BBGuy Essentials 084:
COVID-19 Convalescent Plasma with Pampee Young and Ralph Vassallo
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Pampee: Hi everyone. This is Pampee Young. I am the Chief Medical Officer of the American Red Cross.

Ralph: Hi, I'm Ralph Vassallo. I'm the Chief Medical and Scientific Officer for Vitalant.

Joe: And I'm Joe Chaffin, and this is the Blood Bank Guy Essentials Podcast.

Joe: Hey everyone, this is Joe Chaffin and I want to welcome you to Blood Bank Guy Essentials, the podcast made to help you learn the essentials of transfusion medicine. Now my guess is that some of you hearing this podcast today are doing it for the first time, because of the topic. The topic might have inspired you to listen to this podcast for the first time, and if so, I want to welcome you. I normally interview leaders in blood banking and transfusion medicine with the goal of making sure that people that are learning are able to understand core topics. Now, this particular episode is more of a current event topic though because I've received tons of questions about collection of COVID-19 convalescent plasma. Some people abbreviate that as "CCP," so if I do that, you'll know what I mean, COVID-19 convalescent plasma. For today's episode, I interviewed the Chief Medical Officers of the two largest US blood collectors, Dr. Pampee Young from the American Red Cross and Dr. Ralph Vassallo from Vitalant, to get their perspectives on CCP.

Before we get to that, you should know that this is not a continuing education episode. You can find lots of other episodes where physicians and laboratorians can get free continuing education credits at BBGuy.org/podcast. Just look for episodes there that end with the letter "CE." You can also find those episodes at wileyhealthlearning.com/transfusionnews. And those continuing education episodes at Wiley Health Learning are brought to you by transfusionnews.com, and Transfusion News is brought to you by Bio-Rad, who has no editorial input into this podcast.

Here's how this is going to go: I'm going to spend a few minutes on the front end of this talking just from me to you about the nuts and bolts of convalescent plasma and trying to answer some very basic questions that people have sent me, such as what it is, how it's collected, and the basic ways people can go down a pathway to transfusion of COVID convalescent plasma in the United States.

A note for you guys that are international, I am so sorry: I cannot cover even possibly all of the permutations of this on the international side. I have to stick with what's in the US, because that's been the overwhelming part of my focus for the last six weeks. Please check with your local and

national protocols and make sure that you're comfortable with those. This will be US-based.

After I do that, I will share my separately recorded interviews with Dr. Young from the Red Cross and Dr. Vassallo from Vitalant to get their perspectives on how things are going, to talk to them about challenges and hopefully triumphs they're seeing in their program, and where they see all of this going in the future.

Let's start by answering some of your questions about COVID-19 convalescent plasma or CCP. First, I think the most basic question is what actually IS convalescent plasma? That's a reasonable question, right? Well, that is a pretty simple question. In general, convalescent plasma is just a plasma product that's collected from a person who has recovered from a disease and transfused to a person who currently HAS the same disease. The idea is that the antibodies formed will help to boost the sick person's immune response so that they can recover faster.

It's really in a way a form of passive antibody therapy. In fact, that's exactly what it is. And you may be familiar with that. It's not new. Passive antibody therapy has been around for a century, I kid you not. But currently you see it in things like Hepatitis B immune globulin that's given to people that are potentially exposed to Hepatitis B. Rabies immune globulin is another one. And you're probably even more familiar with it in the form of something like intravenous immune globulin or IVIG. To be clear though, what we're doing with CCP has a lot less evidence than some of those other forms of passive antibody therapy.

As I said, the product that we're discussing today, COVID-19 convalescent plasma, obviously is collected from patients who have recovered from COVID-19 and is transfused to patients who currently have the disease. And we're going to talk a little bit more later about which patients are getting that convalescent plasma. And more on that in just a second.

But the next question, which is really important is: Does it work? Wow. Well, that's a really complicated question, unlike the first one. And right now the answer though is pretty simple and I'll just say it flat out: We don't know for sure. There is a suggestion and I would say it's a little more than a suggestion, but it is a reasonable suggestion in preliminary data from China with very small numbers, no controls, that it might help. Specifically COVID-19 convalescent plasma might help patients. But the truth is we just don't know at this point. What we know is that again, historically convalescent plasma is not new. We've already talked about that. It's been used with previous coronavirus outbreaks. It's been used with previous influenza outbreaks, including the first SARS epidemic in the early 2000s, as well as the Middle East Respiratory Syndrome or MERS, starting in the early 2010s and beyond.

Again, the studies that have been done, I think that if you were objectively trying to characterize their scientific rigor, you would say that they're not incredibly rigorous. But again, there is at least a suggestion of helpfulness. What we don't have right now is a ton of randomized controlled studies that show effectiveness in terms of... certainly in terms of those previous convalescent plasma efforts and definitely in terms of our current COVID convalescent plasma efforts.

The bigger question though, and this is something I want to explore a little bit with my guests a little bit later, is how effective does it HAVE to be to make this process worthwhile? And that's a really, really important question because when it comes down to it, again, this is me editorializing for just a moment, I think the decision point is, do the risks outweigh the benefits or vice versa? And again, because we don't fully know the benefits right now, that question is a little bit challenging. We certainly know the general risks of transfusing plasma. Generally speaking, you have the... of course the risk of non-immune type of reactions such as transfusion associated circulatory overload, transfusion-related acute lung injury, a really small risk of transfusion transmitted disease such as HIV, Hepatitis B, et cetera. In terms of other stuff, there have been suggestions of the possibility of problems such as "antibody dependent enhancement" of COVID-19 disease. That was mentioned in a recent editorial in Transfusion Medicine Reviews by Sunny Dzik.

Again, we don't know, but one thing that I found interesting is that there was an article recently published in the Journal of Clinical Investigation, the lead author on that is Dr. Evan Bloch (I'll put a reference to that in the show page [NOTE: BBGuy.org/084]). And the suggestion from that article was that, all things considered, if this plasma is even 25% effective, that there is potential for benefit there. Again, there's a lot to think about and a lot to debate but I want to explore that a little bit more with my guests in just a few minutes.

A few more things before we roll on. How do donor centers find COVID convalescent plasma donors? This is really important. As I'm recording this, at the end of April 2020, the FDA is strongly encouraging blood collectors in the United States to try to collect this product as soon as we can. They've set out some criteria. The short version is this: A potential donor must have a confirmed COVID-19 infection. Now, most commonly that's going to be done by a nasopharyngeal swab or an equivalent molecular test showing the actual nucleic acid. Alternatively, they can have a confirmed COVID antibody test, and those tests are becoming more available, but they haven't been available before now.

But again, have to be a confirmed positive COVID-19 donor. And THEN the donor has to be asymptomatic for a minimum of 14 days. According to the FDA criteria, if the donor has been asymptomatic, that's again no symptoms or as some people put it "back to their baseline," for at least 14

days, if it's been between 14 and 27 days, then the donor has to have a followup, a NEGATIVE follow-up nasopharyngeal swab or other molecular test, equivalent molecular test. If it's been at least 28 days since the last symptom, then that second test is not required.

And then the last thing is that an antibody test is not required up front. My suspicion is that as antibody testing becomes more widely available, that will probably change, but as of right now, those are the general criteria to find a COVID convalescent plasma donor.

I can speak a little bit to this from my perspective working in a blood center and having implemented this collection process. It is challenging to find eligible convalescent plasma donors, because the other thing I didn't say is that they of course have to meet all the other donor criteria. They have to qualify as a regular blood donor. And getting donors through that, for some places in the United States, New York Blood Center being a shining example, they have been enormously successful. I think for most of the rest of us, there have been challenges. And I want to explore that again with my guests in a few minutes.

A few more things. What products are we collecting? What are we doing? Well, when a donor successfully goes through the process, they're basically donating a plasma unit or more specifically, typically multiple plasma units. We put them on an apheresis machine and we collect multiple units of plasma from them at one time. Most commonly you'll see three or four units, sometimes as few as two or one, sometimes as much as five or so. But generally speaking, in the range of three or four, from an average sized person is what we can get. It takes in the range of 40 to 45 minutes or so on the machine for a donor to do that. Once the product is collected, the product is labeled with...(and all of the testing is done, of course), the product is labeled with a tag or a printed label designating it specifically as convalescent plasma.

If you're in a hospital, how do you get the product? Well, again, we'll explore this a little bit with my guests. But generally speaking, for the most part, you want to try and work with your local blood supplier first, especially obviously if they're collecting, but it's important to understand, this is really important to understand: To a blood center, this is not a research product. We are collecting a product that is a standard apheresis plasma product and we're sending it out to hospitals. But to a hospital, if you're going to transfuse this to a patient in the United States, it must be transfused as a research product. Well, that brings up a whole array of issues.

And many, if not most of you, have already worked through these challenges. Basically, hospitals can get to it one of three main ways: [1] By operating under their own research protocol, your own IRB in other words, or [2] to get on a national protocol such as the Expanded Access Program

from Mayo Clinic, or [3] to request an emergency investigational new drug or "eIND" for each patient that you transfuse, from the FDA.

I have feelings a little bit about which I would prefer, but the reality is each facility has to figure that out on their own. Let me tell you one great website to go to where you can look at these alternatives, if you haven't already. You've got to make a decision on it if you're going to transfuse, but go to covidplasma.org. That is a site that was put up by the AABB. There's a great description in the clinician section of those three alternatives. Further, if you want to look at the Mayo Clinic Expanded Access Program, they have a very similar sounding website. It's uscovidplasma.org. And again, you'll see some of those possibilities there.

Another question people have asked is, which patients should receive COVID convalescent plasma? This really gets a little dicey, to be honest. At present, as I'm recording this, again at the end of April 2020, this product is primarily being prioritized for the sickest patients. In fact, under the Expanded Access Program that I mentioned earlier, that's specifically who the plasma is targeted towards. It's reasonable to ask the question, is that where it's likely to be most effective? And the answer is: Maybe, maybe not. And that's part of the reason that we're studying this, but given the lack of alternatives right now, in other words, blood centers for the most part aren't... their shelves are not flooded with COVID convalescent plasma. We have to prioritize it some way, and it is being prioritized for the sickest patients.

People have also asked, what is "a dose" of COVID convalescent plasma? Well, again, under the Expanded Access Program, a dose is a single 200 mL unit of plasma or roughly 200 mL, not exactly. And that's fairly standard. However, under other protocols that one unit limit is not necessarily there. And, it's important to ask, is that enough? Well, that may be your only option.

And that last question that I want to hit you with is, what is the current inventory status of COVID convalescent plasma in the United States? It's not great, to tell you the truth. Again, this is late April and I hope that if you listen to this podcast, even a week down the line, that answer will change. But as of right now, it is challenging. At the moment, my judgment is that this product is extremely limited. There are pockets where that isn't true, again, New York Blood Center being a shining example of that, but the supply is really limited in most places. And I'll be talking with Dr. Young and Dr. Vassallo about some of the reasons why AREN'T we just flooded with donors? Why are we challenged to get this product on our shelves right now?

So the last thing I will say before I introduce my guests is this: Things are moving FAST! Please stick around to the very end, when I'll do some self-

examination and see if I messed anything up, and give you some updates on things that may have changed since I recorded this on April 30, 2020.

With that background, I'd like to introduce both of my guests, and I'll talk about both of them now so we can go straight into both interviews. My first guest is Dr. Pampee Young. She is the Chief Medical Officer of the American Red Cross. Prior to taking on that role in 2018 she was professor of Pathology at Vanderbilt University Medical Center where she served as the Medical Director of Transfusion Medicine. Dr. Young has over 80 peer-reviewed publications. Her research interests at Vanderbilt were in the field of regenerative medicine using stem cell based cell therapy and small molecular therapeutics. And currently she's interested in research on blood center innovation, product availability and safety.

My second guest is Dr. Ralph Vassallo, who's the Chief Medical and Scientific Officer of Vitalant, based in Scottsdale, Arizona. Prior to joining Vitalant in 2014, he was the Chief Medical Officer of the American Red Cross Blood Services, Eastern Division, based at the Penn-Jersey region in Philadelphia. In addition to his transfusion medicine expertise, by the way, Dr. Vassallo also completed a hematology oncology fellowship at the University of Pennsylvania. Dr. Vassallo is past chair of the AABB Circular of Information Task Force and Donor Health and Safety Committee. He's authored book chapters in "Williams Hematology," "Rossi's Principles of Transfusion Medicine," "McLeod's Apheresis: Principles and Practice," and more than 70 other articles and reviews. I really look forward to you hearing from both Dr. Young and Dr. Vassallo. We will play those interviews consecutively and I'll check in with you again at the end. Enjoy.

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Joe: Hi Pampee. Welcome to the Blood Bank Guy Essentials Podcast.

Pampee: Hi Joe. Thank you for having me.

Joe: Oh, it's my pleasure and my honor. There's a whole lot of people out there that are very interested in COVID-19 convalescent plasma and what the American Red Cross' role has been in moving this forward. I wonder if, just to start though, I know you've had a chance to listen to what I said at the beginning about COVID plasma in general. Are there any thoughts, or concerns, or corrections, or anything that you would like to mention about that general information I covered at the start?

Pampee: I don't think so. That was a very nice overview. No, I don't think I have anything to add.

Joe: Moving forward then, I think it's very safe to say that over the last several weeks especially... and we're recording this everyone on April 30, 2020. And over the last several weeks there's been a huge groundswell and

increasing interest towards COVID-19 convalescent plasma to the point where I think right now it's safe to say, Pampee, that demand significantly outweighs supply. I wonder if you would just take a few minutes to talk about why that is in your view, and what challenges blood centers and your organization in particular have had to overcome to get to the point where we're trying to get CCP on our shelves.

Pampee: Sure. That's a very good and important question. Let's just start with demand. I think that there are very few blood products where the demand curve goes from zero to 60, as acutely as this product has. We were essentially asked to supply this product in the middle of an acute crisis where New York was already peaking and other places were in the process of peaking. It's not as if blood centers have had the luxury to slowly build up or respond to a slow buildup of demand. That's one side of it.

The other side of it is that we're a national blood center. And as such, we're not just collecting in a area that has a high density of people recovering from COVID-19. And that's the population of donors that you need to build up this product. And we can talk in a little bit about why it's hard to get these donors. But from the huge numbers of people that have come to our website to say, "I'm here to donate," there's just a multitude of filters that occur that narrow the actual pool of donors from whom you can collect to just less than 10% of the tens of thousands that have registered.

And we can talk about why that is. And then of that very small 10%, you're having to also make sure that they are qualified to be a blood donor, period, and that they're within a range that is convenient for them to drive and provide the product. And finally that they're comfortable with apheresis collections. Because most people, the vast majority of these donors, are first-time donors, their idea of giving a donation is a whole blood product.

Joe: Right. Yeah, of course. Absolutely. I don't think we should wait. Let's go into right now... Well, first let me say less than 10% qualifying is a startling number and I think that number will really surprise people. I can share with you, from my perspective in my individual center in Southern California, we're seeing basically that same proportion and it's sobering, I'll say. But let's talk about that. The FDA has put out criteria, I mentioned those criteria in the introduction. What, from your perspective, are the challenges associated with that that are leading to so few people qualifying?

Pampee: Well, you have to have some sort of evidence that you've had COVID-19. And so with the shortage of tests, there aren't that many people that have had a diagnostic test for COVID-19. So, that is a major filter that really takes out the vast number of people who have come to you and they feel like they've had COVID-19, they've had perhaps even a clinical diagnosis given to them by a physician that they have had COVID-19, but nevertheless they don't have a diagnostic test in hand.

But even if you take the vast number of 20,000 and you cut it in half, 10,000, that can actually come to your collection site, then you say, "Okay, 10% of that, that's still a high number. And why has it taken us three plus, four weeks to get to where we were collecting a reasonable number?" And that is because we have to have evidence that they have this test. And believe it or not, it is difficult for people to go back and get test results and share them with us, and we ensure that they're in our system. All of that takes time that you don't have to spend in recruiting a regular blood donor.

Joe: It is such a challenge. And that leads to, I know you've felt this as well, Pampee, a lot of what for me have been fairly heartbreaking discussions with hospitals calling me, asking to see if I have any product and in some cases not even having any on the shelf to send out. And that, from a blood banker's perspective, I know you know this, you spent, before you were in the Red Cross, you spent a lot of time at Vanderbilt in a transfusion service. You know how that feels, and I'm sure that hurts your heart, like it does mine, doesn't it?

Pampee: Oh, it's heartbreaking because we have, especially in communicating with family members, we have physicians who are extremely heroic advocates for their patients. And that's wonderful to see that will do anything to try to get a product from us. But then we have the whole number of family members who are just beside themselves with a husband, a mom, a grandmother that is in crisis, and talking to them and trying to explain the situation to them is even more heartbreaking.

Joe: Ah, man. Well, I know that you've had some recent developments in your program that may have an impact on some of this, Pampee. Why don't you tell us a little bit about, as much as you can share, how your program is going right now and how you're overcoming some of those challenges?

Pampee: Right. We have made tremendous progress. We've issued 800 plus units of convalescent plasma and we're at the point where we are manufacturing 250 to 300 units a day. By no means is our progress minimal. It's really been fantastic, but the reality is that we have, still have, a demand that we have not been able to meet. One of the things that we're very encouraged by is that starting this Monday, this past Monday, we were able to start to do antibody testing. Now, very importantly, this is not something that we're offering to all donors, but just as a tool to qualify convalescent plasma units and test convalescent plasma donors.

And why this makes it easy is that first of all, we're not using this as a diagnostic test. That is important because it's not meant to be used as a diagnostic test. What we're doing is using this on donors who have come to us with a confirmed COVID test or a presumptive COVID diagnosis. And we're saying, "Is this donor qualified to give a convalescent plasma unit?" And with that test in place, it really precludes us from needing to get that documentation that we were requiring, of a confirmed COVID-19 test,

and that speeds up the process. And then it also opens up us potentially using that vast number... 60% of our donors had never had testing. It lets us go into that pool and start to evaluate that pool.

Joe: Interesting. So, to be clear, this is not something where you're saying, "Hey, if you don't have a diagnostic test, come to the Red Cross and we'll give you a free diagnostic test." This is specifically a tool for convalescent plasma, people who have already donated? In other words, are you testing something that was collected at the time that the person has donated. Is that how your program works right now?

Pampee: Right now, when we started testing, which is Monday, any products collected on Monday is being tested for SARS-CoV-2 antibodies. And if they don't have detectable antibodies, based on the S:CO ratio [NOTE: "Signal to cutoff ration" indicating reactive testing results], then they won't be used, they'll be converted to standard plasma inventory. And yeah, everything that is issued, or every product that is being collected Monday going forward will be tested by that antibody.

Joe: I gotcha. Okay. Well, that is... Obviously that has potential to help clear some of that, that backlog and that issue. In the interest of time, I'd like to move on and ask you about something else, Pampee. And this is something I've gotten a lot of questions on from my hospitals as well as people asking me things on social media. And it's the ABO compatibility question. Over the last several years, I know you're very well aware that there have been perhaps a little bit of a relaxation in terms of... in particular scenarios such as trauma. For example, using group A plasma as a "universal trauma product".

More recently, something that your organization has been heavily involved in is the use of low titer group O whole blood, again in trauma situations. People have asked me, can you cross traditional ABO compatibility rules in a hospital transfusion service to get a product to a patient when supply is short? For example, I think the easiest example to think of is someone who... a recipient who is very ill with COVID, meets all the criteria according to the Expanded Access Program criteria, but yet is group AB. And there's... there may not be a whole lot of AB products out there. What are your thoughts on... And again, I'm not trying to bind you to this. This is just... I'm just looking for your general impressions on whether or not hospitals can or should consider that.

Pampee: I think that's a good question. It's certainly something that we've dealt with as well. Now, we're a big system and when you order plasma through us, you have to give the intended patient's ABO type, and we find a product that's ABO compatible and send that to you. Now, my suggestion to a hospital would just be to follow your hospital's policy for out of group transfusions.

All of us, not for plasma, but certainly for platelets, we'll give a certain volume of out of group plasma, or titer. Everybody's got... or you might have a policy where you don't give out a group plasma. That's more rare. I think most hospitals have a volume cutoff or a titer threshold where they titer anti-A or anti-B or both, depending. And I would suggest that that is followed for this or that's... were I still at Vanderbilt running a transfusion service, that's what I would have done. What are your thoughts on that, Joe?

Joe: I feel exactly the same way. I have been asked in recent days to consider, as my center does, for group O platelets we will run titers. Now you and I both know that me saying that "my center runs titers" may not mean the same thing as another center that runs titers. The titer... The definition of "high titer" is challenging I think across our industry. But for whatever way, we have defined it at my particular center (and it's 1:100 in saline, by the way). But again, that's not universal by any stretch. We will put a tie tag on those units to say whether or not there are ABO antibodies, which are "high titer". And in my view I feel exactly the same way that a hospital can take that information if they would like and utilize it in whatever way is most consistent with their protocols. I think we're on the same page with that.

Pampee: Yep.

Joe: The second to last question I have for you, Pampee, is this. And this is one that I've heard from blood donors and I'm sure you've heard the same thing. People who either come in or are getting into the pipeline are getting screened to donate convalescent plasma and when they're being asked the questions to qualify them as regular blood donors, they get a little frustrated when they hear about particular criteria. And they'll say things like, "But the FDA changed their donor criteria in April," which is certainly true. "And I know I used to be deferred, but I should be eligible now. Why can't I donate?" What are your thoughts on that and what should people be aware of in terms of those evolving donor criteria?

Pampee: First of all, I think FDA made some very reasonable changes to donor eligibility, especially with regard to malaria and MSM. We're happy to see the changes. Now, I've had this issue come up very recently where a colleague and a friend from a hospital we support, was very frustrated because one of her residents went to donate, had gone to India to give a talk, a very worthwhile pursuit and now was deferred because of the malaria risk, right?

Joe: Sure.

Pampee: And wanted to know why we weren't accepting. And the truth of the matter is that we're a very large center. And I keep saying that, and there's a reason I say that is that we can't make manual exceptions because we run

the very real risk of making errors. And the MAC changes, the BECS changes that are required, the EBDR changes, all the computer, or the IT piece of the process can't be done instantaneously. You've got to get a team together. You've got to have a process team in place.

By the time... Those changes will be implemented at the Red Cross in the next month or two, but nevertheless, it's not right now. And there's a little bit of frustration in that time lag, but that's the reality of our business. We're a highly regulated business. We have to follow protocols. We can't afford mistakes. And in order for that to happen with any fidelity, you've got to have an automated process that can be, where you can run reports and really assess for errors. We can't have one offs. We can't make exceptions because that just asks for bigger mistakes to be made.

Joe: Completely agree. And I have said to people, I love the FDA's intent with this. I'm happy that they've made these changes. I wish... with the retrospectoscope, I wish they had done it about six months ago because it would have been a lot easier than trying to do this in the midst of, as you said, in the midst of a crisis. But yeah, I think your answer is completely correct, Pampee. That's exactly what I'm dealing with here in my individual center.

The last thing, I just wanted to give you the chance, Pampee, to tell us just in general, with everything going on and with everything happening with and surrounding COVID convalescent plasma, what are you most worried about and what are you most excited about?

Pampee: Well, I'm worried about us being able to assess the effectiveness of convalescent plasma. That's one worry. I'm worried about, as a citizen and a human on earth, I'm worried about what does post-COVID state look like? What does this mean for life as we knew it? What is the future state? Is there a post-COVID life? Is it just going to recur and this be drawn out for years? My heart goes out to all the college seniors and everybody. This is just, ignoring the tragedy of the lives lost. I'm not even getting there. I'm just going through all the personal losses that are several degrees removed from the tragedy of losing life. There's a lot that I'm worried about as just a citizen and a person with loved ones and friends that I care about.

What I'm excited about is just what this has meant for, just speaking for Red Cross, because that's really who I'm representing here in today's conversation, it's really shown the best in our team members, and how we've come together, and how everybody has worked as a team to serve each other, take care of each other, serve our hospitals, serve our country. And I think that has been just a real silver lining in all of this craziness.

Joe: That's fantastic. Well, Pampee, I can't even tell you how much I appreciate you taking a few minutes of your super busy day to talk to me about this.

And I know this will be real useful for our listeners. Thank you so very much.

Pampee: Hey listen, you're welcome. And I used the Blood Bank Guy notes when I was a resident, and I think they were pretty instrumental in me passing boards and things like that. I think it would be fair to say, I owe you one.

Joe: Oh my goodness, consider that debt more than paid. Thank you so much, Pampee.

Pampee: Absolutely.

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Joe: Hey Ralph, welcome to the Blood Bank Guy Essentials Podcast.

Ralph: Hey Joe, thanks. So great to be here with you.

Joe: Really appreciate it you doing it. I know that you've had the opportunity to take a quick listen to the information that I provided at the beginning. I wonder if you have any thoughts, or concerns, or anything you'd like to amplify based on that general information?

Ralph: Yeah, I think it was a wonderful introduction. I think what we need to stress is with this disease, with COVID, a lot of the success of convalescent plasma is anecdotal. There's 19 cases reported from China and we've seen a little bit in the United States as well, and people tend to do well, and we're not sure if that's because we're giving it to people who are going to do well anyway. I think it's really important, as you've said, that we have good randomized controlled studies that help us understand the true efficacy of this therapy.

Joe: I want to give you the opportunity to really explore a little bit where you've been with the Vitalant program in the last few weeks specifically. Maybe what lessons you've learned and where you're seeing momentum and movement and excitement in your program moving forward.

Ralph: Yeah, sure. We know that in other diseases, convalescent plasma seems to produce a positive signal, and we as an industry worked incredibly hard to bring this up as quickly as possible. And I'm proud of the Vitalant family because within the short space of two weeks we were able to stand up a website, a recruitment plan, develop procedures, train several thousand people, and make some really complex computer changes that ensure that the process runs smoothly. We started our first donation on April 8th and through today we're coming up on our 200th donation. With three or four products per collection, we've made a good start, but it's only that it's a good start. We really need to kick into high gear and we're making lots of appointments with at least 1,500 donors that we have who have been

qualified and we're ready to get those procedures done, those units out to the patients who need them.

Joe: That is exciting. And one of the things that I think people have struggled with a little bit, Ralph, and I've heard you personally talk about this a little bit before, is in terms of qualifying the donors, in terms of getting people past the initial requirements, I know you didn't get a chance to hear Dr. Young yet, but when she was talking to me, she said that in the range of 90% of the people that were initially contacting the Red Cross were not qualifying for a variety of reasons, I wonder if you could talk a little bit about your perspective on how you're trying to maybe eliminate some roadblocks or some exciting things that are happening moving forward that can help get past that.

Ralph: Yeah, you said it nicely in the intro and that is that requirements that FDA has set up mean that in order to donate convalescent plasma, the donor has to have had a lab-documented case of COVID-19. That occurs by one of two ways, either a positive nasopharyngeal swab test during illness... And we're seeing a very small number, but we're beginning to see more as time goes on with this pandemic in the US, of people who've had antibody testing that indicates that they've not only had the disease but have gotten over it and they're convalescent. That ended up in and of itself as a challenge. We've initially partnered with hospitals or the community physicians and public health authorities, frankly even at the county level, for them to begin referring donors and qualifying them to make sure they meet one of those two requirements and document that for us.

There's also obviously a safety issue to make sure people are not still shedding virus. If you come within 28 days of the end of your symptoms, you're going to need to have some additional testing. But we're really focusing on people who are now 28 days out. And the next wave will be, as you mentioned, the 90% of people who were ill, probably had COVID, many of them, but not all of them. And that's been the conundrum, is that when we look at test positive rates for nasal swabs in the United States, only about 17% or 18% of people test positive. And we know that test has about a 70% sensitivity. Maybe one in every four people who think they had COVID actually had it. And that's the challenge of pulling out those individuals and performing a really good antibody test.

There are two types. There's the rapid finger-stick essay that is fairly good. It's 95% sensitive, and 90% to 95% specific. But frankly, anything less than 99.9% for specificity really starts to mess with the ability to trust a positive test. If 5%, and it's a little high, but 5% of the population have been infected at this point in the US, a test that is 95% specific will have a 50% chance of being a true positive and a 50% chance of a false positive. And if the specificity drops to 90%, which is where a lot of these assays live, it's two out of three are false positives. What we really need to do is develop better assays, and there are a number that are in development,

and frankly within many organizations in the US, the one we use Red Cross, OneBlood, and Vitalant, it's called Creative Testing Solutions, they have a high throughput test that has a specificity in the 99% plus range.

Those results are much better at predicting who's going to have the antibody. And as Pampee probably talked about, the next frontier after we begin to put all of the donors that we know have had COVID disease into the queue to begin donating, and they can donate as often as every seven days, we're going to need more donors, and those individuals probably ought to be the ones with the highest likelihood of having had COVID. That is someone who was exhibiting probably classic symptoms, cough, fever, shortness of breath, perhaps even lost sudden loss of taste and smell, and maybe had a risk factor. They were in contact with someone with known COVID, or they were at a gathering where several people developed COVID at the same time, presumably from that gathering.

That's likely what we're going to start doing is as we clear it, Vitalant has seen about 1,500 donors that we're scheduling and we really want to have appointments to make sure that it's safe for all of our donors to come to a public gathering place, if you will, which not really a public gathering, this is a critical part of the healthcare system. But that's where we are today. We have, as I said, probably made a great start with the units that we have, but we have a far way to go to meet the demand out there.

Joe: Ralph, I want to clarify a little bit on something that you just said because I think that's a really important point. And you had talked about the fact that there is... it is a little bit of... I hardly know how to describe it other than just a massive array of different tests that are available out there for antibodies in particular. Am I understanding correctly that your feeling is that if you combine an antibody test that you research and take a look at it and see if it's a "good test with high sensitivity and specificity" along with the classic symptoms that you feel better about that in terms of qualifying a donor that way?

Ralph: Yeah, and that actually is one of the two pathways. The other pathway, as we said, is people who had a positive nasal swab. And interestingly we've done some testing on the units that we have sent out. It takes a while to get this testing done. It took a while for our lab to bring it up, but we're seeing both at the Red Cross and at Vitalant the same exact number. It's around 5% to 10% of people who've clearly had COVID disease but aren't forming antibody. And remember this is a screening test. We'll talk a bit more about neutralizing antibody in a moment.

But in the screen, this is exactly what they've seen in the Chinese experience that about 5% of people with COVID disease who clearly had it never mount an immune response, and another 25%, they have a relatively weak response. And this is total immunoglobulins IgM, it's IgG. Some tests also look at IgA. It's not neutralizing antibody. Neutralizing

antibody requires not a screening test, but a very complex test usually called a "plaque neutralization test," where it's a cell culture and you either introduce live virus or a pseudovirus and you mix that with various dilutions of plasma to see how it prevents that viral particle or the virus itself from getting into those cells. And this is a test that takes a week. It's available in very few labs across the US because the virus itself requires a biosafety level 3 laboratory and the pseudovirus bio level safety 2. It's not widely available and it takes quite a while. But that's what the FDA has said. They said you would like to have a titer of 1:80 minimum, and 1:160 optimally in these therapeutic units.

Joe: And that's what I think is something that is, I don't know if it's lost on people that aren't necessarily familiar with everything that we do, but I think it's something that's not widely appreciated that the units of of COVID convalescent plasma that have been transfused over the last however long it's been, that the vast majority of them have not been characterized, many of them in terms of antibodies, period, but certainly not in terms of neutralizing antibodies to that point. Is that accurate, Ralph?

Ralph: Yeah, that's really well said, because even if you've had a screen, which is in and of itself, great, and I think all of us as blood providers are moving towards what we hope to be real time screening because it takes 24 hours to get infectious disease results, and then another 12 to 24 hours to label the unit, get it out. So, if we could perform the screening test in that 24 to 48 hour period that it takes to get units out of the blood center and into a hospital, that would be ideal. We would not have maybe up to 10% of them not containing antibody.

Joe: I guess my next question then is, are you seeing a future where people are collected and products are held until those neutralizing antibody titers come back? Or are you seeing what we are now is transfusing and hoping and seeing what the results are when they come back?

Ralph: Well, you almost sounded like, well, "great versus not so great" outcome. Frankly, getting a therapeutic to 90% of the people who need it is an amazing triumph. We'd like that to be 100%. And I think that's what we're headed towards, is real time testing. But there are other mechanisms. We've been talking about other drugs or you've seen it at least in the media, Remdesivir was looking good. Some other early promising medications haven't worked out. But then there are many others that are in the pipeline.

The old people obviously have issues not just related to the virus with the body's response to it. And the "cytokine storm" is yet another thing that we're trying to look into to see if we can remove those things that inflame and start to destroy organ systems. We've had some early experience with plasma exchange. And, frankly our physicians experience within Vitalant,

we provide the services as many other blood centers and hospitals do, has not been as promising as one would hope. But there is a column out there that it removes cytokines and inflammatory mediators, and maybe that may have some efficacy. It probably makes sense to talk a bit more about which patients receive this and what their response is, right?

Joe: Yeah, absolutely. And that is...you read my mind. That's where I was going here in just a second. There's been a lot of debate back and forth and certainly in terms of questions, people have sent me concerns about who is the "appropriate patient to get COVID convalescent plasma". I think we're all aware that the Mayo Expanded Access Program specifies critically ill patients and gives criteria for that. But there's been a little bit of pushback and some concern about, well maybe this would be better given early. What are your thoughts on that?

Ralph: Our reflex, especially when this is a rare therapeutic right now is to give it to the people who are most in need, the people who are on ventilators that we need to get them off in order to give them an opportunity to do well. The problem has been at least in influenza trials with convalescent plasma, we're seeing the same thing here, that many of these sickest of the sick already have antibodies. Perhaps giving them a little more may not be as helpful as one might think that maybe it's the folks who haven't yet developed antibodies and are beginning to have problems getting enough oxygen through the lungs into the bloodstream. Maybe those individuals are the ones we got to target first. The folks who've gone from home to the hospital floor to the step down unit and before they get to the ICU, that might be the intervention that's the best. And we've certainly seen that with influenza, that if you give passive antibody therapy early, it's much more effective than what's given late.

Joe: I guess my concern is, and I don't even know if it's a concern, but the thing that strikes me is, given the current status of inventory for COVID convalescent plasma in the United States, which I think we would all agree is not anywhere close to what we would like it to be, how do we get to the point where we can do those studies, where we can not just be giving it to the most critically ill, but to those earlier to see if it'll have an effect?

Ralph: It's donors, donors, and more donors. We need to have enough people in the pipeline who were vetted as having neutralizing antibody, and to draw that plasma as often as we can. We can actually draw plasma from people every seven days for several months. And it will also help us understand the natural course of the immune response and perhaps how long people have immunity. Certainly, people who haven't formed antibodies are at risk of getting COVID again. I think this is important for the donors to know as well.

And we talk about plasma, but there's another immune therapy. There's hyperimmune globulin. And I've had a number of reporters talk to me and

say, "Aren't we competing to give either plasma to people or get that plasma hyper-concentrated and provided as a concentrate of just the good stuff, not all the other things in plasma."

And frankly, I think that there's not as much competition as one might think. The donor base for fractionators who collect what's called "source plasma" is one demographic in the US and our voluntary non remunerated donors that give to blood centers are a different demographic. And both are critically important to come in and give plasma. Eventually, if you think about it, giving 200 or 400 or more mLs of fluid to someone who has ARDS and already has fluid in their lung may be the most deleterious effect of plasma beyond some of the rare things that you really did a nice job mentioning. Perhaps a hyper-concentrate would be even better and would deliver exactly what you need, the neutralizing antibodies.

Joe: You're absolutely right about hyperimmune and I think we're all waiting with bated breath a little bit. Obviously that's not the industry that you and I work in, but I've heard six months down the line, I don't know if that's true or not, but some of the other things of course out there, vaccines, Remdesivir, things like that. What are your thoughts on how all that might work in together?

Ralph: Yes, indeed. I think our bet is about the same here, that we're hoping within six months we'll have some hyperimmune globulin. Obviously, as you've pointed out, the best immune response is your own immune response with the vaccine. And we're probably 12 months out from that, but I said that three months ago, that we're 12 months away. One of these days I'll actually start the countdown from 12 down to zero. But that is good, passive is just as good if we give it early, all the adjunct therapies really we're hearing now through the media and probably with at least one good study that Remdesivir may be the standard of care right now. There's just so many options available. We just need to get moving with this. And I'll say the word again, DONORS, we need to get donors.

Joe: Absolutely, absolutely. Well, before I let you go, Ralph, I would like to get your thoughts on one question that people are asking a lot and specifically that is what is the most appropriate dose for COVID convalescent plasma? And I know there's been debate about this and I've heard you talk about this before. I'm wondering if you'd just give us your thoughts. Obviously the Mayo EAP dose "is one unit", well approximately 200 mls. Some people say that's not enough. I wonder where you stand on this?

Ralph: I think a lot of the talk around dose is informed by some of the studies that were done with SARS one back in 2003 and MERS in 2012. And if you have a high titer unit, a small amount's all you need, if you have any lower neutralizing antibody titer unit, then you need more. The conundrum here is we don't exactly know what's in what we're transfusing and we're finding out weeks later, hopefully as we go along we'll find out in real time whether

or not the screening test is positive. And if the screening test comes back with a very high positive result, that probably correlates with neutralizing antibody but minimally positive to a very high signal, we really don't know.

So, dose-wise, a really great article, it's by Evan Bloch who is at Hopkins now and who trained at Vitalant Research Institute. Evan's article, and I think you mentioned this, in the JCI, Journal of Clinical Investigation, it really talks about five ccs per kilogram when you have a lower titer. Frankly, maybe lower amounts are okay and three ccs per kilogram that gets into the range of one, maybe two units. And that's what I'm seeing in clinical trials. Anywhere from one to two units.

Joe: Okay. Well, before I let you go, Ralph, again, I really appreciate your time. I am wondering if you would just share with us, the same thing that I asked Pampee at the end which is, what, at this point when we're recording this on April 30, 2020, what are you most worried about and what are you most excited about?

Ralph: Well, I'll start with the second one first. What I'm most excited about is the rapidity with which the blood industry has responded. To get something like this up and off the ground with two or three weeks notice is Herculean. What I'm worried about, though, is we don't have enough. We need more donors. We need to get these donors qualified. We need better antibody testing, more real time testing. But that's coming. We're seeing that over the next three to four weeks, we're probably going to get to an equilibrium point where we can start supplying need as it comes about.

What we often forget though, is the every day blood that is collected beyond COVID convalescent plasma, the red cells, the plasma, the platelets. We have patients who are no longer getting elective surgeries. They're putting off elective procedures, maybe like a bone marrow transplant when they're in remission. At some point we're going to need to open these up and we're seeing the United States is opening back up again. We've seen about a 30% decrease in red cell utilization because of the measures that have been taken with closing down public gatherings, with decreasing elective surgeries, and in many cases eliminating, about a 10% decline in platelets. In the last week, we've seen that rise a bit. And we really need to stress that people need to continue coming in for a whole blood donation for plateletpheresis because it's difficult now. We have appointments to make sure that we socially distance, that it's safe for donors to come into our sites, but we've got to make sure those appointments are filled.

Joe: Absolutely. And I think that is an absolutely perfect place to end. I could not possibly agree with you more on all of that, and especially that last point. Ralph, thank you so much for taking the time to do this with me. I really appreciate your time.

Ralph: It's been great chatting with you, Joe. Thanks.

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Joe: Hi everyone, it's Joe with just a couple of quick thoughts. First, let me confess an error. It's probably not the only one I made in this episode, but in the introduction and more than once in the discussion, I made reference to the fact that in the Expanded Access Protocol or what I sometimes refer to as the "Mayo Clinic Protocol," the "EAP" as it were, that a standard dose of COVID-19 convalescent plasma is one unit. Well, actually that's not completely correct. The protocol has been updated and in fact it now allows one to two units of plasma. I'm pretty sure that Dr. Vassallo knew that, because he made a reference to using one or two units, and he was just too nice to call me a dummy, but I'll do it for him: I'm a dummy and I apologize for the mistake. I hope that didn't cause any confusion.

Next, I want to share with you how quickly things are moving with all of this. I mentioned a couple of times during the interviews that I recorded these interviews and the introduction on April 30, 2020. I'm recording this part right now on Sunday May 3, 2020, and in the interim, like 4 days, the FDA has changed the donor criteria, believe it or not! Specifically, on Friday, May 1, the FDA announced in a new guidance that in their view, donors who have been asymptomatic for at least 14 days are eligible to donate, and that's true even if they don't have a second negative nasopharyngeal swab or another equivalent molecular test. Now, remember, their previous stance and what I talked about in the interview, was that a confirmed positive donor had to be symptom-free for at least 28 days, unless they had that negative follow-up test to make them eligible at 14 days after their symptoms were gone. That is a BIG, BIG change, quite honestly, and to tell you the truth, I'm not sure how it will be received by blood centers. It is possible that some of us may change, and it's also possible that some of us may stick to that 28 day thing; it is just too soon to tell. Like I said, this just came out Friday, May 1st; I'm recording this on Sunday, May 3! So, quite frankly, we will see.

I just can't tell you how honored I was that both Dr. Young and Dr. Vassallo made the time to join me to help all of you understand a little bit more about CCP. Their organizations combine to collect over 50% of the US blood supply. I'm just thrilled that they were able to be here to help you learn. To be clear though, there's a lot of tremendous work going on with CCP all over the United States and from what I understand all around the world. I mentioned New York Blood Center a couple of times, but other major centers like OneBlood in Florida and Versiti in the Midwest, and numerous other centers, I don't want to leave anybody out, I'm sorry. But there's so many places that are doing great work, including places that you've never heard of.

By the way, if you're a clinician, and I want to be clear about this, you may be sitting there wondering why blood bankers seem to be congratulating ourselves for a process that may feel slow to you, and I get that, but you have to understand that almost nothing moves quickly in blood banking. Here's how we work: We think things through, we analyze, we RE-analyze from another angle; we check, we double-check, we TRIPLE-check before we implement really anything. And we do that partly because we're compulsive people (Yep. I admit it. That's what we are!). But we also do it because the stakes are incredibly high with what we do and we have to make it right. And honestly, the speed that COVID-19 convalescent plasma has gained the traction it has so far, is, in our world, STAGGERING!

I hope you'll join me again for the next episode, which will be a continuing education episode featuring Dr. Jill Storry, who joined me all the way from Sweden to talk about one of my favorite topics: "What to do when everything is incompatible." She'll discuss autoantibodies, high incidence alloantibodies, and things that make transfusing compatible blood almost impossible. And that is coming in a couple of weeks.

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.