BBGuy Essentials 087CE:
Transfusion-transmitted Infections with Suchi Pandey
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Suchi: This is Dr. Suchi Pandey from Stanford, and this is the Blood Bank Guy Essentials Podcast.

Joe: Hello, and welcome to episode 087CE of Blood Bank Guy Essentials, the podcast designed to help *you* learn the essentials of Transfusion Medicine. My name is Joe Chaffin, and I'm thrilled to be your host. I'm really excited to take you on a tour of infections that can be transmitted through transfusion and how we go about preventing them, with my friend Dr. Suchi Pandey.

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So, this episode is one that I have really been wanting to do for quite some time. As you've heard me say if you've listened to the podcast before today, my focus is not really on the most advanced or "cutting edge" stuff ["serious announcer voice"] on the far reaches of the expanse of Transfusion Medicine knowledge. I really don't want to do that! I think it's inherent in the name, "Blood Bank Guy Essentials," but I want to cover the essentials, the things that are really core knowledge in this field, especially targeting people who are learning, but also anyone looking to brush up on the important stuff.

To that end, when I was talking with my friend Dr. Suchi Pandey from Stanford, Suchi mentioned that she had developed a talk that hit the basics of transfusion-transmitted infections for her residents there at Stanford. She barely had the words out of her mouth before I was inviting her to join me on the podcast to talk about just that! In this interview, Suchi takes us through the main infectious agents the we worry about being passed along by a blood transfusion, and she does it in a really entertaining and memorable way. I think you will find what she covers to be very enlightening.

I should mention one thing, however, and that's that one of the things we DON'T cover is actually one of the BIGGEST risks of infection, and that is bacterial infection of platelet products. I didn't really want to take time to do that, because I spent a lot of time talking about that in episode 076 with Pat Kopko earlier this… actually, late last year in 2019. So again, check out BBGuy.org/076 for more information on the bacterial guidance.

Let me tell you a little about my guest before we start. **Dr. Suchi Pandey** is currently Chief Medical Officer for the Stanford Blood Center and she is a Clinical Associate Professor in the Department of Pathology at Stanford. She is a graduate of Drexel University College of Medicine in Philadelphia, the UC-San Diego Pathology residency, and the UC-San Francisco/Blood Centers of the Pacific Transfusion Medicine Fellowship. Suchi's interests include donor health, Transfusion Medicine education, and immunohematology. She is on the board of the California Blood Bank Society, and she is co-chair of the Blood Center of California's Medical Advisory Committee. On a personal note, I've known Suchi for a number of years now, and I find her to be just brilliant and an all-around tremendous person!

You're going to love this interview, I think, so I'm very happy to share it with you. Let's get right now to "Transfusion-transmitted Infections."

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Joe: Hey, Suchi! Welcome to the Blood Bank Guy Essentials Podcast!

Suchi: Hi, Joe. Thanks for having me.

Joe: It's so exciting to me to be able to talk about all these infectious diseases that can potentially be transmitted through transfusion and get some clarity on that for our listeners.

I wonder if you can just kind of give us a little bit of a general philosophy, Suchi. I mean, what's the rationale behind how we're looking at screening our blood donors for the potential that they have to transmit an infectious disease?

Suchi: Yeah, so, you know, there are a number of different ways that we can try to make our blood supply safer and mitigate the risk of infectious diseases. So there's screening using donor history questionnaires, there's testing, there's also potential ways you can process the blood, there's pathogen reduction...

So there's numerous ways that we can mitigate and decrease the risk of infectious diseases. And which tools we use really depends on the infectious disease. So for some we, for many, actually, we use, both the questions to decrease the risk of higher risk donors donating. And then, in addition, we also do testing for some infectious diseases. For others, we're only doing screening via the questionnaire and questions that we ask like malaria and there isn't currently any approved test for donor screening. So it really depends on the infectious disease what approach we're going to take.

Joe: I guess we should say from the beginning, well, we should answer this question, which I hope is fairly obvious: Whose rules are we following when we make those decisions? Do blood centers just make those up on their own, or are we following somebody specific?

Suchi: Yeah, we actually, so we have guidance and requirements from the FDA. So the FDA does provide us with rules in terms of which infectious diseases that we are required to screen for, and, you know, which types of infectious diseases we have to ask questions about. And then also we have the AABB. And the AABB

has “Standards” that provide to us all of the questions that we need to ask to blood donors, and they actually have a “Universal Donor History Questionnaire,” which the majority of blood centers in the U.S. are using. And that contains all of the questions relating to risk that we have to ask for donors.

Joe: So those of you that are listening internationally, just please be aware, we kind of have to just cover the way things are done here in the United States in this episode, there are some differences, absolutely internationally. So please check with your local authorities.

A couple of other things before we get to some specific infectious diseases. Let's talk a little bit about something that learners sometimes get a little confused about. So let's just imagine, for example, we're going to talk a lot about different tests that we do today, and in certain cases, certain test patterns leads to certain things happening to the donors versus (in other words, whether the donor will ever be able to donate again), and certain things happening to the unit of blood that's collected.

So can you help us understand the difference between *unit management* and *donor management* from these tests?

Suchi: Sure, and those are two very important things that you always have to consider when a donor does test positive for an infectious disease that we're required to screen for.

So first it's, how do you manage the donor? So depending on the infectious disease result, so there's two things that we do. So one is a screening test. So we are using tests that are approved specifically for donor screening. So we test all donors with that screening test. And then if that donor is positive, then we'll do a confirmatory test. So if the donor is positive for both the screening and the confirmatory, then we do have to inform that donor that they're deferred. And how long we defer the donor really depends on that infectious disease.

So for example, if a donor confirms positive for hepatitis C, then that would be a permanent deferral. If a donor confirms positive for West Nile virus, that's 120 day deferral. So depending on what is the infectious disease and the characteristics of that disease, the donor would be deferred for a certain time period.

But then you also have to think about the product that that donor gave. So when a donor's product or unit is collected at the blood center, it's actually held in a quarantine state until we get the infectious disease results back. If the infectious these results are positive, then that donation that they gave cannot be used.

But in addition, for some of these infectious diseases required to also do, what's called a “lookback.” So you “look back” a certain time period if that donor was a repeat donor, you have to think about, “Are any of the donors prior products that they gave potentially also impacted?”

So that's for product management, you look at the most recent donation and the past donations as well and decide how you need to act on those.

Joe: And you talked about a lot of great stuff in there. I just want to re-emphasize one thing that again, I think, learners sometimes get a little puzzled about, and that's that not every donation gets every confirmatory test. For example, you only go to those confirmatory tests if it's indicated by a positive or a repeat reactive in the screening test. Is that accurate?

Suchi: That's correct. So let's take, you know, HIV. So for HIV, the donor screening test that's approved is an antibody test against a [HIV] 1/2. Now, if that's positive, then you would trigger to a confirmatory test like Western blot or IFA.

Joe: That's important. And I hope that you guys that are learners pick that up. It's a really important distinction in how we manage those tests.

Okay, Suchi, well, we've got a lot to cover and we're going to have to stay kind of high level as we go through these, but I know you have a ton of great stuff to tell us, but let's "tell the story." Let's walk us through. Where did we start? Back in the 20th century, when people started transfusing blood from one human to another, where did we start with figuring out that, "Hey, sometimes bad stuff goes from the donor to the recipient"? Tell us the story of that.

Suchi: Early in the 20th century, when transfusion started to occur, one of the first infectious diseases that was reported to be transmitted through the blood was actually syphilis. And one study showed that by 1941, a total of about 138 transfusion-transmitted syphilis cases had been reported.

So in 1938, we actually had started screening for syphilis, and we still today screen for syphilis, but fortunately we don't see transfusion-transmitted infections. In fact, you know, the last published case that I'm aware of in the U.S. was in 1969. But we still continue to screen because it can also be a surrogate, a sign of risky behavior. So we do continue to test for syphilis for all of our blood donors.

Joe: I think that's an important point. Maybe you could expand on that for just a second. The use of a test that doesn't necessarily by itself tell you that much, because as you said with syphilis, "hmm, nothing since like 1969," something like that, but you're using it as, I think you said the word, a "surrogate."

Can you talk a little bit about that? Are there other examples of that in our history?

Suchi: Yeah, so that concept has been used before. So as I mentioned, syphilis, we continue to test and that's one of the reasons. Another example was, during HIV. So when HIV hit the scene, and, you know, it was a very tragic time, there was still, it took some time for researchers to identify the virus causing HIV and AIDS, and then of course develop the test that can detect it.

But there were tests that they found like, hepatitis B core antibody that could be used as a surrogate, although it wasn't perfect, but it could be used as a surrogate to help maybe identify units, that may have had a higher risk of potential HIV before we had the HIV test available.

That is another example in history. And we continue to do the Hep B core antibody test to this day.

Joe: Yeah, and I have my own feelings about that, but, well, let's just leave [LAUGHS] let's leave that one alone. Those who are wondering why we're laughing, both Suchi and I are medical directors at blood centers. And, both of us, I think, would say that the anti-hepatitis B core test is a little bit of the scourge of our existence. That's, if not the most common repeat reactive test, it's pretty close to it, Suchi, in my experience. Is that the same as yours?

Suchi: Absolutely.

Joe: And it rarely means a whole lot. So let's…we'll get to that one. Let's before we do so, let's *please* leave syphilis. That's another one that I have some feelings about, in terms of the testing, but what happened next? What was the next infection or group of infections that popped onto our horizon?

Suchi: Yeah, so the next was actually, came up during World War II. So during World War II, we had developed some very good preservative solutions that made blood transfusions widely available to soldiers on the battlefield during World War II that were injured. But what emerged was initially called "serum hepatitis," essentially as a major hazard of blood transfusion among survivors of World War II. So really the next disease that was basically reported and caused a significant morbidity in transfusion recipients was transfusion-associated hepatitis.

And there's different kinds of hepatitis. So, you know, there's hepatitis B. And we did have a way to test for hepatitis B in the '70s, but what a lot of these cases were actually "Non A,Non B hepatitis," which we later determined to be hepatitis C.

And so there was a point in time where almost 30% potentially of transfused units could have had either hepatitis B or hepatitis C. and actually. And one of the biggest ways where we decreased the risk was actually, of hepatitis, was that in the early-mid 70s, we moved our blood donor pool to a complete volunteer system. And that in and of itself really decreased the risk for hepatitis, but not completely.

Joe: So why don't you talk to us a little bit about our current strategies? Because you had mentioned "questioning, testing, et cetera." What are our current strategies for Hep B and Hep C?

Suchi: Yeah. So, for Hep B and Hep C, we do use a multi-pronged approach or "belt and suspenders" approach where we do question donors for risk factors for hepatitis. So, for example, "have you had close contact or lived with somebody with hepatitis?" That's one example, and then donors, of course, who answer that they have a certain risk factor for hepatitis B or hepatitis C, they would be deferred.

But in addition to that, we also do testing, and the testing algorithm is the same. You know, we do an approved donor screening test, and the approved donor screening test is both an antibody test and also a nucleic acid test where we're looking for the actual RNA or DNA of the hepatitis virus.

Joe: Let's start with Hep B, maybe. With hepatitis B, Suchi, talk to us about the tests that we use to detect hepatitis B in blood donors.

Suchi: Sure. Yeah. So hepatitis B, we actually have three tests that we're using in blood donors. So first is the **hepatitis B surface antigen**. So this is where you're looking specifically for the viral surface antigen.

The next test that we do, that's also looking specifically for virus is the **nucleic acid test for hepatitis B**. So looking directly for the genetic material of that virus.

And then the last test that we do is an antibody test, which is **anti-hepatitis B core**. So those are the three tests that we're using for hepatitis B.

Joe: This is where the trick comes in. This is me editorializing for just a second. People that write examination questions (and I'm sure you've seen and experienced this, Suchi), they love to try and trick learners by suggesting that we're doing an *antibody* test for hepatitis B surface antigen. I can't tell you how many times I've seen those examples.

So, there are a lot of details there that we could go into in terms of confirmatory testing, et cetera. And I don't want to get too deep in those weeds, simply because they're DEEP weeds. But, I guess this is one place where I could ask you to just talk a little bit about the use of, in certain cases, the nucleic acid test to confirm the results of either the, for Hep B, the antigen or the antibody tests. Could you talk through that a little bit?

Suchi: Sure. Yeah, So, you know, as I mentioned before, so for these blood donor tests, there's usually an approved screening test and then a confirmatory test. So for nucleic acid testing, when we do the screening, blood centers will actually do them in "mini-pools." That means we take multiple donor samples and pool them. So you can either pull 6 samples together, other tests do 16 samples together, and then you do a single test on that pool. If that pool is positive, then we "discriminate" the pool and we try to determine which of those 6 or 16 samples in that pool actually was positive. And that's called "ID NAT" or "Individual NAT."

So that's the confirmatory for the screening mini-pool nucleic acid testing. But in addition, you can also use that ID NAT to confirm your screening Hep B surface antigen as well, or neutralization. So the other option is, you confirm with a neutralization test as well.

Joe: One of the things that people talk about, and we haven't introduced this concept yet, but the concept of the "window period," the period between when a donor is infectious and when we can detect that infection in the laboratory. So what are we looking at for hepatitis B? How well do we do?

Suchi: Yeah, so, you know, great point, the window period is a very important concept in blood safety. So, for hepatitis B, with the introduction of nucleic acid testing, it has actually very much decreased that window period. So right now for hepatitis B with introduction of nucleic acid testing the window period is about 18, up to 26 days.

So that means it takes that amount of time after a donor is exposed and infected for the test to turn positive. So, that's an improvement for, from when we were just doing antibody or the surface antigen testing. When you combine that statistic, you can determine that the residual risk of hepatitis B is about now one in about 1 million per donation; so extremely, extremely low.

Joe: Nice. That's great. Okay. Well, let's move on and talk about Hep C because again, we've got ground to cover, but, I'm guessing Hep C is kind of similar, but not quite the same. Is that accurate?

Suchi: Very similar. So there's a **nucleic acid test** that we do as a screen, also, again, in a mini-pool. And then we do an **antibody against HCV** as well. And both of those, you know, have confirmatory testing we use if they're positive. But when we look at the window period for hepatitis C, this is where we really see nucleic acid testing makes a huge difference. So with the nucleic acid testing, the window period actually is only about 7 to 10 days, versus before, when we just had the antibody testing, it can take one to two months for the antibody to turn positive. So it really has improved blood safety by introducing nucleic acid testing for hepatitis C and now the residual risk is only about one in a million per donated unit. So again, very safe.

Joe: That's great. That's a big change when you, when you look at that graphically, and you see, 7 to 9 days or so versus 60+ days, that seems like that has the potential to make a serious difference. Of course, we're talking about a pretty safe population, right? I mean, that's the thing that I always wonder about when we talk about knocking down these window periods, which is great, but you're already talking about a really safe population. So I'm not sure how many donors fit into that previous window period. Do you have any idea of that, Suchi?

Suchi: I don't actually, but I think you make a good point, because our screening, first of all, the first mechanism we have to make blood safe is it's a volunteer donor pool. So that we know in and of itself brings in donors with low risk. And then in addition, we do all of that questioning, and donors that report any risk factors, they won't proceed with the donation. So with already those two things in place, I think you're right. You know, overall, you're screening already a lower risk population.

Joe: We've talked about hepatitis B and hepatitis C. I assume since we're not talking about Hep A, but somebody is going to ask, that Hep A is not a big deal for us in terms of transfusion transmission. Accurate, Suchi?

Suchi: That is true. You know, if there is a local outbreak of Hep A, then we do have things that we can put into place to decrease the risk in that local area of an outbreak. But in general, that's the only time we really have any mitigation strategy for Hep A.

Joe: Okay, well, so the story continues Suchi, and the next part of the story is not my favorite part because it was not fun at all. And that's when the 1980s came around. Why don't you talk to us about what happened then?

Suchi: Sure. So, you know, really tragedy did strike in the 1980s, and in many ways with HIV and AIDS, and it really did have a major impact to blood transfusion and blood safety. So, you know, the first case of transfusion-associated AIDS was reported actually in San Francisco, down the street from where I live, at UCSF in 1981.

And, by that time, all right, we estimate that in San Francisco, the risk was already at about one in a hundred units, transfused, if you can imagine. So greater than 1% of blood units in San Francisco had HIV in it.

So, it was a major tragedy in the sense that, you know, by 1987, there were about 37,000 AIDS cases identified; about 3% were due to transfusion. And the total number at that time of transfusion-related HIV was over 10,000. So it really was a challenging time in the sense that this infectious disease could be transmitted through blood, but we didn't have really an adequate way to test for it until 1985 was when the first anti-HIV test was licensed and implemented for donor screening.

Joe: I make the comment sometimes to people that it feels like everything we do in blood banking is done through "HIV-colored glasses." And I don't say that to make light of anything. It's just that, because the consequences were so dramatic and so horrible, it really impacted, from my perspective, everything we do until this day,

Suchi: It's absolutely true. I mean, just, any new emerging disease that we become aware of, we have to think of, remember the story with HIV and how that was a disease, an emerging disease that really did have a significant morbidity in transfusion recipients and mortality in transfusion recipients.

So we really, since then, you know, I think there's been a lot more regulations and, you know, a number of strategies put into place to really help maintain blood safety, especially in light of emerging diseases.

Joe: Absolutely. Well, back to HIV for a second: Do we have any idea of how well that…you mentioned 1985, we got the first, that first test. Do we have any idea of how well that worked?

Suchi: Yeah. So, you know, from 1985 to NAT, so nucleic acid testing was also implemented. That was implemented in ’99, but between ’85 and 1999, there were only 49 transfusion-transmitted HIV cases. So much, much fewer. Still, you know, not zero, but much less than we saw before that testing was implemented.

So it did make a huge difference. And then in ’99, that's when the nucleic acid testing was implemented again in, you know, the mini-pool format. But with that, you know, I think when I looked the last reported case, I was able to find since ’99 was in 2008 of a transfusion-transmitted case in Colorado.

Joe: Yeah, I'm sadly familiar with that case. That case led to one of the few times when I've been on the news. And I did not enjoy that, even though my blood center wasn't involved at the time it happened, because it happened in my area, I

ended up giving interviews about that. So yes, that's, to my knowledge, that's the most recent one that I'm aware of as well.

Suchi: But, I mean, it just goes to show like you know, we've reached a point with blood safety with HIV and also hepatitis where it is so rare that when it does happen, it's a big deal, you know, because it's just so rare and we've really tried to make it almost as close to zero risk as we can for HIV and hepatitis.

Joe: Let's talk about how effective we are. You gave us kind of some statistics and it looks at the window period for hepatitis B and hepatitis C. What can you tell us about how all that fits together with our questioning and testing for HIV?

Suchi: Yeah, sure. So there's actually a number of questions that we ask on the donor questionnaire relating to HIV risk behaviors or risk factors. And so we ask all of these questions. And if a donor answers "yes" to any of these, we will defer them.

And there was just a recent change. It used to be anyone that reported an HIV risk factor would be deferred for a year. And now it's actually, the FDA has updated that to three months. So there is that deferral and that length of the deferral is relating to the window period, which we'll talk about shortly.

In addition to the questioning, then we also have the testing. So, HIV, we also have this "belt and suspenders" approach. And for the testing we do, as I mentioned before, a **mini-pool nucleic acid test**. And then we also do an **antibody test against HIV-1/2**. So between the questioning and the testing, the risk now is really one to 1.5 million per donated unit. And the window period with nucleic acid testing is only about 9 days.

Joe: What *was* the window period when we just had antibody testing? Did we have that number?

Suchi: Yeah, it's closer to about 3 weeks, so 21 days. So still pretty good, but not as good as 9 days so that, you know, the nucleic acid testing really has decreased that window period.

Joe: So again, that's great, and it's put us in a position where those transfusion transmission of what I call the "Big Three": hepatitis B, hepatitis C and HIV is not common anymore. In fact, it's really, really uncommon, which is fantastic. And, anything more you want to add about those three, Suchi, before we take a quick tour through the rest of the ones that we worry about?

Suchi: What is the risk of getting hit by lightning? I think that might be more risky than getting HIV or hepatitis from a blood transfusion, just to put it into perspective.

Joe: Exactly! Now that we've covered those three, which again, we spend a lot of time worrying about those in the world that you and I live in, there are many, many other potential organisms that can do damage, many of which we are required, or "guided" by the FDA, let's say, to do testing for. So let's take a quick tour through those. Let's start with, if you don't mind, one of the ones that learners always

forget that we test for, because it's not a famous virus, and that's the **Human T-cell Lymphotropic Virus**. What can you tell us about HTLV?

Suchi: HTLV, there's actually two types, there's type I and type II. And trans transfusion-transmitted HTLV has been reported, but overall it's pretty rare. But, because there is that risk, we do test for both of these viruses, for HTLV. And essentially, what they cause is different.

So for HTLV-I, HTLV-I has been associated with adult T-cell leukemia and also a type of myelopathy. And in 1988 is when we had the first licensed test kit for HTLV antibodies and the FDA recommending that all blood donors are tested for HTLV-I.

Then for HTLV-II, it is also associated with a myelopathy. And in '97, that's when the FDA recommended that we test all donors for HTLV-II. The **testing that we do for HTLV is an antibody test against -I and -II as a screening test**. And this is an example of a virus where we don't necessarily have a screening question specifically to mitigate risk. It's really, the risk is mitigated mainly by the testing that we're doing,

Joe: Any idea of the residual risk from transfusion for HTLV?

Suchi: So it's very rare. And so it's, you know, what I've read is about 1 in 3 million per donated unit. The window period is a bit, it's 51 days, so longer than what we see for some of the other viruses we discussed. But overall, the risk is just so low because the prevalence of HTLV-I and II in blood donors is extremely low.

Joe: HTLV is one of those viruses that when I'm doing donor counseling for people that have it, it's one of the few things that we in blood bank world can actually say, "Yeah, it looks like you may have this, but it's probably not going to mean anything for you in your life." Right? I mean, that's an unusual position to be in when you're counseling somebody about HTLV.

Suchi: It's true. And it's hard, you know, because a donor can feel quite worried that they've now just been told they have this virus, but you know, there's uncertainty if it will actually end up resulting in disease. Because not everyone with these, either HTLV-I or HTLV-II will actually develop…it's just a small percentage of people that will actually develop those clinical scenarios, leukemia or the myelopathy I talked about.

Joe: Absolutely. Okay. Well, the next one that we want to just hit quickly is one that I've covered in a previous podcast, everyone, I spent episode 047 with Dr. John Roback from Emory talking extensively about cytomegalovirus. So Suchi, high level, what do we do for CMV? Do we test every donor for CMV?

Suchi: No, we don't test every donor and, you know, actually a number of just blood donors and the general population have been exposed to CMV and have developed antibodies against CMV. And it really doesn't have any clinical consequence, but if you have a blood product collected from a donor that had CMV, it could cause potential issues in certain patient populations. So for example, transplant recipients or low birth weight infants.

So the way we try to prevent that from occurring is, because we aren't testing all donors, what we do is, there's actually two approaches. So one is that a lot of, the majority of the blood supply in the U.S. is now what's called “leukoreduced.” That means that after we collect the blood, it goes through a filter, to remove a lot of the white blood cells. And we actually call that “CMV-safe,” because CMV is a virus that's associated with white blood cells. So when you remove most of the white blood cells, you're also removing the risk of CMV.

So right now, that's how most centers will transfuse the higher risk patients, with leukoreduced units, to prevent that possible transmitted risks.

We also do test, so Stanford Blood Center, we do test a small proportion of our blood donors for CMV, many other blood centers do that too. And you know, so there is still the option to provide CMV-seronegative products. But in general, most hospitals have now transitioned to really, to prevent CMV transmission in most patient populations, to transfuse the leukoreduced blood.

Joe: There is disagreement on that.

Suchi: There is.

Joe: I have said, and I will stand by what I've said before that, in my opinion, that the risk is functionally the same from getting a CMV negative unit, as opposed to relying on leukocyte-reduced. Is that your position as well, Suchi? I don't want to misquote you. Is that where you stand or how do you feel?

Suchi: No, I think that's true.

Joe: Fair enough. So, let us then move on, because man, there's a whole lot of other stuff, Suchi that happens! My goodness…

Suchi: We have to get into the 21st century now

Joe: You're right about that. So, in our very mobile society, there is a wide variety of other things that can happen in blood donors that could, theoretically, at least, be transmitted through blood transfusion. Some of which we do a lot of work for, some of which we're figuring out what to do work for, and et cetera.

So, let's talk about some of those viruses that are, in some cases, geographic, but again, given our world today, as people move around, at least before coronavirus, things can move from place to place. So let's talk first about West Nile virus, which is, in my opinion, a great example of something that moved, and certainly moved geographically across the United States.

What can you tell us about WNV and what we do for that and what the risks are?

Suchi: Sure. So, you know, West Nile virus is a perfect example of, you know, emerging threats that we're seeing to our blood supply in the 21st century. And, it's actually vector-borne, so it's, you know, mosquito-borne. And as you said, you know, we did see, you know, migration of this disease.

So for West Nile Virus, essentially the first case, actually happened in the U.S. in 1999, but it wasn’t until 2002, where we saw a large U.S. outbreak on the East

Coast. And in that same year, 2002, it was also recognized that this is definitely a risk to blood safety. And there had been 23 transfusion transmitted infections reported. What was really interesting about West Nile, the rapid development of implementation and implementation of testing, **West Nile Virus RNA testing** for blood donors, was very quick. It happened really within eight months of recognition of transfusion transmission of West Nile Virus. So it just showed, you know, a very good example of how fast the industry and transfusion medicine, blood centers can move to develop testing, when needed for a potential new emerging threat to the blood supply.

By pretty much, 2003, U.S. blood centers had implemented nucleic acid testing again in a mini-pool. And since that time, the number of cases, reported cases, did significantly decrease.

And what we also saw was that between 2002 and 2005, we saw this migration of West Nile Virus westward. Nowadays, we actually see it, you know, throughout the country, but in the beginning, at first it really was more focused on the East Coast, but we saw this migration to the West Coast, in around between 2002 and 2005.

For West Nile Virus, the other interesting difference for West Nile Virus compared to diseases from before that I discussed is, it was the first time that the FDA had recommended a "triggering strategy." So what this means is that, blood centers will do the testing in mini-pools. So like I said, we pool maybe 6 donor samples, or 16, depending on the test you're doing, but in times of higher risk, we actually need to "trigger on" to *individual* nucleic acid testing, which increases the sensitivity. And this triggering strategy, moving from mini-pool nucleic acid testing to ID NAT testing, has significantly decreased the number of transfusion-transmitted West Nile Virus cases being reported. It's something where we maybe see one reported every few years at this point, but it's a very different kind of testing strategy that was first introduced in, you know, for West Nile Virus (we later saw it also with Zika).

But blood centers, what it means is blood centers and medical directors at blood centers, we need to be aware of, "What is the West Nile Virus activity occurring in our region?" And so, if another neighboring blood center reports they have a donor that tested positive, then your blood center also needs to trigger on in that region, all blood donors collected in that region and test them also with the more sensitive, ID nucleic acid testing for about two weeks.

Joe: You mentioned this before, Suchi, if someone gets a positive West West Nile virus result and it's nucleic acid testing, as you said, they're deferred for how long?

Suchi: 120 days.

Joe: One other quick question, and that's just for people that maybe don't live in areas where there's a bunch of West Nile, you and I in California are seeing it a lot in recent years, what time of year are we talking about? Is this a "summer disease?"

Suchi: It is absolutely more of a summer disease. So, you know, when we're doing even that many pool testing, usually most blood centers are doing mini-pool testing for most of the winter months, and early spring, but then it's during the spring and summer where we do start to see cases throughout the country. And that's when blood centers are starting to trigger on to that individual nucleic acid testing, which has higher sensitivity.

Joe: Let's move on from West Nile and talk about another odd one where we are also introduced to a brand new way of testing, and I know you'll get to that in a minute, but let's talk about Chagas disease. What's the scoop with Chagas?

Suchi: So, yeah, Chagas disease, you know, this is caused by, the vector that carries this is the reduviid bug or often called the "kissing bug." And it's naturally limited to the Americas. And about 10 million are infected in endemic countries, which are mainly in Central and South America.

In 2007 or so, it was being recognized that there's a lot of people, about 300,000 people in the U.S. that live here and are unknowingly infected with *T. cruzi,* because people can have the infection and be asymptomatic for some time before showing symptoms, so, many years even. And the concern was that, could these individuals possibly be a source of transfusion-transmitted infection in the U.S.? And there have been about 10 cases of transfusion-transmitted cases in the U.S. and Canada. So not a lot, but it definitely is a risk that's there.

So in 2010, the FDA did release a guidance that basically requires blood centers to do one-time donor testing. So this was also very different. And before 2010, we were actually testing all blood donors. But from the years that we were doing that, there was enough data to show that you don't need to test donors all the time, every single donation, because many donors come back repeatedly. You really only need to test them once, and just by doing that, that will increase blood safety.

So this was very different, you know, now, instead of saying you test every donation, every time, blood blood centers have to have a mechanism to know, "We only need to test a donor once, on their first donation." And so that's currently what we are all doing.

Joe: Yeah. And I've got to tell you, when I first saw that guidance, my first reaction was, "WHAT? Seriously? Wow!" I was really surprised because there had been, historically, there had been a pretty big push among blood centers to get Chagas testing implemented. And then we got initial versions of it, and it didn't seem like it was going to be as big a deal as what we had thought. That was the history behind it, anyway. And then FDA came out with a "one-time" guidance and I think most everyone (that didn't have a heads up beforehand anyway) was pretty shocked at that.

Suchi: Yeah, it was the first time, and still the only example of where we're doing a test just on a first-time donor, and then we don't need to do it again. So it's an interesting approach. Blood centers, we have been able to build our computer systems to be able to ensure that we test that first donation. And I think, you

know, from what I recall, the reason why the FDA felt comfortable or went this route is because in, there were the prior years that we were doing testing on all donors or all donations. And what they found is that it was very uncommon for a donor who tested negative to seroconvert at later donations. It was very rare. So that's why this strategy of one time donor testing for this specific disease, is very effective.

Joe: What was also found, Suchi, was that it was uncommon even for people that tested positively (and to be clear, this is an **antibody test**), it was uncommon for even people who tested positively when they went and did the word that you used earlier, "lookback," it was uncommon for Chagas to be transmitted, as well. So that combination, I think, led the FDA to be comfortable with that. So I think we could probably safely say the residual risk is not particularly measurable or pretty darn uncommon.

Suchi: It's rare. I don't even have numbers to really quote, cause it is just very, very rare.

Joe: Gotcha. Okay, well, so let's move on from that odd one. We've, we've done a couple of unique ones with West Nile and Chagas disease, and let's talk about another one that has gotten a lot more attention recently (at least it was getting attention prior to SARS-CoV-2), but let's talk about Babesia and what we are doing now, in certain parts of the country anyway, with Babesia.

Suchi: Sure. So Babesia is another example of a vector-borne disease that has also a transfusion transmission risks. So it's transmitted by a tick vector, *Ixodes* tick vector. And it's a protozoa that's associated with red cells. And most people that get infected with Babesia are asymptomatic, but that period of where the parasite can be found in the blood can actually last for a few months, even up to maybe two years.

And, Babesia is very regional. So the most common, *Babesia microti*, which has been associated most of the time with the transfusion-transmitted cases, it's seasonal and it's in specific parts of the country. So really, we're looking at states in the Northeast and states in the Midwest is where the majority of transfusion or just Babesia cases are occurring.

But really, you know, we started to focus on the risk of transfusion-transmitted Babesia in the 2000s, when we were just starting to recognize more transfusion-transmitted Babesia cases. So pretty much, you know, since, 1980, which is when the first case reported, there's been 200, about 200 cases of transfusion-transmitted Babesia reported, and many of them were recorded after 2010.

It became the next infectious disease that we really started to focus on in the blood banking world, because we were seeing numerous reported cases and also, you know, a high morbidity and mortality from it. And it had about a 20% fatality rate.

Joe: What did FDA do? This is one of the most recent new guidances in terms of testing that we have. So what did FDA decide to do as a strategy to take this on?

Suchi: Right. So, you know, Babesia was recognized as a "relevant transfusion transmitted infection," And, the FDA did provide us guidance recently, in the last couple of years, about, "How can we mitigate this risk?" And essentially this was another kind of paradigm shift in how to approach blood donor testing.

So what we found or what we knew from the data was that about 25% of our transfusion-transmitted Babesia cases are reported from 15 high-risk states and areas. So these are almost all kind of focused in the Midwest and the Northeast.

So the guidance that the FDA released in 2019 recommends that, if you are collecting in any of those high risk states or areas, that you need to perform **year round nucleic acid testing** with a licensed test on all of your blood donations. And if you have a donor who is positive, you have to defer them for at least two years.

Joe: Again, you kind of said this, this is odd and unique in that if you're in a state that is NOT, or an area that is NOT one of those States, you don't have to do it at all?

Suchi: Yeah. So this is our first example of regional blood testing. So where the FDA's recommendation is focusing only on those states and areas that have the highest risk. And even though it is true that it's not, let's say in California, we don't have zero risk. You know, we, I was actually involved in, I believe 2009, with a confirmed transfusion-transmitted Babesia duncani case in the Bay Area. The risk is just so significantly lower in all of the other states that the FDA has really focused their strategy on the highest risk areas. So it is again, kind of a paradigm shift of this more selective testing where based off of a risk assessment.

Joe: By the way, for those of you that are sitting there that are compulsive and are wondering, "what states are involved?", I will have a link on the show page where you can go to the FDA guidance yourself and see if your state is involved. As Suchi said, it's primarily upper parts of the Northeast and upper parts of the Midwest.

So, Suchi, we need to, man, we need to move on and talk about Zika, because that, man, Zika was a big part of my life from way back, it feels like yesterday, but it was four or five years ago now. So, Zika is one of those examples of, and you've uses this phrase before, of an "emerging infection" that the blood industry really had to jump on and really had to develop things in a big hurry.

So, at a high level, just talk us a little bit through what happened with Zika and what we're doing now.

Suchi: Sure. So the Zika virus, you know, was another vector-borne, this time, a mosquito, *Aedes aegypti* mosquito primarily. But it can also be transmitted through sexual transmission and there's this risk of potential transfusion transmission. And there was a big outbreak in South America in 2016, but we also saw that we were having in 2016 or so, local mosquito-borne transmission of Zika virus in the U.S. as well. So it really was a case of a new emerging disease that had a potential transfusion transmission risk.

And I think one of the very concerning things too with this virus was that there was evidence to show that it could cause congenital abnormalities like microcephaly. And so it definitely was a virus we were very concerned about potentially transmitting, let's say to a young woman who's pregnant or someone who thinking about being pregnant, could this cause that kind of consequence if it's transfusion transmitted.

So, you know, I think because of the concerns of the morbidity that this disease could cause, and there was some evidence of it being transfusion-transmittable that really the U.S., we jumped on it again, similar to West Nile Virus, but, “How do we prevent the risk of transfusion-transmitted Zika, especially when there's local transmission occurring also in the U.S.?” And so again, the industry came together and very quickly was able to develop a **nucleic acid test for Zika** virus, which most blood centers had implemented in between August and October of 2016. And even before that, so, you know, this is an example too, what happens sometimes with these emerging diseases, is that because it takes time to develop the test in the interim, what the FDA and AABB recommend are, what are some deferrals that we can put into place to mitigate the risk while the testing is being developed? So for Zika virus at first, when it first, was, you know, an emerging disease and there was a concern of transfusion transmission, some of the first things that blood centers did was implement deferral strategies for people who may be at higher risk for Zika based off of let's say like travel. You know, before the test was developed to and implemented blood centers, we put in certain deferrals to decrease the risk of Zika as well.

So then what happened? So in August, 2016, there was a nucleic acid test that was developed. It was under investigation, but the FDA did put out a guidance in August, recommending blood centers in the U S to implement this nucleic acid test, or, this was also very interesting in this guidance, or implement pathogen reduction. So in this, this guidance was one, I think it was the first that introduced this concept of the pathogen reduction can be used in lieu of the test.

And the guidance actually recommended also this kind of phased implementation, which was interesting. So they identified the highest higher risk States for Zika, and California was one of them. We had to implement within four weeks or so of that guidance, and states with lower risk had a little bit more time, but pretty much I think by October, everyone had implemented individual NAT testing on all donations.

Joe: Yeah. And I think there's been one update since then where things got tweaked just a little bit. Is that right, Suchi?

Suchi: Yeah. So in August of 2018, the FDA did basically tweak their and revise their, recommendation, and it really started to look like what they did for West Nile Virus. So what they said is that, you know, during low risk times or periods, blood centers can do the testing in a mini-pool using a licensed test.

But if there was any evidence of local mosquito-borne Zika transmission in a blood center's collection area, at that point, they had to convert to individual NAT testing, which has more sensitivity.

So, right now, I mean, really there has not been any Zika cases reported in the U.S. or territories in since 2019. And even in 2020, when I looked at the CDCs website if there's any areas in the world right now reporting an outbreak, there actually is not. So right now, all blood centers, we're testing in mini-pools and we've not had to trigger on to the individual nucleic acid testing for some time.

Joe: So Suchi, I wanted to give you a chance to expand a little bit on what you were talking about earlier. And that's what may revolutionize things for us in terms of pathogen reduction. So, what do you want to tell us about what the future might look like with pathogen reduction technology?

Suchi: Sure. So, you know, we've been talking a lot about these emerging infectious diseases and you know, how quickly things have to move when there's a new emerging disease. And you're concerned that there may be a transfusion transmitted risk and, you know, it includes usually a combination of some deferrals and then trying to develop a test, but even developing a test will take a few months.

So really, what is the biggest game changer that I see that can significantly decrease the risk of infectious diseases, especially from emerging pathogens, is pathogen reduction.

So pathogen reduction is a mechanism by which you treat that blood product to be able to inactivate any particles, anything with DNA or RNA to prevent it from being able to cause disease when you transfuse that product into a patient. And there's different mechanisms that are used in different assays and platforms that are out there, many of which use, you know, UV light. So you basically add some kind of, substance into the blood product, like riboflavin, and you then illuminate it with UV light. And that causes the inactivation of any type of infectious disease that may be within that bag. And it does decrease the risk of transmission of infectious diseases that maybe you haven't tested for, let's say it's an emerging disease, or even, let's say it's one of these rare times when a donor gives a donation during that "window period." And it could prevent transmission in that case as well.

So right now in the U S you know, we do have pathogen reduced product and it's using that amotosalen platform for platelets and, you know, I think adoption of the pathogen reduction system in the U.S. has been increasing over the last few years, especially to help us, you know, manage the risk of bacterial contamination, which can decrease that risk as well.

But I think with, you know, emerging diseases, especially, you know, with the most recent one, SARS-CoV-2, which thankfully doesn't seem to have, a major transfusion-transmitted risk, but it's just a reminder that these emerging diseases can happen at any time. And if we had a proactive way to be able to prevent the risk of transfusion transmission for the majority of really most emerging diseases that are a virus, a bacteria, a parasite, it can really enhance blood safety and there'll be less time that's needed to let's say develop, or you wouldn't need to, you know, really rush to have to develop a test per se, because this system would likely be able to mitigate that risk.

Joe: I'm right there with you. It really does seem like that will be a game changer in hopefully in the near future. Folks, if you want to learn more about the history of pathogen reduction, I have a really fun episode that's an interview with Dr. Ray Goodrich who was involved in kind of the development of both of the main platforms in the United States that's episode 079. So please, please check that out.

Suchi, we've just got a little bit of time left. So the elephant in the room right now is we're recording this in early August or mid August of 2020 is SARS-CoV-2 and the COVID-19 pandemic. So, I know people will have questions about that. So what do we know about that in terms of about SARS-CoV-2, in terms of specifically the risks to our blood supply?

Suchi: Sure. Great question. So just like when with any emerging disease that comes up, that we start to see, you know, cases in the US, we have to always ask that question: "What is the risk of transfusion transmission?" And there's actually numerous work groups that will specifically discuss and determine whether a new emerging disease like SARS-CoV-2 is considered a transfusion-transmitted infection or considered a "relevant transfusion transmitted infection" that would require more strategies to be put in place.

There's basically two questions that has that's asked for any emerging disease. First is, can you have asymptomatic, healthy blood donors having viremia? So that means the virus can be detected in their blood. And what we know so far about SARS-CoV-2, is that it's very rare. And when it has been detected, let's say in studies that have been performed in blood donors, the viral load that's detectives is extremely low.

So there's been, you know, some studies that came out of Wuhan Blood Center. They did report a few donors, blood donors that had a positive PCR. And Stanford blood center, we actually recently reported, because we were also doing a study protocol, testing blood donors, and we did detect one blood donor. But it's very rare and the viral load is very low.

So that's the second question is, even if let's say donors may have viremia is it actually *infectious*? So will it actually cause disease in a patient if it was transfusion, if it was transmitted? And so far, fortunately for SARS-CoV-2, there's been no evidence that this virus, if, you know, transmitted through a blood product, would actually cause clinical disease.

So of course, you know, more studies are needed, but right now there is really no evidence for this. And that's why we haven't been working on developing a test per se for SARS-CoV-2 that would become widely implemented for blood donor screening.

Joe: If there's been any good news about SARS-CoV-2, in the last four or five months, that sounds like the one little bit of good news that we'll hang on to. Right? Yay! Something good!

Suchi: Yes. Yeah, I think it is good news. I mean, I will say that, you know, it's not a requirement, or it didn't come out in a guidance, but you know, the AABB did say

that medical directors at blood centers may want to consider having some deferrals for COVID-19. So for example, a donor should not donate until 14 days after being symptom free. They weren't requirements, but I know many blood centers in the U.S. have implemented these basic deferrals

Joe: You're 100% right. And it's interesting though, Suchi, I think a lot of that from my perspective, just to editorialize for a second, I'm not sure how much of that is to prevent virus in the blood versus protecting staff members and fellow donors.

Suchi: Yes, that's actually a great point. So, you know, with this emerging disease, what, you know, we're not only thinking about transfusion transmission, which, you know, fortunately, as we just talked about, doesn't seem to be a big risk or a risk, but protecting our team members, other donors in the donor center with this specific virus, that's a primary concern.

Joe: Well, Suchi, you have, you have done a great job taking us through this really fast and an excellent tour of transfusion transmitted diseases. I want to thank you for hanging out with me for this last hour and going through this. I really, really appreciate your time.

Suchi: Thank you, Joe. This has been great. So thanks for having me and happy to do it again.

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Joe: Hey everyone, it's Joe. I hope you will hang with me for a few moments for a couple of quick closing thoughts.

Once again: This *is* a continuing education activity, so if you're a physician or a laboratorian, go to wileyhealthlearning.com/transfusionnews to get your hour of totally free continuing education credit. My thanks for that continuing education sponsorship, as always, to Transfusion News, to Bio-Rad who brings you Transfusion News, as well as, of course, to Wiley Health Learning.

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This episode is being released, as you know, in the middle of December 2020. I am going to try to get one more episode out before the end of the *hellstorm* that has been 2020! I appreciate all of you who have written with encouragement. 2021 HAS to be a better year, and I will do my best to contribute to that with new episodes covering, as always, the *essentials* of Transfusion Medicine!

But until then, my friends, I hope that you smile, and have fun, tell the ones that you love that you DO, and above all, never, EVER stop learning. Thank you very much for listening. I'll catch you next time on the Blood Bank Guy Essentials Podcast.