Immune

With Vincent Racaniello, Cindy Leifer, Stephanie Langel, and Brianne Barker

Episode 31: Immunology of COVID-19, Part 3

Aired May 8, 2020

www.microbe.tv/immune/immune-31/

Transcribed by Kim Barker

Content on Immune (microbe.tv/immune) is licensed under a Creative Commons Attribution 3.0 License.

{Music}

VINCENT: From Microbe TV, this is Immune, Episode number 31 recorded on May 6, 2020.

{Music}

VINCENT: I'm Vincent Racaniello, and you're listening to the podcast about the body's defenders against disease. Joining me today from Ithaca, New York, Cindy Leifer.

CINDY: Hello again!

VINCENT: How've you been? Well?

CINDY: I have been well. Healthy. Working from home, not leaving the house much. But it's very interesting, I think I can get almost everything done that I need to get done here. I just am excited to get people back in the lab. We got some pilot COVID funding so we're gonna look at some interesting things coming up.

VINCENT: Good! From Durham, North Carolina, Steph Langel.

STEPH: Hey there! Good to be back. Part three of our COVID immunology conversation.

VINCENT: How many parts is it gonna be like 100?

STEPH: Well yeah I know we really could just keep this going for a long time, I don't know when people are gonna wanna hear about different things but, for now, there's quite a bit to discuss.

CINDY: I don't know about you, but putting it in context, you know I'm teaching an advanced immunology class right now and sort of using this as a method to, you know, as a way to teach the information. The students are really appreciating that, because they're getting some information about this current thing that's going on but then putting that in the context of their learning. I think it's a unique and really exciting opportunity.

STEPH: For sure.

VINCENT: Yes, I agree, I agree. And from Madison, New Jersey, Brianne Barker.

BRIANNE: Hi, it's great to be back with you guys.

CINDY: Yay!

BRIANNE: I'm excited to talk more about the immune responses to coronavirus.

VINCENT: What's that? [laughter] If you like what we do on Immune and all the other podcasts, consider supporting us-microbe.tv/contribute. Let's do some e-mail first before we talk about immunology.

CINDY: That's a great idea.

STEPH: Yeah.

CINDY: I think the listeners have been writing in like crazy and we've been just discussing normal stuff, so.

VINCENT: So Lucian writes: *There was some discussion on Immune 30 about the feasibility of driving across the US in about a day. This is a known time trial called the Cannonball Run, and has been done! As you all pointed out, this requires driving for long hours in great excess of speed limits, and so is both very illegal and very, very dangerous. Nonetheless, it's been done. Here's a story of one pair of racers from Wired Magazine in 2007* [provides a link]: *httpSTEPH://www.wired.com/2007/10/ff-cannonballrun/ As always, thank you all for your insights and humor during these very strange times!* Yes indeed. I guess the humor would be the Cannonball Run...

CINDY: I think, you know what, I don't...yeah, I don't know that anybody's gonna beat the record that these guys set while the pause was in effect without...cops out there and the cars out there. I don't know if it's gonna be able to be done. I think I looked at that article she put up and I think they did in 37 hours and I think I remember saying it was 27, so I don't know if that's gonna be doable again. Do you...was it before you were born, but do you remember Cannonball Run the movie?

VINCENT: I do. I do.

CINDY: It was a comedy movie. But it was probably, I don't know if Steph and Bree know...

STEPH: Yeah that I'm not...

CINDY: ...probably too young.

STEPH: I'm not...

BRIANNE: I am not familiar with it.

CINDY: Oh no! That's terrible.

STEPH: That's very sad.

BRIANNE: I'm checking...oh I was born!

CINDY: You were born, oh yay, good.

STEPH: What year, Brianne?

CINDY: I don't feel quite so old.

BRIANNE: It was in 1981.

STEPH: Okay.

CINDY: I was pretty young then, I was pretty young.

STEPH: I was...someone's memory for seven years and then I was a thought seven years later then I was here.

CINDY: Oh dear.

STEPH: Oh boy. But that's interesting. Yeah I mean now that people are at home, I mean, I wonder...people could, not that I'm promoting doing an illegal and very very dangerous activity, but if you do it now you might be able to beat that record.

CINDY: Just don't go through some of the states they've opened already, right?

STEPH: Well that's true.

CINDY: Wear a mask.

STEPH: So yeah we we do have a couple more e-mails, I'm jumping down, that we could address before we kind of get rolling. It's easy to get rolling and then we don't get a chance to get to those e-mails.

CINDY: Yeah that's what we've been doing.

STEPH: So...

VINCENT: Sophie's first.

CINDY: I think...is Sophie first or Jessie?

STEPH: Oh you know, Jessie we'll talk about in the context of that conversation.

CINDY: Sounds good.

STEPH: So if you wanna read Sophie's that's fine.

CINDY: Oh sure. Okay. Sophie writes: Dear Immune, *I am a student in Bi 115 (Virology) at Caltech [*hopefully I said that right*], and we recently discussed the bat immune system. One thing that I found quite interesting was that bats have to suppress their immune response due to the inflammation caused by their high metabolic activity. Could people with higher metabolism (which I believe is associated with exercise) also have increased inflammation that could lead them to have a suppressed immune system that would allow them to tolerate the virus in a similar manner to bats?* So I think this is really interesting. And I think that one of the things we have to think about is the metabolic activity issue. So there's metabolism that you think about where skinny people have a quote unquote high metabolism or exercisers, right? But the metabolic activity that we're talking about here I think, I tend to think of it a little bit differently. It's how we're using glucose within cells. And so there was an interesting thing with in connection between inflammation and glycolysis. And that might be different but I'm not sure that the runners are gonna have a suppressed immune system? I think they'd actually have a more active immune system, I don't know what you guys think about this? But I know that...go ahead.

BRIANNE: I think so. I think that the changes in bats are quite a bit more dramatic...

CINDY: Yeah.

BRIANNE: ...than what we see in people because they're associated with flight.

CINDY: Yes.

BRIANNE: As bats being the only flying mammal. And so I think that it's longer term.

CINDY: Yeah.

BRIANNE: Than we see in people and much more dramatic. And with bats, that, this has led to sort of some long term evolution of their immune system.

CINDY: Yeah.

BRIANNE: In terms of changes in immune genes that I don't think we would see happening long term in humans who were running.

CINDY: Right. And some of the things that the bats have are like changes in their innate immune recognition signaling mechanisms, right? Cause I found an interesting paper that came out last year I think on STING.

BRIANNE: That's such a great paper.

CINDY: I love it. I love it. I think we should do it on our Immune podcast. But yeah so they have defects in the signaling responses to viruses, which, you know they seem to be more resistant yet have a lower immune response, which is kind of a fascinating thing.

BRIANNE: It is.

CINDY: And I think there's just so much more we need to know about bat immunology, right?

STEPH: Yeah. Definitely.

BRIANNE: I know, I have learned that they are actually missing all of the genes in the family that I study in my lab.

STEPH: Oh wow.

CINDY: Is that right?

BRIANNE: And so I have, I often flirt with the idea of starting to do some experiments on that.

STEPH: Oh you should!

CINDY: Unfortunately, I don't think NIH is gonna fund them!

STEPH: Yeah.

BRIANNE: I know!

VINCENT: Why, you can use bat cells right?

STEPH: Yeah you can use...are there bat cell lines? Probably.

CINDY: There are! Definitely.

STEPH: Okay.

BRIANNE: There are.

VINCENT: Yeah we have one, we just got it from Ian Lipkin.

STEPH: Oh good.

CINDY: Oh cool!

BRIANNE: Yeah I've thought about getting some, because yeah that whole the entire gene family that I study.

CINDY: And which family is that?

BRIANNE: All of the PYHIN proteins, so IFI-16 and AIM2, all of those PRRs.

STEPH: Oh nice.

CINDY: Yup, DNA sensors.

VINCENT: The problem with studying bats, and I talked about this with Linfa Wang, a TWiV we did a couple of years ago, you know they have bat colonies right?

CINDY: Yup.

VINCENT: But they don't fly around, they're in cages.

STEPH: Right.

CINDY: Whoa...

VINCENT: So they're always resting. And so yes it's an issue because you cannot get them to the point where they're flying and they're like 105 degrees Fahrenheit temperature, it really cranks up. So it's hard to study.

STEPH: Yeah unless you're doing field work and capturing bats, of course, that's gonna be a stress induced response because they're not gonna wanna be captured.

VINCENT: Yeah.

CINDY: Right. They do have large cages in which they house bats some certain places for research.

VINCENT: Yeah but you know these labs can't afford so many of those, right? Cause...

CINDY: Right, right right.

STEPH: I imagine it's very expensive work.

VINCENT: So I was supposed to go to a bat meeting this summer in Fort Collins, and of course it was cancelled, but they were gonna give me a tour of the bat colony and that would've been cool and then I could speak first hand.

STEPH: Very cool.

CINDY: Neat.

BRIANNE: So cool.

VINCENT: I can imagine them putting the bat on a long leash and letting it fly around.

CINDY: Did you ever see those things for Halloween where you hold it and the thing flies around in a circle on a string?

VINCENT: Yeah of course.

CINDY: That's what it reminded me of.

STEPH: We could definitely do this paper. We could also try to get, I mean Linfa Wang is probably pretty hard to get a hold of right now with COVID but we could try a post-doc or another...

VINCENT: Well there's a guy in Fort Collins who invited me, he's a bat guy. I can't remember his name...

CINDY: Oh yeah!

VINCENT: ...but he would do it.

STEPH: That would be great.

CINDY: Yeah.

VINCENT: He could do it sooner than Linfa.

STEPH: Yeah sure.

VINCENT: And the time difference with Linfa is difficult.

STEPH: Yeah, for sure.

CINDY: Yeah.

STEPH: And yeah I touching back to, I think we had discussed exercise induced inflammation before and we had made the point where it really is a difference between an acute versus a long-term effect...

BRIANNE: That's right.

STEPH: ...of inflammatory proteins on your body. And also, you know, thinking about excess adipose tissue...

CINDY: Yes!

STEPH: That also comes with its own inflammatory milieu. So...

CINDY: That's right.

STEPH: I think it would be very challenging and probably why exercise immunology is really...that's a difficult field...

CINDY: Yep.

STEPH: ...to try to parse through. So...but great e-mail, because I think it's going to lead to an episode or two.

CINDY: Yeah! Thanks, yeah.

VINCENT: So why don't you take that next one, Steph.

STEPH: Yeah sure. Whitney writes: *Hello! My name is Whitney Sloneker, a Bi 115 student from Caltech.[*Seems like they're in the same class.*] I had a few questions based on your Immune 29 podcast. You mentioned that enveloped viruses tend to be more unstable than other types of viruses, but coronaviruses seem to be stronger in that they enter the digestive system. What mechanism would you theorize is responsible? Do you think the differences regarding how IL-2 reacts in these different regions plays a role in ensuring we see stronger symptoms in the lung versus the gut? Are there different levels of SARS-CoV-[*She put 19 but I get it, I think she's saying like COVID-19 and SARS-CoV-2]...

CINDY: Let's hope we're not at 19.

STEPH: No, no we're not. ...*19 in both regions due to the structure of the virus and does this play a role in the effects we see if present?* So yeah, I mean coronaviruses, they can enter the gut even though they are enveloped viruses. So clearly they have enough stability that they're able to last through the pH of the digestive system. And then after that it's really all to do with the receptor, which for most of these is an enzyme, as to whether they're gonna bind and cause disease. You know comparing coronaviruses as a more stable virus than others, I hate...I don't know, I don't know if I wanna speculate in that way other than just to say for coronaviruses it seems fine. And then what mechanism would you theorize is responsible...well you know, I imagine if we were to break down so the structural proteins, the membrane and the envelope, I'm gonna assume those play a role in keeping that virion intact. And if we compare between families maybe that's where we would see differences, so you could kind of focus on those structural proteins. And differences in how IL-2 reacts in the lung versus the gut... I don't know about IL-2. I mean, maybe she meant IL-6? Because that was a driver of pathogenesis?

CINDY: Yeah I'm not sure.

STEPH: Not sure about IL-2.

CINDY: But we know IL-2 is important for T cell proliferation.

STEPH: Yeah, right. So they IL-2 definitely play a role in those two organs. Let's say it was IL-6 that she meant: I think that IL-6 is driven by macrophage infiltration, which can have negative effects both in the gut and in the lung. So you can think about immune infiltrates coming in during inflammatory Crohn's Disease or IBD, inflammatory bowel disease. So they definitely play a role, just in a different way. Her last question- different levels of SARS-COV-2 in both regions...so that's interesting, because we know the receptor ACE-2 is expressed both in the lung and in the gut.

BRIANNE: Yup.

STEPH: And there are high viral titers in the gut. I don't know if we can say with much confidence the transmissibility of that quite yet.

CINDY: Yeah.

STEPH: Because a lot of these studies are not using our favorite plaque assay to determine if they're infectious. But it may play a role. I think we're gonna learn more as papers come out.

CINDY: What do you think about the studies that are looking at like in hospitals they're saying that the highest levels of virus that they can detect, the viral genome that they can detect by PCR are in the bathrooms. Do you think it could literally be only just non-transmissible form that they're detecting just because it's massive amounts people are pooping out?

BRIANNE: I think that could be viral remnants.

CINDY: Yeah?

VINCENT: Yeah, Christian Drosten said they can't find infectious virus in stool. At all.

STEPH: Which is...

CINDY: That's interesting...is it just...oh, go ahead.

VINCENT: It may be pieces, yeah.

STEPH: Well, so, and I know coronaviruses in general need greater genomic content to form an infectious plaque.

VINCENT: Yeah.

STEPH: Like I would have to add more than another RNA virus. And then if those are all degraded I guess that could contribute to this high load. But right, I'm still wondering like why is there so much there? Even if it is degraded.

CINDY: Yeah.

VINCENT: Well it's a...this is becoming a general phenomenon with RNA viruses that you get a lot of pieces of genomes. Because now we can detect them independent of the plaque assay...

CINDY: Yeah...right.

VINCENT: ...infectivity assay. And Diane Griffin thinks that this happens with basically every RNA virus infection. There's a tail, after the infectivity is gone you still have this tail of pieces of RNA that go on for a long time.

STEPH: Sure.

VINCENT: Maybe months.

CINDY: How much do you think coughing and swallowing of virus might lead to detectability in feces for example?

VINCENT: No that too, sure. You can get flu in the feces, flu RNA.

CINDY: Right.

VINCENT: Cause people swallow it, yeah.

CINDY: Yup.

VINCENT: You swallow your mucus. That's how you, you know your ciliary elevator brings the mucus up and you swallow it.

STEPH: Right.

VINCENT: So yes, that's what I think when people find, oh we got flu in the feces, it's just swallowed virus. But for this, in this case it seems to be reproducing in the gut.

STEPH: Well that's the thing, I was gonna say, you know, to get this high of titers as what we're seeing in pre-prints and papers, it would have to undergo replication at least one cycle. But maybe it doesn't have an additional...I mean there's other enzymes, cathepsins, the TRPRS system.

VINCENT: Now when you say titers, you mean RNA copies.

STEPH: I'm sorry, RNA copies. Yeah Yeah.

CINDY: Yes. Yeah yeah.

STEPH: Not infectious virus.

CINDY: We can't get sloppy just because we're on Immune right. You've gotta keep us in check there, make sure we use the right viral terms.

STEPH: I know.

VINCENT: No because there's this paper on saliva- did you see this paper on saliva detection a couple weeks ago from Yale?

CINDY: Yes.

VINCENT: And they call it virus titer and I wrote to Akiko, I said no you can't say that, it's absolutely wrong.

CINDY: Oh no.

VINCENT: I don't wanna yell at people, but please use your terms properly, because the public is really watching now.

STEPH: Right right.

CINDY: Oh yes. And they're armchair experts now.

VINCENT: And the thing that's funny is that, it's not even genome copies, right? Because you're just amplifying a small piece.

STEPH: You don't know if you have every part of that virus.

VINCENT: I guess it should be amplisomes, amplisomes per mL or something.

BRIANNE: Right.

CINDY: Right.

VINCENT: It's very, very, what's the word...very...I can't think of the word.

STEPH: Nuanced? Is that what...

VINCENT: No...it's...

CINDY: Precise? Specialized?

BRIANNE: Technical?

VINCENT: No not precise it's...unwieldy, it's an unwieldy term to say amplicons per mL.

STEPH: Oh I see, yeah.

CINDY: Oh oh oh oh yeah yeah yeah. Replicons...

VINCENT: I can no longer think.

STEPH: We've reached the point where it's just like, it's too many Zoom meetings, too many papers.

VINCENT: By the way, these two from Caltech, so we learned over on TWiV that they're part of a virology course and the instructor assigned them to send in e-mails to podcasts.

CINDY: Aw, yay!

VINCENT: TWiV and Immune, so that's where the...I forgot what the instructor's name is. Do you remember, Brianne?

BRIANNE: Was it Pam Bjorkman?

VINCENT: Yeah Bjorkman yeah.

CINDY: Oh yes! Oh great.

VINCENT: Yes.

CINDY: Yeah, she's fantastic.

VINCENT: Yeah she's having her students...and in fact they don't, we don't even have to answer them as long as they send them in.

STEPH: Well we'll be sure to answer them. Yes. Do we feel like we answered Whitney's question appropriately?

CINDY: I think so.

VINCENT: Yes.

STEPH: Okay.

CINDY: I think you did a great job. Anything that you wanted to add Vincent?

VINCENT: No, we're good.

STEPH: Okay.

VINCENT: Maybe Brianne can take the next one.

STEPH: Yeah Brianne can take the next one.

BRIANNE: Okay. Matt writes: Hello, Brianne Barker recently noted there was a third type of immune system, which is distinct from the innate and adaptive immune systems.
I recall it had something to do with memory cells. I would love to hear you discuss this on a future episode of This Week in Immunology. Keep up the great work! *Matt.* So, I think that this is a reference to a comment I made on TWiV about trained immunity. Which is not actually distinct from innate and adaptive immune systems, I wish I could take credit for coming up with a third type of immune system, that would be pretty great.
STEPH: Don't forget about us when you win the Nobel Prize for your...
BRIANNE: I definitely won't I definitely won't. So I think this is when I was discussing trained immunity, which is this kind of new area of study that people are looking at, which is kind of an innate memory response.

STEPH: Yeah.

BRIANNE: So it's not really distinct from the innate and adaptive system. It is part of the innate immune system. It involves innate immune cells, but they are acting in a way that we normally associate with the adaptive immune system in that they are acting differently upon later exposure or after exposure to pathogens. So a newer area of immunology, something that I've been reading up on a bit since most of it was really understood after I left graduate school, making me feel old. But...

CINDY: Oh please, don't even.

BRIANNE: But I'm pretty sure that that is what Matt is asking about. We can talk about trained immunity but I don't think it's something distinct. At least...

STEPH: Right.

BRIANNE: If I, if I knew about a third type before I don't know about it now.

CINDY: But it was a fundamental shift in our thinking about innate immunity, which I think is just absolutely fascinating.

BRIANNE: Oh yeah it's really fantastic. And there have been a couple of sort of therapies that people have been talking about with COVID-19 that seem to take advantage of trained immunity. I've really enjoyed kind of taking all of this as an opportunity to learn a little bit more about it myself. And it's a total shift and it's totally fascinating. But does also tie into the fact that we know about lots of different organisms that don't have adaptive immune responses, and they also seem to have these responses where we see changes after infection. And so this may be kind of a very broad type of immunity that's present in many organisms.

STEPH: Yeah, yeah. And so Brianne brought up a good point that people are looking at this trained immunity as a mechanism to boost people's protection against coronaviruses and so if you guys are fine with it we can roll into that conversation...

CINDY: Yeah sure.

BRIANNE: Yeah!

STEPH: Particularly with two types of vaccines, so one that we call BCG and the other, polio, which Vincent did a recent TWiV about this, so, I think 604 is the number if you're interested in learning even more about this concept. But involving different reprogramming of innate immune cells so whether that be epigenetic or metabolic is the concept behind a non-specific vaccine boosting your immune system against another type of virus. And we were going back and forth and conversating about this, and I can appreciate that this would not provide herd immunity, because it's not specific. This is not gonna be specific against the coronavirus. But, there's some evidence out there, and maybe Vincent and Cindy, you guys can talk more about that evidence, but showing that countries that have the BCG, so this is the oh what's the French word for BCG...Bacillus...

BRIANNE: Bacille?

STEPH: Yes, Bacillus Calmette Guerin. So it's an attenuated strain of *Mycobacterium bovis*, so it's against tuberculosis. Gosh it's been around for a long long time.

BRIANNE: Yeah they started using it in, you know, the early 1900s.

STEPH: Yeah. And it's the only tuberculosis vaccine we have. And it's used in countries that, not in the US, that have high rates of tuberculosis so comparing countries that have populations that had gotten this vaccine, they had seen some evidence that maybe it could be protective against other viruses. But does anybody have any...I think Cindy might be one of the top...

CINDY: So I saw another paper that when they broke it down so there are certain countries that stopped using it, and if they looked at, if they broke down by age group for those who would have had it and would not have had it because after they stopped using it as a vaccine they didn't see any correlation with the incidence of disease. So I would take that to mean that looking at these bulk countries, you know, like saying that one country uses BCG and they had lower levels, and another country doesn't use BCG and they have higher levels, but when you look at the country that did and you break out the population that had had the vaccine or had not had the vaccine there was no difference. So...I'm I think that this is not...I wouldn't say debunked but I think it's quite questionable whether this is true.

BRIANNE: Yeah.

CINDY: That being said...if you look at the basic level, what the active or most active component of BCG is from Coley's toxins way back when, is DNA. And DNA triggers TLR9, and there have been studies for example from the lab in which I did my post-doc, where we found that, you know, just injecting CpG DNA or a TLR9 ligand repeatedly over time and then challenging animals they were more resistant to infection with a variety of different agents including bacterial agents and viral agents. So the idea was, and this was way before we had this idea of trained immunity or any other innate immune memory or anything, was just we had the idea that

triggering TLRs on a, you know, on a regular basis kind of kept your immune system like primed to some degree and so would make you generally able to respond more quickly and more robustly to any kind of insult, didn't matter what it was. So I don't, I'm still not convinced but I mean if you, if you looked at people who had recently had that BCG vaccine versus ones who had it years and years and years ago, maybe there's a difference, but I don't know.

BRIANNE: Yeah that's my take as well, I think that there are kind of two sets of studies on this. One that are sort of epidemiological studies where you're looking at the bulk country data as Cindy mentioned, and some where people who have recently had a dose of BCG have been examined. And there are some clinical trials going on where healthcare workers are being given BCG. There are some pros and cons to that because of issues with BCG. But the idea of trained immunity, at least from my extensive learning from reading two reviews, is that this seems to be a change in innate immune cells that lasts between three months and a year.

CINDY: Yeah.

BRIANNE: And so perhaps people who have recently had BCG might have a sort of improved activity of some of their innate immune cells, particularly monocytes or macrophages, that let them act a little bit better against some of these viral infections. So it's not specific, it probably wouldn't lead to herd immunity, but perhaps it's some way that people at higher risk might be protected from the short term.

VINCENT: There are 8 clinical trials ongoing in 6 different countries to test this. All for, mostly healthcare workers but not all of them. So we'll see if it has any effect.

STEPH: Yeah, we'll see.

CINDY: Yeah-go ahead.

STEPH: And I guess if it's healthcare workers, maybe it would not be people who were...I mean they're at high risk for being in contact with high amount of virus but maybe not high risk age group wise, So I do wonder about boosting your innate immune response for a disease that is known to be most severe in people who cannot control their innate immune response.

BRIANNE: True.

STEPH: So the trade-offs there, I just don't know if we know, you know, what this would do to a person who's already susceptible because they don't have the ability to control their macrophages infiltrating into the lung. So, I think it'll be yeah, interesting to find. Now with poliovirus Vincent, I mean there's two different types of vaccines, and so this would have to be the live attenuated version to have effects?

VINCENT: Yeah I mean that's what Kostya Chumakov said. You don't get this effect with the inactivated polio vaccine. So, yes, it's OPV and you know, he's trying to do a trial, I don't know where that stands now.

STEPH: Sure.

VINCENT: But, you know it'll be relatively safe.

CINDY: Are they doing these trials prospectively? So are they enrolling people and then vaccinating or not or are they doing these retrospectively where they're looking back at charts and...

VINCENT: No they're doing prospective trials. And they would be in healthcare workers too yeah.

STEPH: Okay.

VINCENT: Yeah healthcare workers are the real target.

STEPH: Sure.

CINDY: Right right.

VINCENT: You just need a couple of months of protection, right? That would be good.

CINDY: And with BCG the concern to re-introduce that vaccine into countries that aren't using it, my understanding is that we sort of use this as a surveillance, right?

BRIANNE: Exactly.

CINDY: So TB, multi-drug resistant TB spread is a real concern worldwide, and not being able to do surveillance for individuals who might have TB versus those who don't is a problem.

VINCENT: Yeah, yeah.

CINDY: And we use the TB test, you know, the tine, you know, pricking your wrist and doing the delayed type hypersensitivity reaction to determine if you've been exposed. You'll test positive if you've had the BCG, which creates a whole nother layer of surveillance to do lung, you know, radiographs and things to determine whether you actually are harboring the bacterium or not.

BRIANNE: Right, but I think...

VINCENT: It's interesting that the BCG trials are getting so much traction and I just looked there's no OPV trial in clinical trials.

STEPH: Hm, that's interesting. Do you think that's because they wanna stop using OPV? Because the issue of...

VINCENT: No, I think Kostya is just not as forceful as the other people involved.

BRIANNE: I think that's part of it, and I think that sort of coincidentally, a lot of the original work on trained immunity has been done with BCG.

CINDY: Yeah.

STEPH: Right, we understand it better.

BRIANNE: Yeah.

VINCENT: But remember, listeners, these trials cost money.

STEPH: Oh my gosh.

VINCENT: Someone has to pay for them. And so if Kostya has an idea, it doesn't just happen. So...

CINDY: Right.

STEPH: Yeah.

VINCENT: I think these BCG trials are in many different countries.

STEPH: Sure.

VINCENT: So clearly their countries are behind it, so that helps.

STEPH: So I mean big picture, okay so let's say that we could get a boost in immunity for 3-9 months with the BCG vaccine. In healthcare workers I could see that'd be beneficial. I don't foresee this being anything that we could roll out to a large, you know to society or to the large group. Just because I don't think we know enough in particular the high risk groups. But if it was focused and it did show it worked, I, you know, at least to tide us over, because what we're gonna talk about in a little bit is that a vaccine against SARS-CoV-2 is gonna take some time. Contrary to what you may have heard.

CINDY: You also might have been quite on the young side, but in 2001...

VINCENT: Still is!

CINDY: ...when we had September 11 and then we had the anthrax threats.

STEPH: Yeah.

CINDY: So that was when I was in this lab, and we were talking about stockpiling CpG DNA...

STEPH: Hey...

CINDY: Whether we could, you know inject ourselves to give a boost of immunity for anthrax exposure.

STEPH: Sure, do what you gotta do.

BRIANNE: We're never gonna go to my lab, right now.

CINDY: We never did that, but the point being though that you know, if a primary active component of BCG is DNA, it's somewhat safe, right? So it wouldn't have to necessarily be just BCG, which could have its own problems, but you could use DNA.

STEPH: Yeah.

BRIANNE: Yeah I think that would be much safer than using BCG. I would be concerned about using BCG in whole populations.

STEPH: Sure.

BRIANNE: But something else with DNA would work.

VINCENT: Yeah, but there's some component of being, it's a live bacterium and it's infectious.

CINDY: Yeah.

VINCENT: Polio virus...

CINDY: True.

VINCENT: ...and the inactivated vaccines don't have the same effect.

CINDY: Agreed, agreed agreed.

VINCENT: So it's not just DNA right?

CINDY: But you know, a little boost is...

STEPH: Better than nothin? I guess?

CINDY: Well that brings up a very...that's not a very...

VINCENT: This brings the question, if you have influenza now, will it protect you for a couple of months...

CINDY: Yes.

VINCENT: ...against SARS-CoV-2 infection, right?

CINDY: I would say...

VINCENT: That's the effect of virus.

CINDY: Yeah...I would say no.

STEPH: No.

CINDY: Because...

VINCENT: Why not? If just general boosting is the idea.

CINDY: Well it's general boosting, except that influenza's infecting the, you know, same target cells in the lung and causing tissue damage, which is, I don't know that that's gonna boost immunity or make you more susceptible.

STEPH: I would go with yeah, I do...the concept of boosting innate immunity, but then I think influenza particularly infecting the same cell type and then you're gonna follow up with this virus, I think it would predispose you potentially.

BRIANNE: Yeah pathology in the same place twice...

VINCENT: Well Kostya seemed to...Kostya seemed to think that Flu Mist would have the same effect, because that's not damaging cells. I guess maybe that's...

STEPH: Could it be...

CINDY: Oh, but you know what? We could probably find that out, because they did reinstate Flu Mist this year, didn't they?

VINCENT: Yes.

CINDY: So there will be a cohort of patients...

STEPH: Yeah.

CINDY: ...who received Flu Mist versus the regular flu and we could look retrospectively to see.

STEPH: But how could we...sure, but we couldn't decipher...yeah no we could do that. You're right. We could.

CINDY: You could look at people who didn't get a vaccine versus Flu Mist versus inactivated and see whether there's any difference in attack rate with SARS-CoV-2.

STEPH: Okay, well who wants to write that grant? Ready go. Cindy your post-doc studies, when you were able to see, induce the effect of multiple CpG injections, did it work if you just gave it one time? Or was the multiple important?

CINDY: So I didn't do those studies and the challenge studies, but it's...the general consensus was, you inject you would get a little boost for about 2 weeks and then it would start to wane. So they tried to do this thing where they were gonna boost every 2 weeks, but if you continue that for very long you end up with some spleen issues, cause you get some...

STEPH: Yeah, true.

CINDY: ...overzealous inflammation and splenomegaly and lymphadenopathy.

STEPH: Not fun.

CINDY: No.

STEPH: Well good. Okay so we feel like we covered BCG, polio, trained immunity pretty well?

BRIANNE: Yes.

CINDY: Yeah.

BRIANNE: And the fact that there is no third immune response.

STEPH: Yeah.

CINDY: No Nobel Prize yet, you gotta keep working.

STEPH: Keep going.

BRIANNE: Sad.

STEPH: So the next thing is something that I've gotten asked about a couple of times and Vincent recently did a TWiEVO about it if I'm not mistaken. But there's a potential mutation in the spike protein and a lot of conversation about mutations in coronaviruses, which we've discussed on this podcast too. You really can't say without functional studies whether or not a mutation is weakening the virus or making it more, you know, transmissible. And Vincent, I'll kind of let you talk about this if you want, but, it's been something that's been in the news because of this emergence of this particular mutation within more European strains that had seeded into New York and then went back to Europe. So...

VINCENT: Yeah so this is a pre-print, now that's the problem, it's a pre-print.

STEPH: That's the problem, yeah.

VINCENT: And as it is written it will never be published using the same language. It's out of Los Alamos.

STEPH: Sure.

VINCENT: It's a computational biology analysis. They have a pipeline for looking at changes in the genome that may persist. And they identify this amino acid change in the spike, which they think has been spreading extensively in certain areas. Okay that's fine. But then they say: it's alarming spread and in the title it says this mutation, this amino acid change, enhances transmissibility, which is where it just falls apart because there's no evidence. Just because a change is persisting doesn't mean that it's doing anything, it's just...so there have been a number of discussions about this. What's the guy's name in Washington? Trevor...

STEPH: Trevor Bedford.

CINDY: Trevor Bedford.

BRIANNE: Trevor Bedford.

VINCENT: He agrees that it is probably a founder effect, which means, and I told a reporter this yesterday, when you get a virus infection, you're full of marbles. Imagine each marble is an infection, a virus, and they're each different colors. You transmit one of those, you transmit a blue marble, and now that person will transmit blue marbles. And so it's just random, and has nothing to do with any property, in fact in the paper they didn't look at any biological properties at all. So I think it's fine to report this, it's interesting that a particular change has been sustained, but it is really irresponsible to say it enhances transmission, because all the papers are picking that up, all the news sources are picking that up and they're scaring people! And I have to say this is not the first time this has happened. It happens, it happened with Ebola virus, it's happened with Zika virus. People seem to want to watch the virus change and get worse, I don't get it. Anyway, Nels and I talked about this yesterday, but the fact that Trevor agrees that it is a founder effect, which means whatever virus gets into a population, all the others are derived from it, right? They have similar mutations. And it's no, there's no evidence of what we would say positive selection, which would be if this confers some property on the virus that's selectable. And I think that's the other aspect you have to think about. If you wanna say a change increases transmissibility then you need to show me what's the selection for that? Because last time I looked, this virus is pretty transmissible, it's doing a great job.

CINDY: Yeah it's doing a very good job. We do know though there had to be a mutation in order to get it into humans, right?

VINCENT: That's right. A long time ago, maybe last year, yeah.

CINDY: Right, and then there's probably a mutation that allows it to spread from human to human, right?

VINCENT: Yeah.

CINDY: Because they...

VINCENT: And as Nels said all that probably happened long before we saw it.

STEPH: Right.

CINDY: Right. Yeah.

VINCENT: Cause to see it working in people it's already gone through all of that change.

CINDY: Right.

VINCENT: And we would love to be able to watch that in action, but we can't.

STEPH: Yeah. Well and...

BRIANNE: We'd need to know a lot more about all the viruses in all sorts of different organisms.

STEPH: Yeah!

BRIANNE: To do those things.

STEPH: Yeah we should be funding more bat research.

VINCENT: Oh, you mean we shouldn't be cutting it?

STEPH: I was gonna say.

CINDY: Yeah! Seriously, geez. Go figure.

STEPH: So I say okay yeah, I agree. I think while there's a hypothesis and while that could be plausible, we have no evidence right now that that would be the case. So people listen to TWiEVO to get more info on that, because that would be pretty good conversation. And you know, talking about vaccines and vaccine development, I think one of the things we all get asked a lot because gosh it's just such a part of the conversation in the media is when are we gonna have a vaccine?

CINDY: Oh yeah.

STEPH: How long is that gonna take? You know, I just think it's irresponsible and I even think Tony Fauci did say this although I'm a big Tony Fauci fan, he did say at one point 12 months. And I just think that's irresponsible to say, because 18 months would be a dream based on what we know about how long it takes to produce vaccines. I think looking at this chart that maybe 10, 11 years...

CINDY: Yeah.

STEPH: ...was the fastest that we've been able to do. And I don't wanna scare people to say it's gonna take that long, because there's a lot of investment going into creating a vaccine for basically the entire world, but we just gotta be careful and really what speeding up a vaccine production would mean is maybe skipping out on some safety trials, which I don't know.

CINDY: Yeah so I think that there is there is some acceleration pace of development, right? So you know, computers and technology all kind of follow that same exponential phase.

STEPH: Sure.

CINDY: I'm not saying that it's gonna be 12 months or 6 months, but if we're using platforms that have already been developed and are shown to be safe, they're going right into almost phase 3 trials with these, so the vast majority of the research that would normally be done, the basic level and setting up to get to those phase 3 trials is all being skipped, right? And so we're still going to have...

VINCENT: You have to do, you have to do phase 1. Even in accelerated you have to do a phase 1.

CINDY: Yeah but it's a combined, right? Isn't it?

VINCENT: No it's a phase 2/3 that's what.

CINDY: Oh phase 2/3.

VINCENT: Yeah but phase 1 you have to do it because you can't go into two, three-hundred people immediately because if you have side effect you're screwed.

CINDY: Yeah...I thought they were already starting those...

VINCENT: And no one will ever take the vaccine. No they're all phase 1, the mRNA vaccine is in a phase 1, the ChAdOx, the chimpanzee adeno from Oxford, that's in phase 1, all phase 1. But then if it looks good you could do a combined 2/3, which would mean...

CINDY: Got it.

VINCENT: ...dosing in large numbers for efficacy.

BRIANNE: Yeah I think the furthest I've seen is people trying to do some paperwork to be ready for that phase 2 as soon as their phase 1 is finished.

CINDY: And how long do those phase 1s usually take?

VINCENT: Two months, right?

CINDY: Two months.

VINCENT: To just do the trial, not to recruit and do the paperwork and get approved and then afterward look at the data.

CINDY: The analysis, right.

VINCENT: The two months you wanna look at them for two months and so, and now the virus levels are going down...you hear China doesn't have enough circulation to test its vaccines now.

CINDY: Yeah.

STEPH: That's so interesting. Yeah.

VINCENT: Will the US let them test theirs here? Huh, what an interesting idea.

STEPH: I don't know. No, I mean politically no. That's never gonna happen. But it would be good for public health. Yeah and you know, Cindy's right I mean there's a lot of technology that has sped up particularly the beginning part of the process, I mean an mRNA vaccine you just need the sequence. But there's no mRNA vaccines licensed, correct?

BRIANNE: Correct.

STEPH: So we actually don't really know the safety profile in humans. So...

CINDY: That's right.

VINCENT: No.

BRIANNE: Right. And that's why they're working on all of those right now.

STEPH: So anyways just a little, you know, blip about...

VINCENT: Where did the longest vaccine that ever...what's the longest time a vaccine ever took, Steph?

STEPH: Well, I'm gonna say based on your background, the polio vaccine.

VINCENT: 50 years.

STEPH: 50 years.

VINCENT: From 1906, 1908 to 1957. And lots of false starts. Now granted, we are better at technology as you said right now, so it shouldn't be 50 years, but we still don't have an HIV vaccine.

CINDY: Yep.

STEPH: Yeah.

VINCENT: And it's not from lack of trying, right?

CINDY: That's right.

STEPH: Right?

BRIANNE: No, definitely not.

CINDY: Yeah.

STEPH: So, we we'll keep people updated you know, each week we can do a little vaccine brief even if we start to diverge to different topics, because it will be obviously it's something on people's minds. But that Vincent is interesting, that they don't have enough circulation in China to be able to test their vaccine, that's interesting.

VINCENT: Yeah now it's becoming a political issue right?

STEPH: Yeah, sure.

VINCENT: Because they wanna go somewhere and this country is destroying, what do you call that when you destroy your ties with a country?

STEPH: Oh...diplomatic...well if you think of the term you can let us know.

VINCENT: Yeah so that's unfortunate because, I have to say that when Albert Sabin made his polio vaccine candidate, the US wouldn't test it. They said no, we have IPV, we don't need it. So he went to Russia. He went to Chumakov's parents in Russia, who had visited cause they were interested in infectious vaccines and they said sure come over! And they did 100 million plus people clinical trial in Russia. Sabin brought over his viruses and they did it. Can you imagine?

STEPH: Interesting.

BRIANNE: Wow.

VINCENT: I mean that's because they had the people and the wherewithal to do it. Why can't we do it today you know?

STEPH: Yeah.

BRIANNE: Yeah that would be great.

VINCENT: But people have to fight. Burning your bridges behind you. Something like that. Then you have to turn around and go back and your bridge is gone.

STEPH: Yeah. Yeah for public health it definitely is not ideal. So we will have to keep an eye on that. And that leads to, you know immunity in general and vaccine and are you immune? And Cindy might wanna talk about this because she has recently taught it in her class but there has been a lot of conversation about serological studies. We have talked about serological tests, and in-between I think our last episode and this one there was a couple serological studies I think they're pre-prints...I don't think they're published but they're pre-prints, came out of Santa Clara and then Los Angeles. And there was a lot of conversation about whether or not this accurately predicts your positivity and can you do that with these tests? Because there is, you know, a sensitivity issue.

CINDY: Right. So I think that there's a couple of really important points related to this. The first one is that it seems from a lot of these studies that there's prolonged detection by PCR, right? So we've already discussed, at least in feces, whether that would indicate that you're transmitting or not, because people aren't doing the plaque assays, right? But the idea that, you know, we seem to have detectable virus for significantly longer with this particular infection that with some other infections, and more importantly is that some of these studies are showing that even if people seroconvert-that means their immune system is now recognizing the infection- starts to make antibodies, you can still detect the virus bits that we were talking about before for quite a long time. And so the other issue is that it seems like some people just aren't seroconverting. So even if they are infected, their body is having a hard time recognizing this infection and inducing an immune response. So those are two issues. But then the important issue that everybody wants to know is once we seroconvert, and you become PCR negative, so this means your immune system recognized the infection and presumably you have now cleared the infection, are you actually immune? Right? This is this is the basis of vaccines, this is the basis of what we talk about with memory and the immune system. But the answer is we don't necessarily know yet. So there's many different reasons why. With flu we know we need the new vaccine every year, but that seems to be because the virus itself changes, so our immunity doesn't protect us, right? But what if our immune response to this virus doesn't fully protect us? Now that gets into some nuance, right? Because even if you're quote unquote fully protected, we don't...we never fail to be infected again, right? So if you're gonna breathe in more virus it will go into a couple of cells likely, but you're not gonna transmit much and you won't get sick. But the question is you know, what does this seropositivity actually tell us? And can we use this to give these people these you know, passports, right? That's the whole idea that they wanna use this, they wanna say if you're antibody positive we now know you can't be infected, you can't infect anybody else and you're good to go, you get a passport you go out in public and you don't have to worry about things anymore. And I think there's a lot wrapped up into that that we don't really know yet.

STEPH: Yeah. Yeah wow. That's a great explanation. And the immunity passport thing, because we don't know protective levels, we don't know if that associates with neutralization of the virus, and just how different people are in terms of their immune response in general. I am gonna read an e-mail that was sent in because it has to do with this immunity passport conversation and we can kinda go around...

CINDY: Yeah!

STEPH: ...and give our opinions on that. But, so this e-mail is from Jesse Mangold. Side note, he does, he's a, well he's going to do his M.D./Ph.D. but he's an undergraduate at Duke who works in our lab. And he said: *Dear hosts of Immune, thank-you for continuing to deliver timely and trustworthy science communication that I can rely on to cut through the noise. My name is Jesse Mangold, and I'm a research tech at Duke Human Vaccine Institute.* He's an incoming first-year M.D./Ph.D. at Mount Sinai so I think he'll be potentially involved in some of the exciting work that's going on at Mount Sinai in regards to viral immunology. *What I miss the most about the lab while working from home is listening to Immune while workin in the hood and having the luxury to pick Steph's brain when I have a burning question.* And I have to say, walking into the lab and hearing your own voice is a bit disconcerting. I'm usually, it takes me a minute to realize that it's me and then I typically will just say you know what, Jesse? You keep listening, I'm gonna go over here cause it's just, you know, listening to your own voice.

CINDY: It's weird.

BRIANNE: Yeah, that is.

STEPH: It's weird. Makes me sweat. Anyways. T*his time I will write in*-oh *big Permar and Fouda* -and those are our PIs- *lab style, shout out to Steph*. Thanks Jesse. *This time I will write in a question. What are the key dos and don'ts around the design of a SARS-CoV-2 population serosurvey and their interpretation to inform policy? Do you have concerns with the circulating concept of immunity passport to return to working society. For example, a biased sampling method could reinforce existing structural inequities by conferring more immunity passports to those people with greater access to testing. This brings a whole new meaning to the term immune privilege. Looking forward to hearing your insights. Thanks and stay well.* Yeah that is a huge part of it is access to testing. And those populations that are not going to have, I mean they generally don't have as great of access to healthcare. So then you're determining their ability to work based on that.

BRIANNE: Right.

STEPH: In addition to what we described, we don't even know...and for most infections, I don't think we would ever know enough to make this a public policy.

BRIANNE: No, I agree. And I also really worry when I hear about this discussion of immunity passports, not just about thinking about people with greater access to testing, but I wonder about people who are seronegative who really wanna go back to work and who now seem to have some sort of incentive to go get themselves infected.

STEPH: Oh yeah. Like a party.

CINDY: Yeah, that's right.

BRIANNE: Yeah that seems like a really bad idea to me. I really wanna go back to my lab and I do not wanna be in a situation where I have to think hmm should I go do something dangerous to get infected?

STEPH: Right, right.

CINDY: Right.

BRIANNE: That just seems like a terrible idea.

CINDY: It is a terrible idea. But also I mean there's just like think about who is in the forefront of interaction with the public. I mean these are people who are working in grocery stores, and restaurants and things that are still open right now. And so if they're negative does that mean that they're not allowed to work anymore? These people are not being paid a lot anyway and they've been forced to work through this whole thing, and now you're gonna tell em only if they're positive they can work? I just think that there's gonna be a huge societal inequity if something like this were put in place. And I would say like one other issue that I think is really important to consider when we're talking about these kinds of serological testing or even any testing in general, was as I was talking about this with my class the other day, there's a really important thing that we often don't think about. And that is the prevalence of the disease actually in the population.

STEPH: Yeah.

CINDY: Right? So if you have a high prevalence, so there's a lot of people that are actually positive, when you test there's a good chance that a positive test is actually positive. And there's a reasonable chance that a negative test is actually a false negative. But on the flip side, if we only have a small portion of the population that's actually infected, so the prevalence is really low, if you have tests that aren't so specific, now you all of a sudden have people testing positive that aren't positive.

STEPH: Right right.

CINDY: Right? So...but a negative's a good chance that it's a negative. So as we're testing the population now, with relatively low prevalence in a lot of areas, then a negative test is probably reliable. But as we cross a threshold and a lot more people are actually positive, a negative test becomes less reliable.

STEPH: Yeah. For sure. And you know I don't know if these conversations were brought up because...I don't know who started these conversations of immunity passport, if it was actually from a government official or if this was just general think pieces that people were publishing. But people have seemed to come off it and and I think it's because what we're seeing from these serosurveys is it's very difficult one to get a test with the specificity that you want and then two to rely on that. So. I don't know if we'll have these conversations much more but.

CINDY: I don't know, I think those conversations are still happening. They're happening locally here in Ithaca.

STEPH: Okay.

CINDY: Because...and at Cornell University and other universities, because they're trying to figure out a way to reopen, right?

STEPH: Yeah that's true. And healthcare workers.

CINDY: So we need something, people are like something's better than nothing.

VINCENT: But we do have...we do have a test called PCR that will tell you if you're infected.

CINDY: That's right.

VINCENT: And that can be used to quarantine people and do contact tracing and limit outbreaks. But we don't seem to want to do that in this country. I don't get it.

STEPH: Yeah, if we can't even implement widespread testing to see if anyone even has the virus...

VINCENT: Yeah.

STEPH: Then to tie it to the ability to work, we wouldn't have the capacity.

VINCENT: You know these serosurveys...go ahead.

CINDY: I think the reason...go ahead.

VINCENT: The serological surveys historically have never been used to determine who is susceptible or not. They've been used to say who's been infected or who's encountered the virus, right?

STEPH: Right.

CINDY: Right.

BRIANNE: Right.

VINCENT: And now for some reason we wanna use them to say you're okay. I don't get this, I don't get where this is coming from. It's the wrong use of a serosurvey.

STEPH: Yeah I think people are just really wanting to, you know, go back to work and reopen the economy and make money, and I can appreciate that but it would be irresponsible to.

BRIANNE: Yeah I think that it's in some ways wishful thinking that people wanna get back to work and open things back up. But I just don't have any idea of exactly how much antibody is needed to be protected and whether or not we're measuring protective antibody versus just any old antibody and things like that.

VINCENT: Yeah. We have no idea.

STEPH: Yeah.

VINCENT: Never for any virus have we to do that...

BRIANNE: Nope.

VINCENT: Unless you do a neutralization assay.

STEPH: Right.

CINDY: Yup. Not...yeah.

VINCENT: So on TWiV someone wrote in from...I don't know...Taiwan, South Korea, and they have never shut down, they've done extensive PCR testing...

BRIANNE: That was Taiwan.

VINCENT: ...yeah and the other day someone, oh Jeff Shaman talked about the South Korean experience where using extensive PCR they could limit infection by quarantine and contact tracing.

CINDY: Yup.

VINCENT: And it seems to me, we are just forgetting about that. We shouldn't!

CINDY: Nope.

STEPH: Yeah, so, I think that that's a good point we could transition, we could read a couple more e-mails or we could kinda roll into this last section of well we have a couple more sections but testing, prevention and control. Do we have any preference? Whether we wanna do e-mails...

VINCENT: Let's do a couple of e-mails.

STEPH: Sure.

VINCENT: Whatdya think?

CINDY: Sure.

STEPH: That bounces us back to...last one was Matt's so that bounces us to Ben. Benjamin.

VINCENT: Right.

STEPH: Vincent, you can read it if you want.

VINCENT: Benjamin: *Good Afternoon! It is 62F in Washington DC. I work in a lab for the department of defense, and while I am not working in Immunology or Virology, your podcasts have encouraged me to look into it.*

STEPH: Do it!

VINCENT: *You have been talking on both TWIV and Immune a lot about the possible lack of sterilizing immunity that could be acquired from the immune response to SARS-CoV-2. What impact would this have on the efficacy of a vaccine? Do vaccines still work (at least through the mechanism of "artificially" increasing herd immunity) if they don't give sterilizing immunity?* Maybe we should stop and answer that.

STEPH: Yeah yeah I think so. I mean if you're gonna decrease overall...cause we can assume that this vaccine will not cause sterilizing immunity, and I don't know that most vaccines do...I still think you have low circulation. But if you're lowering it then you have less people infected and then you can reach whatever your herd immunity percentage is. I still think you can reach herd immunity with a non-sterilizing vaccine.

VINCENT: Yeah. I think if you look at the experience with the common cold coronaviruses, and Jeff Shaman just put out a paper on this. They've been doing a survey in New York City for these for infection with these virus and they find people getting infected, they get low level of serum antibodies and then they keep getting reinfected and reinfected every year with mild or no disease. So...a vaccine could do the same thing. It could just give you this low level immunity. You don't get sick but you get infected, the virus circulates, I don't think that's a bad situation, right?

STEPH: And I should clarify just in case- cause' I'm assuming people know what sterilizing immunity is, but it's the idea that you would not get infected, there would be no replication, there would be no symptoms. And then non-sterilizing immunity is you maybe would get low level of infection but you're potentially not spreading it, you might...it would be mild in general.

CINDY: Yeah I would agree with that. I think that, you know, this is something that I encounter, I don't know about you Vincent, in the anti-vaccine crowd, is that they seem to think that vaccines are useless and herd immunity doesn't exist if people could potentially still get infected even if they're immunized. And I think that it's a...it's a really hard thing to explain that, you know, if you have a more robust and a more rapid immune response because you have pre-existing memory, you're going to dramatically reduce the amount that you would spread. And so you decrease the load and what you would be able to transmit. So it still works. But you know, it's an argument.

VINCENT: You know what the problem is Cindy? They...I think people equate infection with getting sick, in a way.

CINDY: Yes.

VINCENT: And they don't understand that you could be infected and not get sick.

CINDY: That's right.

VINCENT: And in fact we have an e-mail where someone says, how can that be? Right.

BRIANNE: Yes. I would say that that is one of those things that's a little bit of a soapbox that I think all of my students get to hear a lot when I'm teaching. I talk about it all the time, is how infection does not equal disease.

VINCENT: Yeah. Cause you know, as you well know Cindy, the point of a vaccine is you get an immune response without getting sick.

CINDY: That's right.

VINCENT: And then you subsequently get infected, you may get some virus in you but you don't get sick! So why don't they get that, I don't understand. Well they don't want to get it, really. That's.

STEPH: Yeah that's right, I don't know if...

CINDY: Well they want to say that that means that if you don't get sick, that you will still continue to spread and so that the idea of herd immunity is irrelevant. And I don't...and that's just not true, because if you have someone who is not...doesn't have pre-existing immunity who would shed 100 particles and someone who does have pre-existing immunity would shed 1 particle, the probability of transmitting to another person is dramatically reduced. So it does, that's exactly what herd immunity is. You know while we're talking about this, one of the other arguments is is that if you are targeting, you know, pathology in an individual and not necessarily transmission, so let's say we were...we have some vaccines that are generating immunity against the toxin rather than the bug itself, and they're like oh but that's only gonna affect the toxin and not the bug. And how do you explain to someone that the toxin is there because the bug uses it to gain a foothold on the immune system...

VINCENT: Yeah.

CINDY: ...and the host! And so if you block that, the bug is crippled and doesn't replicate as efficiently and doesn't transmit as efficiently.

STEPH: Yeah it seems like what I've learned from science communication is it's all about the long game. But it's very hard to build these conversations because they're so nuanced. I mean gosh, you know, I feel like the more I learn the less I know kind of thing, so...

CINDY: Yes.

STEPH: To be able to translate that to the public is very it's very challenging. But I guess persistence, right? And having over 600 episodes of podcasts helps.

CINDY: It helps.

STEPH: Yes.

CINDY: Did you wanna read the second half of that e-mail?

VINCENT: Yeah Ben continues- *I'm wondering if you knew of anyone doing cool vaccinology/immunology/virology type work in a fish or non-mammalian animal system that you could suggest? I am looking into graduate schools, and any suggestions would be appreciated!*

CINDY: Steph?

STEPH: Yeah! Oh yeah so if you listen to Immune 28, we had an excellent time interviewing Irene Salinas, and she is a really good immunologist working in fish models and non-mammalian animal systems at University of New Mexico, so you should contact her, listen to that episode, and see what if there's any opportunities there. And I visited that campus, it's beautiful, it's in Albuquerque, and she has fish in her office, there's fish downstairs, there's fish all over the place, it's so cool.

CINDY: We also at Cornell have some researchers who are doing fish research as well, which is kinda cool. So you know, we're at a vet school, so I would encourage you to look at some of the vet schools.

STEPH: Yeah for sure.

CINDY: The veterinary schools, because they would have companion animal or non-traditional model systems or you know, systems. There's also people who use zebrafish for various different innate immune studies. And then Brianne, you were mentioning somebody...

BRIANNE: Yes.

CINDY: ...that I know also who does really fascinating research.

BRIANNE: Yeah so one of my friends who did a Ph.D. in virology then wanted to look at fish immunity and did a post-doc at Maryland with Martin Flajnik, so. I know that he really enjoyed that. Yeah.

CINDY: Yeah he does tests of comparative genetics work, yeah.

BRIANNE: Yup. And so I know she was really enjoying his lab and actually one of my students in my research lab got into the Cornell program and was particularly excited about all of the opportunities-that was the thing he liked about Cornell was all of the people who were doing sort of non-mammalian types of immunology.

CINDY: And the cool thing is is like they're doing it in the natural animal, right? So we often think as immunology we look for animal models. But they're actually studying the disease in the animal for the sake of understanding and developing therapies for the animal. Which is different than I grew up as an immunologist, but it's really fun to see. And sometimes there are things that they're trying to develop in the animals that then they can translate into human, because there's certain studies and samples and things that you can do in animals that you can't do in human patients.

STEPH: Yeah for sure. Cool, alright. Well we could do Lizzie is next.

VINCENT: Sure, yeah. Go ahead.

STEPH: Go ahead? Okay. *Hello Immune Team!* This is quite long, so, we could answer questions as we work through this. *I am a healthcare worker currently assigned to care for patients in an ICU designated solely for Covid-19 patients. I work in one of the academic medical centers enrolling "frontline" healthcare workers in a randomized hydroxychloroquine vs placebo study through the HERO trial. I and many of my coworkers are intrigued by the study as a possible opportunity to both get tested for SARS-CoV-2 to see if we are pre-symptomatic and potentially, though not proven, to prevent becoming infected or ill, which is a daily concern for us. While I appreciate reading about the possible side effects of hydroxychloroquine including GI upset and QT prolongation arrhythmias, I wanted to do a little more digging of my own before I decided to enroll. I found many articles about the use of hydroxychloroquine to treat an array of autoimmune diseases and other non-malaria disease processes. I'm wondering if you all would be interested/ willing to discuss the immunomodulatory effects of taking hydroxychloroquine for a person who is healthy and likely not infected with SARS-CoV-2. I gather from my research that there is quite a bit that happens at the cellular level as the body responds to this drug and I'm curious about the potential "silent" side effects.* So we can tackle this and then I can read the rest of her e-mail in a bit.

CINDY: I can say, I can say a little bit.

STEPH: Yeah, go for it!

CINDY: So first of all, thank-you Lizzie!

STEPH: Yes, thanks Lizzie.

CINDY: Thanks to you and all of your co-workers. You know we really, we can't say thank-you enough.

STEPH: Yeah.

CINDY: I have studied innate immune receptors and signaling and regulation mechanisms for a long time, and so one of my interests is in the innate sensors that are recognizing nucleic acids, and Brianne you do too, and so a lot, some of these are toll-like receptors, which we've talked about in the past. And it's interesting because they seem to recognize their nucleic acid ligands inside endosomes or phagosomes. And hydroxychloroquine does block signaling through those receptors, and that's thought to have something to do with pH changes, you know neutralizing pH and so forth in the endoplasmic er, in the endosomes and the phagosomes. And so that has been studied as one of the potential mechanisms why those drugs are good for autoimmune disease. Because we know from studies from Ann Marshak Rothstein and others that TLRs, especially these nucleic acid sensing ones, when they recognize their ligand in B cells, they prime the production of autoantibodies. And so there's this feed-forward loop where nucleic acid recognizing antibodies bind nucleic acids, internalize them, trigger the TLR, and promote more production of autoantibodies. And so the drugs work in part by disrupting those signaling processes, and so that's one of the reasons why they really work well for autoimmune diseases. They're also naturally quote unquote immunosuppressant, whatever that might mean, whether that's actually through their TLR mechanism or other mechanisms, I'm not sure.

BRIANNE: Right. Right.

CINDY: So I don't know what other people wanna mention on that too.

BRIANNE: I mean I think the only thing that I would say is my understanding is that the autoimmune diseases that are used, that this is used against are predominantly things like lupus.

CINDY: Yes.

BRIANNE: And lupus might have a little bit of a nucleic acid part to its pathology. And so it may not be something that's...it may be working specifically for lupus because lupus may involve this nucleic acid/TLR/endosomal signaling as part of its pathology.

CINDY: That's right.

STEPH: Yeah...and I don't know...

CINDY: So what's gonna happen to a healthy person? I don't know.

STEPH: Yeah, I don't know either. I think both of what you said is excellent, and I don't really have any additional things to add other than if it were me, not that you should do what I would do, but I think that there are many upsides to this. You know, in addition to seeing if you...you say get tested for SARS-CoV-2 and what I'd be curious if she's gonna get tested for the virus of if she's gonna get tested serology for antibodies. That would be...

CINDY: I would guess both, it's a large trial.

STEPH: Probably both. The only reason I didn't know is because I remember Daniel Griffin, M.D. on TWiV was talking about their hydroxychloroquine study, and they just went ahead, and Vincent correct me if I'm wrong, just did PCR testing because they hadn't picked a serology kit yet they were happy with for the...I don't even remember what his trial was called but either way, yeah both would be great. And potential silent side effects? I you know...

VINCENT: PATCH trial. The PATCH study.

STEPH: PATCH, okay the PATCH study.

VINCENT: Sorry.

STEPH: Oh it's fine. That's hard to say. I guess if they're silent, you don't have to, you know, it's not something, you know it's something happening at the cellular level but it's not symptomatic. So, you know we're not M.D.s here but if you think that it would be worthwhile and, you know, would be an interesting way just to contribute to science in general.

CINDY: What, I mean what do you guys think about this hydroxychloroquine?

STEPH: Yeah.

CINDY: I thought, at first I said hmm that's interesting, because if there is acidification required for spike protein activation and fusion then that might block fusion, right? And on top of that if immunopathology is induced in some small way through TLR signaling, which we don't know, that's totally hypothetical, then maybe it might dampen that and then you know you would have dampened inflammation and potentially less immunopathology. However, a lot of the studies that have come out have, you know, have conflicting results and so I'm glad that they're doing a larger control trial but I'm a little concerned whether it's actually gonna work or not.

VINCENT: So this PATCH trial, which stands for Prevention and Treatment of COVID-19 with Hydroxychloroquine, they're gonna see if it prevents and treats COVID-19, right? So both see if it can block infection and if you give it to an already infected patient. And I think Daniel has said that the problem is it's immunosuppressive.

BRIANNE: Right.

CINDY: Right.

VINCENT: So, if you give it too soon, you're gonna get too high virus loads.

CINDY: But if you...

VINCENT: So you have to really give it later when the immune response is higher and the virus loads are low, but then it doesn't...if it's antiviral...I mean.

STEPH: Right.

BRIANNE: Yeah.

VINCENT: So, that's why you need a really good trial and the first trials that were published were not really well designed to address these nuances basically. So his is really big, multi-state and should answer these questions.

BRIANNE: Right and I think it's important for us to look to our M.D. colleagues to understand some of the other things that are going on outside of the immune system. I seem to have read a bit about effects on the cardiovascular system with the heart with this drug

and that is really not my specialty, so I can't tell you how that is happening, but I think that that's something that we need to think carefully about in terms of use of these drugs in healthy patients and look to our M.D. colleagues to help us out a bit.

STEPH: I would agree with that. Yeah so hopefully what we were able to say maybe guides you in a way, but obviously there's gonna be, you know, consultation with enrolling in this and so you would just wanna make sure that you were already baseline healthy, don't have heart problems or already immunosuppressed in some way because those are things to consider. I can read the second part. So *On a side note, I'm a huge fan of TWIV and Immune (as well as the other podcasts) and have been interested in virology since listening to Vincent's Virology lecture series in 2012. I read Spillover by David Quammen in 2015 and his chapter on SARS-CoV-1 has made me fear a corona virus pandemic ever since. As a result, I ended up joining the Communicable Disease Response Unit at my hospital the next year.* Wow that's great*. This is a sort of volunteer unit used for quick mobilization of regularly trained healthcare workers who received additional training for a potential Ebola or MERS outbreak. I owe my personal preparedness for the current crisis we're facing to the Microbe TV team and can't thank you enough. I share your podcasts with everyone on my unit and I don't know what I would have done had I not been able to turn to your podcasts for trusted information. Best Wishes, Lizzie.* Well Vincent, that is so cool!

VINCENT: Yeah isn't that great.

STEPH: That is great.

VINCENT: Makes you keep going with this.

STEPH: Ah that's right!

BRIANNE: Yeah.

STEPH: Wow, thanks Lizzie.

VINCENT: You have all the naysayers and anti-vaxxers and people who don't believe what you say and think it's make in a lab and then people like this come out and you feel like it was really worth it.

STEPH: Ah, I know. The warm and fuzzies. Well we should print this off, you know this part.

CINDY: Yeah.

BRIANNE: Yeah.

STEPH: If we're feeling discouraged...

CINDY: I also think it was really, I also think it was really nice that they had this kind of preparedness team.

STEPH: Yeah!

CINDY: That you know, it just goes to show you that a little bit of preparedness goes a long way, right?

STEPH: Yeah for sure.

BRIANNE: Well thank you Lizzie but also thanks to Lizzie's hospital for having this foresight.

CINDY: Yeah, thank you, thank you.

STEPH: So we could, do we want, we've got we've been going for about an hour and 15, do we just want to wrap up with e-mails and then have a part 4? What do we think?

VINCENT: Yeah, sure, let's do that.

CINDY: Sure, okay.

VINCENT: Maybe Brianne is next, right?

BRIANNE: Okay. Jacob writes *I have enjoyed both your virology and immune podcasts. They have helped me push my understanding of both subjects to a much higher level. I recently read a paper on how SARS-Cov-2 infects T cells. I came across this paper by accident while I was searching on another subject. The paper is enclosed. Is this a reasonable explanation of why we are seeing lymphopenia in Covid-19 patients? I have never heard of the CD 147 receptor. Do you know what role it plays normally in T cell function? I have been following this story since January. I find it very interesting. It gets more interesting every week. In your most*

recent immune podcast a question was asked on the role of proning. Patients are turned on their stomach every 4 hours to help match blood flow to open alveoli. This decreases shunting, which is a major cause of hypoxemia. When lying flat alveoli on the front of the chest are open, but there is less blood because it has pooled in the back. So you turn the patient over so blood flows to where the alveoli are open. Then you switch them back. I am interested in your thoughts on the paper. Thanks, from Jay. So I am checking, looking at the paper now.

CINDY: Yeah.

STEPH: If I remember correctly, because there's only there's been one T cell big T cell paper that kind of popped out, and I think that it was roundly criticized by immunologists for...

BRIANNE: I...this is that paper.

STEPH: Okay so...

BRIANNE: Yup.

STEPH: They really did not show that it infected primary T cells. Maybe, I don't remember, maybe they showed a T cell cell line...

BRIANNE: They do. They use a T cell cell line and show infection and there are some questions about some of the ways that they show infection.

STEPH: Yeah...

VINCENT: And I think these are not productively infected.

STEPH: No.

VINCENT: They don't make, they don't produce new virus particles either right?

STEPH: I don't think we have evidence that yet it infects lymphocytes.

VINCENT: So what is the...

CINDY: I still got interested cause I was like CD147 what is that?

VINCENT: Yeah.

BRIANNE: Yeah I...this is the one that I sort of ranted a little bit about one of their figures being not the way I would have done my flow cytometry.

VINCENT: So what's the connection with CD147? Do you know?

CINDY: Well they're saying that it's a receptor, but all I know is I did a little bit of digging and it's expressed on a couple of different types of T cells but primarily on T regulatory cells. And so it's thought that it might have some role in regulation of T cell responses.

VINCENT: But they published previously...

STEPH: Yeah and then mostly pre-prints...

VINCENT: They say we recently reported this to be a novel invasive route for SARS-CoV-2. CD147, which as far as I know, it's a pre-print, nobody is buying.

STEPH: No.

CINDY: Well that paper that he put up is in Cellular and Molecular Immunology.

VINCENT: Oh, published, yeah?

STEPH: Yeah yeah.

CINDY: In a Nature journal.

BRIANNE: The T cell paper.

VINCENT: No I'm talking about the CD147 as an alternate receptor.

BRIANNE: Right.

CINDY: Yeah. Yeah.

BRIANNE: So he...they cite a pre-print in this...

VINCENT: Yeah.

BRIANNE: ...Cellular and Molecular Immunology paper.

CINDY: Oh oh oh oh oh okay.

BRIANNE: Citation number 9.

CINDY: Ah, okay.

STEPH: Yeah and so I don't think that CD147 has been shown to...

VINCENT: Yeah. I agree.

STEPH: ...play a role. We'll have to see. It's very...

CINDY: It could still infect T cells, yeah?

STEPH: Yeah...I mean sure...

BRIANNE: Maybe.

STEPH: Yeah. I think...

VINCENT: May I ask...

STEPH: ...you have to have a high bar when trying to determine receptor and actual productive replication of cells.

BRIANNE: Right.

CINDY: I guess...

VINCENT: I asked Susan Weiss last week on TWiV if T cells are infected. She said no.

CINDY: Oh, really?

VINCENT: Remember Brianne?

BRIANNE: I do remember, yes.

STEPH: I mean at least they're, I don't think we have evidence? It's not to say it's impossible.

VINCENT: No, no.

BRIANNE: I would agree. There's not evidence and I don't really think that this paper would be evidence.

CINDY: So does it...is it...the virus doesn't get in at all?

VINCENT: Well according to this paper it gets in, but doesn't...the cells don't make new virus particles, right?

CINDY: So my question would be do you need to? Because if you make viral proteins and since it's an enveloped virus, if any of those viral proteins get to the surface you could still have...

VINCENT: Mmm yeah.

CINDY: ...depletion of T cells even if they're not productively infected. You know replicating and secreting virus, right?

VINCENT: Sure. Sure. Sure. And the proteins...

CINDY: So even if they just get some proteins...

VINCENT: The viral proteins could kill the cells themselves, right?

BRIANNE: Right.

CINDY: That too, yeah.

STEPH: Sure.

VINCENT: So yeah, it's possible, but these are cell lines you guys said, right?

BRIANNE: Yeah. Yes.

STEPH: Yeah.

BRIANNE: It's cell lines and I think we need some more evidence.

STEPH: Yeah.

CINDY: I would agree with that.

STEPH: Alright.

CINDY: Should we do one more?

STEPH: Sure, you wanna take that one?

CINDY: Sure. So Marion writes *Dear Immune @ Microbe.TV – and the team over there. I hope this email finds you well. I have been following your organization's work and want to let more in Asia learn from you. If you have more recent findings do let me know. I want to disseminate only the best science and medicine in these times.* So he goes on to provide some resources that he has available to him, and *In partnership with the World Health Organization's Global Outbreak Alert and Response Network (GOARN)...*

STEPH: I thought that, when I read that quickly, I thought that said GROAN, I was like...good acronym, but ok, got it. GOARN.

CINDY: *...my medical school has launched two public education initiatives on Covid-19. We have a webinar series that reaches out to doctors and scientists and shares the most up-to-date information from medical and research experts on the ground in Singapore – so very real and transparent.* And then also there is...where was the second part of that...there's educational comic strips for lay public communication. And there's some links here that I suppose we could put up to their information that they're putting out for their webinars.

STEPH: Well I'm glad if there, if he or she...I don't know if Marion is he or she.

CINDY: Oh that might be a woman, yeah.

STEPH: It might be. I don't know, it's fine. ...is looking towards Microbe.tv for information, that's great! And hopefully...

CINDY: Yeah.

STEPH: ...helps facilitate education. So yeah we could post these if you think that that would be fine with.

VINCENT: These are cool comics.

BRIANNE: That sounds good.

STEPH: The comics are cool.

VINCENT: The COVID-19 chronicles. So National University of Singapore I visited last December.

STEPH: Nice.

VINCENT: It's a campus of Duke's Steph!

CINDY: I was gonna say! It is.

BRIANNE: It is.

STEPH: It is, yep, mmhmm.

VINCENT: Duke and US, yep.

STEPH: Yes.

CINDY: Yeah.

VINCENT: That's where Linfa is actually, who we mentioned earlier.

STEPH: Yeah, Linfa Wang. And then I don't know if you're familiar with Ashley St. John? She does macrophage...

VINCENT: Yeah! Yeah. I met with her, she was on, you know, I did a TWiV with her and a few others.

STEPH: Yeah.

VINCENT: We still have to release it, because...

STEPH: Oh really? Okay.

VINCENT: ...yeah she was really very interesting.

CINDY: Yeah for sure.

STEPH: Well I know it's hard to release non-COVID related...

VINCENT: I'm gonna start doing it because otherwise they'll be 2 years old by the time they come out, and it's not good. Do you wanna...can we take a few more or do you wanna stop?

CINDY: Sure. Oh yeah, let's go.

VINCENT: I don't know who's next...Steph you wanna come in?

STEPH: I can do Steve, yeah sure. *Hi Vincent et al, Good to see these early results from China, on infusing critical CoViD-19 patients (n of 5),* so I mean...like let's be a little careful what we say...good results *with convalescent plasma. This reminded me that I have been wanting to ask about the business of using antibodies from donor blood in general. I had wondered why antibodies from another person weren't treated as foreign by our own immune systems, so that we'd make antibodies to the antibodies (*Or anti-antibodies*)?* And we can answer that question first. So I think that that is something that is considered as a potential risk factor. Although you would, you would be infusing convalescent plasma to do some sort of therapy so the risk would be low and the reward potentially saving your life would be high. So that's like a risk/reward ratio. But also I don't know if convalescent plasma would be in your blood long enough to develop auto-antibodies? I don't think there's much evidence for that being true, I think it's more theoretical. What do you guys think?

BRIANNE: So I...yeah I think the idea is that yes those antibodies would be treated as foreign by your own immune system, but you're probably not getting multiple doses of them.

STEPH: Right.

BRIANNE: And having them over a really long time. So it's entirely possible. You could image in kind of theoretically if you got convalescent plasma and then five years down the road you got SARS-CoV-3 and you happened to get convalescent plasma from the same person...

STEPH: Right.

BRIANNE: Which, you know, is a stretch, perhaps you would have antibodies to their antibodies and make a response. And I talk about this because we do use passive antibody therapy where we're getting antibodies from other organisms in a few different cases in humans, one of them is black widow spider bites and I always tell my students that, you know, if you get a black widow spider bite and then you get one again, you might have trouble getting that class of antibody treatment. But that seems unlikely.

CINDY: Yeah.

STEPH: Okay.

CINDY: I think that, you know, each individual...well the interesting thing is each individual develops their own repertoire of antibodies, right? Because we have the randomness of the recombination that we've touched on in the past. And so yeah, you you could develop antibodies to another individual's antibodies. Probably it's not gonna happen to a huge degree, you're more likely what you were saying Brianne about like if you were using protective plasma that was developed in another animal then...

BRIANNE: Right.

CINDY: ...you're definitely going to have an issue.

STEPH: Right.

CINDY: But the other thing is we have to remember that it's not infrequent that humans can actually develop antibodies to their own antibodies. So we get anti-idiotypic antibodies, and they are a marker for autoimmune disease.

STEPH: Right.

CINDY: And they can propagate, the disease, they're very, you know, they're common in lupus once you develop lupus. So, it happens, you know, the tolerance is broken, so it, yeah. It's not unheard of to have something like that, especially if you have a bolus that's introduced all at once.

STEPH: Right. And maybe people who have an autoimmune disease would be ruled out from convalescent serum.

CINDY: Maybe, yeah.

STEPH: If they're more predisposed.

CINDY: I don't know.

STEPH: So moving on, *And, following on these new results, and on general testing in the wider population seeming to turn up quite high prevalence of symptom free infection: might it be possible to make transfusions mixed from batches of plasma from recent blood bank donors, rather than relying on those who had been recently ill (whom blood banks would, presumably, turn down as a rule)?* And so I think we also mentioned on a previous episode that some of the criteria for donating blood or plasma being recently infected is that you would wanna have high titers. You wouldn't wanna give somebody lower titers because maybe it wouldn't be protective or maybe it would actually induce pathology if you were to get infected, although we don't know much about that quite yet. So I don't think it would be probably something people would do to take blood bank donors just because at least for this you would want the titers to be high.

CINDY: Yeah because you're gonna be just diluting anybody who might have titers with lots of people who don't.

STEPH: Yeah.

CINDY: Unless the prevalence is really high. So.

STEPH: And I don't know if we can say that there's a quite high prevalence of symptom-free infection.

CINDY: We don't know that yet.

STEPH: Yeah I think we know based on epidemiological evidence and other evidence that there is asymptomatic patients and people, but I don't think we can say what the prevalence is of transmission from those people yet.

CINDY: No.

BRIANNE: Right.

STEPH: *Also: is it possible for people to be infected with a virus and neither be ill, nor mount an immune reaction–virus just goes through without gaining entrance to any cells? This way, some people could be 'immune' to viral exposure without any evidence of this in their blood?* And so yes I think that that would be considered sterilizing immunity, what we discussed earlier. But I don't...you know in terms of a primary infection in a sero-negative or at least a non-protected individual, I had always thought that that was very rare, that if you were going to be infected, you were going to have, you were gonna be symptomatic.
BRIANNE: Well I think it depends on the virus.

CINDY: Yeah.

BRIANNE: There are certainly many viruses where you can be infected and have no symptoms. There are some viruses that 90 plus percent of the human population seems to be infected with.

CINDY: Right.

BRIANNE: And we have no symptoms. We often might mount an immune response although I don't know that I have looked enough to say that we would always mount an immune response. So I think it is very virus dependent.

STEPH: Oh I see what you're saying. Yeah yeah you're right, I was thinking in the context of the bugs we know that make us sick and would somebody...

BRIANNE: Right.

STEPH: ...could they be infected with influenza and never have a symptom, but you're right, like, EBV you can have...

CINDY: Well in this case they're saying not...without gaining entrance to any cell. So...I guess the definition of an infection is that you that a pathogen gains entrance to a cell and replicates?

BRIANNE: Right...I usually think of infection as colonization.

CINDY: Yeah there might be some that don't go inside a cell. But yes colonization is a better word for it. But I don't know though...do any people have polymorphisms in the receptor that protect them?

VINCENT: That's a good question.

BRIANNE: Good question.

STEPH: Yeah. Good question.

CINDY: I haven't seen that yet.

VINCENT: People are looking at that I'm sure.

STEPH: Yes, yeah.

CINDY: Yeah.

STEPH: I know there are a lot of polymorphisms in the innate genes that can protect against coronaviruses in general. A lot of the interferon-induced genes are highly polymorphic but ACE-2 specifically I think yeah, we'll learn a little bit more.

BRIANNE: Yeah and so I guess that would make sense there are people who have mutations that make it so that HIV cannot or certain strains of HIV are not able to enter their cells and so in that case they might be they would be neither ill nor mount an immune response as Steve mentions here.

CINDY: That's right.

STEPH: Yeah, sure. And he ends it, this e-mail *Hope these aren't too dumb questions for you and the 'I Team'.* Definitely not too dumb, no questions are. *Wash your hands (scrub under your nails too), Steve.*

CINDY: Cool.

VINCENT: You wanna stop there? Is that good?

CINDY: Sure.

STEPH: Yeah that's good.

CINDY: We covered a lot of ground.

STEPH: We sure did.

VINCENT: Okay.

CINDY: God there's a lot of e-mails.

STEPH: There are. There are. Brianne this just might be...you just might be with us for a while, if we continue our COVID.

BRIANNE: That's fine!

VINCENT: I don't think Brianne minds.

CINDY: Although she definitely has to be here when we talk about the bat thing.

STEPH: Yes! I know.

BRIANNE: The bat stuff is I think we talked about that paper on TWiV.

CINDY: Probably.

VINCENT: Really. So we'll try and get the bat guy.

BRIANNE: But it's so cool.

STEPH: Yeah, Vincent do you wanna reach out to him? You said he's at Fort Collins.

VINCENT: Yeah. Yup I will do that.

STEPH: Okay. Sweet.

CINDY: So we should at least do one more where we go through the rest of the topics and some more...

VINCENT: Sure.

STEPH: Yeah, part 4.

VINCENT: And then COVID pandemic will be over, we can go back to normal.

STEPH: Yes the COVID pandemic will be over.

CINDY: What are you gonna do when you're not doing four TWiVs a week on COVID?!

STEPH: Yeah!

VINCENT: It's fine I don't...I mean I'm doing it to help people.

CINDY: Oh I know.

VINCENT: I will go back to one a week, that's fine. But I think it's gonna be awhile, because, well maybe, you know, if you look at the curves they're going down and the models predict end of June is really negligible circulation, so it might be quiet over the summer, we'll see. Unless when we go back...

CINDY: In New York or everywhere?

VINCENT: Well in New York and many places there haven't been many infections at all, rural places for example, like Ithaca.

CINDY: Yeah we...no hey, we had, I was just hearing so I don't know if we're still recording you're gonna put a break in here, but my husband is on local government official calls, and they were talking about we've had 1 case in the last seven days.

VINCENT: Yeah. That's good!

CINDY: So yeah they're ramping up, we have thousands of tests being done and like a hundred and thirty-three cases so far. So not too bad.

STEPH: Okay.

VINCENT: That's good, you should monitor, I mean that's a good thing to do, monitor and make sure. They you see a case you quarantine them, that's the way to keep it down. But I think...

CINDY: Yup. And they're doing a lot of contact tracing.

VINCENT: Good! That's what they should do.

CINDY: Yup.

VINCENT: Everywhere. Not just in Ithaca but, you know, it's out of my control, I'm not the governor. If I were the governor I'd be doing it more. I'm surprised he's not frankly. But, if he's maybe...

CINDY: Well I think they're counting on the local health departments to be doing this.

VINCENT: Mmm not sure that's good but, anyways. Alright Immune 31. All the notes and letters at microbe.tv/immune. Send us your questions and comments, immune@microbe.tv. And if you wanna support us financially, microbe.tv/contribute. Today on Immune, Cindy Leifer is at Cornell University. cindyleifer on Twitter. Thanks to sax...wait wait lemme say that again, thanks Cindy!

CINDY: Thank-you!

VINCENT: Aye yai yai. Steph Langel's at Duke University, stephanielangel on Twitter. Thanks Steph.

STEPH: Yeah thank-you this was fun.

VINCENT: And Brianne Barker's over at Drew University, bioprofbarker. Thank-you, Brianne.

BRIANNE: Thanks it was great to be with you guys.

VINCENT: I'm Vincent Racaniello. You can find me at virology.blog. The music on Immune is by Steve Neal. Thanks for listening to Immune, the podcast that's infectious. We'll be back next month.