BBGuy Essentials 059:
Antigen Matching for Future Moms with Meghan Delaney
Released October 29, 2018

Joe Chaffin: Hi everyone, I am very happy to welcome you back to Blood Bank Guy Essentials, the podcast designed to help you learn the essentials of Transfusion Medicine. This is episode 059. My name is Joe Chaffin. Today I'm interviewing Dr. Meghan Delaney to see if we can finally get an answer to a really important question. That question is this: How much before red cell transfusion should we be matching ladies who could potentially have babies later for things other than RhD, which is the main Rh antigen?

But before we get there, you should know this is not a continuing education episode. You can find other episodes where physicians and laboratorians can earn those fabulous continuing education credits for just no charge whatsoever at BBGuy.org/podcast, it's pretty simple. You just look for episodes that end with the letters "CE." You can also visit wileyhealthlearning.com/transfusionnews. The continuing education episodes there at that site 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.

I think, at least I hope, that most of us are fairly well aware of how hemolytic disease of the fetus and newborn happens, at least in the traditional sense. The classic story is an RhD negative mom who delivers an RhD positive baby. A little bit of baby's blood mixes in with mom's blood at the time of the delivery, primarily, and mom forms an anti-D. Then during the second pregnancy, the anti-D crosses the placenta and really starts damaging the baby's developing red cells, and you have the classic hemolytic disease of the fetus and newborn. That's just obviously the bare essentials. If you need a little more information or a little review, please check out BBGuy.org/038. That's an interview I did with Greg Denomme on a ton more details on hemolytic disease of the fetus and newborn.

Anyway, that whole interaction with RhD negative mom and RhD positive baby, and the mixing of the blood, that's what Rh immune globulin is designed to stop, and it's done a really great job. Roughly 3 to 80 per 100,000 deliveries happen in the United States with RhD hemolytic disease of the fetus and newborn, which quite frankly, is still more than any of us would like, but is way down from what it used to be.

But, one thing that we've been trying to figure out for quite a while is, what about *transfusion's* role in this? I mean, the classic story is mom having a baby and getting immunized, and then the next baby is damaged, but what if mom gets a transfusion that immunizes her?

Interestingly enough, there have been very different approaches in the United States and in different countries around the world in terms of how ... I don't want to say how seriously we take it, but how we try and prevent those interactions. In the United States, generally speaking, women of childbearing years are not

specifically prophylactically matched for really any red cell antigens. But, in other countries, for example in the United Kingdom, females of childbearing potential are matched for the K (or sometimes called Kell antigen) if they're under 50 years or so years of age. In Sweden, not only do they match for K but also C. The Netherlands, K, c, E... you see where I'm going with this. Internationally, the rules are different and the way things are handled is significantly different.

I think it's a very important question to ask: Is that [matching] effective or is it not effective? And, Meghan Delaney led a group with the BEST Collaborative that took a real close look at this. They creatively titled their study the "AMIGO Study." That's "Blood Group Antigen Matching Influence on Gestational Outcomes." I love that. And, Meghan and her group decided to take a look and see whether or not we could tell whether this prophylactic strategy aimed at decreasing the risk of non-D alloimmunization in females of childbearing potential was effective. Meghan is here today to talk about her role in that study and to tell us what they were able to find out. So, I won't make you wait even one more second, here's my interview with Meghan Delaney on matching for Kell.

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Joe: Hey Meghan, welcome back to the Blood Bank Guy Essentials podcast!

Meghan: Thanks so much Joe, it's great to be here.

Joe: It is an honor, once again, to have you. Everyone, you may or may not know that Meghan joined me back in March 2017 for one of my, well, it's in the top 10 of the most popular episodes I've ever done, Meghan, on molecular testing in the transfusion service. That's episode 29, at BBGuy.org/029, and I'm sure you're having a hard time dealing with all the fame that, you know, being on the podcast has brought to you, am I right?

Meghan: Oh, absolutely, it's been amazing.

Joe: Ah, that's awesome. Well, actually, I'm not kidding about the fact that ... I am kidding about the fame, I'm not kidding about the fact that what you did there has really, it's made an impact. I get emails often from people that have listened to that episode and talked to me about how useful it was, practical it was, so I've said this to you before offline but officially in front of all these people listening, thank you again for doing that episode.

Meghan: Well, thanks so much for having me, I was really glad to do the episode and I'm excited that people have found it useful, so thank you.

Joe: Yeah, no sweat. So, today Meghan, I'm really, really excited to talk about this particular study and ironically, I didn't even realize this at the time, you were on the podcast in March of 2017, and the study that we're going to talk about today, which is the "Blood Group Antigen Matching Influence on Gestational Outcomes," or "AMIGO (I love that) study", was published that same month, March of 2017, in *Transfusion*, so dummy me for missing that at the time.

But, I'm very very happy to talk to you about this because I think it's the start anyway of an answer to a question that has somewhat bedeviled us in Transfusion Medicine for a while. So, Meghan, we need to set the background on this. We're talking about essentially against a background of hemolytic disease of the fetus and newborn, or "HDFN," and I wonder if you wouldn't mind, before we get to the specifics of your study, just give us the Meghan Delaney high level thumbnail view of what hemolytic disease of the fetus and newborn, what HDFN is, and what are kind of the general questions that we worry about with this, and how this led to your study.

Meghan: Sure, I'd love to. So, hemolytic disease of the fetus and newborn is a consequence of red blood cell alloimmunization in a woman who is pregnant. The problem occurs when a woman has red cell alloimmunization, and that could be due to previous pregnancy or previous transfusion, and then when she is pregnant with a fetus that bears the antigen that her antibodies are directed against, those antibodies can cross the placenta into the fetal circulation, and destroy or take out precursors of the fetus' red cell line.

When that happens, there's grades of severity of what this could mean for the fetus. When the infant is born, they have a positive direct Coombs test, and more exacerbated neonatal hyperbilirubinemia. Or, it could mean a much more severe presentation, where the anemia is really profound while still in utero, and that can cause all sorts of physiological changes, such as significant anemia that leads to high output cardiac failure, extramedullary hematopoiesis, as well as fluid collections in different body cavities, because of the significant anemia, and even can lead to the demise of the fetus.

We sometimes hear the term "hydrops fetalis," which is denoting that when a fetus in that severely effected state actually has ascites and extravascular fluid accumulation, and those are usually the most severe forms of the disease. So, it has a very wide range in clinical presentation, but it all starts with maternal alloimmunization.

Joe: Okay. And Meghan, typically or classically you mentioned that we're talking about that alloimmunization, which antigens are we most commonly talking about?

Meghan: So, just like any other study of red blood cell alloimmunization, our most common offenders are in the Rh blood group system, but also one antigen or antibody that's a particular problem in HDFN is the Kell or "K" antigen. The reason for that is that in HDFN, the Kell antigen is expressed in very early red blood cell precursors, and so instead of presenting as a hemolytic anemia in the fetus, it presents as a hypoproliferative anemia, because the red cell precursors can be severely effected with an anti-Kell antibody in the mother.

Joe: That's something that I think, I want to make sure people grasp the significance of that Meghan, because I've had many teaching sessions with people about HDFN caused by an antibody against K, and what I always tell people is that, yes, it's HDFN, but you emphasize the hypoproliferative part. There's not necessarily, a

frank hemolysis like you might see in other forms, like the classic HDFN due to anti-D, so what's the big deal about that, why do we care about whether you get hemolysis, or whether there's suppression, what kind of a difference does that make to the baby?

Meghan: So, I think about it, I draw those distinctions though two places. So one is that, in the "olden days" and I smile when I say that because I certainly was in the lab when this test was being done, we used to do amniocentesis to look for bilirubin levels, to look for HDFN. We don't do that anymore and we'll talk about that later. But, when you have hypoproliferative anemia, there's not elevated bilirubin, because there's just the red cells not growing. So, that is one difference. The amniocentesis method of picking up bilirubin is not going to help you.

In today's world though, we still do use titers, and so titers in the mother, of her antibody, is somewhat problematic, because it's hard to reproduce, but when the same lab is doing it over and over again, we're watching to see if the antibody titer is increasing, and we have what's called "critical titers," which is somewhat arbitrary but where we to note that that fetus might be really affected by HDFN.

In the case of Kell, because we really are kind of in the dark about how much it's affecting the fetal red cell precursors, we consider the critical titer for Kell to be either no critical titer, or for instance, with D, we might use 16 or with e, or c, we might use 32. With Kell, we might use nothing, just say ANY Kell titer could be dangerous, or we might use 8, so for instance we're basically saying, at that critical titer where HDFN could really severely be impacting this fetus, Kell is more dangerous, we're putting that threshold lower.

Joe: And, Meghan, just for the folks out there in my audience who are sitting there going, "You know, I've heard that term before: Titer," can you give us the plain English definition of what we mean when we say titers of an antibody?

Meghan: Sure. So, a titer is really just mixing the patient's blood and the reagent cells in dilutions of each other, just a straight dilution the way we would do in any sort of mixing study in our biology or chemistry labs, but in this case we're measuring it against, if the patient's antibody agglutinates the reagent red cells that bear the antigen, at basically "neat," so in the straight amount that we would use for a regular test, and then diluted by half, and diluted by half again, or double, depends on how you think about it, but each time it's a dilution of 50%. And then, seeing where that agglutination is no longer detectable, and whatever that number is of dilutions that you've done for each of those subsequent test tubes, we would say that that's the titer.

Joe: Got it. Forgive me for that little definition sidelight there, Meghan, but I just want to make sure that people are right there with us. So, you were saying that with Kell, it's difficult to define a critical titer as we maybe can for other antibodies. With anti-K, what I hear you saying, and correct me if I'm wrong, is that really any degree of having this antibody is a potential problem, and it's harder to potentially to monitor than it is with other antigen systems involved. Is that a correct assessment?

Meghan: Yeah, that is correct. We do have more modern ways to look at the fetus using ultrasound now, which we probably won't talk about a lot today, but in general laboratory testing for a fetus affected by anti-Kell HDFN is a bit more problematic to determine if the fetus is at risk or not using the laboratory tests.

Joe: Alright Meghan, thank you for taking the time to go through that with me. I wonder if, before we get again to the details of your study, let's again thumbnail the two kind of generally accepted pathways or causes of HDFN that partly led you guys to do this study?

Meghan: Right, so, you can be sensitized to foreign red cell antigens by being exposed to foreign red cell antigens, so the two ways that that occur are either through red cell transfusion, or through previous pregnancy, if you're a female.

Joe: Okay, and do we at least traditionally, have we had any thought of which one of those predominates, or have we known?

Meghan: Well, so that's a really good question. The idea about which one predominates is something that's always interested me. When I was a resident applying to be a blood bank fellow, I went to Sweden and went to Lund University to study with Martin Olsson and Jill Storry about red cell genotyping, actually, and I also got to hang out in their transfusion service, and I was very struck by the fact that they provide Kell negative and sometimes Rh-matched red cells to females that are receiving red cell transfusion for the purpose of preventing HDFN.

And that always stuck with me. But if you back up for a moment, and you think about what all of us are taught in blood banking, really "Blood Banking 101," is that we actually are, by transfusion policy, protecting women from HDFN, because who do we save the Rh negative blood for in emergency transfusion? It's always for the women of childbearing potential. And so, there are threads of it, but it's often easy to overlook, because we're not really thinking with intention about why we're doing it. And so that trip to Sweden really got me thinking about it and wondering why, going back to the United States, in our very advanced blood banks, how we don't match for more than D for women, and why is that, and does it matter?

Joe: First, what a great experience for you. You said you were not even yet a fellow and you got to spend time with Martin Olsson and Jill Storry?

Meghan: Yeah, they were very generous and let me come spend some time with them, yeah.

Joe: Wow. That's a relatively good start for you in blood banking I would say, Meghan. Nice call. Wow!

Meghan: Yeah, no, it was a great experience, and I definitely am grateful and still in close touch with them and they've always been mentors from afar for me. It's been great.

Joe: Yeah, wow. That's awesome. So, that leads us, Meghan, to your study. So, I love the fact that this is something that was kind of tickling in the back of your mind, this whole concept that in other places, and certainly I'm sure there are places in the United States that do match females of childbearing potential for different antigens, but I think mostly, it seems anyway, from my perspective, that there's not a lot of that, and in the United States, but there does seem to be more of that in the European countries.

So, with that kind of tickling in the back of your mind, I'd love for you to just set up how your study came to be. Again, folks, we were talking about the fabulously named AMIGO study that Meghan amazing group of fantastic blood bank professionals published in the journal *Transfusion* in March 2017. So, Meghan, how did this come about?

Meghan: So, it came about when I was also becoming a member at BEST Collaborative. And that group is a really interesting group because it has transfusion scientists and physicians from really all over the world that work together to try and improve and study transfusion safety. And, I thought to myself, "Wow, this is a mixture of centers that do this type of matching or prospectively providing antigen negative blood to women, and don't." And so, I proposed to them this idea of what became the AMIGO study, and I'll also give a shout-out to Sunny Dzik, he's the one who came up with the AMIGO acronym, which was brilliant.

Joe: I was guessing either Sunny or Yazer, one of the two, but that's awesome.

Meghan: Yeah, so, what the AMIGO study set out to do first was to just determine, you know, you ask "What do we know about red cell transfusion causing HDFN?" And the answer is not that much, but there are some papers published. They're generally single center papers and I felt like they potentially were over- or underestimating, it's very hard when you have a single center study to broadly generalize.

And so with that idea in mind, I said, "Well, let's first define what patients we're going to study." And so what we did is we defined that this was "Severe HDFN," defined as either needing a neonatal exchange transfusion after birth, or needing an intrauterine transfusion. So, those severe ones. And then, looking back into their record and to find out: Were they transfused, were they not transfused, or were they previously pregnant? And then categorizing them into those categories. Really, the first goal was to say, "How much of this severe HDFN can we attribute to transfusion, can we attribute to pregnancy, or are we unable to discern?"

And then the next part, which we'll continue to talk about, is then to say, "Okay, of the ones that were transfusion-related, and we can say that because there was no previous pregnancy (so it's trying to be a very "clean" population), how many comparing those between the centers that provided matched blood and the centers that did not, to try and get that question of "Did the matching have an impact?"

Joe: Got it. Okay, and so you mentioned that you were looking at an international group of locations for this. Can you describe where those locations were?

Meghan: Yeah, absolutely. So, we had 14 total centers, we had the centers that did not match were in the United States, there were seven of them, and then there was one in Canada. And then the centers that did match were, four of them were in Europe, so the UK, Sweden, Netherlands, and Switzerland, and then also we had Australia in the match.

You know, what's interesting about the MATCH centers' policies is, and you can see this in the paper, is that actually none of them are exactly the same. They all use different age cutoffs for what is considered a female of childbearing potential, ranging from 45 up to 60, and then they all match for different antigens, with the UK only using Kell, whereas Switzerland can match for up to Kell, C, c, E, and e. So, even just trying to do a retrospective comparison was a challenge, and ultimately our comparison about the impact of transfusion matching ended up being only able to compare around Kell.

Joe: Okay. That's really the one they had in common, even though there were slight variations on it that was pretty much the big one that was left in common for all those five centers, right?

Meghan: Yes.

Joe: Meghan, in terms of the centers themselves, were these all hospitals that we were talking about, or were there differences in what the facilities were doing?

Meghan: That is a good question. We learned a lot about how care is provided. You know, this AMIGO in many ways was trying to get a denominator of all the women out there who have pregnancy, how many are impacted by HDFN, how many are impacted by transfusion-related HDFN. And it's an almost impossible number to get, because if you think about the US, for example, you might be diagnosed with the positive antibody screen by your local family medicine provider, who also could be someone who delivers babies, but that person probably [would] not take care of a pregnancy affected by HDFN, and so that would be referred to another center. And so, if you look at all patients treated, it's a difficult number to ascertain.

However, if you look at a country like the Netherlands, in general, they are a smaller country and they do have one or two referral centers where all of their severe HDFN is referred to for the whole country, and so their denominators were cleaner. And so, because we couldn't really get that, we had to deal with what we could get, which was the cases, and just compare case to case at different sites, and not really have a rate, if you will, which would require a denominator.

Joe: Okay, okay. And that actually, that answers a question I was going to ask, which is, I was going to mention, as I look at the study and as I read this study, it seems a little light on the details of how you found out those numbers and how you found out the cases. I mean, I guess that kind of explains it, because you were in

different places, you were dealing with different challenges in finding the cases, right?

Meghan: That's right. So, the center in the United States who is doing high-risk OB care, we did it based on a time period of as many cases as we could find, and then we looked at each, categorized those subjects into, was it due to a transfusion? Was it due to previous pregnancy? Or, [was it] unable to discern, and that's an important category, because that's both, they could have been transfused and pregnant earlier, and those are classically the women who had a previous pregnancy with obstetrical hemorrhage. So, there's no way to determine when she has alloimmunization with pregnancy number two or three, which place it came from. But yeah, the analysis section is an important part of the study, it is a challenge because of what data is available.

Joe: Okay. So, Meghan, before we get to exactly how many women you found to be included in your study, there was one thing that caught my eye that I wonder if you'd clarify for me. There's a statement in the methods section of your study that, I'll read it to you, and you help me understand what you guys were saying here. And it says, "If medical record revealed that a transfusion attributed to a MATCH center's subject was found to have potentially been administered outside of the MATCH center's catchment area, the transfusion was still attributed to the MATCH center." So, help me understand what you were saying there.

Meghan: Yeah, absolutely. Yeah, this is something that we've put a lot of thought into. So, people may be familiar with the idea of "intention to treat," in studies, an intention to treat analysis, so once you're allocated to a study group, regardless of if you get an off-study intervention, you're still in that study group. So, this was the same idea.

So, if you were a woman who had severe HDFN and you were treated in the Netherlands, that's a MATCH center. But when we did the deep chart review, which really is what we all did to figure out where this antibody came from, looking at their OB medical records, we might have found out that actually, she came from Somalia, and this is pregnancy number seven, and there seems to be a history that she was transfused there, which Somalia is not matching, right, once she is in the Netherlands, being cared for there, as a blood bank doctor, again kind of going back to initially made me interested in this is as a blood bank doctor, what can I do to prevent HDFN? Can I do anything? And so as a blood bank doctor in the Netherlands, I'm matching, because I'm trying to prevent HDFN.

Now, my policy, though, is broad across all patients, and many of them, this will never impact their future, because they're not going to go on to have children, but we're still broadly implementing the policy. So, I'm still at a MATCH center, but I have taking care of a woman who had a transfusion somewhere else, so this was more of that we wanted to know, does the policy work? And so we weren't going to erase the women who had HDFN due to transfusion that we knew was elsewhere because they were being cared for under that same policy, if you will. And, ultimately, at the end of the paper, you'll see that this ends up being a pretty

significant finding that quite a few of the women were transfused outside of the match catchment area.

Joe: Got it, got it. Okay, so I noticed that in another place, you used a couple of kind of key words or phrases, you used "real world application" and "pragmatic", and both of those terms I guess would just imply that this is what you're dealing with in the real world, right, I mean, this is reality, as you just described, whether or not someone got all their transfusions in one of those centers or not, you're still seeing, does this work, does this have an impact?

Meghan: That's right. Because if you looked at it differently and said only women who've ever been transfused with matched blood, that's somewhat of a different study, it's more of a physiological study, which I think most of us as blood bankers believe, that if you have never been pregnant and you only get Kell-negative blood, you probably are not going to have anti-Kell HDFN (probably). But, this is really the "I'm a blood bank director, I'm trying to figure out if I should be matching the way the Netherlands does or not, what's the impact of my policy?"

Joe: That's awesome. And in my role as an educator, Meghan, I talk to people from different parts of the world, and I have gotten this question many, many times, I can't tell you how many emails I've received from people, asking variations on a question of "What's wrong with you guys in the United States, why don't you guys match all these women?"

That is why I was really excited to talk to you about this study, because of the fact that you guys were trying to make an answer to that, trying to take a practical look on how all this fits together, so I've gotten you down deep in the weeds of the setup of your study, and I apologize for that but I'm a nerd that way. So, forgive me for dragging you through that, but let's hit the meat of it. What did you guys find? How many women did you guys discover, and what was interesting about it?

Meghan: Absolutely. So, and by the way, I love going in the weeds about the study because it really...it's a lesson in how to design a study in many ways, and how difficult it is.

So, first and foremost, what we found when we broadly categorized the severe HDFN into transfusion caused, previous pregnancy caused, or unable to determine, is that the vast majority of women had never been transfused before, and their severe HDFN was only able to be attributable to previous pregnancy. So the number there was 83%. So when you talk "80/20 rule," you know, over 80% of HDFN that goes on to be severe HDFN is caused by previous pregnancy. And having myself done some of the chart review for my center that contributed data, I can tell you that that story I told about a woman from a different continent coming in, or even from North America, there were highly multiparous or "grand multiparous" women in this cohort, you know, quite a few pregnancies.

So, then going on, the transfusion that we could say no previous pregnancy, only transfusion preceded this event, was 3%, or eight patients. So, very, very small. Now, the place where there's gray is the "unable to determine." So about 14% of

the cohort, or 42 of these women, had both previous pregnancies and transfusion preceding their severe HDFN, so we really were unable to say which caused the presentation.

Joe: Got it, got it. So, just making sure that I have those numbers right, 83% of these patients that you found with severe HDFN, you said it was 293 subjects, was that correct? Do I have that number right, Meghan?

Meghan: Yeah, so it was 293 women, yes.

Joe: Okay, so out of those 293 women, 83% of them, and these are, by the way, again just to re-emphasize, everyone, these are women by definition in this study that had what we could consider a "severe form of HDFN," as manifested by the fact that they needed either the baby needed either an intrauterine transfusion, or a neonatal exchange transfusion, after the time the baby was born. So 83% of those women had a previous pregnancy exposure only, 3% had transfusion exposure only, and 14% of them you're kinda like, "Oh, crud, they have both." Is that an accurate summary?

Okay Meghan, so that really puts us in a situation where I guess we need to try and answer one of the questions, anyway, that you guys were trying to ask, which was, "Does this antigen matching actually work? Does it actually help?" So how did you guys go about trying to answer that question?

Meghan: So that was the second point of the study, and as I described earlier, we used the "intention to match" analysis approach, and we divided those same 293 women into that had been transfused, and were either a "MATCH" center and a "NOMATCH" center, and we compared them to see, were there more Kell caused HDFNs in places that are matching for Kell, compared to places that are not? And so, what's interesting again is that, so remember I said 14 centers across the world, we scoured our records for severe HDFN, and we only found 293 women who qualified, so right there is also an important part of the study, is that this is not that common in general.

Joe: And Meghan, can I interrupt you for just a second? I can't remember if we said, and maybe we did, but over what time frame are we talking about? 293 women in over how long?

Meghan: So, we looked at records from between January 1st 2000 and December 31st 2012, so 12 years of records.

Joe: Wow, so, 12 years, 14 centers international with only 293 cases. That actually is a surprisingly small number. I guess it makes sense, we think that this doesn't happen all that often, to have severe HDFN, Meghan, but were you surprised at the small number?

Meghan: I was surprised. But, you know, also, remember that I didn't do all of the United States, I just did seven centers. And I'm sure that there were some in the different countries that we- because it was one center per country, some of them were

national level data like the Netherlands, but most of them were not. But yeah, still gives you that idea that this level of HDFN is not that commonly encountered.

Joe: So Meghan, I distracted you there for a second, why don't you head back into what you were describing about the effectiveness of transfusion matching?

Meghan: First of all, going further with the uncommon level, how relatively uncommon it is to find these women, there was really in our cohort of 293, 50 women had been transfused, a total of 63 transfusion episodes. We counted transfusion episodes as essentially if you got four units because of an OB hemorrhage, that was a "transfusion episode." So, only 50 women were really eligible for us to do the comparison between does Kell matching prevent HDFN due to Kell or not.

And, so, if you look at the paper, it's a pretty complicated table, but in table 6, it compares all of the different antigens, Kell's the biggest one because remember that's the one that all the MATCH centers matched against, although we did do the statistics on the other antigens, and essentially of the 50 women who received red cells, only 17 were alloimmunized to K, 13 at the MATCH center and 4 at the NOMATCH center. And so, we're getting to the very small numbers here, and 12 of the 13 of the Kell sensitized women at MATCH centers had partners who were Kell positive, suggesting that the causal stimulus was not transfusion. So those are the ones in that unknown, they were transfused and pregnant before.

And so, of the women who received the red cells who had partners that were Kell negative, the number attributed to transfusion, are really too small to be able to say that the transfusion was causal. So, you get very small very quickly. So, we weren't able to prove... I mean essentially you could say AMIGO is a negative study, because we started off wanting, me honestly saying "Hey, I want to show that antigen matching is a great idea, because let's match these women and prevent HDFN as a blood bank director, let's make the transfusions safer," and we were unable to do it.

But the devil's in the details. Going back to that intention to match, if you look at how many people who had got transfusion, who received that transfusion outside of the MATCH centers, like my example, a woman from an African country who emigrated to the Netherlands and that's where her HDFN was treated, that that was actually 49% of the MATCH center subjects, had actually received their transfusion outside of the MATCH center's catchment area. And that's reality. I think that was one of for me the biggest learning points, is that, if we want to have an effective policy, to be able to prevent all HDFN due to transfusion, which again, is in the minority of cases, everyone has to match, the whole world, to be able to have something that's effective in that way.

Joe: Right. That piece of data jumped out at me, Meghan, the other thing that you mentioned about in that setting of the 13, I'm going to try to quote the number right, but of the 13 K-negative women who, 13 K-sensitized women at the MATCH centers, 12 of them had partners who were K positive. I mean, that seems like logically that that would point in the direction that previous pregnancy was the

cause, but I guess what you're saying is, because they got transfusion as well, it's difficult to say that with 100% certainty?

Meghan: Yeah, that's right. And then the other thing is, our Dutch colleagues also let me know that they felt like the data they submitted was weighted more toward the women who had partners that were Kell positive. Either way, the numbers get small and the take home still to me is actually about that intention to match piece, that you clued in on early, is that people move around the world a lot, and so for transfusion policy to be effective, your one hospital making a decision, you really want to make it on the context of our global world.

And I know that sounds maybe too high-minded, but as a blood bank director in one hospital in America, it's difficult to say, "yeah, we should do it," just because of that reason, and we all know, especially in the United States, that we have a lot of people moving around hospitals and describe that referral pattern. But I do know that as a country like Canada I think is considering moving to more matching, and as a country, if you're going to make the decision, to me it would make the decision to at least do it as a country. You know, back again to blood bank and our antigens that we love, if you're going to match for anything, Kell is probably the easiest, you know, because it's not a prevalent antigen, and so therefore it should be easier.

So all those things have to be taken into account when a blood bank director is making a decision about how they're going to transfuse women and girls.

Joe: Well, so Meghan, there's really a lot of rich data in what you guys discussed and what you guys discovered. I wonder if by way of summary, if you wouldn't mind just, and it's totally fine to go over ground that you've already covered, but let's kinda make this the audio summary slide for this particular study, if you had to pull three, four, however many points you feel you need to make to kind of summarize what you guys found and what this means for now and potentially for the future, I'd love to get that from you.

Meghan: Yeah, absolutely. So, the conclusions from the AMIGO study were that, in a very broad sampling of women who had severe HDFN across seven nations, we found that most HDFN is due to previous pregnancy, that the minority of HDFN is attributed to transfusion, and that also we found that there's a really low rate of chronic transfusion in the cohort of women who are having children, which makes sense, because generally women who have children are typically healthy and able to become pregnant.

We also found that we were not able to prove a protective effect of MATCH center policies, and this was attached to a number of different things. One of them is, there was few transfused subjects, and that the matching policy are probably effective if you are always under that catchment area. When you are not, there is really no way for them to be effective, and therefore the efficacy is diluted. And so, back to what I was interested in is, you know, should we be doing this, how can I protect patients at my center, and really think it should be a discussion around,

energy around broad-based antigen matching policies throughout the world, that this could improve results, but doing it in very surgical, small areas probably is not going to provide the protection that we would think that we wanted to.

The study has some limitations, there are a small number of subjects overall. However, it was a very broad based sampling, so I don't think it would be a challenge to make a bigger study. And that in general, severe HDFN is a rare disease, I think that's a good summary. A couple of other commentary points is that we didn't look at low-grade or mild HDFN, which probably would have made our population quite a bit larger, and maybe we would have had more power to detect a change. But it does show that when you look for that at that most severe form of really true HDFN that we know that that's what it is, that you have to be really thoughtful about what your policy's going to be and probably making decisions at the national level is probably the best way.

Joe: I'm curious, Meghan, if we can venture completely into "opinion territory," and just for absolute clarity here, everyone, what I'm going to ask Meghan for is just her personal opinion, not her speaking on behalf of any organization or me speaking on behalf of any organization. I'm just curious as to your thoughts. You've been around this industry for a while, as have I, me longer than you because I'm tremendously old, but, in your heart of hearts, Meghan, do you think that we could be looking a few years from now at a national policy of prospectively matching females of childbearing potential, at least for K, is that something that you foresee happening in the United States?

Meghan: So, I think my answer is “maybe,” right? I mean, AABB…

Joe: That's a good answer.

Meghan: …Yeah…I mean, our standards are constantly evolving, right, every few years we get a new issue of *AABB Standards*, which many of us ascribe to, and if not that, then CAP [*NOTE: College of American Pathologists*], and they generally march in close step to each other. And I think that the answer is "maybe," and I'll give you one background thing that I am constantly thinking about and have been working on separately.

It will be much easier to do this at the transfusion service level if the blood suppliers can put the antigen on the label, right? Because then we don't have to be retyping, and so the FDA is moving that way, and suppliers are moving that way, and then of course the hospitals which are the clients of the suppliers are demanding it, are really trying to push. And so if someday it really is quote unquote easier than it is now to get your Kell status on the unit, which is what I saw in Sweden again, so many years ago, is that the antigens were just on the unit, then then it becomes just a transfusion service function that's more doable. Right now I think that the barriers to that are pretty high, and so unless you have one supplier that is one of the suppliers that are doing it, then you're faced with a challenge of having to buy more typing antisera, do extra testing, and in our world today that's a big challenge. So I think that that's one of the big drivers.

Joe: That is such a huge point, and I'm really, really glad that you made that point. For the folks that are learning, Meghan, again, I don't wanna go too deeply into this because I know we need to wrap this up, but I can't let that go without having you explain it a little bit more. You've worked in the blood center environment, I know, for quite a long time, and you're now in a hospital, I was in hospitals for a long time and I'm now in a blood center. Can we make sure everyone understands the importance of what you just said about how, if the antigen profile is on the label, how that makes a difference for a transfusion service?

Meghan: Yeah, absolutely. So, the traditional rules are that the unit is typed on the current donation to be able to put it on the label. The FDA is moving to be able to and has moved to be able to allow that if you've typed it two separate times, that you could put the historical type, meaning you didn't type the current donation, on the label. So those rules end up being really important, because first of all, the blood supplier has to be able to execute those rules.

It's a challenge for a blood supplier to know the antigen typing of two types ago, basically based on our BEC systems that we have, the computer systems, and the blood suppliers, but once you can get it on the label, then when it arrives at the blood bank, at the transfusion service, it's there and the transfusion service doesn't need to take a segment, do a typing, write it on the label, or label it separately, because that's a whole additional piece of work that is a challenge for our transfusion services to meet.

So, if it's already there, then it becomes another inventory issue that we've having to manage, which I will say is not necessarily going to be easy, but it takes away the piece of additional testing and additional work that has to happen at the transfusion service.

Joe: Definitely potentially removes a barrier that is currently there, and I think that's the way you put it earlier, and I completely agree with that. That would change the dynamic if and when, and I'm going to say "when" hopefully that type of, our ability to do that becomes a reality in the near future, I hope.

Meghan: Right, and I think that people who create the Standards think that way. I mean, I think that if we're five, ten years in the future, just guessing, and that it's quote easy to get those antigens on the label, that after that's out there for a few years, I could see the creators of Standards and the CAP requirements to say "Okay, now we think this is what you should do." But I think it will play out in that order.

Joe: And that, Meghan, that partly goes to one of the things that, well, I mean, the last time you joined me when you talked about molecular testing, is that potentially as our ability to do molecular testing on a grander scale, as things get easier and easier to do that, then we have the potential to have more and more things that we could potentially prospectively match people for. So, the future of that really has some exciting possibilities, it seems to me.

Meghan: Yeah, I couldn't agree more. I mean, that's really the way that the donor center is now, donor centers are now doing more red cell genotyping, but the information is difficult to transmit to the transfusion service under our requirements and regulations, and our computer systems, so that stuff needs to get sorted out, become more efficient, and when that day comes, I think that our ability to do the matching for women, for our sickle cell disease patients, or other chronically transfused patients, that we will be able to improve the care in that way.

Joe: And when we get there, Meghan, I have no doubt that you're going to be one of the people leading the charge, so I'm, as always, incredibly honored that you're willing to take the time to hang out with me on the podcast and to share what, and I'm not sucking up here, which is, you just have an incredible level of expertise and I'm so happy to be able to talk to you. Thank you so much for joining me.

Meghan: Well, thanks so much for having me, it was a real pleasure to talk about the study and to talk about these issues, it's always great to talk, Joe. Thank you.

Joe: Thank you.

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Joe: Hey, this is Joe with just a couple of things to share at the end. Remember, you can find quizzes, videos, a host of other free resources at BBGuy.org. In addition, you can find references and other useful information on the show page for this episode, at BBGuy.org/059. You can also listen to previous and future episodes directly on the website, on Apple Podcasts, Google Play, Stitcher, Spotify, really wherever you get your podcasts. Speaking of that, if you have a chance, I'd really appreciate it if you'd head on over to Apple Podcasts and give this podcast a rating and a review, and subscribe! It will really help get the podcast out in front of lots more people, which is what I'm trying to do.

So, I do have another episode coming very soon, in which I'm going to discuss some really interesting and creative ways to manage blood inventories with Dr. Nancy Dunbar from Dartmouth. Nancy's been on the podcast before, and she's also published some really useful things that might surprise you, and some of the conclusions and recommendations that she makes might surprise you. Really, our discussion I think is full of super-useful tips for you. That episode will also come by the way with free continuing education credit for doctors and laboratorians, and it's on the way very soon.

But until that day arrives, my friends, as always, I hope that you smile, and have fun, and above all, hey, never, EVER stop learning! Thank you so much for being with me today on the Blood Bank Guy Essentials Podcast, we'll catch you next time.