Ruth Adewuya, MD:

Hello, you're listening to Stanford Medcast, Stanford's CMEs podcast, where we bring you insights from the world's leading physicians and scientists. If you're new here consider subscribing to listen to more free episodes coming your way. I am your host, Dr. Ruth Adewuya. This episode is part of the COVID-19 mini series addressing up-to-date insights on COVID-19. In today's conversation I'm joined by Dr. Bali Pulendran. Dr. Bali Pulendran is the Violetta L. Horton Professor of Pathology and of Microbiology at the Stanford University School of Medicine. Dr. Pulendran's work focuses on understanding the mechanisms by which the innate immune system regulates adaptive immunity and harnessing such mechanisms in the design of novel vaccines against global pandemics. Dr. Pulendran, I have been looking forward to our conversation today on vaccines and immunity, thanks for chatting with me.

Bali Pulendran, PhD:

Well, Ruth, thank you so much for inviting me to this conversation. It's such a pleasure to be with you, and I'm so thrilled that you're actually doing this podcast on COVID vaccines.

Ruth Adewuya, MD:

Fantastic. I have a lot of questions and I would like to cover a lot of key themes around this issue. So I'd like to jump right into our discussion and I wanted to start with a term that I've heard a lot in the news and clinicians have been talking about when it relates to vaccines. People have been talking about Operation Warp Speed, I would love for you to be able to share with us, what is Operation Warp Speed as it relates to COVID-19 and vaccines?

Bali Pulendran, PhD:

Operation Warp Speed is a major initiative, it's undertaken by the United States government in partnership with companies. Essentially the US government launched a Manhattan Project style project called Operation Warp Speed, and really the broad goals of that project are to deliver several million doses of the safe and effective COVID-19 vaccine, they say by January, 2021. And really this is part of a much broader strategy to accelerate the development, manufacturing, and distribution of a portfolio of COVID-19 vaccines.

Bali Pulendran, PhD:

So this is led by the US Department of Health and Human Services in partnership with the Department of Defense. And it's just been a tremendous effort in the sense that it truly galvanized the development of COVID-19 vaccines. And this is progress at a pace that is unprecedented in the history of vaccines. Typically to develop a vaccine from a concept to a phase three efficacy trial can take years, typically five or more years and sometimes as long as 15 years. What's happened under the auspices of Operation Warp Speed is that this timeline has been considerably shortened.

Bali Pulendran, PhD:

I have to tell you that the traditional vaccine development paradigm that involves preclinical testing in animal models followed by clinical testing and phase one, phase two, phase three clinical trials typically takes years, sometimes up to 15 years. But what's very unique about Operation Warp Speed is that this entire process has been accelerated tremendously. So that it's happened in a matter of months from the first identification of the SARS-CoV-2 virus, sometime in January of 2020 to where we are now, which is a number of phase three clinical trials in progress. It's been what, 10 months? That is truly

unprecedented in the history of vaccines. So that's what Operation Warp Speed is, As I say, its goals are truly ambitious to deliver tens of millions of doses of SARS-CoV-2 vaccines by the end of the year, early next year, and as many as 300 million doses, hopefully by middle of 2021.

Ruth Adewuya, MD:

Thank you so much for that overview of Operation Warp Speed. And we've all been hearing about different press releases of several companies that are racing to come up with the vaccine, and the first vaccine that would be available. Are you able to share with us kind of at a high-level which vaccines are currently in phase three trials, and maybe even what are the differences between the types of vaccines that are being developed right now?

Bali Pulendran, PhD:

Yes, I think first we should discuss what exactly phase three clinical trials are. So phase three clinical trials typically involve tens of thousands of people, and the goal of the phase three clinical trial is to test whether the vaccine really works. In other words, how efficacious is it? So what happens is that people are given the vaccine or a parallel group of people are given what's called a placebo. Placebo is any substance that you inject, but that doesn't evoke an immune response, so it's a control. And the ultimate goal of the phase three trial is to ask, what was the incidence of disease in the vaccinated group compared to the placebo group? And then you can calculate the efficacy of the vaccine based on that data.

Bali Pulendran, PhD:

There are currently eleven vaccines that are being tested in phase three clinical trial. In the United States we have several candidates, so I'm sure our listeners have heard of the Moderna messenger RNA vaccine, which Moderna developed in partnership with the NIH. There's a phase three clinical trial that's ongoing with 30,000 subjects, including 7,000 people over 65 years old. Another messenger RNA vaccine candidate is the vaccine developed by Pfizer in collaboration with the European company BioNTech, And this phase three trial involves some 43,000 people in the United States and in other countries. And I think earlier this month, Pfizer announced that it had received FDA approval to enroll children in this trial, children as young as 12 years of age in their trial. So this expansion is aimed at understanding whether the vaccine would be safe and effective in the adolescent population as well. So those are the two messenger RNA vaccine candidates that are being tested in phase three trial.

Bali Pulendran, PhD:

Then we come to the viral vectors. So these are DNA constructs made from viruses in which you can express a gene in coding with SARS spike protein antigen. And really the two viral vector candidates that are being tested in phase three clinical trials are the ones developed by Johnson & Johnson, and this candidate has been developed in collaboration with scientists at Beth Israel Hospital. And it has provided protection in experimental models of COVID in monkeys, and so Johnson & Johnson are conducting a large phase three trial with 60,000 people. And what's unique about this particular vaccine is that it is the only vaccine candidate that only requires a single dose rather than two doses. You see all the other vaccines so far require two doses to see really strong immune responses and protection in non-human primates. So the other viral vector candidate is the one that's being developed by AstraZeneca in collaboration with Oxford University. And again, this candidate showed efficacy in the non-human primate model. Currently the phase three trial is ongoing in United States and some other countries, I think Brazil and South Africa.

Bali Pulendran, PhD:

And then finally we have the recombinant antigen. So recombinant antigen is essentially a protein from the SARS-CoV-2 virus that is used as your vaccine candidate, and this is given with something called an adjuvant. Now, adjuvant is a substance that is added to a vaccine to make the immune response stronger and last longer. So the recombinant vaccine candidate that's being tested currently in phase three trial is one made by this company called Novavax, which is a Maryland based company. And so again, they are very promising results in monkeys and in the phase one trial in humans, so that's ongoing. And then the other recombinant vaccine candidate that will be tested in the coming months in the phase three trial is the one that's being made by Sanofi in collaboration with GlaxoSmithKline, so that's another recombinant protein antigen candidate. And again, they're using an adjuvant developed by GlaxoSmithKline called, AS03. So those are the phase three trials that are ongoing in the United States currently, but there are others in the pipeline as well.

Ruth Adewuya, MD:

Are the vaccines that are currently in phase three clinical trials being developed to be age specific? I know that you mentioned that there was one of them that got permission to include children.

Bali Pulendran, PhD:

We should clarify that the vaccine that we mentioned that had FDA approval for testing in children, these are the children above the age of 12, okay? So they're not for infants or they're not for neonates but these are for preadolescence. Now the majority of vaccines are currently being tested in the healthy young adult population between the ages of 18 and 45, some of them are also being tested in people above the age of 65. So I think the initial focus is on assessing the efficacy of vaccines in these two populations. And the question of whether they would work as well in children, that is something that will be addressed in followup studies. Right now I think the major focus is on assessing the efficacy of these vaccines in the healthy adult population or in people above the age of 65.

Ruth Adewuya, MD:

I think that's interesting though, because for all intents and purposes, when they started talking about people who were at risk for it or more at risk for it, we were talking about people over the age of 65. So I think it's interesting to me then that the vaccines that are currently being developed are kind of initially focusing on an age range that is below that, is that odd or is that just the norm in terms of how vaccines are developed?

Bali Pulendran, PhD:

Typically what happens in vaccine development is that one tests your candidate vaccines in the healthy young adult population, and then extends this to other demographics such as the very young or the very old, and so that's what's happening here. What's encouraging though, is that based on the phase one study data from say, for example, the Moderna vaccine, the immunogenicity of the vaccine, in other words the strength of the immune response induced by the vaccine appears to be quite similar in the healthy young adult population, as well as in people above the age of 65. So that's an encouraging sign that these vaccines could work quite well in both these demographic groups.

Ruth Adewuya, MD:

You had mentioned earlier, that kind of two goals, if I understand you correctly, two goals of vaccine, one is preventing against severe COVID infection and one is protection against infection. When you look through these vaccines that you've mentioned that are currently in phase three trials, generally speaking, are they trying to do both things or are some vaccines kind of focused more on protection versus symptomatic uses?

Bali Pulendran, PhD:

That's a great question. I think virtually all of these vaccines, the phase three trials aimed at testing protection against the development of symptomatic disease and with a particular emphasis on severe disease. However, it's possible that at least one of these candidates will also plan to look at protection against infection. As I said, that's more difficult because of course it's easy to see who are these subjects who have developed disease symptoms. You get sick, you exhibit many of the symptoms of COVID, right? But it's much, much more difficult to ask, well, there are these people who have been prevented from infection because there's no overt symptoms in the majority of cases. As it turns out, I believe that at least one of these candidates may plan to look at protection against infection. That's also relevant from the perspective of the immune response that's induced by these vaccines you see, because the kind of immune response you would need to ameliorate symptoms may not necessarily be the same kind of immune response that you need to prevent infection.

Ruth Adewuya, MD:

So can we talk about that in terms of what kind of immune response would be needed for protection?

Bali Pulendran, PhD:

I think the major mechanism by which the immune system fights against infection and in the control of virus is the neutralizing antibody. And that is the method or the mechanism by which the vast majority of our successful vaccines against a whole range of different infections have been developed. And so if you look at all the licensed vaccines that are so effective in fighting other infectious diseases like measles or chicken pox or mumps, or smallpox, or yellow fever, all of these vaccines work so well because they use and maintain a high enough level of neutralizing antibodies.

Bali Pulendran, PhD:

Of course, in some vaccines in some cases, especially the live viral vaccines, such as smallpox, yellow fever, measles, they also induce T-cell responses that work hand in hand and they synergize with the neutralizing antibodies to control infection. So the aspirational goal of COVID vaccines is to develop vaccines that induce a high enough titer of neutralizing antibodies and to maintain that titer for some period. Some of these vaccine candidates also induce cytotoxic or killer T cells that can synergize with the antibody response to prevent and control infection.

Ruth Adewuya, MD:

There have been some cases, or at least I know at least one case I think in Hong Kong, and you can correct me if there's more since then, where there's been re-infection after COVID-19 recovery. So my question is, does infection with COVID-19 induce natural immunity, and if so for how long?

Bali Pulendran, PhD:

That's a terrific question, I'm glad you asked that because it's something that's been discussed quite extensively, not only in the scientific community, but on social media so I think it's a good opportunity for us to talk about that. This question of whether there can be reinfection with COVID-19 is a very important one because it goes to the heart of the issue of whether we acquire natural immunity to infection and how long lasting this is. Natural immunity is the fundamental feature of the immune system against many viral infections, such as measles, mumps, chicken pox. The half-life of the antibody response against measles virus has been calculated to be 3000 years. So that is why when people, some of us now, fortunately we have a very good measles vaccine, but back in the old days when we didn't have that, many of us developed measles when we were very young and then we were effectively protected for life because the immune system remembers that, there's natural immunity.

Bali Pulendran, PhD:

So the question is, is the same true for coronaviruses? And the answer to this question is not so clear. Well, there are multiple strands of evidence. You see, there are animal model studies in monkeys where people have infected rhesus macaques with SARS-CoV-2, and then after about a month, reinfected the same animals for the same virus and they show significant protection. It's not sterilizing protection, by sterilizing protection I mean there's no virus that enters the body. There's a little bit of virus that does infect, but it never seems to establish very strong infection, so it's cleared after a few days. So this suggests that at least in this animal model, that infection with SARS-CoV-2 does induce some natural immunity against reinfection. Although the caveat here is that reinfection happened so quickly after the initial infection, only one month and one month is not a very long time.

Bali Pulendran, PhD:

Then there's evidence from what we called controlled human infection studies, not with SARS-CoV-2 but with other coronaviruses. As our listeners might know, many of the common cold viruses are also in the coronavirus family. So these are viruses such as [inaudible 00:18:43] 229E or OC43. So what people have done, and this happened in the mid 1980s, early 1990s in England, they did controlled human infection models. So these are healthy humans who were deliberately infected with one of these common cold coronaviruses, And then after some time they were reinfected with the same virus after about a year or so. And the data from those studies suggests that infection does induce some natural immunity, but maybe not a very persistent natural immunity, nothing like what we might've expected from measles or chicken pox or mumps.

Bali Pulendran, PhD:

And then finally, as you mentioned, we have the example of reinfection with SARS-CoV-2 itself. You mentioned the individual from Hong Kong, I believe this happened sometime over the summer, where there was an individual who had an initial bout of infection several months ago and then was reinfected. And it was a bonafide re-infection because they could sequence the virus isolated from this individual and show that the genetic sequence of the virus that caused the reinfection was so different from that that caused the initial infections, it wasn't as if there was some lingering virus that hung out in the body for some time, it was truly a re-infection. What was interesting about that individual in Hong Kong was that reinfection didn't cause any symptoms, so this person was asymptomatic. In fact, he wouldn't have known that he was reinfected, except for the fact that he was returning from Europe back to Hong Kong and he was tested at Hong Kong Airport, and then they realized that he was positive so then he was admitted to the hospital and monitored.

Bali Pulendran, PhD:

So since that time there have been a few other documented cases of what appear to be real re-infections. There was an individual in Austin that also appears to have been reinfected and then a couple of other cases. And unlike what we have seen with the case in Hong Kong, some of these other individuals did develop symptoms upon re-infection. So it's not clear whether the initial bout of infection had used any level of immunity, that clearly it hadn't induced immunity to prevent infection [inaudible 00:21:09], but it's not clear whether the immunity was sufficient to prevent symptoms. So it's still very early days, as I've said, there are multiple strands of evidence suggesting that there could be some natural immunity, but how long lasting it is and whether people differ in the capacity for the immune systems to launch natural immunity is still unclear.

Ruth Adewuya, MD:

We know that flu vaccines are roughly around 40 to 60% effective. One, I'd like to get your thoughts on that in general, just because when else will I get a vaccine expert to talk to me about that. But also what does that mean for COVID-19? Is that the win for us, 40 to 60?

Bali Pulendran, PhD:

That 40 to 60% is better than 0%, right? I mean, imagine we were doing a test, if we got 40 to 60%, it's not a very good score but I would certainly be happy compared to somebody who got 0%, so I think we need to view this as the context. Every year, the World Health Organization sets up a team of scientists and clinicians who analyze epidemiological data that they receive from health authorities throughout the world, in terms of what particular strains of flu viruses are circulating during that season. And based on this, then they make a guess, if you will, an informed guess, a recommendation that they then provide to the vaccine companies to say that their guesstimate is that the vaccine companies should include these three or four strains in their flu vaccines. So this is what is subsequently produced and then given to the public.

Bali Pulendran, PhD:

Now, very often the guesstimate made by this body of clinicians and scientists is quite good, so there's a very good match between the flu virus strains that are circulating and the ones that are contained in the vaccine. So when there's a good match, there's good efficacy. Good efficacy could mean anything above 60%, that's a pretty good efficacy. Now the question is, even if there's a good match between the vaccine strengths and the circulating strains, why is it that we only have a 60% efficacy sometimes, why not a 99% efficacy? So I think the reason for that is that the seasonal flu shot that we get is not a very strong vaccine compared to some of these other live viral vaccines. Firstly, it doesn't give you long lasting immunity. If you get the flu shot today, you would develop really a good antibody response that would protect you for some time, maybe three or four months, but it really doesn't last very long.

Bali Pulendran, PhD:

The other reason is that we talked about different populations, the very young and the very old, the efficacy of the vaccine can vary quite dramatically in these different demographics. You see the immune system in the elderly population may be going through what we call immunosenescence, so the capacity of the immune system to respond strongly and robustly against the vaccine may be diminished as people get older. So in such cases, what you need is an adjuvant, an immune boosting agent that can be added to your vaccine to boost up your immunity, and that's not contained in the seasonal flu vaccine.

So these are some of the reasons why the efficacy of the flu vaccine can vary quite substantially from year to year.

Ruth Adewuya, MD:

Does that have any implications for how the COVID-19 vaccine is being developed?

Bali Pulendran, PhD:

The same principles apply to the development of any vaccine. So we talked about how strong of an immune response, can you induce, how long lasting would this immune response be, the same principles applied to COVID-19 vaccines. So that is why this issue of durability has featured quite prominently as we think about COVID-19 vaccines, because in the vaccines we've discussed the messenger RNA vaccine, the viral vector vaccine, the recombinant protein vaccine, the neutralizing antibody response is at one month after vaccination, it looks pretty good. The question is how long lasting is that going to be? And that's an uncertainty, we don't know that. Why don't we know that, just because it's just been so recent, how can we? I mean, we only develop these vaccines just four months ago. We've only be testing them in phase one and phase two trials for a very short time.

Bali Pulendran, PhD:

So that's an uncertainty, how long lasting is it going to be? That's where this concept of the adjuvant, adjuvant are substances that you can add to a vaccine that can induce the strength, but also the durability. That's going to be very, very relevant here to you to see whether those adjuvant can actually not only amp up the immune response, but maintain it for quite a long time.

Ruth Adewuya, MD:

We just started developing vaccines a few months ago and we talked about Operation Warp Speed, which in enough itself the title says that we're moving very, very, very quickly. I have a question about safety because my understanding is vaccines usually take a long time to develop, sometimes years, if I'm not mistaken. And now with this COVID-19 vaccine we're moving through the phases, at least to the outsider, who's not in it... And you could correct me if I'm wrong, it seems like we're moving through it in a matter of months. Do you have any concerns about safety or how would we know that it's safe?

Bali Pulendran, PhD:

It's very understandable that people may be worried that vaccine development has been rushed through and shortcuts might have been taken. But I think what we need to understand is that although the process of vaccine development has been accelerated under the [inaudible 00:27:05] of Operation Warp Speed, it's occurred without compromising safety or product quality. We have one stand why and how the timeline has been so accelerated. I think there are two main reasons. One is that the development of new technologies such as the messenger RNA technology meant that you could literally go from the identification of the genetics sequence of SARS-CoV-2, which happened sometime in January of 2020, to the first testing in a phase one trial within the matter of 60 days or something, that's unprecedented. So that acceleration happened simply because it was this messenger RNA technology, you didn't have to produce GMP material of your protein, you didn't have to express it in the cell line. So that was a major step in enabling this accelerated speed.

Bali Pulendran, PhD:

But even more important than that is the fact that the government was able to provide financial resources to allow the vaccine companies to make their vaccines, GMP quality vaccines that could go into subjects even before the results of their clinical trials became apparent. See, normally what happens is that there's a sequential process. First you test in animals, such as mice and non-human primates. After you get the results of that then you go into a phase one trial, which can take a year or longer. After you get the phase one trial, then you start your phase two trial and which can take several years. And then once you know the results from your phase two trial, then you start your phase three trial, and then only once you know the results of your phase three trial do you now start making a vaccine, so it's a sequential process.

Bali Pulendran, PhD:

What happened with Operation Warp Speed was that the US government said, "No, we are willing to provide financial resources for these companies to manufacture their vaccines in parallel with the phase one, two, three clinical trials." So effectively it was financial de-risking of the companies.

Ruth Adewuya, MD:

So given the advancements of technology and what you said around this parallel development of things, realistically, do you think we would have a vaccine in January of 2021?

Bali Pulendran, PhD:

Well, I mean, since I'm not in the process of making any of these vaccines, I can only by what I've heard from Dr. Moncef Slaoui, who is the head of Operation Warp Speed, and some of the other vaccine manufacturers from what I gather the goal is to make available at least several million doses of vaccine by the end of the year, ultimately building up to 300 million doses by the summer of 2021. So I wouldn't be surprised if by the end of the year, we have several million doses for emergency use authorization for certain high risk populations, such as healthcare workers for example. My hope is that by the summer of 2021, the vast majority of the population, not just in the US but in many countries would have had access to vaccines and that the vast majority of people would have been vaccinated.

Ruth Adewuya, MD:

To close out our conversation my question to you is what can clinicians say when having conversations with patients that will allow them to overcome those fears?

Bali Pulendran, PhD:

I believe that it is important for clinicians and for us scientists to engage with the non specialists and with the public in this discussion. We're all in this together, we're all learning together, and I think there shouldn't be any barriers of communication. So that means it's important for the clinicians to keep up to date with the data that's emerging about the safety of these vaccine candidates and how effective they are at controlling or preventing infection, and to discuss this with their patients or with the public.

Bali Pulendran, PhD:

You see, I think there's nothing complicated here. I mean, the science of it could be explained to a nonspecialist in a way that they could understand and engage in this discussion. I feel that it's really a paramount importance for us scientists to do this and learn together because I think the whole vaccine landscape is so dynamic and evolving so rapidly, there are so many trials on the horizon, sometimes it

can be overwhelming for the non specialists to look at the media and try and understand what's going on. So I think it's all the more reason why we scientists and clinicians should really reach out to the lay person and to engage in a very constructive and productive discussion and to understand the very understandable fears and hesitation that people may have in taking some of these vaccines.

Ruth Adewuya, MD:

Well, thank you so much Bali for sharing your insights on this topic with us today.

Bali Pulendran, PhD:

Oh my pleasure. It's been wonderful talking with you.

Ruth Adewuya, MD:

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