The Path to a New Vaccine Isn't All Paved

OnMedicalGrounds

PODCAST 7

Dr. Jill Sellers:
Welcome to the *On Medical Grounds* podcast. I'm Dr. Jill Sellers, your host. *On Medical Grounds* is a casual, friendly place where you can find an authentic, audible blend of timely scientific and medical knowledge. We talk with experts about their experiences and knowledge, the utilization of new therapies and challenges within the world of healthcare. Select podcasts offer continuing medical education credits for those of you needing an additional why-you-should-listen. We provide perks to all posted podcasts by linking content so you can drink in more if you so choose.

Our guest today is Dr. Margaret Liu. Dr. Liu is known internationally as an expert in the fields of gene delivery, vaccines, immunotherapy and global health. Dr. Liu obtained an MD from Harvard Medical School and completed her clinical and research training at Massachusetts General Hospital, Harvard Medical School, and the Massachusetts Institute of Technology. She currently holds a variety of positions with one of them being the chairman of the board of the International Society for Vaccines.

She is also known as The Mother of DNA Vaccines and is the scientific lead for the World Health Organization drafting group writing the guidelines for mRNA vaccines. I will link to Dr. Liu's full bio in the show notes. It is an honor and a privilege to have her with us today. Welcome to the *On Medical Grounds* podcast, Dr. Liu.

Dr. Margaret Liu:
Thank you Dr. Sellers, Jill, and thank you for your kind agreement to take the honorarium that you offered and donated instead to the Lazarex Cancer Foundation. Lazarex helps individuals participate in clinical trials for their cancers when they have failed existing therapies. Lazarex helps reimburse the ancillary costs such as bus fare or parking that otherwise would be a barrier for these people to participate in the clinical trial. So thank you.

Dr. Jill Sellers:
Well, I know the Lazarex Cancer Foundation, thanks to you for your generous gift as we do also. We are going to discuss vaccines today, and before we get into the finer details, let's provide some foundational information for our audience. What are the different types of vaccines and how are they developed?

Dr. Margaret Liu:
There are several different technologies for making vaccines. These include killed version of the pathogens, live, weaken strains of a virus, pieces of the pathogen, such as the outside sugar or outside protein and other viruses that themselves don't replicate, but can deliver a gene coding for the antigen of the target virus. These can take a long time to develop. The chicken pox vaccine, for example, took nearly three decades to develop because it required growing the virus many times to make it weaker and weaker.

Of course, we are fortunate now that with recombinant DNA and new vaccine technologies, we can develop vaccines much more rapidly. However, the time it takes to make any new vaccine depends not just on the vaccine technology, but also on what kind of immune responses are needed for protection against the given disease. This isn't always known. So sometimes even after decades, we don't have successful vaccines such as has happened for HIV.

Whereas for other diseases, vaccines have been made much more rapidly. And of course, when a vaccine simply needs to be remade due to strain changes such as what happens yearly with influenza, the revised vaccine is made in a matter of months after the surveillance has determined which strains of flu are most likely to cause the yearly seasonal epidemic. Another factor that affects how long it takes to make a new vaccine is how prevalent a particular disease is. For example, in the efficacy trial for proving that a vaccine works, you need to have a certain number of people get infected in the placebo group, hopefully, to determine the percent efficacy.

If the disease incidence is low, it will take you longer to collect a number of cases. In the case of COVID-19, the pandemic meant that there were so many cases happening, that the studies rapidly gathered enough cases to determine efficacy. So that was kind of a silver lining for the pandemic for vaccine development, that the unfortunately high incidence of disease meant both that doing a 30,000 person study, instead of say, a 70,000 person study, could demonstrate efficacy.

Plus, the number of people getting infected in the placebo group happened more quickly than, for example, with a disease like hepatitis B, thus the high incidence meant that the clinical trial phase of the vaccine development could be faster than for other diseases.

Dr. Jill Sellers:
Which was good for us. And because of the pandemic, there has been much discussion recently about the mRNA vaccines. So how are mRNA vaccines different from the ones we have previously been exposed to?

Dr. Margaret Liu:
mRNA vaccines are different from many other vaccines, but they actually share a key point with another type of vaccine. So let me explain. Usually, vaccines themselves provide the target, the actual antigen or piece of the pathogen against which you make the very specific immune responses. For example, some influenza vaccines use an influenza virus grown in chicken eggs; then that virus is killed prior to giving it to people.

In contrast, an mRNA vaccine simply uses a string of mRNA that codes for the antigen. So your body makes the protein and then your immune response develops against the protein. The J&J COVID-19 vaccine uses an adenovirus one that causes the common cold, but which has been altered so that it cannot replicate itself. It also then delivers a gene coding for the SARS-CoV-2 spike protein. So the J&J vaccine also results in your body making the antigen; neither the mRNA vaccines, nor the J&J vaccine are the SARS-CoV-2 virus antigen themselves. They just deliver the gene either in the form of mRNA or in the form of a viral gene to the person. The person then makes the protein themself and subsequently the immune response.

Dr. Jill Sellers:
Are there circumstances or diseases in which a specific vaccine type is preferred?

Dr. Margaret Liu:
Yes, there are, for example, for bacteria such as *Haemophilus influenza*, a polysaccharide that has then been chemically conjugated to a protein carrier is the best type of vaccine, but for other diseases, different technologies have been successful for this same disease. For example, we have inactivated, recombinant and live attenuated influenza vaccines. So different technologies but all targeting influenza.

In contrast, sometimes technologies that we thought would work didn't work. For example, Merck Sanofi and GSK stopped work on their COVID-19 vaccines because it didn't appear that they would work even though they were using technologies that had been used successfully for other vaccines. The ultimate proof is what works in humans rather than simply based on immunological theory or even past successful vaccines. However, there are certain types of immune responses that are thought to be better for certain diseases. For example, the mRNA in J&J vector vaccines for COVID generate antibodies. Plus they also generate a specific type of T-cell immunity.

This type of T-cell response, which helps develop certain types of antibodies and other T-cell responses are important. And so for COVID-19, a specific type of T-cell response called a T-helper 1 rather than a T-helper 2 response is what scientists wanted to make for the COVID-19 vaccine because actually of specific concerns about what type of antibodies might be generated if a vaccine made a T-helper 2 response instead of the T-helper 1 response. And this actually was based on prior work with respiratory syncytial virus.

So, you can't definitively say that one type of vaccine will or won't work until you do the efficacy study, but you do select a technology based on prior experience that should generate the type of immune responses predicted to work for that particular pathogen.

Dr. Jill Sellers:
That is so very interesting. What kind of data is collected on the tested vaccine prior to approval?

Dr. Margaret Liu:
Well, data collection starts in the laboratory with both in vitro tests and animal testing, and then progresses to clinical trials. So in a clinical trial and in the animals, you look for immunogenicity, that is you look at antibody and T-cell responses. You look for protection, even in the animal models where an immunized animals then are challenged, that is infected with the virus. And you also look at safety, which includes many measurements, such as blood tests, as well as systemic effects.

A huge amount of additional data is collected that relates to the manufacturing process. And that includes characteristics such as purity, sterility, consistency of one manufactured lot compared to another manufactured lot, the stability of the vaccine and so forth.

Dr. Jill Sellers:
Are there standards for data collection or results interpretation for vaccines?

Dr. Margaret Liu:
This is a key point, so thank you for asking. There are very strict standards for the different steps of the process. For example, manufacturing for clinical use is done under what is known as GMP or good manufacturing

practice, which are established FDA regulations. Similarly, clinical trials have to be performed under GCP or good clinical practice. Statistical calculations need to be established for the trial ahead of time, so that enough people are enrolled in both the vaccine and placebo groups to get a statistically significant proof of efficacy.

And of course, the study is double blinded, meaning that neither the participants nor the researchers know what an individual received. There are many components to GCP or good clinical practice, and they are all designed so that the researchers cannot even subconsciously influence the outcome. There are also two key aspects of what happens next for presenting to the FDA. So the first is that the point at which the vaccine is determined to protect against COVID-19 is predetermined and agreed to in advance with the FDA. So, the people performing the trial just can't change their trial design or their efficacy endpoint on the fly.

Secondly, the group that reviews the data and informs the company of the results is actually an independent group called a Data Safety Monitoring Board. So it isn't the company that decides what the results show, it is an independent group.

Dr. Jill Sellers:
I think that's a key point for people to understand. What type of data is submitted to the FDA for vaccine approval?

Dr. Margaret Liu:
Well, first I want to clarify that when you use the term approval, the usual process for full approval, whether it's a vaccine, a drug or a device, is approval for which a company submits what's called a BLA, a Biologics License Application. The emergency use process is different in that it's called Emergency Use Authorization, not approval. And the acronym for that is EUA. This process actually was established in 2004 in response to concerns of bioterrorism raised after 9/11 and after the subsequent anthrax attacks.

So, this really wasn't driven by pandemics per se, but by bioterrorism. EUAs have been used though since then, mainly for medical equipment and drugs, but they did have find usage in the H1N1 influenza epidemic of 2009. So the process isn't new and actually was used over a dozen times prior to the COVID-19 pandemic. And it's important to note that the EUA or the Emergency Use Authorization is only valid until either the product is licensed or until the emergency is over, such as when the H1N1 influenza epidemic of 2009 disappeared.

So an EUA submission will include the immunogenicity and efficacy data and all the safety data accumulated from phase one and two studies, and from a specified number of participants and for a certain length of follow up for safety for phase three participants, looking for any adverse offense. In addition, enough information about the manufacturing process to ensure quality and consistency is needed. This is referred to as CMC or Chemistry, Manufacturing and Controls. The FDA will evaluate whether GMP has been fulfilled by reviewing records, by visiting manufacturing plants, and by looking at the prior history of the manufacturing facility.

So once an EUA request has been submitted to the FDA, both FDA scientists and members of a committee of outside experts called the Vaccines and Related Biological Products Advisory Committee or VRBPAC

evaluates information. And of course, these outside experts are screened for conflict of information, and they're all very prominent individuals in the vaccine and scientific community.

Dr. Jill Sellers:
I asked these questions so our listeners understand that there's a lot that goes into vaccine development and then the authorization and or subsequent approval. So, does the data submitted to the FDA differ for emergency use vaccines?

Dr. Margaret Liu:
Thank you for asking this question because it's very important that people understand this. So, for licensure, that is the BLA, the FDA does require longer follow up of trial participants for vaccines, at least six months of safety data. But it's important to remember that most adverse events such as fever or achiness, those types of adverse events occur really within the first six weeks. So going out six months for data is actually really longer than is seen for the typical adverse events and even including any of the adverse events that have been seen with all of the billions of people who have gotten the COVID vaccines.

For the EUA, the requirement was two months of follow up after completing the immunization protocol of at least half of the vaccinees. Plus, the phase three safety data from over 3,000 vaccinees followed specifically for one month for adverse events. So this really is the time course where they would've seen the serious adverse events. But secondly, for BLA, for the actual licensure, the FDA does require more manufacturing information. And that's specifically the CMC information of Chemistry, Manufacturing and Control data, and includes requiring facility inspections.

This, as you can imagine, generates hundreds of the thousands of pages of data, which takes months to go through. So, because in an emergency, many people would actually die or become severely ill during the time needed to process all the information, the EUA process was developed to provide the key safety and efficacy evaluation, and to show that the manufacturing process was consistent in the context of the benefits of an EUA vaccine outweighing any risks, not yet observed. Because otherwise, if they just waited the full months for all of the information for a BLA during those months, people would still be dying and getting severely ill.

And so, the idea is if the benefit clearly is there to have this emergency authorization to protect people while additional information is not only gathered, but looked at for a full approval.

Dr. Jill Sellers:
How much clinical trial data is required for Emergency Use Authorization for a vaccine?

Dr. Margaret Liu:
Well, the efficacy of the phase three study that's needed for an EUA, for emergency use is actually technically the very similar to what's needed for a BLA. As I said, there is a little bit longer period of safety follow up, but in fact, you still need to determine that a vaccine has efficacy. So the terminology that's used is that, "may be effective and that the known and potential benefits outweigh the potential risks." And of course, an important point is that, at that time point for the EUA, that there's no adequate approved available alternative. So, really is a benefit risk ratio that is determined.

Now, if you recall before any of the COVID vaccines got their EUA, what happened was the FDA had said, "Well, we'll probably authorize a vaccine as long as it has efficacy around over 50%." So when the results of the mRNA COVID vaccines showed over 90% efficacy, and in fact, the J&J one also showed very high efficacy, the issue of any difference in efficacy between an EUA and a BLA was not an issue, because the efficacy was actually just tremendous and much better than people had been hoping for.

So, there was no question about saying, "Well, we'll accept an inferior vaccine for an EUA even though for a BLA we might want more because, in fact, the efficacy for all three of the vaccines that have their authorization was just much better than anybody expected." So an EUA requires that monitoring and reporting of adverse events will still be required even after the EUA is granted. The main issue is that with such tremendous efficacy, the concern was that it would be unethical to withhold the vaccine from placebo recipients just to continue having a placebo group for following differences in long term safety.

So that was the only issue, in fact, that people discussed, is how do we get the safety data over a longer term period when we really need to offer potentially the opportunity for the placebo recipients who voluntarily offered to get the vaccine? Fortunately, because there have been no large numbers of any serious safety events, and because, as I said, usually any safety events occur in the initial period of time in the first six weeks or so, this hasn't ended up being a problem in terms of continuing to demonstrate the safety and to look at the minority of adverse events that have occurred.

Dr. Jill Sellers:
Well, you answered the question I was going to follow up with. So I'll go on to my next question. What were some of the previous vaccines that held the designation EUA or is the COVID-19 vaccine the first to have emergency use only authorization?

Dr. Margaret Liu:
Well, so I mentioned that in fact there were devices and drugs that actually have had EUA designation in the past. So the only vaccine that previously held an EUA was actually AVA, which is called anthrax vaccine absorbed. Now, that actually was a licensed vaccine for anthrax, but the reason it got an EUA was because the people that the license was for didn't extend to the population of people that the EUA covered in addition.

So, in fact, what the EUA was for was, people that the Department of Defense deemed to be at risk for inhalation of anthrax. So this now included people, for example, like mail carriers, because as you recall, the anthrax attack occurred by people putting in anthrax spores in envelopes. And so, it was really an extension of the use of an existing vaccine to be given for people for whom it hadn't actually been licensed for.

Dr. Jill Sellers:
So, really for the COVID-19 vaccine, EUA is the largest one apparently, that's as far as how massive it covered, like the massive population. Right? Because this other one for the AVA was strictly for Department of Defense people or people who were deemed by the Department of Defense. So that was a smaller population than the mass population. Right?

Dr. Margaret Liu:
Yes. Absolutely, right. Although it was … but the other point is that these, in fact, were new unlicensed vaccines. At the same time certainly by this point when we've now had people who've been getting the vaccines for a year because of the clinical trials, there have been so many people who've gotten it, billions, literally around the world. Now we have a much larger denominator than you usually would have by the time you were filing for a licensure of a vaccine.

Dr. Jill Sellers:
Right. Has there ever been a vaccine developed where you questioned the efficacy and safety?

Dr. Margaret Liu:
Well, the issue here is that everything is a benefit risk ratio. So you always want to make sure that the benefit vastly outweighs the risk. In fact, you could question, for example, the malaria vaccine that the WHO just approved because it only has a 30% efficacy against severe disease. So some people would say, "Wow, that doesn't sound very good. Even though it's really safe, is it worth having approval and distribution when it's only got 30% efficacy?"

However, it's important to know that actually for data, going back to 2018, which is one of the most recent years for which there's good data, nearly half a million people died. So 411,000 people died of malaria. And of those, 23,000 children a year die. So you can say, "Well, 30% isn't very good." But 30% of 400,000 people is a lot of people. And so, the benefits then are still really significant. On the efficacy side, that somewhat low percentage compared to over 90% with the COVID vaccines, for example, still is very much worth having that vaccine.

Regarding safety, of course, the benefit always has to outweigh the risks. As we've seen with the COVID vaccines, there are some very rare safety adverse events that do happen. But, I'll give you an example where it's a little more complex because of the specifics of the issue. So there's a dengue vaccine, which is actually very effective at preventing disease. So if you were to use it in a dengue endemic region, which tend to be regions where you have a lot of mosquitoes, it turns out it, on a population benefit, would really do a lot of good because dengue is a very severe disease, and a number of people die from it.

The problem is that, for really young children who've never ever had a single dengue infection, and there are four main strains of dengue, sometimes because the vaccine generates certain antibodies that can help the virus enter cells, then sometimes these young children will end up having worse disease if they've been immunized. So the vaccine is safe for the majority of the population. It will have a benefit by protecting the majority of the population, but it does have a very specific safety issue for a minority of the population who are mainly children.

And so of course, what is proposed to do is to test people before you give them the vaccine. Particularly test the children, and if they haven't had dengue before, then they could not take the vaccine, and so, they would still be at risk for dengue, but at least the vaccine potential risk of worsening subsequent disease wouldn't be there for that subset of the population. So, just to summarize, for every intervention, whether it's a vaccine or whether it's a drug therapeutic, decisions are always made on a benefit and risk ratio. So fortunately, the COVID vaccines have a fantastic ratio of being incredibly effective and incredibly safe.

Dr. Jill Sellers:
We studied the benefit risk ratios in pharmacy school *ad nauseam* so I understand that. Speaking of the COVID-19 vaccine specifically, is there anything you were pleased with and or disappointed with concerning the rollout?

Dr. Margaret Liu:
This is a great question. Before I answer it, do you mind if I go back and just make another comment about benefit risk that I should have thought of at the time? And that is that everything we do in life is a benefit risk calculation.

Dr. Jill Sellers:
Yes.

Dr. Margaret Liu:
So most of us, in fact, drive cars, even though there are 30, 40,000 deaths a year of people who drive cars. Everything is based on, "Do we think that we derive more benefit than there is risk?" And so, if you look at some of the incidents of adverse events with the COVID vaccine, such as the rare cases of clotting with the Johnson & Johnson vaccine, it turns out that actually there are many, many people who spontaneously have clotting, and this happens from people who fly on airplanes, it happens in pregnant women. It happens for no known reasons some people have, and they often can get pulmonary emboli, they can die, they can have other disorders.

So, the incidents that has happened with the Johnson & Johnson vaccine is very, very low compared to certainly, I think, it may be something like a 100,000 people who have these thrombi anyway in the United States each year. So, I just wanted to make it a little more clear that this isn't just area of benefit risk for medications, it's actually everything we do in life.

Dr. Jill Sellers:
Right. I agree. I totally agree, and I appreciate you clarifying that.

Dr. Margaret Liu:
So to get back to your question, though, you had asked, is there anything I was pleased with and or disappointed concerning the rollout? I think that all of us in the world were just blown away by how wonderful the vaccines were in terms of efficacy, and combined that with really a very small and limited amount of adverse events. I mean, some people felt fevers and they had to maybe take a day off work, and that's a big deal, but compared to getting COVID and dying, or even having a long haul COVID, these adverse events were so minor compared to these 700,000 Americans who have died of COVID.

But, there were two things that I was actually disappointed with. And the first is that there's so much vaccine misinformation and politicization that have resulted in an incredible amount of vaccine hesitancy and outright refusal. So, huge numbers of people are dying unnecessarily, and they're becoming disabled with things like lung transplants or other long lasting disabilities when they don't need to be. This to me is really a travesty; it's particularly sad in the United States where we've had a disproportionate number of deaths per population, compared to other countries, including countries that are much poorer than we are.

The second thing I've been disappointed about is that there's not been enough effort to immunize the whole world. So, this is obviously wrong from an ethical standpoint, because we are all brothers and sisters with every other human being. But, even from a selfish perspective, we have to remember that no one is safe until we all are safe. And that's because variant strains that arise anywhere in the world can rapidly spread over the entire globe. And we've seen this with the Delta variant, we saw this with SARS-CoV-2 itself, of course, and these strains may actually be resistant to the vaccines and to the monoclonal antibodies.

But even if they aren't resistant, more virus means that we all have to worry about getting infected even though the vaccines protect us from severe illness and death. So, it's just something that had we been able to eliminate a lot of the disease amplification, then we would as a world and as individuals be in a better position.

Dr. Jill Sellers:
I want to come back, and you mentioned variants. I want to come back to that later, but I have a question right now, at what point in the vaccination rate curve do we transition from a pandemic to endemic?

Dr. Margaret Liu:
So, sadly the term endemic used to most frequently be used to refer to a disease that was confined to a particular region without input from outside that region. So as polio was getting eradicated, which it hasn't been yet, but it was limited just to one or two or three countries, and it was said to be endemic there. But now we're using the term endemic to refer to the persistence of COVID-19 globally. So not just at a lower level than now, but still at some significant level.

So I don't know if we'll actually ever even achieve that for SARS becoming endemic and whether or not, there will be a need to keep boosting or keep reformulating the vaccines. To me, it's really sad that it would've been easier to contain the virus earlier in the pandemic when there was less virus, fewer people infected overall. I mean, we're now celebrating the fact that there are, say, 70,000 people a day getting infected in the United States, getting diagnosed in the United States.

And it turns out that a year ago we thought that was a terrible number; it's only because we've reached such higher numbers before. So, it would've been nice if we could, in fact, have eliminated it just as SARS-1 in 2003 was actually contained and disappeared.

Dr. Jill Sellers:
Yeah. It is interesting how the perspective changes when the numbers change, but it's still a lot of people.

Dr. Margaret Liu:
Right. Absolutely.

Dr. Jill Sellers:
I think the COVID-19 vaccine has been highly politicized, despite that, what advice would you give to healthcare professionals as they educate and counsel patients regarding the COVID-19 vaccine?

Dr. Margaret Liu:
Well, your audience, that is physicians and healthcare workers, are still considered by people to be the

trusted sources of information for their health and including for vaccines. So when dealing with vaccine information, actually physicians in particular are well positioned to help people become comfortable with the vaccines. However, it's clear that simply providing scientific information isn't enough, and it's really important that the patient not be spoken to condescendingly. So the patient needs to feel listened to and to have their personal concerns addressed. But physicians are very well positioned to play a key role for this.

Dr. Jill Sellers:
Agree. What should physicians say to people who think they don't need the vaccine because they already had COVID-19?

Dr. Margaret Liu:
Oh boy, this is really a great question. So, some of the confusion here is because there actually have been different publications that have said, "Oh, having infection protects really well or better than the vaccines." And certainly for some diseases like measles, you get really good, pretty much lifelong protection. However, the problem with COVID is that there is a wide range in antibody titers and in responses to infection, whereas completion of a primary vaccine series, especially with the mRNA vaccines, typically leads to a more consistent and higher titer initial antibody responses.

But it's also important to know that, very recent, CDC data from a large network. So this is why the data is more important, more relevant and believable is that they actually show that looking at 187 hospitals in a network, when they looked at 7,000 COVID like illnesses, they found that if they had been infected or vaccinated, either one, three to six months ahead of time, that for the people who were previously infected, that they had a 5.5 times higher chance of getting infected again, compared to fully vaccinated patients getting infected. So in other words, immunization protects better than prior infection.

Another key point to tell your patients who already had COVID-19, but are unimmunized, is that when they get the vaccine, they're actually going to have a really powerful immune response to the vaccine. So the illness primes their immune responses, but the vaccine will then really boost it.

Dr. Jill Sellers:
I believe this point has led to a lot of confusion. So, help me understand how it is possible that the COVID-19 vaccine can be more effective and or durable than having the disease.

Dr. Margaret Liu:
Well, there are many ways that a vaccine can generate more immune responses than actual infection. Although the reverse for other diseases can happen as well, but it appears not to have been this way for COVID-19. So in the case of COVID-19, one issue maybe that when someone is infected, they make immune responses against so many parts of the virus, and yet only certain of the immune responses are protective.

The vaccines that we now have are focused on the spike protein because you want antibodies to block the virus from binding to and infecting cells, and the virus does that through the spike protein. So, you want to target the outside protein, the spike protein for killing by antibodies before the virus even tries to bind to cells. So if you make a strong immune response focused on the protein that's best for that purpose, that is the spike protein, you could see how the immune response could be better because it hasn't been diluted by making an immune response against all these other viral proteins.

This would be kind of like an action hero movie where the hero stops the guys in the getaway car by shooting out the tires rather than shooting at the chassis of the car. It's a focused response. I always find myself watching a movie going, "Just shoot out the tires." And that's exactly the approach that the vaccine does; it focuses the response on the spike protein, that is the protein that is how the virus infects cells. But there are many probable factors that involve the way vaccine stimulate other parts of the immune system, and that includes what's called the innate immune system, which is like your early warning system. It would be like your burglar alarm that detects whenever you've had an intruder come in.

So it turns out that both the mRNA vaccines and the J & J vaccines actually trigger innate responses, in addition to the antibody and T-cell responses that are part of what's called the adaptive immune system that is very specific. But this innate system, which is more nonspecific, actually helps the adaptive response be better. So the bottom line is that what's been observed, that is by seeing who's getting sick after infection compared to the fewer people who get infected after they've been immunized, means that for these reasons and possibly others, because there's a lot of complex immunology going on, the vaccines have actually been able to protect better from subsequent infection and disease.

Dr. Jill Sellers:
You mentioned variant COVID-19 strains a bit earlier, and I want to revisit that now. How do variants arise and spread?

Dr. Margaret Liu:
Variants are actually always arising; because they happen during the replication process when progeny virus are made, there's just errors that occur during the process. So some of these errors just randomly make the virus less viable, but obviously then those viruses don't go on to survive and spread. So, other errors, just by chance, make the virus better able to, say, bind to receptors on the cell, or they make the virus able to replicate more quickly, or they might even change the parts that are targeted by antibodies so that the antibodies don't neutralize as well.

Well, those viruses then would be able to outcompete the original virus in certain situations, and so they would spread more quickly. That's apparently what has happened with the Delta virus, where it is able to make a lot more virus particles, it's estimated maybe a thousand fold more virus particles. Therefore, it just spread more quickly, and that's how it's so quickly came to dominate the cases in the United States.

Dr. Jill Sellers:
Interesting. That really is interesting. Does prior immunity from high rates of infection help select for variants?

Dr. Margaret Liu:
Well, the hope, of course, is that if there are enough people who have immunity from immunization or a combination of immunization and prior infection, even though that immunity may not be as good, then the virus wouldn't be able to infect enough people to spread, and the pandemic could die out or at least new variants wouldn't spread as easily. However, it is thought that some of the variants such as the P1 from Brazil and one from South Africa may have arisen in populations that had a lot of infections with the early strain of SARS-CoV-2, but their immunity apparently wasn't good enough to completely eliminate the virus from their community.

So a variant that arose that was able to spread outcompeted and so even previously infected people then apparently became infected with these variants. There is some thought that the prior immunity just wasn't good enough, either because the rates of people wasn't high enough or that even in the people themselves, their immunity wasn't good enough, and so then the variant strains were able to propagate. But, this is still an area that is under study.

Dr. Jill Sellers:
The term variant of concern has been mentioned by the CDC regarding the Delta variant of the COVID-19 virus; what does this mean, and how did this variant gain this recognition?

Dr. Margaret Liu:
So the CDC has a rating system. It's kind of like in the Olympics gymnastics, they give scores. In this the CDC has four levels of variants. So they have variants that they're just monitoring. They have variants of interest that they're following. They have variants of concern of which the Delta and related strains are the example of, and then variants of high concern. So fortunately, there are no variants in the U.S. currently that are considered of high concern.

But why the Delta variant is a variant of concern is because of its increased transmissibility, because of its potential reduction of neutralization by some monoclonal antibody therapies and the potential reduction in neutralization by antibodies generated from vaccination. So, this actually was one of the factors that played into why the decision was made to permit boosters, was because it seems that you need to have these higher titers for good neutralization.

Now, there are other reasons that a variant could be called a variant of concern, and that's if it evades existing diagnostic tests or if it could cause more severe disease. So the Delta virus hasn't convincingly caused more severe disease, although there is concern that it might be doing so because of the increased number of young people, children and younger adults even who have become ill, but that's still a matter of debate. It's definitely more contagious, but whether or not it actually causes more severe disease, there's a little bit of disagreement about.

Dr. Jill Sellers:
When someone is vaccinated, what are the desired vaccine induced immune responses that we are looking for?

Dr. Margaret Liu:
Well, we've all of course heard about and focused on the antibodies and particularly neutralizing antibodies. I'd like to emphasize that actually there are several ways that antibodies work to either destroy the virus directly or to block the virus from binding to cells so that it can't infect the of cells.

But in addition to the antibodies, vaccines induced T-cells, and we talked about these earlier about how there were two main types of T-cells. But of this cells, the T-cells, the first type that I mentioned earlier called T-helper cells, and T-helper cells do just what their name implies, which is that they help B-cells make antibodies. And they actually also help other T-cells that are called cytolytic T-cells. They do this by producing cytokines. So they're like the vitamin manufacturers that help the other cells do what they need to do.

Now, cytolytic T-cells can kill virally infected cells. So, they don't kill viruses directly like antibodies can do. But what they do is they kill the virally infected cells that are making new virus particles. So effectively, they're shutting down virus factories if you want to think about it that way. So they limit the number of new virus particle made. The nice thing about T-cells, both helper and cytolytic T-cells besides what they do, is how they do it, and that is that they recognize peptides from various parts of the virus proteins.

So, even though variants may have mutations say in the receptor binding domain, which would be very important for escaping an antibody response, the T-cells can recognize parts of the virus that are more conserved. So these are parts of the virus that are kept the same between different variants. It's like people look different on the outside, we wear different clothes, we have different colors skin, we have different hairdos, but we have the same internal organs. We all need lungs and a heart.

So T-cells, in fact, can target these conserve proteins that the virus needs so they can target the ones that are functional for reproducing the virus, for example. So if the vaccines are designed that way, the T-cells could target them, but even for the spike protein, there are regions that are more highly conserved even with the variant spike mutations on the variant vaccines. So, while T-cells can't prevent infections, they can limit infection by killing virally infected cells so that more virus can't be made. So this is like an additional line of defense that we have besides all the antibodies that you hear talked about.

Dr. Jill Sellers:
So knowing that, we know that vaccinated people are still getting COVID-19, and I want to talk about that for a little bit. So, what does the COVID-19 and or the Delta variant of COVID-19 look like in a vaccinated patient versus an unvaccinated patient?

Dr. Margaret Liu:
This is such a huge important issue to make sure everyone understands, because when we think about what we want a vaccine to do, we normally think that we want it to protect us from getting sick or to protect us from dying. That's the most important. Success of any vaccine is to prevent them from dying and to prevent them from getting significantly ill. The COVID vaccines do that really well, even against the Delta variant.

In fact, when the Delta variant became the predominant strain in the U.S., immunized people were 10 times less likely to die or need hospitalization from COVID. And immunization meant that people were five times less likely to even get infected. So, we don't usually ask a vaccine to completely protect us from getting infected without any symptoms because for most diseases, we wouldn't even know if we were asymptomatically infected. You could imagine that someone with a few respiratory symptoms from, let's say, flu might think they had allergies instead of the flu. And so they wouldn't go get tested.

And yet we get tested now because of the public health importance of not taking COVID into our workplace. But somehow people in the United States started expecting that the 94% protection meant that people wouldn't even get infected at all, rather than understanding that that 95% really was looking at serious illness and death. So, people can still get infected for two reasons. One, is that the vaccine is given intramuscularly. So the immune response is actually largely systemic, that is within the blood.

As you know, there's influenza vaccine that is given in the nose, that's a live vaccine, and the whole reason that was developed was to have a mucosal response so that you have a strong response right at the gates

where the barbarian COVID virus, influenza virus in this case, is trying to enter. So with the vaccines that we have now that are systemically given, the virus could infect an immunized person mucosally, but then antibodies and T-cells do a great job of protecting them from systemic illness.

So the second reason people can get infected is that circulating antibodies may decrease over time. In fact, they do decrease over time because unless someone has active antigen present, the B-cells don't keep making a lot of antibodies. And this actually turns out to be an important part of how your antibody responses develop because as antigen goes away, it turns out the B-cells that have the highest affinity, the tightest binding like the super glue antibodies, are the ones then that keep developing by the whole immunologic process. So actually, it's a good thing that this happens, because then we end up with the really super-duper antibodies that are the most powerful.

But, fortunately for us, not only does this development continue, but both B-cells and T-cells have memory. In other words, if someone now is exposed to the SARS-CoV-2 virus, these memory cells wake up, they start pumping out antibodies, the T-cells get reactivated. So someone might get infected, but then the memory response shuts down the virus. So, this was actually one reason why there was so much debate about whether to authorize booster doses for people, because the boosters will raise the circulating antibodies and they will protect people right away more from the Delta variant, which seems to require maybe higher titers of neutralizing antibody.

But the memory responses still would've played a protective role without the booster. So the question was whether that response without a booster shot, but with the memory response, would've been inadequate. Now, a number of vaccines actually need up to three shots like hepatitis B. In fact, these third shots that people are getting wouldn't necessarily have been called a booster shot even for the immunocompromised for whom the third shot was for authorized, and now the booster dose given to the elderly and certain other groups has definitely been deemed beneficial and thus authorized. But it doesn't mean that these weren't good vaccines because this is a very normal process for other vaccines that need to have multiple injections.

Dr. Jill Sellers:
Oh yeah. When I go to have an annual physical and I have a titer drawn to see if I need any boosters, that's why they draw titers, right, to see if you need a booster. So, it's the same thing here. Right? I mean, can you even do titers with COVID-19? Can you even check titers? I don't even know.

Dr. Margaret Liu:
It is the same thing, although, for most vaccines people don't draw titers. Like if you think about your hepatitis vaccine, there's just a recommendation that you need to get your booster every 10 years, unless if you stick yourself with a rusty nail, you'd need it sooner. You can get titers checked, and, in fact, particularly for people who are immunocompromised, like they're on immunosuppressive drugs, they may be undergoing chemotherapy or have had a bone marrow transplant and therefore are immunosuppressed.

Those people certainly can have titers checked, but, I mean, other people can have them too, because physically the tests exist. But those are the people who would be most potentially in need of checking, or, of course, now the authorization has been given that they should just get their third dose and that other people at risk such as elderly people should also then just get the boost. I say that term, elderly, just

out of habit because I'm in that group now too, and so, it's not meant to imply that it's only people who passed a certain level of immune functioning, but the reality is all of us, once we hit puberty, our immune systems actually start declining because our thymus starts involuting around the time of puberty. So, it's all over for us immunologically, the older we get, although, clearly everybody still has, they're not decrepit immunologically, but I say this partly because many people in their twenties and thirties think that they still have superpowers.

Dr. Jill Sellers:
They're invincible.

Dr. Margaret Liu:
But the reality is if they're past their adolescence and their puberty, then already their immune system has started and its way down. And that's why the pediatric dose of the Pfizer vaccine that just got authorized is one third the dose of the adult dose because the kids actually have more powerful immune systems than we do as adults.

Dr. Jill Sellers:
Right. Will the COVID-19 vaccine need to be redeveloped annually as the flu vaccine does?

Dr. Margaret Liu:
Well, we don't know that yet because, for example, the Delta variant, we've been really fortunate that it still is neutralizable by the antibodies developed by the vaccines, and actually by a number of the monoclonal antibodies as well. So, there may be new variants that will require different vaccines to be made, and of course, this is done for influenza. But another approach might be, and people are working on this, is to develop a pan-COVID vaccine that could target even future variants of SARS-CoV-2 and maybe even other coronaviruses.

And the reason that people hope this may be true is in fact, one of the monoclonal antibody therapies that's used for COVID-19 was actually derived from a patient infected in the first SARS epidemic in 2003. So it suggests that there are actually regions even between that SARS-1 virus and the SARS-CoV-2 virus that we're having now that are highly conserved, and so they're identical or similar regions that could be used for possibly a pan-COVID vaccine.

Dr. Jill Sellers:
I am so glad we have physicians, scientists, people such as yourself that are researching this. So these vaccines can be developed and we can understand and use them to prevent another pandemic or to become healthy or stay healthy. We've covered a lot of ground today regarding vaccines. So I was wondering if you have any final thoughts for those listening regarding vaccines, their immune responses, variants or anything else?

Dr. Margaret Liu:
Well, I think you've actually raised so many key questions, but I would just like to say two things. One is that we're still learning about this virus, and so, hopefully as we learn more, we will also continue to both develop, let's say, vaccines that are pan-COVID if that turns out to be needed with new variants. And also that we'll be able to help convince more people about the real benefits; we are just so fortunate to have

these vaccines. I don't think people haven't realized that the number of people who have gotten these vaccines safely and the number of deaths and serious illness that's prevented has really been something that has never occurred on such a scale before. So we're really fortunate we live in the 21st century.

But the second point I'd like to make is, I'd actually really like to thank your listeners for all they are doing daily and for such a long time now to care for patients above and beyond their prior careers because they're really helping them at a difficult time and helping to educate their patients about vaccines. So those of us who aren't on the front lines are really appreciative of all that you are doing, and actually I'm just in so much admiration for your dedication and persistence in this difficult time.

Dr. Jill Sellers:
Well, thank you so very much for being with us today. I can't tell you how much I have learned, and I know that our audience has learned, and with all of the information that's been out there on vaccines, you have clarified so much. So, thank you for educating us on this vaccine development and approval, and more specifically about the COVID-19 vaccine, its disease variants and immune responses. Just thank you so much for being with us today.

Dr. Margaret Liu:
Well, thank you Dr. Sellers for asking such great questions.

Dr. Jill Sellers:
And thank you for listening to the *On Medical Grounds* podcast. We know your time is valuable. The resources that were referred to in this podcast can be found at onmedicalgrounds.com. In addition, please be sure to click the subscribe button to be alerted when we post new content.