is to lower the cost of vaccine development.

> Dr. Sharon Egan
> *We're really excited to work with colleagues in Vietnam as well, to open new collaborative links, and to share research knowledge between both our institutes. We'll be sharing some of the technological advances that we have and combining with some of the things that they're doing and have a more grounded and holistic approach to vaccine development, rather than us sitting in the UK trying to develop something that might not work for them in their country*.
>
> *For some of the other methods and techniques that are out there, you need to buy specialist sequencing machines, you need to have a specialist bioinformatician who can manage all the data. With our process, you don't necessarily need that. For some countries where funding may be a bit more limited, it's a more user-friendly approach. It allows them the access and the ability to utilize this technology, whereas maybe they might not have had it before.*

EB – They're even building a dashboard to help with this.

JK – Who doesn't love a good dashboard.

> Dr. Sharon Egan
> *It's a user-friendly interface: people can then upload their sequence data, and they can do some really quick comparative analysis. So it takes out some of the mystery and hard work. You get a really nice visual output of your data as well, and it's really super fast. So it gives you an overall package that makes you feel a bit more confident about the data that you're handling*.

JK – That sounds really cool.

EB – I also spoke to Sharon and Adam's colleagues in Vietnam to hear about their side of the project.

> Dr Nguyen Thi Bich Thuy
> *My name is Thuy, full name Nguyen Thi Bich Thuy. My position is deputy director of National Institute of Veterinary Research, which belongs to the Ministry of Agriculture and Rural Development of Vietnam. So, my major is the bacteriology field and we focus on vaccine development and research.*

EB – Here's how Thuy described to me how she hopes the transfer of technology will lead to the development of a vaccine against strep suis.

Dr Nguyen Thi Bich Thuy

We really need the advanced techniques from international collaboration. That's why we try to find the partner from a developed country to collaborate. So, we can apply the advanced techniques to help us to find a good gene or good antigen so that we can get the good results after we apply the vaccine. The disease in our country currently appears often. So we can, we can take a sample, but we when we collaborate with Nottingham University, they can help us to develop the good technique and find the good protein or gene. So, I we really hope that by this project we can find the good candidate gene or protein to apply and we hope we can make a good vaccine to get a good result.

EB – But like for all of us, COVID-19 has thrown a bit of a wrench in the project team's plans, and it's making international research collaboration a bit trickier than usual and delaying the Vietnamese team's plan to organize training workshops in the region.

Dr Nguyen Thi Bich Thuy

Last year in 2020, almost our activity was pending because of COVID. On the Vietnam side, we are not so affected, but on the UK side, they have they have been locked down for a long time. So, it really is a threat to our project. That's why trainings and also conferences and workshops have not been organized yet. I really hope that this year we can do it. However, it is good that we already collected the sample and transferred to it to the UK already. So now we wait for the UK side to apply in Vietnam. Because of COVID it takes like half a year to try to transfer the simple strain and also the DNA to UK. I can tell you that now with we have done this work we are a little bit happy

Dr Nguyen Thi Bich Thuy

If we succeed, I think it's very, very good for our country. But I think it's good not only for our country, but for other countries as well that can apply the technique and learn to develop vaccines for sows. We only need to use a vaccine for sows, but the piglets also have an antibody transfer from the sow. That I think is a very good idea. If we succeed, we can announce or we can share with other groups and other countries about that.

JK – This is great, both the teams sound like they are onto some very promising approaches.

EB – Yeah, they're all harnessing the power of international cooperation and cutting-edge technology to make strep suis a thing of the past.

JK - But let me be pessimistic for just moment: what happens if a vaccine against strep suis isn't developed in the near term?

EB – Well, the stakes are pretty high. There are two scenarios to consider here. In the first, we continue using antibiotics to prevent and treat strep suis in pig production at the same rate we do today. In the second, we severely restrict antibiotic use in the pork industry to protect their efficacy. Which scenario would you pick?

JK – Sounds like a choose your own adventure books! Ok, let's say governments restrict antibiotic use so that they stay effective for humans.

EB – Well, it turns out that some countries are moving in that direction, including Vietnam.

Dr Nguyen Xuan Huyen

Hello my name is Huyen and I am head of the bacteriology department.[5]*. And in this project my role is technical specialist.*

Dr Nguyen Xuan Huyen

AMR is a big problem in our country, especially in animal production. In our country, our government has a plan to step-by-step restrict antimicrobial usage. We restrict, using limits, antimicrobials for animal production and in feed. So right now, I would encourage the research institutes find a way to develop a vaccine for prevention.

EB – The problem is, the incidence rate of s. suis is currently kept way down due to antimicrobial use.

Prof Mariela Segura

There is no effective commercial vaccine to prevent this disease in swine and people. We keep the incidence rate of disease in animals down, which normally could be around 20%. But it is kept lower than that, it is reduced to up to 5% of incidence because of the extensive use of antibiotics in a preventive way.

In Southeast Asia, like in Thailand, the governments are trying to make a measure to reduce the use of antibiotic as preventive measure, which means reducing the use of antibiotics in feed in livestock production. But what happens if you remove the use of antibiotics, which is what is being done right now in Europe, for example, you will have an increase in clinical cases of streptococcus suis. *So, you will have more disease in animals, and if you have more disease in animals, you will have more zoonotic cases in the human population. So it will be a kind of chain reaction. So yes, we remove the antibiotics as we are expected to do and then if we don't introduce a vaccine to protect the animals against the disease, then the animal will get sick, and if the animal gets sick more people can be contaminated as well.*

[5] Of the National Institute of Veterinary Research in Vietnam

JK – Wow, so based on what Mariela mentioned, infection rates could quadruple, from 5 to 20 percent.

EB – Yeah, more sick pigs means more pig mortality, and also more sick pork producers and handlers who are in contact with these animals. And lots of economic hardship, too.

JK – Alright, so that scenario is no good. What about the second option, where antimicrobial use in the pork industry doesn't change and an alternative way of preventing strep suis isn't developed. I can hear the AMR alarm bells ringing.

EB – Well, what are they saying?

JK – It's the same story we talked about in the primer episode, really. Areas where pork production is highly concentrated become evolutionary accelerators for strep suis. More and more resistant strains of strep suis emerge, and the antibiotics become less and less effective, so the incidence and mortality rates start to climb.

EB – Right, so then we're basically back to the impacts of scenario 1, but with fewer effective antimicrobials and more resistant bacteria.

JK – And knowing what we know about gene swapping, strep suis bacteria that have developed resistance genes could pass them along to other species, including some that are even more dangerous to humans.

EB – Yeah, and that's a major reason why strep suis specifically is such a focal point in the AMR problem.

> Dr. Sharon Egan
> *The streptococcal species are really good at swapping around their DNA between each other and also to related bacteria.* Streptococcus suis *causes problems and causes meningitis in humans. But, there's a number of other related human streptococcal diseases: streptococcus pneumoniae, for example; streptococcus pyogenes and agalactiae, and they all cause various respiratory meningitis septicemia diseases in humans. If we start getting this swap of all these antibiotic resistance genes between different species, we're going to have an issue with the antibiotics that we use to treat our diseases not working for us either. So not only would they not work in the veterinary world, but they won't work in the human medicine world either. And it's really scary. Really scary.*

JK – This begs the question, how much resistance is already out there? Was that something any of the researchers talked about?

EB – Yes, Adam has some pretty concerning numbers to share.

> Dr. Adam Blanchard

I found a really interesting paper, and it was based in Vietnam. It was saying that about 99% of strep suis have at least one resistance gene. So, each isolate is resistant to one gene, but about 5% have 17 different resistance profiles. There could be multiple resistances in one isolate. The project looked between 2006 and 2016 and saw a 20% increase in resistance to cephalosporins, which are human important; a 20% increase to resistance in gentamicin; a 4% increase to a 90% resistance to oxytetracycline, which is one of the most commonly used ones for veterinary medicine; and also a 10% increased resistance to penicillin. So that was nearly five years ago now, so if that same level of resistance increase is happening, in a couple of years, antibiotics aren't going to work against strep suis infections.

JK – The case for vaccines seems pretty clear.

EB – Yes. And luckily, it seems that legislators and potential users are already on-board to promote and use this vaccine when it becomes available, provided it is effective.

Dr Nguyen Thi Bich Thuy

The quality of the vaccine is also very important. If the quality is both good, even if the price is little bit high, they would still use it because comparing the use of vaccines with using antibiotics, farmers still choose vaccines because it gives a good result.

EB – But there will need to be some significant cross-sectoral collaboration and educational campaigns as well.

JK – Right, we can't really talk about vaccines without talking about educating and dispelling myths, can we. These projects are still relatively early in the vaccine discovery process though. So, when is the right time to start working with end-users to understand potential concerns to get ahead of any pushback?

Dr. Sharon Egan

Once we think we've got it right from our clinical trials, then, for the next step, we need to make sure that we're engaging with the smallholder farmers, and we're getting them on board with our vaccine trials as well. Because if it's there at the grassroots, we've got more chance of identifying any problems in communication, but also getting the right message across through them as well, which I think is really important. I suppose that at the moment, antibiotics are considered cheap and cheerful, aren't they? But at the moment, they still work and they do a really good job in protection, and they can be made at relatively low cost. Vaccines are going to be more expensive, because of all of the import into the safety and how you make them and making sure that they are effective, but also safe for use.

EB – When talking about vaccines at this current point in history, it's hard not to draw parallels with the COVID-19 pandemic. So, one other worst-case scenario that was mentioned was the risk that a new pathogen that's incredibly dangerous to humans and

highly transmissible emerges – for instance, a bacterial disease that has picked up some of strep suis' resistant genes.

JK – That's a scenario we can now all conceptualize very clearly.

EB – And this just shines a spotlight on how incredibly important it is to invest in this type of research, on preventative solutions for neglected diseases of livestock, in terms of global health, livelihoods and pandemic prevention.

> Prof Mariela Segura
> *I guess what COVID provides us with, in the positive, is that people now understand science more. It's much easier now to explain what we are doing. It's much easier now to explain why we need a vaccine, and in a way, it's much easier for us to explain that we have bad variants, and the vaccine may be good or not against variants. So it does help a lot.*
>
> *Vaccines are important and are amazing tools that we have, and they have been proven to be extremely successful to eradicate diseases. So we need to keep doing research on vaccine development, because it's the future. And for animal diseases, we need also to think ahead of having an outbreak. Because when the outbreak appears, it's too late to develop a vaccine. COVID was an exception, because we have vaccines developed in less than one year, but it will not be the case for all the diseases, and it will not be the case for diseases in animal or in veterinary medicine. So, we need to be prepared, and we need to work in advance and not wait until the fire and then to try to erase it because it will be too late.*

EB – But these projects really showcase why there's reason to hope when it comes to these kinds of major human and animal health crises

JK – Because minds from all over the world are putting their heads together to work on them?

EB – Precisely, emphasis on the word together.

> Dr. Sharon Egan
> *I think one thing it has highlighted is how well we could all work together if we have funding. And if we share our ideas and we share our resources, how fast we can turn around something that could be considered really negative, a devastating disease. But if we all pull together and share our resources, plan together, share our ideas, which is what happened with COVID, like that turnout of papers and the discussion and the collaboration between labs, that has led to us being able to have a number of fantastic vaccines that are actually working. If we could apply that collegial approach and not be fighting each other for funding or fighting each other to get those papers out and work more together, then you know what, maybe we could make more progress a lot more*

quickly on some of the things that we're working on in the animal health world but also in the human medicine world.

JK – Team work makes the dream work.

EB – Indeed it does

JK – Maybe that's a good thought to leave on. This concludes our series on antimicrobial resistance and the international researchers who are working together to develop alternatives to antibiotics.

EB – Or does it? Stay subscribed and find out. There may be a bonus episode in the works.

EB - For everyone wanting to learn more about the podcast, read the transcript or get in touch, visit us on the podcast's home page linked in the show notes. We'd love to hear your thoughts.

JK – Thanks for listening. Bye for now.

[end]

*Note that some of the quotes throughout this transcript have been lightly edited for readability.

SHOW NOTES

More than a mouthful, the *Streptococcus Suis* bacterium is a leading cause of mortality in the pig industry worldwide and drives high volumes of antimicrobial use. With its sugar capsule and its multiple and varied strains, this sneaky pathogen evades attempts to control its spread. In this episode, we dive into the cutting-edge of vaccine development and learn about glycoconjugate vaccines and using big data to find hypothetical proteins.

Innovating Alternatives is a serialized podcast that will delve into the issue of antimicrobial resistance, a slow-moving pandemic that risks erasing the last 80 years of modern medicine's progress. We will take you right to the cutting edge of science, where researchers are developing new and surprising alternatives to antibiotics and innovative solutions to reduce the use of antimicrobials in livestock and aquaculture production.

Get in touch and let us know what you think of the podcast by email innovetamr@idrc.ca or on twitter @Livestock_IDRC

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