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Expert Interviews

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Syphilis: Immune Responses & Vaccine Development

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The body’s immune response to syphilis and how the response impacts the development of a vaccine is complex. Dr. Tara Reid from the University of Washington Division of Allergy & Infectious Diseases delves into the various responses and the difficulties of vaccine development with Dr. Meena Ramchandani.

Topics:

- vaccine
- CD4
- CD8
- serology

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Disclosures

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Transcript

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intro**[00:00] Intro**

Dr. Ramchandani

Hello, everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STI [sexually transmitted infections] review for health care professionals who are interested in remaining up to date on the diagnosis, management, and prevention of STIs.

Welcome, everyone. For this episode, we are excited to introduce Dr. Tara Reid. Dr. Reid is an acting instructor in the Division of Allergy and Infectious Diseases at the University of Washington. Dr. Reid did her MD and her PhD at the University of Washington, and her area of focus is bacterial pathogenesis and T cell immunology, specifically looking at the immune responses to syphilis. So, welcome, Tara. We're so excited to have you on this episode.

Dr. Reid

Thank you for having me. I'm excited, too.

syphilis-immune-response**[00:50] Syphilis Immune Response**

Dr. Ramchandani

Well, let's just start out with some background for our audience, and I want to know what's been discovered around syphilis immunology and syphilis vaccines? Can you tell us a little bit more about that?

Dr. Reid

Right, so a lot of what we know about syphilis immunology, specifically, stems from studies that started in the early '60s and the '70s and that work has been ongoing but has been a little bit slower in the past decades. But from that, we know that in syphilis lesions, the bacteria that causes syphilis, *Treponema pallidum*, is cleared by a combination of host immune responses. So, there is antibody against the organism that binds, and then that helps facilitate phagocytosis, or removal of those bacteria from the lesion by macrophages. So, really, there's cellular responses and humoral or antibody responses that are important for clearing the bacteria from the body, and these responses are what we're trying to target with vaccinology.

Dr. Ramchandani

That's really helpful. Why do you think there has been so little data recently on the syphilis immune response in the human host?

Dr. Reid

Yeah, so there's a lot of different reasons. I'll say that much of the work that we do to understand *Treponema pallidum*pathogenesis, we do in the rabbit model of infection. So, we use rabbits for a few different reasons, but it's a limited model. We don't have strong immunologic tools to further define the immune response using

that model. That's one reason.

The second reason is, it hasn't been as easy to do this research in humans. So, we can get different biologic samples from people that have syphilis and do immunologic studies, and that work has been ongoing, but some of these finer, deeper dives into the immune responses are just starting to get off the ground.

Dr. Ramchandani

And also, probably the syphilis rates, they started increasing around the early 2000s, but before that, there were very few syphilis cases. So, I wonder if that also had an effect in terms of research during that period of time because there were so few cases, not many people did research in that area.

Dr. Reid

Yeah, there were relatively few cases, particularly in more affluent countries. As a side effect of that, there was less social investment into understanding syphilis pathogenesis, syphilis immunology as well. As we've been in this ongoing growing epidemic of syphilis, there is renewed interest and more support with different sources of funding for this research.

vaccine-syphilis**[03:46] Vaccine for Syphilis?**

Dr. Ramchandani

Can you tell us a little bit more about the benefit of a vaccine against *Treponema pallidum*? For example, why is there such a strong interest in a need in the development of a syphilis vaccine?

Dr. Reid

Right. So, as I mentioned, and as you know and as our listeners know, we have year-on-year increases in syphilis cases here in the United States, across the world. And this isn't for a lack of trying to stem this ongoing spread, right? There's a multitude of government local programs to help reduce the spread of syphilis. We've got great diagnostic studies that are widely available to most people. We've got excellent curative antibiotic therapies. But despite all of these great things, we still have more and more and more syphilis cases. So we, and most people in the field, are excited about the prospect of getting an effective syphilis vaccine to add to this repertoire of tools that we have to stop syphilis and get control of this epidemic.

Some of the finite benefits would be one, to decrease the severity of syphilis lesions. So, if somebody did acquire syphilis, we would want those lesions to maybe not ulcerate and be less infectious. Again, if somebody was to acquire syphilis but they've been vaccinated, maybe we'd be able to limit the amount of dissemination of the bacteria through the body. So that would have a lot of personal impacts. So, if you had less dissemination, you'd be less likely to potentially develop neurosyphilis, or ocular syphilis, or any other body-wide sequelae from infection.

As an offshoot of that, if a woman or a person of reproductive capacity was infected with *Treponema pallidum* and they were vaccinated and they weren't disseminating the organism throughout their body, they might be less likely to transmit that bacteria to a gestating fetus. Right? So, then we'd hopefully limit the numbers of congenital syphilis that we see.

Dr. Ramchandani

Are there any vaccine candidates for syphilis currently in clinical trials?

Dr. Reid

Oh, sadly, no, not yet. So, some of the vaccine candidates that we've identified, we've done so in rabbit studies, and those have been great. We've got really exciting candidates on the horizon that are able to produce partially protective immunity, again in this animal model, but haven't made it through to human trials yet. And part of the reason is we're still working on optimizing these vaccine constructs. Part of the reason why we haven't developed a vaccine to bring to human trials yet is we are optimizing the treponemal antigens that we're targeting, as well as optimizing adjuvants to help shape the immune response to what we think will be the most protective.

Dr. Ramchandani

And why use rabbits?

Dr. Reid

So, although *Treponema pallidum* can grow in multiple different model organisms, including mice, and hamsters, and guinea pigs, none of them develop the skin lesions and other sequelae of infection like humans do. So, rabbits develop a syphilis lesion similar or analogous to what we see in human infections. So, it recapitulates human infection the most completely of all these other model organisms.

prototype-vaccines**[07:30] Prototype Vaccines?**

Dr. Ramchandani

Have there been any prototype vaccines used in animal models, and what were the findings?

Dr. Reid

Yes, so for prototype vaccines in rabbits specifically, there's been individual protein subunit vaccines. So, an individual recombinant protein might be used to vaccinate animals. Many of those studies have shown either no protection at all or maybe partial protection after you immunize an animal and then try to challenge them with active live bacteria.

There's also been a number of multi-subunit vaccines where you're using maybe two or three different *Treponema pallidum* proteins as the vaccine and then challenging. And most of those studies we do measure a partial protection. So, none of these studies have shown full sterilizing immunity, but it's still very exciting because after challenge of these immunized animals, the lesions are attenuated. So, either they take much longer to ulcerate, or they never ulcerate, and maybe they heal much faster. So those are all great results from a vaccine.

And then, in other trials or even in the same trial, we've been able to measure a decrease in the ability of *Treponema pallidum* to disseminate within these vaccinated animals.

immune-response**[09:01] Immune Response**

Dr. Ramchandani

What do we know so far about the immune response to *T. pallidum* infections? You mentioned a little bit about antibody response and cellular immune response. What are some of the findings of those areas?

Dr. Reid

The way that I like to approach it is understanding what happens at the interface of our immune system and the bacteria. So, at that interface, often in the skin or mucosal sites where we find like chancres developing, we know from prior studies that the bacteria are opsonized or coated with antibodies. So there's antibodies

covering the organism, and then macrophages in the tissues will come in and phagocytose or gobble up, almost like Pac-Man gobbling up whatever Pac-Mans gobble, and removing those bacteria from the lesions. So, it's a complicated dance between the bacteria and the immune system. But part of the components of our immune system that are fighting the bacteria, again, include our antibodies, the cells that make the antibodies, our B cells and plasma cells, and then our T cells, which we think function in a couple of ways. So, there's multiple types of T cells, but I'll focus here on CD4 T cells. And these are really important because they provide help to those B cells that are producing antibodies, and they produce interferon gamma that activates those macrophages to do that Pac-Man action and gobble up those treponemes and remove them.

Dr. Ramchandani

Are antibodies protective?

Dr. Reid

Great question. So we think that they can be, and all of those immunization studies that I mentioned oftentimes will measure antibody against the immunogen, against the protein that we're using as the vaccine. And the antibody levels oftentimes will correlate with the protection or relative protection that we see. There are older studies, decades-old studies, using passive transfer of antibodies. So taking antibodies from one animal that's been infected for a long time and they've cleared bacteria, taking sera and antibodies from that animal and then infusing that into a second animal, and then challenging them and measuring protection. So, in those types of studies, those older studies, we also find that antibody response from rabbit A is protective in rabbit B.

serologic-response**[11:30] Serologic Response**

Dr. Ramchandani

So how does that relate to a serologic response to syphilis in terms of the treponemal antibody tests? Because those don't seem to be protective, but they help us diagnostically.

Dr. Reid

Yes. I love that question. So, and it's important to understand the treponemal tests measure a couple of things. So, there's different treponemal tests, right? Our fast high, throughput treponemal tests, like the EIAs [enzyme immunoassays] and CIAs [chemiluminescence immunoassays], really only measure antibodies to three to four treponemal proteins. So, three to four. The TP-PA [*Treponema pallidum* particle agglutination assay] and things like the FTA [fluorescent treponemal antibody] measure antibodies across the whole organism. But, if we're just thinking about an EIA test, for example, antibodies to those three *T. pallidum* proteins aren't protective. We know that. But in those prior vaccine studies that I mentioned, some of the targets that we use in our vaccines are putative or known outer membrane proteins. And so, if you imagine the outside coat of the bacteria, if you want antibodies to stick to the bacteria and have any impact, they have to be targeting something that's exposed on the outside of the bacteria. So, these are the outer membrane proteins. These are the ones that we use in our vaccine studies typically, in contrast to what we use in our diagnostic studies, right? Those actually tend to be proteins and lipoproteins found kind of underneath the outer lipid membrane of the protein.

Dr. Ramchandani

So, there are antibodies that the immune response makes to interact or to clear the infection. Some can be protective, and some are not.

Dr. Reid

Right. Part of what predicts whether they're protective or not is where that protein is in the bacteria.

cellular-immunity**[13:30] Cellular Immunity**

Dr. Ramchandani

What about the cellular immunity? For example, CD4 T cells and the CD8 T cells? You described a little bit about CD4 T cells. How do they play a role in the immune response to infection?

Dr. Reid

So, a lot of what we know initially about the immune response to syphilis comes from immunohistology, so actually taking a piece of a lesion and looking at it under the microscope. And even early lesions, so we think about chancres, for an example, you'll see an influx of lots of immune cells but a lot of T cells. So that includes CD4 T cells, and CD8 T cells, and other subtypes. But, that very initial influx of T cells, we call a delayed type hypersensitivity reaction. So typically, this is like a TH1 CD4 T cell response to bacterial antigens, and it happens quickly. Right? So that's the first immune response that you see. That will mature over time and you'll see these CD4 T cells and also CD8 T cells infiltrate lesions along with B cells, and as a subset of B cells, plasma cells that are actively producing antibodies.

Dr. Ramchandani

Do we also see an influx of these cells in the skin, for example, if someone had a rash?

Dr. Reid

Correct. So, as you know, that rash can present differently in different people, but when we biopsy and look at that rash under the microscope, typically we'll see again that same CD4, CD8 T cell infiltrate, along with phagocytic cells, dendritic cells, macrophages, and K cells as well, in addition to those plasma cells, as I mentioned. So, it actually looks quite similar to what we see in the primary chancre.

Dr. Ramchandani

That's helpful. So primary and secondary, we'll see these infiltrates, all these immune cells to the skin, especially if someone had secondary rash.

cd8-cells-role**[15:38] CD8 Cells Role**

Dr. Ramchandani

What about CD8 T cells? Do we have any evidence that they play a large role in the immune response to syphilis?

Dr. Reid

That's such an important question, and it excites me. The CD8 T cell response is not well defined, to be honest. So, we know that they're there. We know that they're in lesions. We can measure CD8 responses in the circulating blood as well. We know that during neurosyphilis, there's CD8 T cells in the CSF, the cerebral spinal fluid, as well. But we don't know exactly what they're responding to and what their effector functions are. We know that they make interferon gamma, so presumably, they're an important source of interferon gamma to activate those macrophages, again, that are doing that Pac-Man action. But there's a lot of work that needs to be done to better understand and define that, right? If it's a really important and protective response, it'll be so beneficial to know it and understand that and utilize that as we're thinking about building a maximally effective vaccine.

Dr. Ramchandani

Yeah, so it'd have to have some sort of protective antibody response, elicit an immune response from CD4 T cells, but then also CD8 T cells as well.

Dr. Reid

Potentially, if it turns out to be something that's truly physiologically important.

stages-immune-response**[17:04] Stages of Immune Response?**

Dr. Ramchandani

Do we have any evidence that the immune response changes during different stages of syphilis? For example, those with primary syphilis might have a different immune response than those who have latent syphilis. You talked a little bit about the cellular immunity to the skin, but what about the immune response in general?

Dr. Reid

The lesions of early syphilis are similar. So, we'll see a TH1-predominant CD4 T cell infiltrate, and also antibody producing cells. That's limited to our ability to target those tissue types, biopsy them, and look at them under the microscope. During latency, by definition, there is no active lesion, there's no outward sign of infection, no tissue to target to look at those pathogen- or bacterial-focused immune responses. There are studies that describe the circulating response. You can measure these different cell types, but in latency, it can be difficult to assign causal relationships. Latency, because you don't have any lesions, it can be difficult to age that latent stage, right? How long has this person had latency? What was their primary infection like? Did they have a chancre? Did they have secondary syphilis ever? Yes, no, maybe? And so, there are exciting and really helpful data. It's just hard to say, "Oh, you know, in primary syphilis, the circulating immune response looks like X versus Y in secondary syphilis versus Z and latency."

Dr. Ramchandani

Yeah, that makes sense in terms of how difficult and challenging it is to study the immune response to syphilis because you have these different stages, there's different clinical manifestations. Also, different clinical manifestations even within one stage, and so all of that is variable. And in the latent stage, no one has any clinical manifestations, and so then it's hard to ascribe whether the immune response is due to syphilis versus something else. There's probably a lot of variables.

Dr. Reid

There are. Add into that all the other things your immune system is responding to just in your life, day-to-day life, right? So, whatever respiratory virus you might be exposed to can alter what we're measuring as a general immune response in the blood. Maybe you were vaccinated against something. All these things can change the levels of different immune cell types in the blood.

impact-past-history-syphilis**[19:37] Impact of Past History of Syphilis**

Dr. Ramchandani

Does the immune response differ in people who have had a past history of syphilis? Is there any evidence that a past history of syphilis might be protective?

Dr. Reid

That's a great question. So, one of our colleagues here, [Dr.] Christina Mara, actually published a really great report on this, suggesting that people that have had a prior history of syphilis are more likely to develop early latent syphilis upon reinfection. So what that means is, if you've had syphilis before, you've had the bacteria in your body, you may have developed enough immunity, such that if you were exposed to the bacteria again, instead of developing like a primary chancre or secondary syphilis lesions, you develop an infection, right? We know this because the RPR [rapid plasma reagin] will go up, but there's no outward sign of infection, there's no lesions during that latency. This is important because we really have good evidence that those syphilis lesions, the early syphilis lesions, are the most infectious stage of syphilis. You're much, much, much less likely to be transmissible if you've got latent infection, be it early latent or late latent.

Dr. Ramchandani

That's really exciting because it does suggest that there is some protective effect of a history of syphilis in decreasing those more advanced clinical manifestations, and that's encouraging.

Dr. Reid

It is encouraging. I'll share a big caveat, though. There's also evidence that the increased incidence of early latent infection might be due to our testing and screening patterns. So, if we're screening people more frequently and our screening programs are just becoming more and more robust, we're screening more people, we're more likely to detect early latent syphilis or late latent syphilis.

Dr. Ramchandani

That's a good point. And in someone with a history of syphilis, we tend to screen them more frequently and within a shorter period of time.

Dr. Reid

Correct. So, I like to think that, yes, as we are treated for an early syphilis case, that we develop some protective immunity. This is my hope. My hope is that we are indeed developing some protective immunity that we can capitalize on with a vaccine and that will help protect people in the future.

Dr. Ramchandani

Very encouraging.

ideal-vaccine-response**[22.11] Ideal Vaccine Response**

Dr. Ramchandani

If one were to develop a syphilis vaccine, what do you think would be the ideal type of immune response?

Dr. Reid

The ideal type of immune response would include multiple components, but one would be a robust antibody response. We think that antibodies are so, so important, as I mentioned, to clear treponemes, right? So, we want to get those antibodies to outer membrane proteins. So that's the first thing that we're after.

The second component of a robust immune response would be the cellular immune response. This is kind of an umbrella term to include the CD4, TH1-type immune response, and then also potentially a CD8 T cell response. Again, more data are coming.

And then lastly, I'll add that we want all of these immune responses to be durable. We want it to last and last

and last for years and years and years, so that we're not having to constantly boost with immunization. But if that's the case, then so be it, but a durable immune response is key.

Dr. Ramchandani

Well, we appreciate you being on this episode, Tara. It was fantastic, and I learned so much from you.

Dr. Reid

Thank you.

credits**[23:25] Credits**

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