The Curbsiders - COVID Vaccine

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SPEAKERS

Matt, Molly, Dave, Stuart, Chris, Paul, Monica Gandhi, MD, MPG

Molly 08:17
Absolutely. So we have Maria, she's a 35 year old woman and she is coming in and wants to ask if what you think about getting the COVID vaccine. So kind of to take a step back? What are the currently approved COVID-19 vaccines in the US?

Monica Gandhi, MD, MPG 08:29
So right now, and it's really interesting, the word approved is not the right word, but they're authorized. So someone corrected me on that very sternly, but it's there under emergency use authorization. And we have two in this country, three in other parts of the world, and they are what are commonly known as the Pfizer biontech vaccine is one and the second is the Moderna. And those are the only two vaccines that we have authorization for in this country. And they're both very similar.

Chris 08:57
Now, there is a couple other vaccines that you said and some other countries. I know there's the one from is it University of Oxford AstraZeneca one, but that's a little different from the ones that have been approved for emergency use in the US. Is that right?

Monica Gandhi, MD, MPG 09:11
Yes. So there's actually three approved worldwide if you want to say, you know that there's more than one and then there's some in, there's one in Russia and one in China that we don't know as much about the third one, like you said, is the University of Oxford AstraZeneca vaccine. And it does have a different mechanism of action than those first to the Pfizer in the Moderna. It's an it's a, it's adenovirus. So it's like a it's a very benign cold virus from a primate. And inside that adenovirus which really becomes the vector to bring it into your body is its DNA that codes for the spike protein of COVID-19. And so it is a different technology. It's only approved in the UK and India but there are some major advantages to it. But it hasn't yet been authorized here partially because there's some very weird things about the trial which I can get into

Paul 10:06
which I think we'd love to hear about. And then I think you mentioned sort of the mechanism of action of the big two that I think we're most familiar with being the mRNA vaccines, which I think a lot of hay has been made about, do you mind just sort of talking us through exactly how that works now is different from vaccines that we typically use?

Monica Gandhi, MD, MPG 10:20
Yeah, there is never been a vaccine for a pathogen before that, that uses this mechanism that the Pfizer, biontech and the Moderna one do, which is called an mRNA vaccine. So it's, it's, it's, you know, messenger RNA, that is codes for the spike protein, and it's embedded in this lipid bilayer. And so you inject it in the arm it very easily, because our cells, of course, you know, have a lipid interface, merges with our cell and releases mRNA into our host cells. And then the

translational machinery of our cells is harnessed to make protein, you know, that mRNA goes through our ribosomes and goes through the endoplasmic reticulum, just like any mRNA would. And then we make ourselves make the spike protein in bounds, like lots of it. And it's really efficient. And then your body's like, oh, I've never seen the spike protein before. And then it will trigger the appropriate immune response, both antibodies, and T cell response against the spike protein. So it's super unique, never been used before it has been used for tumor vaccines, but not for a pathogen. And it's pretty amazing technology. Usually vaccines are like bits of protein from the virus, or the bacteria or it is even a live attenuated form of that pathogen. But to take mRNA and put in a lipid bilayer are really unique and very exciting. And then the AstraZeneca is different. Actually, it's more along the lines of how each of the vaccines we've been trying to develop for a long time, but it's taking a virus is the vector, benign virus, this cold virus, adenovirus causes colds and chimps, and it brings it into the cell. So the adenovirus gets injected inside it has DNA, not mRNA. But it's the DNA that codes for the spike protein. And then it's essentially that DNA gets incorporated into your into, essentially, that DNA is coded eventually to mRNA in your body, and then you go ahead and produce protein. So it is, by the way, the virus doesn't replicate in your body, so that I know you don't even get a cold from it. And that has been explored before and adenovirus vector, actually really super familiar with that in HIV, we keep on trying it. It has never worked. So that that is not as novel of a technology.

Dave 12:46
I feel like it's almost the novel nature that is making some people maybe a little bit nervous, I think intuitively it makes sense that you put a piece of something into the body that it says that doesn't belong there. And then it gets excited and builds an immune response. Like I feel like that's really understandable for a simpleton like myself. But the mRNA it's complex, it's seems more complicated. It's exciting. And it's interesting, but also the fact that it's so novel, I think, makes people a little bit nervous about it. So I guess the first question, why don't we start with why it's working now, if it's been something that we've looked at before, so I guess that's a good place to start. So why are these vaccines effective with this mechanism, when prior vaccines attempting and have not been, have not seem to have caught on?

Monica Gandhi, MD, MPG 13:19
You know, Dave, it's only been attempted really for tumor vaccines and tumor vaccines have notoriously been more difficult, obviously, to develop because the tumor has elements that look like yourself. So this is the first time you're right, that it's been used for a pathogen. However, there's this onion article, actually, I'm sure you all saw, but it's like someone hitting their forehead and saying, Oh, my gosh, the answer was here, all along a lipid bilayer with an mRNA in there, and, you know, like it like we could have done this like. So it is it is really amazing. It is really new technology. However, I think its simplicity is what, for me makes it seem so safe. And what I mean by that is when you inject you know, of course, if you inject a live attenuated vaccine, there's always this chance of going back to the real, you know, virus. And we've seen some very terrible examples of that, in the case of measles vaccine, for example, subacute sclerosing Pan encephalitis that could occur very later on. We don't give live attenuated vaccines for pregnant women or immunocompromised individuals. And so that's one mechanism. And then if you give a protein, you had to give it so often like so if you think of, if you think of some vaccinations, you are just giving it so often, and you often you have to give a booster. So it's kind of ingenious, to think, well, instead of giving like a piece of the protein, I'm going to give a piece of the genetic material that harnesses your very own system to produce scads of the protein. I think that's just such a unique idea. And then you produce So much protein that the immune response is quite robust. Now, it's not robust enough, unfortunately, to have given it as a single dose. And I do think that's a really important point that think of any vaccine in the world, like, there it is, it is usually we need more than one dose, because you're sort of generating this immune response, you're starting to form your memory cells. And then if it gets re stimulated with a second dose, then you get a really strong and robust memory, immune response. So I don't think we're ever going to get away. And we can, we can later in this in this if you are if you want, we can talk about the conversations that are coming about out about delaying the second dose, but we're which actually approve of, but we're not going to get away with not giving two doses for these two mRNA vaccines. And that is true of the AstraZeneca as well, it is also a dual, it's a two dose vaccine.

Chris 15:53

Can you speak a little bit I've heard a lot about the manufacture and distribution of these mRNA vaccines. So as mRNA vaccine, you don't need like a chicken egg to culture. And so production can be a lot faster. But then there are some distribution issues in terms of freezing. Could you speak a little bit about that?

Monica Gandhi, MD, MPG 16:12
Yeah, I mean, for anyone who has worked in a lab, in undergraduate, for example, and you worked with genetic material, and you remembered how kind of unstable it is. People are like, Oh, you're so brave to work with RNA, because it actually has to be kept super cold. So that is the issue. And that is why AstraZeneca - there are going to be advantages to it. So the Pfizer biotech vaccine has to be kept at negative 70 at all times, and if you think about like what's in your house, that's a two to eight degree fridge. I mean, sometimes people get down to one, but that's typically a four degree fridge. So if you think about all your clinics out there, many of us have clinics with fridges to store samples, or urine or whatever, but that that's at four degrees, negative 70 is what you'd have in a research laboratory. So it really is really freezing. And so it brings in this complexity of having to ship it on dry ice, having it in these special containers that have dry ice, bringing up the expense of it, the one good thing and that's Pfizer biotech period, like negative 70 period, you know, there was a story in yukata. Ukiah yesterday that they were going to lose their vaccine because it was getting too warm and they like quickly vaccinated 850 people, you just can't let it get warm. Now, the Moderna has advantages. And I don't know, if the Pfizer didn't study it, or there's something inherent about the Moderna that is more stable, it can be stored at for longer at higher temperature. So it can be stored at negative 20 degrees for six months, which negative 20s you don't really have those sitting around either. But it can be stored in a regular fridge 4 degrees for 30 days. To me, that is you know, that really involved that really will allow for full distribution of vaccines, or like using a cooler in a mass vaccination campaign or being out in the field because I am really envisioning and hoping that we're going to have fields and parks and convention centers and people getting mass vaccination, when we open it up to phase one B. So the Moderna has that advantage, but the Astra Zeneca can be in a regular fridge for like kind of indefinitely, six months as how long they've studied it. So that does have advantages in rural settings. And in other places where 30 days may not be enough.

Molly 18:24
And once the vaccines actually given when I originally heard about this new technology a couple months ago, it honestly sounded a little creepy to me. I mean, we're injecting foreign DNA or RNA, but it sounds like it, it really degrades pretty quickly and it doesn't enter the nucleus. Is that correct?

Monica Gandhi, MD, MPG 18:38
Yeah, I mean, that is the best part is that like, think about HIV as a virus that goes in intercalate into a chromosome and you can never get it out. This is literally an mRNA that goes straight to the cytoplasm goes to your ribosomes, you know, use their translation, magic and make it into protein. And then it's in and of itself, like all mRNA just immediately degrades. So when I think about pregnant women, which we can certainly talk about, I know your patient is 35 I don't know her interest in childbearing. But it's very reassuring to me that it's never going to stay around in your body. And so it is it degrades quickly. I can't imagine a scenario where the you'd have long term, scary genetic side effects from it, you know, and so I feel very secure about it safety.

Molly 19:28
Yeah, I mean, the research data looks very, very exciting in terms of just how effective it is. When Chris and I were kind of talking beforehand, he sort of had a question about efficacy versus effectiveness. Was that your phrasing?

Chris 19:42
Yeah, I've heard both praises and seen in some of the literature and saying that they're not the same and I was wondering whether you would be able to speak to that if there is a difference and how what that means.

Monica Gandhi, MD, MPG 19:53
I mean, actually, so you know, that phrase in general usually refers to sort of efficacy is in phase three trial and effectiveness as we roll it out to put it really sort of simply. But there is a weird aspect about this in what they decided their endpoint was, that has led to some confusion about it, right, because both the Pfizer biontech and the Moderna

trial, they started up in like July, and they got their results in November. So it was really fast. However, to have that sort of expediency, which I think was necessary, given the nature of the pandemic, there were shortcuts taken. And one shortcut that was taken Is that the kind of one bizarre aspect of SARS COVID 2 is that we know that you can have asymptomatic infection, you can feel perfectly fine and be shedding the virus in high rates from your nose and mouth. And that's fundamentally the crux of the problem with this virus. It's why it's spread so quickly. It's why we need face masks. It's why one person can carry it and be fine, and they can give it to someone who's more vulnerable and they can get really sick. And that particular outcome of just being infected in general was not an outcome of either the Moderna and for Pfizer study was an outcome of the AstraZeneca trial, but we'll talk about that. So the outcome that was looked at was specifically developing symptomatic COVID-19. And how would you know, if you were symptomatic people, like reported in Hey, don't feel well Oh, really, Okay, come in and get swapped. So there was not routine, swabbing that occurred that we do, for example, in schools for teachers wasn't routine, swabbing at all. It was like, if you don't feel well come in, and we're going to test you for COVID. And so in the Pfizer biotech study of 170, people who ended up being tested and they had COVID-19, 162, were in the placebo arm and eight were in the vaccine arm. And so that is an 95% effective rate, meaning, you know, not many people had symptomatic COVID in the vaccine are they most of the symptomatic COVID was in the placebo arm. But it doesn't actually necessarily tell you if you have asymptomatic infection, say you were in many of these patients were high risk, especially in the Moderna. And by high risk. I mean, like health care workers, essential workers, they were out, they had to be working. And so you could have been infected, but you would never know if you're asymptomatic and going along with that symptomatic outcome, because I think that's a really important outcome. We don't want people to get sick, but that I loved this other secondary outcome, which was having severe disease. Of course, as physicians, that's what we really care about. And almost all of the people in all three trials who actually had severe disease, there were four in the Pfizer trial who had severe disease, and almost three out of four, were in the placebo. And in the Moderna trial, there were 30 people that severe disease, and all of them, all of them were in the placebo groups and zero severe disease in the vaccine group. And then in the AstraZeneca, trial looks like there were 30 as well. So fewer outcomes, and all of them were in the placebo group. So I love this idea that like the most important thing to prevent severe illness, this vaccine works amazingly, it works really well for symptomatic disease. And I actually am going to make the assumption and I'll tell you about that with the AstraZeneca that it actually prevents asymptomatic infection. But that wasn't proven in the Pfizer in the Moderna vaccine trial.

Dave 23:23
So one of the things that I'm taking away from this already are just sort of scripts for people who are maybe hesitant to consider vaccination. So you've given what is it going to prevent? Exactly. So that was incredibly helpful to go through? You talked about the new technology and how it's not that new and also how it's relatively benign and seems very effective. And I think I wonder if you wouldn't help me with the script for the people who are concerned about how quickly this came about, you know, we hear about, you know, drugs and vaccines, and really any kind of medical treatments taking years and years and years to come together. And I feel like some of the, I don't wanna say conspiracy minded, but the people who are nervous about things just feel like this feels markedly different, because it seems to happen so quickly. Do you have something that you tell patients when they raise that specific concern?

Monica Gandhi, MD, MPG 24:00
Yes. What I say to them is in 1918, when they were trying to develop an influenza vaccine, it was 1918. We're in 2020, the entire world was focused on getting a vaccine, you take everyone in the world who has any ability to produce something and they all put their minds to a problem. It's this stop the world in its track. And also there was precedent for mRNA vaccines. They just hadn't been developed, but they had been thought about like you said for a while for influenza for Zika for rabies, actually for MERS another Coronavirus, but MERS kind of went away on its own. So the technology was actually already there. And then you kind of give this challenge to the whole world like do you want to get us out of the misery and get winning Nobel Prize and become the most famous person ever? Yes, like people are going to be on it. And, and it and it went through. I mean, we're in the year 2020. And I think it went really fast because we're in a highly technological age. We had precedent People there was never there wasn't a real issue to use it for influenza, we have other ways to do influenza, there was no hurry. Now there was a huge Hurry, and why not use this incredible technology? So I do not think it was I mean, I it was developed fast. And I just found that found that an

amazing kind of the amazing power of technology, science and how miserable we are all are because until, we get mass vaccination, and the world is just on hold, and it is just affecting every facet of society.

Molly 25:30
I love that answer. Oh, sorry, Chris. Go ahead.

Chris 25:33
I was just gonna say that, you know, so one of the reasons I heard we were able to fast track this so fast is because with the different phases and trial, and we were obviously the EUA was approved after phase three trials was that each trial phase actually overlapped instead of doing it subsequently. Is that correct?

Monica Gandhi, MD, MPG 25:51
Yeah. So if you think that's a great point. So the first step was actually phase one seeing if, if, if this mRNA 1273, for example, what which is the official name of that Moderna vaccine triggered immunogenicity, and it did and right as soon as that was noticed, okay, then we'll go into phase two and see what's the right dose. And then as soon as the dose didn't, you know, cause too many side effects. Okay, let's go right into phase three, and started giving it out to people. The other thing is that if you look at the endpoints, there were some shortcuts taken. And I can't again, I cannot blame them. I'm so delighted to have these vaccines that I'm amazingly grateful. But I think you know, what kind of short cuts while they didn't swab everyone weekly in the in the Pfizer or Moderna with phase three trials. they did in AstraZeneca. And I'll tell you about that. And so we don't know if it prevents asymptomatic infection again, biologically, it actually makes sense that it would prevent asymptomatic infection. But when you hear people say wear masks, and still distant until everyone around you is vaccinated. I think that's frankly, a fair point until we can ensure that the other person that we're wearing a mask in front of his vaccines as well, because there is this possibility. So that was one shortcut. Second shortcut was to give three weeks between doses was probably speeding it up a little bit. I there's been I'd love to talk about this. If we had time. This controversy that's circulating right now about if you can delay the second dose, actually think usually delaying the second dose creates more immunogenicity. This is just true for many viruses, we actually care way more, if someone comes in too short of an interval versus too long of interval. It's why we don't start childhood vaccinations all over again, if someone missed a year, we're like, okay, we'll just take you where you left off. Same thing with hepatitis B. So there's something good about delaying time between two shots. And I'd love to tell you a little more about AstraZeneca. To explain that I think that that AstraZeneca trial really showed that. And because of that, I'm giving it everything, giving it three weeks or four weeks was another shortcut probably would have been like 12 weeks if we had all the time in the world. And then the other shortcut was that these outcomes were given just two weeks after receiving the second dose, which is pretty fast. And so the fact that we have such amazing outcomes means these are amazing vaccines.

Paul 28:14
All right. I feel like you've been teasing the AstraZeneca trial for a while now LAUGHTER

Monica Gandhi, MD, MPG 28:18
I've been hinting that I want to tell you two things.

Paul 28:22
We'll let ya loose. laughter Tell us about it. I'm excited to hear.

Monica Gandhi, MD, MPG 28:24
Okay, I really wanted to tell you something about the AstraZeneca trials, because I think they give us hints about what we could expect from the Pfizer, Moderna, because frankly, those trials will they've been criticized, did some things really well. So one thing is that the Lancet paper, which was on December 8, which published the literature on the trial, so far, the AstraZeneca trial, and it was in the UK, Brazil and the United States, that data that was given to us is kind of halfway through the phase three trials. And they did a couple of things were great. They swapped everyone every week. So then you really could say, Okay, well and they had himself swap. So then you could really say, okay, does it reduce asymptomatic infection? Okay, why would anyone even dream of this because in influenza, you don't really have

asymptomatic infection. The reason that we need to do this swabbing, and it's important is that it's possible that a antibody response or T cell response can minimize symptoms of an infection, but not totally block the infection, which is why in the past, we were wondering if COVID antibodies to other coronaviruses, not COVID antibodies, but antibodies to other coronaviruses were conferring some protective immunity against getting symptomatic COVID. So even though you think, oh, it totally block infection, there's still an idea that maybe these antibody responses wouldn't, and you can still get asymptomatic disease and you could still pass it on to people. So AstraZeneca did things right. They actually swapped everyone every week. And one thing that came out that I think is really important is that AstraZeneca also decreased the rate of asymptomatic infection by 59%. So I'm going to assume and extrapolate that that's true of all these vaccines. The second thing that it did, weirdly, and it was like an accident. And that's why people have been kind of suspicious about it is that in the UK, they accidentally gave half, they gave people the half dose, and then a full dose, it was an accident, they noticed that they'd given them half dose because no one was having side effects from the half dose. And then they noticed that and then they said, oops, you got to have those full dose, it turned out that that dosing regimen was actually more effective. For those individuals that have that dosing regimen gave an effectiveness rate of 90%, whereas it was 62% in people who got full dose full dose for a combined effectiveness of 70%. Now, I will say one thing that just came out. And it wasn't actually in The Lancet paper. But it just came out from the data that the UK had reviewed, that allowed them to pass the AstraZeneca vaccine, which is that the people got half dose, actually, were more likely to have a very long period between doses because there was all these mistakes made. And they're like, oh, and so actually was 12. On average, they had a longer period between doses. And what the investigators are speculating about is it was likely that that that increased spacing between doses that led to the increased immunogenicity of the half dose/full dose. And in fact, the UK approved it for 12 weeks between doses. And so when we're having this argument about Moderna and Pfizer vaccine that like oh, gosh, we have to give it between you have to give it three and four weeks respectively. And maybe extending it, if we extrapolate from AstraZeneca would not be a big problem. In terms of immunogenicity.

Chris 31:50
Very interesting.

Matt 31:52
The trial sounds like mess I just I can't imagine right. But like if there was a half dose now we're adjusting the timeframe. Like I think just analyzing the data, there's some probably a roomful of statisticians just losing their minds. I hopefully so.

Monica Gandhi, MD, MPG 32:06
I think they were I mean, the other good thing when you have people who are like a questioning about the data, is that the AstraZeneca was published on December 8, in Lancet, and the Moderna and the Pfizer biotech data were published on the December 30. In the New England Journal, like we have full peer reviewed data to look at, we have 54 page documents, 100 page documents that were submitted to the FDA, like, there is a lot of data there. You know, these are these are well done, studies and we can all look at the data and feel comfortable with it. So I just I'm like, this is like the only good thing happening in the world right now. So let's love that vaccines.

Molly 32:45
Forget about it, it doesn't look likely that the AstraZeneca vaccine will be approved in the US or authorized,

Monica Gandhi, MD, MPG 32:50
you know, I'm I am I'm a little concerned that a won't be because not yet, because of this, it did look kind of fishy with the half dose/full dose, and then like it was a mistake. And they admit it was a mistake. And then beyond that, that somehow the only people got half those photos were less than 55. And so the United States Yeah. It wasn't given to anyone who was older than 65. So the United States AstraZeneca trials ongoing, the US FDA is not going to authorize it until we're done with the United States AstraZeneca trial, and now it will be done in by March.

Chris 33:28
Should we move on to what's going on with Maria?

Molly 33:32
Sure. I actually just have one other question. Are we hopefully gonna get the data that at some point soonish around Pfizer and Moderna if it does prevent asymptomatic spread?

Monica Gandhi, MD, MPG 33:42
Yeah, I mean, it does. So it wasn't it literally wasn't in the design. I mean, you can't go back and swaps. However, they have promised in quote phase four, phase four means rollout to take segments of the population and swap them. And then we'll be able to see if it's if asymptomatic infection is rolled out. So like, for example, health care workers, like a bunch of people are getting swapped. And so we'll be able to know that soon.

Molly 34:08
Yeah, cuz that would be wonderful to take off our mask from Yeah, our goggles. Laughter

Monica Gandhi, MD, MPG 34:13
I mean, I honestly, you know, the thing is, and I really, you know, it's a very interesting thing. Like, if I was in a social gathering, and the two people had been vaccinated, I think you can be very comfortable taking them off. I mean, it's just the truth. But the issue is that we're at the beginning of this rollout, and all of our patients haven't gotten vaccinated yet. And so yeah, we have to keep it on for now, even though we most likely won't pass it on, but we just can't know for sure.

Molly 34:38
Great. So coming back to the case, Maria from Kashlak, and we're talking to her a little bit more. And in reviewing her history, we find out she's on Humira for psoriasis, and she has a history to anaphylaxis to peanuts, and she's considering pregnancy in the next few months. And should we still recommend that she gets vaccinated, so, I know that's a lot of different qualifications there. But just to kind of talk about it what certain populations maybe should not receive the vaccine at this point?

Monica Gandhi, MD, MPG 35:04
No, yeah, I love how these cases they just like have everything. So um, yes. So you know, at this current moment, there's not a single population that probably should not receive it. Now, that doesn't mean that all these groups were studied in the trials. So pregnancy was actually excluded from trial participation, which is, you know, huge oversight. By the way, it just because, you know, the FDA has been saying for years that pregnant and breastfeeding women should be included in such studies, and then they let it pass that there was an exclusion criterion. But um, but on the other hand, the reason that I would not be concerned about pregnancy is because when I think about all the things that we just talked about the mRNA degrading quickly, it's never going to intercalate anywhere, it's not going to be able to go and you know, cross to the fetus, it's, the protein is really specific meaning there isn't anything about the spike protein that looks like a human element. So that you when you produce antibodies against the spike protein, we haven't seen people having autoimmune reactions to natural immunity, for example. So there's just a lot good about the idea that pregnancy, I would really approve it and encourage Pregnant Patients to get it. And then the idea, of course, that SARS COVID is not a good thing to get for pregnant women, there is some evidence that there are more severe outcomes in pregnancy. So all that combined, I would advise pregnant women to get it with the caveat that we didn't enroll them in trials and very sad about that, in terms of HIV. Or being on immunosuppressants, again, there was no subgroup that was big enough to like stratify to say, oh, does it work as well. There was like 176 people enrolled in the 43,000, Pfizer biotech trial with HIV. But there's just no biological reason to think that it wouldn't work as well. And in fact, as you have been, you know, immunocompromised to a certain degree, and it actually depends on what immunocompromised you have, can predispose you to worse outcomes with SARS COVID, too. So, I would encourage immune immunization of those individuals quickly. And then what was her third thing that she had, besides

Molly 37:05
that she has a history of anaphylaxis

Monica Gandhi, MD, MPG 37:07

Yeah, that's actually really important. So um, so, you know, the anaphylaxis issue was really interesting. And it was raised, not in the trial. So actually, went back and looked at the really long documents that were submitted to the FDA, and really saw there was no hypersensitivity reactions in about 21,000 people in Pfizer, and 16,000 people in Moderna, who got either these vaccines, no anaphylaxis, so then you think there's going to be no anaphylaxis. And then it just happened to be like, among the first healthcare workers, there was a couple of episodes of anaphylaxis. I mean, that was really dramatic, because it was kind of coincidental was just when people are getting so much attention on the vaccines, we haven't seen a lot of those anaphylaxis since there's been total of four that I know of. So, it's not like it's really that common, we've given out now, there millions of doses that have been given out. So, it's not at all common. It just was, you know, it just happened in a dramatic way. And so, you think that anaphylaxis is more highly associated with these vaccines. And the CDC put a caveat on them and said, you should sit in the doctor's office and wait for 15 minutes after your vaccine. And in fact, wait for 30 minutes, if you have a history of anaphylaxis to any vaccine or injectable, I think that's overkill, given what we've seen now. And I think for people like health care workers who likely have enough knowledge, I would probably let them leave right away. And you know, they have the knowledge to where you can be concerned about that. And in addition, peanuts, or seafood, or chicken, or egg allergies don't seem to be anything to do with those couple of cases of anaphylaxis. In fact, it's not that at all, it's more that we think it could have something to do with the PEG, which is a polyethylene glycol that was in the that's what's being looked at, at least, that was in the vaccine formulation. So, someone who has a peanut allergy, I'm not worried about them at all.

Chris 38:57
So, my question is about, and this is a question I'm getting a lot of, with our patients, you know, because we're nearly a year into this infection course. I have patients who had COVID at the beginning of the course or even more recently, I had actually had a health care worker who had the COVID vaccine, was diagnosed with COVID a couple days later, because she probably caught it somewhere else. And now it doesn't know what to do about the second dose so that I think I know what you're gonna say about that. What do we do with our patients who've previously had COVID? What do we tell them about the vaccine?

Monica Gandhi, MD, MPG 39:29
Yeah, I mean, you know, the ACIP CDC recommendation said really clearly that if you've had COVID, please try to go more to the back of the line. Because they actually said 90 days, but there was an amazing study in the New England Journal. Just last week, about health care workers who've had COVID. And antibody protection lasts at least six months. So right now, the CDC recommendation is to wait three months before getting it. Not because there's any like severe reaction to yourself. But kind of out of altruism that we need to, we need to, you know, reserve doses for people who need it, and you are protected. If you've had natural COVID, you have natural immunity for at least three months, more and more likely six months and even more likely longer. Why do we only have out to six months, we haven't had this this long, we're gonna keep on looking, it's probably much longer. So, I would really hope, you know, the health care workers or others have had COVID could please wait 90 days after their COVID so that, like their fellow teacher could get it or fellow healthcare worker can get it?

Matt 40:33
And well, we'll get to the side effects are the possible side effects of vaccination later on. But since we're on this topic now of patients who've been who had previous COVID infection, are we seeing increased side effect responses with vaccination with those patients? Is that another population we've looked at? Since they already having more immunogenicity and just feeling kind of crappier after the vaccinations? Or is that not something we're seeing necessarily?

Monica Gandhi, MD, MPG 40:54
That's actually a great, great question, because, as you know, there are many people who don't know that they've had COVID. And so, there are actually some pretty, I mean, to be fair, there's probably more adverse injection site reactions to especially the Moderna vaccine, then there are to the influenza vaccine, and they did not rule out. Well, okay. So, in that infection, in the trial, they did stratify if you had had prior COVID infection or not. And there wasn't, at least in the small number of people that had COVID, more of an injection site reaction. But in the world, it's a great question. If people who have more severe side effects could be having a more profound reaction. Because that anytime you get

boosted with a vaccine, or even seeing the natural infection, you have a very robust immune response. And maybe that's causing more severe side effects. It's very interesting. I have not thought about that. But at least what they looked at in the trials, because they did know some people who had had COVID, it did not look like they had more severe side effects.

Molly 42:04
And maybe we could jump into the side effects what whether we counsel patients that they should expect after the first dose, and then after the second dose?

Monica Gandhi, MD, MPG 42:11
You know, I yeah, I think it is fair to say that there probably more side effects with this than influenza with both of these mRNA vaccines. And the most common side effects were injection site reactions, and they were up to 94% of people in the Moderna trial after the second dose. So, it's pretty it's really, really common, but they're not severe meaning not that many people really called it severe. And even either whether you what's called solicited or unsolicited, so there was solicited and unsolicited, like, did you get an injection type reaction? They're more likely to say yes, but even unsolicited people describe the pain so there is going to be some pain and you know, this whole Tylenol, acetaminophen after vaccines, probably not before, based on how you would know more, Chris, based on the pediatric data, I think we don't give some theoretical aspect about acetaminophen before in kids, but in children, but people plenty 20% of people took antipyretics after the Moderna vaccine, the others that were more common, but still not that common were fatigue, and fever, and headache. So those three, and again, not that common, and not that bad, like the severe side effects were very rare. But a fair amount of people said they had fatigue. And anecdotally, I've had like some coworkers around me, they're like, I like to fall asleep after by vaccine for like, like two hours and it really hurt. So, I don't know, I'm sure you guys are hearing the same thing. But I do think it's a little different than influenza . It's a little more, I like it, because I think it means it's working. And I think you can take antipyretics and I think the main thing to remember is nothing was very severe, and nothing was too bad. And I genuinely don't think for example, they were like rotating them. So, like some people in the ER got it and others didn't just in case you had to be at home. You know, after getting the vaccine, this is in no way that bad. Like it's you can totally work with it. Usually.

Chris 44:10
I would say from anecdotal evidence, I had a colleague who got his got a second dose. And unfortunately, he spiked a fever that night. And then he couldn't go into work in the ICU the next day, because he had to be fever free for 24 hours before he could go to work. So, they did. So, you know, I think that's something that different departments have at least are trying to keep in mind to know that that can happen. So, I think

Monica Gandhi, MD, MPG 44:28
that's fair. And you're absolutely right, that instead of like things getting better after the second dose, they're worse for all for both, both of them that their higher rate of side effects of the second.

Matt 44:38
It's right because I have not been fatigued since probably February of last year. I'm not even sure I know. Like I think I noticed my stopping fatigue more so than doing tired.

Monica Gandhi, MD, MPG 44:47
Now Actually, that's so true. I have a chronic headache.

Molly 44:51
I think it was like 30% of the people in the placebo group had a headache too. So, you're not alone.

Monica Gandhi, MD, MPG 44:56
That is very fair. The problem with many of these trials Including not at these trials naturally as you, you, you solicit them, you ask them if they've had it and like, yeah, people are like people are miserable right now. So yeah, they had side effects. Right? That's a very fair point.

Chris 45:11
Do you mind if I put my peds hat on for a second? So, you know, these?

Monica Gandhi, MD, MPG 45:17
Remember, I didn't get an honors. Laughter

Chris 45:21
Laughter I know, I know. And I know that, for at least the big trials, the phase three trials for these three big vaccines, the two mRNA. And then the AstraZeneca trial, they really excluded basically all pediatric populations. I think the Pfizer trial did go up to go down to like a 16-year-old or Modera. I can't remember one of them went down to 16-year-old but by and large, they excluded pediatrics. Do you have any idea if they're doing pediatric trials or and what to expect on that? And in terms of I trying to reach a herd immunity for like our general population? Is it important to get these children immunized in the future?

Monica Gandhi, MD, MPG 45:57
No, this is a great question. So, in the middle of the Pfizer trial, it got approved to go down to 12. But by the time age of 12, but by the time there was approval, given it just was too late, and that, and the youngest age was 16. And then same in the Moderna. And so, what happened is that this is now currently both vaccines have only been approved for 16 and older. There has been an approval to go forward for pediatric immunization trials. And hopefully they'll enroll, there's some concern that they may not enroll as readily because parents are more - In general, this is not an infection that has as much of a devastating effect on children. And people often weigh lots of things when they decide to enroll their child into a vaccine trial. So right now, only till 16. So, then the way that the CDC is designed, the rollout is there's phase 1a, 1b, 1c and 2. And 1a is of course, healthcare workers and long term care facilities and staff in those long term care facilities. 1b is aged over 75 years old equals or older. And also, really frontline essential workers, like grocery store clerks and public transit workers and teachers and educators, and people who are out food and agriculture, meat processing plants. And then phase 1c is 65 to 74, just period, or 65, to 74, aged 16 to 64, if you have a preexisting condition, and then all the other essential workers, like people are out more like media or communications or it or waterworks, and then two is everyone else. And two means anyone over the age of 16. And so you're right that the way that the current scheme works is a child whose 810 12 will not be vaccinated by these vaccines in this country, it doesn't mean that these trials won't enroll, they won't go forward, and hopefully they will they were approved for the child vaccines. And, and there may be many people who will say You look like you're 16, you know, like, I'm just gonna give this to you. Like, you know, there may be people like you who straddle the world between med peas that you're gonna give your 14 year old this. And then you're right, that herd immunity, which is a very important concept, you know, has to be it really does not require 100% of the population to be immune. It requires. I mean, there's some models that say 60%, I would say the safest way to think of it is 70%. And so between all those people that fit into phase one, ABC and two, and then between the fact that children may have gotten it and got some immunity, and then between the fact that a teacher is actually teaching a child that she her or he herself is immune, I think we will get to herd immunity by the time we get to phase two. And I'm not worried that we have to go out and do little children. That's great question from the pediatric world. It's a great question.

Matt 49:00
Perfect. And then, Molly, how are we with this being?

Molly 49:05
I think we are. I mean, we've covered a ton, this has been great. I would love if we have time to spend just a little bit of time on the ethics. And you kind of open that up with talking about the tiers for distribution. And I know that a lot of people went into thinking about how to decide those tiers. And it just seems like an incredibly complicated thing of how actually that's going to happen in practice. And, you know, does that make the most sense in terms of keeping the highest number of people safe? So I don't know if you have any thoughts about the tears or just insights that we might need to know.

Monica Gandhi, MD, MPG 49:38
I mean, that day when they released the tiers, which was you know, the Sunday after authorization occurred for the Moderna, I could not think of anything else the whole day because I puzzled and puzzled and thought about them and I have to say that I really liked them. And the reason is that the CDC clearly put out Very strong principle at the beginning of the slide set that they put out about the tiers. That said, we are going for both protecting the vulnerable and getting society functioning again. And those are the two hardest things going on right now: is that older people are susceptible to severe outcomes. And so where people with comorbidities, but society not functioning right now, and children not being in school, is getting increasingly impossible for just this much time out of learning, and so forth. And so it was quite a surprise, and not knowing ahead of time that they put teachers and educators in phase one B, which should theoretically start, as soon as and let's admit it, we have had a slower vaccine rollout than we should have, but will theoretically start at the end of January. And that is kind of an amazing concept to get children back to school. And yes, then where the criticism came in is, well, we I'm 74, like I'm I have to wait to 1c, when 75 where's this arbitrary cutoff of not being 65, I thought that was all the older people were going to be put into phase 1b, but the way I thought of it is you can't actually do anything that's perfect. There's never a right way to do things. And I believe this society not functioning grocery store clerks being at risk or meat processing plant workers, or agricultural workers or children not being in school, a lot of that is really difficult and scary for them. And so I kind of liked it, I actually liked it. And I know it's not perfect. And I probably would have tweaked the ages and gone down lower. But I it's hard for me to criticize people who are making such complex decisions. And that, of course, you could go really fast. If we had a different country, you could go really fast. And you can get to 1c, really quickly, aka Israel. And so we need to go faster. And that means, you know, I think when we if we really think about like, sort of the capitalism, how come? I mean, I just to make a comment about capitalism, I think it failed us with our public health response. Because we didn't pay people to stay at home. So people had to go and work, then it really benefited us in terms of two vaccines. One thing to give credit for is the private public private partnership of operation warp speed, which was, you know, which really wasn't impetus, there was a lot of money put into so that was a good thing for capitalism. But Third thing about capitalism is that once people have gotten the CEOs and stock options, and people have gotten money, it didn't actually incentivize anyone getting into the arms of people. And we're so decentralized in this country with our health care, which we really saw, during this pandemic, that we don't have this some central system to just decide how to like do mass vaccination campaigns, how are people supposed to find out? If they're or don't have any insurance, how they get their vaccine? How do they, we can understand that if you do have insurance, you can call your doctor's office and say, Do you have it? Do you have it yet? But what about people who are uninsured or underinsured and so we really need now departments of public health to think about mass vaccination campaigns for their undocumented immigrants for under insurance for medical for Medicare, that the ones that DPH is are responsible for, and I'm envisioning these parks. In in San Francisco, I'm envisioning convention centers in Chicago, big spaces, where you like, go in like you were voting. So we can use voter registration for those who are documented, go in, get logged in, say, while you're in one be and go in and get your shot. And then maybe Wait a minute, 15 minutes if there's any question and go away.

Stuart 53:38
I love that. That sounds great. That sounds like utopia. Can I can I ask about the preexisting conditions I remember sort of early on in the course, there's a lot of hay being made about obesity being risk factor, and things kind of surprises like chronic kidney disease seem to be disproportionately affected. So what, what pre existing conditions are they looking at that will actually put you into sort of the faster track?

Monica Gandhi, MD, MPG 53:56
That's a great question, because they haven't actually specified that exactly. So if you look at another CDC webpage and look at "conditions" that increase your susceptibility to COVID-19, it's some of these that you named but some of them I don't think do so. For example, like you said, COPD, cardiovascular, heart disease, chronic kidney disease, like you said, came out diabetes, obesity, then hypertension to a certain extent, but then on that list, unfortunately, was having ever smoked. And, you know, I mean, say you smoked, like, you know, like in college like I mean, I I'm concerned that that people can get around the rules that I am susceptible. My patient. Yeah, I'm gonna write a little note for them that they really need this because they smoked. So I think by the time that we get to 1C, which is again, when that 16 to 64 year old get on with susceptibilities, get to get it first. I would really try to I hope the CDC will Got a very clean list about what qualifies you. Cancer should be on that list. Chemotherapy and receiving chemotherapy should be

on that list. But asthma hasn't come out clearly as a risk factor, and neither has just the fact that you smoked. I mean, you have to have COPD from your smoking to get to that list. So I hope that gets honed. Right now. It's a little too big.

Matt 55:20
It'll be like seven people left at the end.

Monica Gandhi, MD, MPG 55:23
Yeah, I mean, I keep on thinking that like, it's like it, it's not as if like sub 20 year old is not going to go get it and say they have something right. Like I mean, and that's I mean, so maybe 1C is going to be more of a free for all, but it may. Yeah, well, it's gonna be interesting to see. That's why we need mass vaccination campaigns.

Molly 55:40
Do you have any sense of where that timelines looking right now, like, when those 1C people might anticipate like, March, April or more like May June?

Monica Gandhi, MD, MPG 55:50
Well, so the way the CDC put it out. And this was again, on December 16, it looked amazingly fast, it looked like we'd be done with phase one A, which has helped coworkers by mid January, five weeks, and then we'd start on one B, and then we'd be done with that by mid February, and we'd launch right into one C, like it looked so fast. I think that this audience is aware that now, all reports are on how we are not moving as fast as we thought we should think there's 1.7 million doses in California and 450,000 shots have been given out as of yesterday, that is simply not fast enough with the with what our supply is. So we are struggling with the logistics of our kind of fractured healthcare system, I think, and we got to be get super creative and innovative. And we got to get these out faster. So at least by the CDC timeline, we were going to be done by July for phase two. And I meant like done like phase 1C would have taken a long time. So would have taken from March to June. And then we would have done phase two, and we would have been done. But it's gonna take longer if we go at this rate. So I hope I hope we can think creatively and go faster. Because the vaccines are there. The government bought the doses we have the vaccines, there's not, there's actually not an issue there. we have them.

Stuart 57:06
I'm sorry, if we missed this, but do we have? So let's assume everything is going to go perfectly from here on out? Because by all accounts, I mean, what can possibly go wrong? But do we? Do we have a sense of how long the vaccines will provide immunity? Like, are we expecting waiting? Are we gonna need boosters later on? Does anyone have any idea who's gonna have to sort of play it by ear?

Monica Gandhi, MD, MPG 57:24
Okay, so I think my personal feeling, and I've really looked at the immunity literature, is that it's going to last at least five years now, maybe even 10. Now, again, that's sort of extrapolation for what curves look like, like when you see waning T cell responses. And so right now, it's true that we've only followed out people for say, like, longest six to nine months, and we're seeing still seeing good immunity. And then we're extrapolating that it's going to be five to 10 years. Do I think that we're going to have to have boosters in the future? Maybe, maybe, like five years from now, but I don't think it's never going to be a yearly vaccine. Why? Because the only yearly vaccine that you ever get has a unique property, which is that it has these two little spiky proteins that influenza virus, H and N and they change all the time. And the only reason that we give, you know repeat vaccinations is we have to figure out what strains are circulating at the time. That's not true of Coronavirus. It is true that there is mutations happening. it's not like this hasn't been in the news. And there are like three, I mean, one that didn't get as much attention but the D 614 gene mutation occurred over the summer that made the virus more transmissible then there's this UK variant, B117. That is, seems like maybe up to 60% more transmissible because it causes higher viral loads in your nose. And then there's this South African variant. Luckily, I do not think these variants so far are going to affect the efficacy of the vaccine, though I don't know. the South African one, we have to watch. why? at least the B 117, which is the predominant strain in the UK right now and came to Colorado and then California and is going to be here. It's just a single mutation in the code on and the mRNA that you put in the body is quite a big chunk and it makes your body produce quite a bit of the protein and it doesn't span that

codon and so Pfizer very clearly said you know - it's a proprietary information. Clearly we don't know exactly where the mRNA is, but the Pfizer and Moderna CEOs came out and said, we really do not think that, and they have to know, we really do not think that the efficacy of these vaccines will be reduced by this UK variant. But it speaks to the rapidity about which we have to get these out because if now we have something more transmissible which let's admit it like it seems like something's more transmissible because this surge has been so much faster. We need to get these out because herd immunity - all it means is that the virus is looking around and it can't find anyone else to infect. Or it takes a long time to find anyone to infect. That is the state we need to get there. So, um, yeah, I think it's, it's gonna be every five or 10 years, and maybe that maybe will eradicate it altogether. And we wont need more vaccine boosters that will remain to be seen.

Molly 1:00:21
Well, this has been great. Do you have any other questions, Chris or Paul?

Chris 1:00:25
well, I just have one last question and I like to usually end episodes with sort of like a future looking for things or what are the cool things in the future? Especially a lot of like these mRNA vaccines? Are we going to see, now that we've seen good, you know, possibly great efficacy on COVID-19? Will we see like, other coronaviruses, like the common cold or HIV or, you know, tons of other viruses? I mean, has this opened the door to just like a new way of combating viruses and an infection?

Monica Gandhi, MD, MPG 1:00:58
I think it could, I really think I could so common cold, you know, that's kind of like the see is some companies gonna have to invest in that because people don't care about that. But, um, HIV is the one that I'm most intrigued by, and that happens to be my interest because I'm an HIV doctor. We've been trying to develop a vaccine for HIV, because Tony Fauci is the person who happened to be in charge of that. And so he's been looking for a vaccine elusively for 25 years. He personally, his lab actually works on this. And they've just all failed. And no one's ever tried an mRNA vaccine for HIV. So that was like, one of the first things that came out last week, someone's like, Oh, I'm gonna try this. So I think HIV is the one I'm most excited about. I don't know about you, there's a nature paper in 2018, that they tried it for influenza, and rabies. I mean, it would work for all of these things. And probably we may be able to refine, you know, make better some of our vaccines that don't work very well. Maybe someone should take a look at influenza sometime. Because this getting it every year is a problem. So maybe, maybe it will be looked at for influenza. So influenza and HIV are the two that I would vote for.

Matt 1:02:05
All right, Monica, this has been tremendously helpful, like fascinating. I could probably hear about this for another two hours, but we won't trap you here. I'm wondering if you could give us maybe a few take home points for our listeners. So the really important takeaways from what we talked about tonight.

Monica Gandhi, MD, MPG 1:02:19
I think my takeaways are that these vaccines, at least the mRNA vaccines have effectiveness, and I'm using that word because it was one outcome, beyond my wildest dreams. I did not think that we'd have 95% effectiveness, I thought it'd be 70%. And this this is these are very highly effective vaccines against one of the most important things that can happen, which is getting sick. So I'm really excited about these vaccines. I think they're gonna work and I think they're gonna work well, and I think they're gonna give durable immunity. Number two is that they just mechanistically there's not anything about them that's scary or scientifically sci fi or anything that, you know, I would worry about having long term side effects in the future. They just scientifically, I think they're going to be very safe. And three, I would as internists, you know, my biggest goal would be to reassure patients that so sorry, it's not here yet for you, but as soon as it is, I'm gonna let you know because I think these are wonderful vaccines and then four is whether there's a delay between the first and second dose or not. Both doses have to be given.

Matt 1:03:27
Great. Thank you so much. This was fantastic.

Monica Gandhi, MD, MPG 1:03:29
Okay, thank you.