# Vaccinations After a Diagnosis of a Rare Neuroimmune Disorder

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[00:00:00] **Roberta Pesce:** Welcome back, everyone. For our final talk of the day on vaccinations after a diagnosis of a rare neuroimmune disorder, I'm delighted to be joined by Dr. Benjamin Greenberg, a professor at UT Southwestern Medical Center, Director of the Transverse Myelitis and Neuromyelitis Optica Program, Director of the Pediatric CONQUER Program at Children's Health, and SRNA board member. Dr. Michael Levy, Associate Neurologist at Massachusetts General Hospital and Harvard Medical School, and Dr. Carlos Pardo, Professor of Neurology and Pathology, Division of Neuroimmunology and Neuroinfectious Disorder and Director of the Johns Hopkins Myelitis and Myelopathy Center at Johns Hopkins University School of Medicine. Hello Dr. Greenberg, Dr. Levy and Dr. Pardo. Welcome, and over to you.

[00:00:55] **Dr. Carlos Pardo:** Thank you very much, Roberta. Glad to be here.

[00:00:59] **Dr. Benjamin Greenberg:** Good to see you, Michael, Carlos, thanks for joining in. This should be the most fun and least controversial session of the entire symposium because today we're going to be talking about vaccines and vaccinations, and before we get into the content, I do want to remind everyone, a little bit of a shameless plug for some of the talks coming tomorrow that will be COVID specific. And while I'm sure we're going to reference the COVID vaccine today during this talk, there'll be another opportunity for us to discuss COVID vaccinations and COVID relative to these conditions tomorrow.

[00:01:38] But I'd like to start off by just acknowledging the fact that the topic of vaccinations remains a hot button topic, not just within our community, but frankly now worldwide, and just to ease ourselves into it, I'm curious, I know both of you have clinics, essentially every week, several times a month. In what percent of your clinics on any given month does the topic of vaccination come up with your patients or families? Mike, is this a topic that comes up frequently or infrequently?

[00:02:11] **Dr. Michael Levy:** I would say it's somewhere around the 110 percent range.

[00:02:14] **Dr. Benjamin Greenberg:** Okay. Because sometimes people ask twice in the same clinic, so 110 percent. Carlos, are things the same in Baltimore?

[00:02:20] **Dr. Carlos Pardo:** It's the same, actually it's one of the most important and favorite topics in our clinics, particularly in the past 18 months, yes.

[00:02:32] **Dr. Benjamin Greenberg:** And I think what would help for the purposes of this conversation is to split the topic in two parts. I think it would be worthwhile for us first to talk about what's known and unknown about the potential associations of vaccinations as a causative or contributory factor to the neuroinflammatory disorders that we all treat, transverse myelitis, neuromyelitis optica, ADEM, et cetera. And then separately I think it's worth us addressing the issue of for our patients who already have had an inflammatory event, the relative safety or concerns or approaches to receiving future vaccinations.

[00:03:09] So if it's okay with you, I'm going to start with that first topic, and it's fair to say there have been efforts over time to examine the potential role of vaccinations relative to these conditions, and we all struggle with the fact that A, not all vaccines are the same. So, we're talking about very different agents as we move from vaccine to vaccine, and within quote "one vaccine," the influenza vaccine, it actually changes every year, so there is no single flu vaccine year after year, and then the conditions we treat are rare, and so there aren't, thankfully, large numbers of events that happen at a time.

[00:03:46] So Carlos, starting with you at a high level, as you've looked over this literature over the time that you've been personally involved in efforts to examine this, what's your general takeaway of the state of evidence around vaccinations as a causative or contributory factor to the development of some of these conditions that we treat.

[00:04:09] **Dr. Carlos Pardo:** Thank you Ben, it's a very fascinating question, since unfortunately I'm one of the seniors in this group, I need to tell you that historically vaccines actually have been a very important topic of research about neurological complications. Particularly because at the beginning of the introduction of many vaccines, there were some reactions that were adverse reactions, and that was known historically, for example, for rabies vaccination, that was known historically for other type of very well-known vaccines, like yellow fever.

[00:04:49] And we need to take in account the historical perspective, because during the 20th century when vaccines started to be massively used, the production of vaccines actually went in different type of steps and approaches. For example, in the '60s and '70s, vaccinations were based on products that were produced on, for example, cell cultures or brain tissue cultures that unfortunately contaminated some of those vaccines and produced reactivity because there were antigens or protein from those brains in which they were produced, and that obviously generates adverse reactions.

[00:05:36] **Dr. Benjamin Greenberg:** So, Carlos, just because I think you're making a really important point that I think gets lost on a lot of folks, that historically to grow the virus that you wanted to use in the vaccine we literally were using brain tissue or nervous system tissue to grow the virus in. And what you're saying is historically, so if you look at the old literature that talked about a post vaccination ADEM or myelitis or whatever the case may be, some of those reports came from vaccine that was literally potentially contaminated with brain proteins or nervous system proteins.

[00:06:12] **Dr. Carlos Pardo:** Exactly. Exactly. And here in the United States, in 1968, '69, the major concerns of vaccination for influenza actually was generated precisely in that contamination, because there was a contamination of particles associated with myelin in many of those vaccines, that generate Guillain-Barré cases.

[00:06:30] **Dr. Benjamin Greenberg:** Okay.

  

[00:06:31] **Dr. Carlos Pardo:** The good news is immediately that was discovered, there was a major change in the production of vaccines, and those mistakes from early stages of vaccination production were corrected, to the point that that situation that generated a lot of concern, for example, for flu vaccination back in the late '60s and early '70s was immediately corrected, and the production of vaccines have been, or entered a level of safety that is really important. And one of the major roles, and we love and hate FDA, but actually FDA has a role here, a role because they actually watch very carefully for the way that the vaccines are produced and the safety profile.

[00:07:24] So when we move now to see about potential complications, we can say that we went from having a great index of adverse reactions to a very low, minimal index of adverse reaction, and the answer to that is because we learned in the past 2 or 3 decades, all of the mistakes in the past, and those have been corrected. And the reality is for neurological complications, and I will add this probably later, I don't believe that we're seeing the magnitude of neurological problems with the current vaccines as we used to see with flu vaccination back in the '60s or '70s, or with rabies or yellow fever vaccination. And in other areas of the world, like Japanese encephalitis it is same story. So, I will stop here, but I want to make sure that everybody who is listening understand that safety in the production of vaccines have improved dramatically in the past 20, 30 years.

[00:08:26] **Dr. Benjamin Greenberg:** Yeah, and I appreciate you giving a shout-out to the FDA and their role in maintaining safety. And while it's easy to often feel frustration in their role overseeing safe production of biologics of medicines and vaccines is critical. There was what was called the Cutter incident in the 1950s, which was a manufacturing error of polio vaccine, and instead of inactivating the virus, live virus was contaminated, was administered as a part of the vaccine, and so I think you're right, we've seen a large evolution in the oversight and appropriate regulation of manufacturing to make them safer.

[00:09:04] But even as we move into the modern era of vaccines, the last 40 years let's say of vaccines, Mike, I know you face the question quite a bit, somebody comes in and there's a temporal association between vaccine X, like Dr. Levy, I got my flu shot in October, and in November I had transverse myelitis. Didn't the flu shot cause my transverse myelitis? Can you walk us through kind of the science, the understanding or lack of understanding around if A precedes B can we really show causation between those two?

[00:09:40] **Dr. Michael Levy:** Yeah. Chronology is probably a very important consideration about whether a vaccine triggered an event. I think most people accept within 30 days as being possibly linked. Sixty days is a little farther out and 90 days is a long stretch. But even if it does occur within 30 days, what the FDA has asked us to look for is a systemic reaction to the vaccine that was adverse, like a rash or fever prior to the transverse myelitis or optic neuritis or something like that, and that it occurs within something about 7 days or so.

[00:10:18] When it happens within 30 days, we still feel like there could be a link, but it might not be as specific. And by that, I mean that whatever is in the vaccine may not be as important as the general activation of the immune system. So anytime you activate the immune system, whether it's with a vaccine or an infection, you activate the whole immune system, and then there's that rogue element that attacks the spinal cord or the optic nerve, and that can be triggered by any activation of the immune system, including a vaccine sometimes.

[00:10:52] **Dr. Benjamin Greenberg:** And so, we're often left with this temporal association that you talk about without knowing or being able to prove causation. When we've looked in different populations, there's literature on this from multiple sclerosis, which is a much more common inflammatory disorder of the central nervous system that failed to show associations between vaccinations and onset of relapses, and I think our challenge in our community has been due to the rarity, thankfully, of conditions, it becomes even harder. It's

  

I think worth noting that obviously the overwhelming majority of the hundreds and hundreds of millions of vaccines, billions of vaccines that are administered worldwide every year, we don't see an obvious pattern of association. That if the association is there it's an exceedingly rare alignment or misalignment of stars.

[00:11:45] **Dr. Michael Levy:** Can I add one more thing to that? Because I think another way to think about it is that maybe the immune system was on the threshold, on the precipice of attacking the spinal cord or the optic nerve, and it really just needed one more push in that direction, and that may have been the trigger. The vaccine could've just kind of pushed it over that threshold and allowed the autoimmune activity to happen. That's another way to think about it.

[00:12:13] **Dr. Benjamin Greenberg:** And so, it raises that natural concern that like you, I probably have this conversation at every clinic, at least with one patient per clinic, I get asked, Dr. Greenberg, whether or not my prior event was associated with a vaccine, is it safe for me to go ahead and get my next shot, my flu shot, my COVID vaccine, whatever the case may be. And in fact, what I've heard, which has been a little bit concerning to me is I've heard understandably patients and families having concerns, natural concerns, but I've also heard of patients being specifically told by physicians or health care providers " Oh you have an autoimmune disease, do not get vaccine X or Y." And I'm going to hold my comments for a moment and ask Carlos in terms of your counseling for patients and understanding of the data about the relative safety, need or lack of need for taking a vaccine after you've had one of these rare conditions.

[00:13:20] **Dr. Carlos Pardo:** So, thank you, Ben. Actually, before I answer that, I'd like to extend some of the comments that Michael made. There is one word that I actually have been using more often in the past few months, it's what we are seeing in terms of neurological complications in the setting of vaccination is mostly the unmasking of disorders that were previously established, and the vaccination is basically prompting the immune system to trigger more immunological reaction and unmasking that, and actually it's very frequent, when we explore a couple of years ago issues of vaccines and transverse myelitis in our registry in our center actually what we found is that actually the majority of patients in which there was this temporal onset of myelitis in the period of 2 to 30 days after the vaccination, actually the majority of patients, they basically end up having multiple sclerosis. Not because the vaccine triggered multiple sclerosis, but the vaccine probably unmasked the underlying disorder.

[00:14:32] But it's extremely important to understand this because obviously the patient is going to be very concerned about what is next. Do I need to be more cautious about following with the next vaccination? The answer and the advice that I always provide to our patients is you should get vaccinated. Viral diseases, particularly the viral diseases like influenza, or any other viral disease, actually may produce more harm if you are not vaccinated.

[00:15:05] In other words, flu is a killer. We didn't pay too much attention to the flu mortality until the current pandemics, and actually people never pay attention that in the United States there were thousands of people that die of flu in the previous years. And this was no magnitude to the pandemic like we are seeing right now, but it's quite amazing to see that there were more than 100,000 people dying from flu in the United States, and most of them actually young people, and it's extremely important to keep in mind that a lack of vaccination, a lack of immunity against some viruses that basically are transmitted frequently like flu, actually is more dangerous than the vaccine that is concerning at the moment.

[00:16:00] **Dr. Benjamin Greenberg:** Yeah, it's interesting this topic of uncovering or aggravating an underlying autoimmune event. I think it is worth noting, just to push back a little bit to show that there's variable data on this, if we take multiple sclerosis patients, so these are individuals whose immune systems are primed to attack the brain and spinal cord, so they have an underlying autoimmune disease, they have a perpetually

  

confused immune system. The studies have been done looking for risk of relapse relative to influenza vaccine, the one you're talking about, have shown that as you get vaccines, it doesn't change your risk of relapse.

[00:16:35] That equal number of people who didn't get the vaccine during the same period of time had relapses versus those who did, and I will point out there's a study that doesn't get cited often when they were looking at risks of vaccines to disease, but people who got the diphtheria and the tetanus vaccine had a lower risk of developing multiple sclerosis than people who didn't, and those studies don't get cited in certain circles and certain websites, where in fact vaccination not only was safe but statistically was associated with lower rates of a condition. But it comes up all the time, and Mike, I know you've published on this in the setting of neuromyelitis optica, and if I remember correctly, you looked at risks of attacks in people who were vaccinated versus not vaccinated. Could you walk everybody through what you found in your data set from MGH?

[00:17:28] **Dr. Michael Levy:** Yeah, so remember NMO patients have a predisposition to attacking, to relapsing, and what we looked at is we lined up everybody's relapses with their vaccine history, and what we found is untreated patients, there was a statistical association with vaccines, especially at the onset. So, it may unmask your NMO, or it may have pushed you over the edge, or it may have finally brought it on. Or if you were untreated and you got a vaccine then there was a higher risk of relapse. But if you were treated on rituximab or whatever, then your risk with a vaccine of a relapse went down, and that suggested to us that it wasn't the vaccine that was providing the, the vaccine was triggering relapses in those who were untreated, but preventing relapses because it would prevent infections in people who were treated, so it's a little bit complicated, but I think the overall balance of risk, it depends on how likely you are to get infected.

[00:18:37] And I think with flu, which is high chance, and certainly delta variant of COVID is very high chance, you have to consider, okay, is it more likely that I'll get a relapse from the infection like COVID or is it more likely that I'll get a relapse from the COVID vaccine or the flu vaccine, the vaccine being a lower trigger than the infection.

[00:18:57] **Dr. Benjamin Greenberg:** And on analogous lines, when we looked at, and there will be some data coming out in the future on this, are patients with idiopathic transverse myelitis different than neuromyelitis optica, because they aren't in the high-risk category for having relapses. When we looked back at our patient population, for people who had had transverse myelitis and subsequently had vaccines. So, they got their annual flu shot or they got their hepatitis B vaccine, or varicella zoster vaccines. I have yet to document a single relapse in an idiopathic transverse myelitis patient following a vaccination.

[00:19:41] Anytime somebody has had a relapse they were either later found to be positive for the aquaporin-4 antibody or the MOG antibody or something else, but I'm not aware of individuals with idiopathic transverse myelitis having relapses after vaccination, and important for our pediatric patients, I am not aware of any of our acute flaccid myelitis kiddos, mostly kiddos having relapses after vaccination. Carlos, I know you lead the AFM working group. Have any AFM relapses come across your radar after a subsequent childhood vaccination?

[00:20:20] **Dr. Carlos Pardo:** I am not aware about that, but it is something obviously that everybody's paying attention. Yeah.

[00:20:28] **Dr. Benjamin Greenberg:** And so as were getting to the end of the hour, and I know all of our participants have had a long day and may have questions, I'll just ask the very straightforward question to each of you. So, you have a patient in your clinic, assuming there are no extraneous factors, allergies, or other issues, is your recommendation to go ahead and get vaccinated for things like flu, COVID and so forth? Or do you put a lot of caveats on that? Michael, I'll start with you.

  

[00:20:58] **Dr. Michael Levy:** Treated patients, almost certainly. Untreated patients, there are caveats.

[00:21:03] **Dr. Benjamin Greenberg:** Okay, Carlos?

[00:21:05] **Dr. Carlos Pardo:** I need to agree with Michael, it's the same basically. It's a very straightforward answer for that.

[00:21:13] **Dr. Benjamin Greenberg:** Okay, and so I think hopefully what people are hearing is there's a lot of confidence in the safety of the vaccines and that there are ways to manage risks and get people protection against these dangerous infections that we want for everybody. So, Carlos, comment?

[00:21:30] **Dr. Carlos Pardo:** I need to emphasize is we are using vaccines because we'd like to prevent the viral illness that is probably more dangerous. That is one thing that all our patients need to understand. If they cross with influenza virus, if they cross with other viruses that have the potential to produce disease, the consequence of those infections are going to be dramatically bad, because it's very difficult to control an influenza in a patient with neuromyelitis optica or multiple sclerosis. So that's the reason we are very, very proactive in recommending that patients need to be vaccinated.

[00:22:20] **Dr. Benjamin Greenberg:** Great. Well, thank you both for this. I'll check in with Roberta to see if we have questions from our community online. Roberta, has anything popped up?

[00:22:30] **Roberta Pesce:** Yes, we have a question here. Are there cases you're aware of where the vaccine was indisputably the cause of the event, or is the closest we get a high probability?

[00:22:44] **Dr. Benjamin Greenberg:** I think that's a great question, and Michael, you were talking about kind of the standard of evidence around causation, and I think we break it into, correct me if I'm wrong, maybe three levels. So, one is a temporal relationship. You got exposed to a vaccine and within 30 days you had an event, and at best people would say a possible. Michael added the caveat that if there is a systemic reaction to the vaccine, a rash, and all sorts of things, and then that maybe it's possible or probable, although I think there's some controversy on what language to use.

[00:23:23] I think in order to provide indisputable causation we would need certain blood samples and spinal fluid samples to show that the immune response to the brain or the spinal cord was overlapping with the cells that were responding to the vaccine, and to my knowledge that has never been done before, and so we are always left with these statistical associations based on time courses and population data. So, I'm not aware of any instance where there's an indisputable cause. Michael or Carlos, are you aware of any cases where it was just cut and dry, no questions asked?

[00:24:02] **Dr. Carlos Pardo:** So, I am not aware. One thing that actually, causation is a very difficult item to demonstrate in these types of situations, and the only way to demonstrate causation is to perform case control studies that basically evaluate carefully the different factors that may be associated with the complications. But I like to introduce one element that unfortunately we need to recognize. That fortunately is very rare, but we need to recognize, is that our genetic background may prompt us to react differently to different type of environmental challenges, infections, or even vaccines. And we are not able to control.

[00:24:50] The only way to control probably in the future is to establish a very comprehensive genetic analysis and determine who is going to be a higher risk, but at this moment, this is impossible. We don't have the technology to predict that, but there is always a concern about causation. Yes, it's possible that in one in 10

  

million we may have that link with causation, but if you're taking into account that this disease is killing 2.5 percent of the infected patients around the world, are you thinking about that? Are you thinking one versus 10 million versus 2.5 percent of mortality in a disease? This is one thing that people don't think about, that possibility.

[00:25:41] **Dr. Benjamin Greenberg:** OK.

[00:25:41] **Dr. Michael Levy:** I would just add that there are criteria put out by the Vaccine Compensation Injury Board, and you can go online and see them, and there are criteria whereby, if you meet them, it is considered not indisputable, but you get the cash payment, and nobody challenges it. And it's a high threshold, you have to have all those features that I mentioned. And then if you don't, then you go in front of a panel, and they review your case individually.

[00:26:07] **Dr. Benjamin Greenberg:** Yeah, and I'm glad you brought that up, Michael, because I actually find some people get confused on this. The Vaccine Injury Compensation Panel was formed to indemnify companies against lawsuits, because otherwise we wouldn't have vaccine manufacturers. They would just prove litigation, be shut down, and so there were just decisions made of what would be fair, what level of threshold of evidence would be fair to just say we don't know if it was the cause but let's compensate an individual. And I think it was actually a critically important thing for us to do in the United States to help make sure we had an access to vaccine manufacturing. I think it still leaves us with questions to both your points we may never be able to answer in terms of proving causation.

[00:26:56] **Roberta Pesce:** Excellent, thank you so much. We're getting quite some questions so I'm going to keep going if that's okay with you. Do you recommend getting the shingles vaccine since shingles infection can lead to nerve damage pain?

[00:27:10] **Dr. Benjamin Greenberg:** Michael, you want to take this one?

[00:27:12] **Dr. Michael Levy:** Yeah, so kids now get vaccinated against varicella zoster to prevent the infection from establishing in the first place. Grown-ups like me, and certainly Dr. Pardo, who's much older than me, were infected as children, and the virus lives inside of our nerves forever. And the point of the shingles vaccine is to keep our immune systems capable of containing the virus to the nerve, not letting it extend out to the skin or into the spinal cord. The new shingles vaccine called Shingrix is very, very safe. It uses an adjuvant from the bark of a Chilean tree, and before the whole RNA vaccine thing, people were talking about using that adjuvant in all future vaccines because it was so safe and effective. And now since the RNA vaccine has proven so safe and effective people are saying well, forget that Chilean tree bark, we're going to go with RNA. But I do recommend it in almost every circumstance. Again, the only caveat being people who are untreated. And in that case, there may be some caveats.

[00:28:13] **Dr. Carlos Pardo:** Yeah, and I'd like to add one thing that all our patients and family need to be aware, is that the CDC has recommendations on their website and frequently the age limit between six to 65, but the reality is the majority of our patients that are undergoing a specific treatment for NMO to multiple sclerosis and other things, actually they need to be aware about the risk for shingles and they should be proactive in the process of vaccination for shingles.

[00:28:52] **Roberta Pesce:** Excellent. Thank you. Another question, should vaccinations be spread out rather than given on the same day? For example, the annual flu shot, shingles, should they be given all at once or spread out? Who would like to take this?

  

[00:29:10] **Dr. Benjamin Greenberg:** Yeah, so I think it's fair to say we don't have randomized data on this. In general, I think it's safe. Safe from a neurologic perspective to do things on the same day, but from a side effect perspective you're going to feel worse the more vaccines you have at once. And we haven't had a chance to mention how common it is for our patients to have a re-emergence of their old symptoms after a vaccine because they get a low-grade fever or they're feeling bad. So old numbness or weakness may come back and if you take multiple vaccines at once, the chance of that happening is probably higher. I say probably higher because I don't know for sure.

[00:29:49] So from a quality-of-life perspective, people may want to space it out, but from a safety perspective I think it's probably fine to do it on the same day. I leave that to the discretion of patients and their, it doesn't worry me too much, and it also depends on what we're taking. So, flu shot, seasonal, Shingrix, you have touched the shingles vaccine, which we use Shingrix, a name brand frequently. You can do that at a different time, so it's not necessary to get it at the same time. I think this question is going to come up mainly over the next several months for COVID vaccine and flu shots overlapping and whether or not to space out. We've been doing it for comfort reasons, not for grave concern reasons. Mike, you may disagree with this.

[00:30:41] **Dr. Michael Levy:** Well, I don't have any data either, I'm only basing it on rationale that each vaccine could sort of add to that step wise activation of the immune system. It may be that all vaccines activate to a certain level, and you could put everything in there and immunize to all once, but the fact that we don't know makes me a little bit leery of giving multiple shots in the same day, and so without any data I've been advising people to spread them out.

[00:31:09] **Dr. Carlos Pardo:** I do agree with that actually, I am advising patients actually to avoid multiple shots, because the problem is, as Ben said, is the comfort. When patients are receiving two or three different vaccines in the same day, we don't know the reactivity of those vaccines in a specific patient population. So probably the issue of reactivation of symptoms is concerning, so I prefer to space out a little bit those doses.

[00:31:44] **Roberta Pesce:** Alright. Thank you, all. Another couple of questions. Are there studies that explore whether the unvaccinated have a higher rate of development of these diseases?

[00:31:53] **Dr. Benjamin Greenberg:** So, I think that the...

[00:31:57] **Dr. Michael Levy:** Neurological?

[00:31:58] **Roberta Pesce:** Yeah.

[00:32:00] **Dr. Benjamin Greenberg:** Yeah, I think the challenge with that is unvaccinated is a broad term. Meaning somebody who has not had any vaccines whatsoever versus have they not had certain ones. So, I am not aware of any study showing a totally unvaccinated population relative to their rates of these conditions, versus partially vaccinated versus full vaccinated populations. I thankfully I think our rates of totally unvaccinated populations is very low, and so I think it would make it hard to do that study, but Carlos or Mike, are you aware of any study that focused the reverse, looking for people who have never gotten a vaccine?

[00:32:51] **Dr. Carlos Pardo:** So, I am not aware about the specific studies, however there is a lot of interest in immunology about that situation, particularly because last year there were some studies and some observational studies that went out that people that got a BCG were possibly more resistant to coronavirus infection, COVID-19. And the hypothesis was that the early exposure to BCG that was used for tuberculosis may have induced some protective immunological factor for that population. But again, I don't believe that there are serious studies or very detailed studies to answer that question, and it's extremely difficult to

  

answer that question as well, because remember, in addition to not being vaccinated, a patient may have been exposed to viruses already in a pathogen, so answering that question is going to be challenging.

[00:33:51] **Roberta Pesce:** Yeah, thank you. The last question, I promise, I know that we are running over. Do you recommend one vaccine over another? I believe here we are talking about the COVID vaccines. We have a talk going on tomorrow, but I just wanted to address this question today since it was asked.

[00:34:12] **Dr. Benjamin Greenberg:** Yeah, if I can read into this a little bit, I think what's in the background of this question is there seems to be differential rates of concerns with the mRNA vaccines produced by Pfizer and Moderna. The Johnson & Johnson vaccine, which is the third of the vaccines that's available in the United States and has a different approach to inducing immunity, and then what we hear about the AstraZeneca vaccine that's available elsewhere. I guess what I'll say is what I say in the clinic, we have much more experience and data with the mRNA vaccines than we do with the other, just real-world experience. And so, my ability to comment on the relative safety of the mRNA vaccines is bolstered by the hundreds of millions of doses of people who have received doses in the United States and beyond.

[00:35:04] I've been cautious to not say it has to be an mRNA vaccine because I want everybody to get vaccinated, and I think the safety data for the Johnson & Johnson is quite good, but there have been the reports of clotting events. Particularly I believe in young women, and so I lean towards the mRNA vaccines, but if somebody told me their only option was the Johnson & Johnson I'd say absolutely, take it, and would feel very comfortable taking it myself. I don't know, Carlos, if you have a different take on this, or if you're adamantly recommending one versus another COVID vaccine.

[00:35:46] **Dr. Carlos Pardo:** No, I agree with you completely. It depends where you are. I frequently get messages from out of the country from Latin America and other countries, and I always say just get the vaccine that you have been offered if there are no other options, because what we need to do is to make sure that people get vaccinated.

[00:36:12] **Dr. Michael Levy:** Carlos, what do you think about the vaccine in South America from, I think it's from China called Sinovac.

[00:36:18] **Dr. Carlos Pardo:** Very interesting question. I think that the data is a little bit mixed. Particularly data generally in Chile appear to show that there is a good degree of protection. I think that the reality is the problem is nobody's going on in other countries is the availability of vaccination. It's very sad that many countries around the world don't have access to vaccines, so I think that the effort to cover the population with other vaccines including the Sinovac vaccine is very important. The Cuban scientists have developed vaccines and Cubans are very well done to have a very good technology to develop vaccines, and they are exporting their vaccines to other countries like Vietnam and other South Pacific countries.

[00:37:13] So I think that as many vaccines we have available that is where we need to go. Unfortunately, if the mRNA vaccines are available for all countries around the world, fantastic. The reality is as we've seen in the past few days with research that has been done is none of those vaccines are widely available in other countries. It's very sad that we still are waiting for a full vaccination of many areas in the world.

[00:37:43] **Roberta Pesce:** Indeed. All right. Well, I think this concludes this talk. Thank you all so, so much for being here and doing this. I know we've gone over by 15 minutes, so it has been very generous for you to stay on this additional time. We really appreciate you as an integral part of our community, so thank you very much.