

COVID 19 in South Asia – A Practitioner’s Workshop Tests and Vaccines

Transcript Begins:

Salman Rafay: Hello everyone, Thank you for joining both in the U.S and in the South Asia region. My name is Salman Rafay, I'm the program coordinator at the Mittal institute at Harvard University. I'm one of the main partners for hosting this workshop series. I'd like to give thanks, in a moment, to our speakers, but also to our partners on the series, namely the Lancet Citizens Commission, on reimagining India's health system, Harvard T.H Chan school of public health, and the Swasth community science alliance. This is the third part of a three-part series aimed towards practitioners in the region, who are currently on the front lines of what is one of several waves of the COVID pandemic, and we want to host a series of scholars and practitioners from around the world to give a series of best practice-style advice sessions to those on the front lines dealing with the pandemic. As mentioned, this is the third part in the series, following parts from the past couple of weeks. This particular session is going to focus on tests, vaccines and variants. Moderating today, previously we had Manoj Mohanan from the Duke university scheduled to moderate, but due to a last minute change of plans he was unable to attend. However, we very gratefully have Shitij Arora, who was a previous speaker during part two, for stepping in to moderate. Shitij is an associate professor of medicine from the Albert Einstein college of medicine, and I'll turn it over to him to introduce the rest of our panel, and to moderate our session. Thank you all for joining us.

Shitij Arora: Thank you. Thank you Mittal institute. Thank you everyone for joining. We have an absolutely fantastic session ahead of us. The topic is extremely interesting, it's focused on testing vaccines and variants, something which is of particular interest in where we stand today in this pandemic. And, we have an absolute star line-up. I'll introduce them. We have Anu acharya. Anu is the founder and CEO of Mapmygenome, a leading genomics company headquartered in India. Previously, she founded Ocimum bio solutions in the year 2000. With 20 years of global genomics experience, and whose companies have been involved in infectious diseases like TB, COVID, H1N1, along with personal genomics and clinical genomics. Welcome Anu, thank you. Then we have Priya Sampathkumar. Dr Sampathkumar is a consultant in the division of infectious diseases at Mayo clinic in Rochester, in Minnesota in USA. She leads the infection prevention and control program at the mayo clinic. Then, we have Rebecca Kahn. Dr Kahn is a post doctoral research fellow in the center for communicable disease dynamics at Harvard TH Chan School of Public Health. In her research, she uses infectious disease modelling to enhance epidemic preparedness and response, with a focus on vaccine trial design and analysis for emerging infectious diseases. Prior to her graduate studies, she worked with the US President's emergency plan for aids relief and for partners in health in Sierra Leone, and on the ebola response and health systems rendering programs. Welcome Priya and Rebecca, it's great to have both of you here as well. I'm Shitij Arora. I'm an associate professor in medicine at the Albert Einstein College of Medicine, new York. My focus of research has been corticosteroids in COVID-19 over the past year, and more recently I have been studying Mucor mycosis and the clinico-epidemiologic factors associated with it. So, I'll be moderating the session today. For all our audience, thank you for joining and please feel free to use the chat session for questions and answers, and we'll be happy to address it at the end of the talk.

So, there will be three segments today - Testing, vaccine and variants. The first segment would be testing, and the first question under that segment is- "What are the types of tests available in India and Southeast Asia? And this question is for Anu.

Anu Acharya: Right, thank you Shitij. So, if we just had to look at the types of tests that we typically find in India for covid, I think there are three main categories of tests. One is to actually find and detect the antigen. There are many types of tests that we have, which are antigen based tests, and then you have the ones that are more indirect, trying to find the antibodies. And the third, of course, is blood tests, and CT scans, and other things that we want to sometimes use in conjunction with these tests in case the report is inconclusive. So in India, I think since the start of the pandemic when we had very few tests. I think today you find that if you look at the broad category of the antigen tests for instance, which includes your RT-PCR, your LAMP and CRISPR and variety of different techniques to be able to do that. I think RT-PCR is the gold standard, and has been used in, you know, there are about 167 odd test kits that have been approved for use in India, and at the start of the pandemic, we had very few, and now I think we have, you know, it has come to a point where we pretty much have a choice in terms of what kind of test kit that you want. There are tests that cover many different parts of the regions of interest. We also have what are the point of care sort of devices, and these are extremely useful in situations where you need to do quick reporting of results. So you have tests like the ID now from Abbott. You have the gene expert, and you have trunact, which are the three main categories of the point of care devices for rapid testing which uses either an isothermal way of testing or a PCR based test. So that will be another category of tests that are there. There are also tests that have been approved which use CRISPR as a backbone. So there is the feluda test, that has been developed by IGIB. And then there are the rapid antigen cards which are used both, a large number of them, I think about 60 or 100 or so tests, are approved and most of these are the ones that you would use in a lab with the person actually taking the swab, but there are three tests that have recently been also been approved for testing at home, and then that would include like my lab and also there's another one called merit. So those would be the broad category of antigen based tests that are being available in India. I might have missed one or two categories that might have been there, and then of course there are the antibody tests, and then in the antibody tests we have, most of the commonly used antibody tests would be the ones that you would go to a lab and get your blood drawn and get the test done for IGG typically. So some do IGG, some do a combination of these different IGGs, but also you can find neutralizing antibody tests, and you would also find that there are the rapid cards as well. So, you know, that would be these two categories, and of course, the third category I'm not really going into details, but the blood based test. So in case a doctor finds that you've got a negative RT-PCR, but you still have symptoms, they are likely to also recommend a few kind of blood tests like a CRP, d-dimer and IL-6 or even an HRCT. So that would be dependent on mostly for symptomatic patients, but maybe I think that would be a good start to at least that sort of broad set of tests that are available in India.

Shitij Arora: Yes, absolutely. So we have antigen based testing, antibody based testing and the conventional RT-PCR which is how we how we started. Are these freely available even in rural areas and semi-urban areas?

Anu Acharya: So, I think in cities like Hyderabad, and Delhi and all, it's very freely available. You have a choice of labs, you have a choice of technologies and everything. Of course, during the second wave that had become a little bit of challenge in a few cities like Bombay and Delhi, but I think in large, over the last one and a half years it has not been very difficult to get access to a test once testing became more freely available. Especially in the last, I would say, seven or eight months, it's not been, and it's also become very affordable. But when you look at rural testing, and a lot of the testing in some of the smaller towns, I think many of them still don't have a lot of the RT-PCR capabilities over there. And while that has changed tremendously, I think when the start of the pandemic I think very few labs actually could do an RT-PCR. But I think today there are more than 2,300 or so labs that that can do an RT-PCR, which means that, and I don't remember, I didn't see it in the last couple of months, but I think that's sort of the scale that we have developed over the last 18 months or so. So there is a significant increase in the amount of testing that has happened, but a large majority of the tests done also in the rural areas and other places are also antigen based tests. And that is both good and bad, because of sensitivity issues and other things, but at least there's an availability when it comes to testing that can be done. And I think the introduction of home based testing has brought about a little more change in terms of how people can access these tests especially in remote areas.

Shitij Arora: That's very good to know. With these multiple forms of testing available, are there specific scenarios where one test would be recommended over another, Priya?

Priya Sampathkumar: So yes, like for diagnosis of infection of, you know, with COVID, like Anu was saying, a PCR is the gold standard. It's probably the most sensitive test and you can also have different specimens that you test by PCR. A nasopharyngeal swab tested by PCR is probably the most sensitive test. Under other circumstances you can use the other tests, including the antigen test. They generally lower sensitivity, but the advantage is that the test comes back quicker. You get results quicker. So during the second wave in India, although tests were available, I know that for the PCR test sometimes there was six-seven days delay in getting the test results. So under those circumstances that, you know, the testing is not very useful and most cases were actually diagnosed by symptoms. Anyone with fever and respiratory symptoms was assumed to have COVID, and almost always the test did come back positive, but it was six or seven days turn-around time. So, the advantage of the antigen tests are that they are much more rapid. If they're positive, they're very helpful. Especially when bed availability was low and you needed a positive test in order to find a bed, having that rapid antigen test was very helpful. Because of the lower sensitivity of the test when you have a negative test on a rapid antigen test, it doesn't rule out COVID. So that's something that you need to keep in mind and, you know, follow it up with a PCR test, if you truly think that a patient has COVID, if you're able to. These at-home tests can be very helpful for control of outbreaks because if you do a test at home, you don't have to go out, stand in line, wait to get a test done and potentially expose other people. So these at home tests, although they're not as reliable as the lab-based PCR test, they have a role to play in reducing exposures and especially if they're rapid tests that come back quickly, which all the home-based tests are, then you can immediately, you know, ensure that you're staying in isolation, inform people that you might have exposed, and all of that helps to prevent further transmission. So, gold standard test PCR, that's what you would do for a hospitalized

patient, but the rapid antigen tests and the home-based tests especially also have a significant role to play.

Shitij Arora: Thank you Priya. That's very interesting. You know, we have been fascinated by PCRs and just because they're so sensitive, but with this emergence of home-based testing, compromising a little bit on the sensitivity, it does bring an important question up for Rebecca next. Should we just have adopted these home-based tests sooner to have a better control on the outbreaks at a community level? Would that have been a reasonable strategy?

Rebecca Kahn: Yeah that's a great question. And thank you so much for having me today. So, as the others have mentioned, I think, you know, testing is critical for achieving epidemic control particularly in the absence of widespread vaccination and the earlier people can figure out they're infected and take the necessary precautions, the better. But as Anu mentioned, you know, there are many barriers to testing, you know, transportation, the time it takes to get to a test, the availability of testing and then, as Priya mentioned, the delays and results especially for the PCR tests. So I think home-based tests are a really important tool that can overcome a lot of these barriers and permit more frequent testing. So as is mentioned, PCR is the gold standard, but often the choice is not between, you know, PCR and a lower sensitivity test. The choice is between a lower sensitivity test, versus no test. And in this case, you know, I think home-based testing can be a really important tool. Many mathematical models including some that I've worked on, have found that the frequency of testing or the turnaround time of testing can be much more important in controlling epidemics than the sensitivity of the test, because, you know, with COVID a lot of transmission occurs early on in infections, so the earlier people can know that they're infected, the more transmissions that can be prevented. So, you know, I think sensitivity is a really important factor, although I think it's important to kind of distinguish between sensitivity for any infection. You know, PCR tests can pick up infection with very low levels of the virus, kind of long after people are infectious, and I think when you compare sensitivity for when people are infectious, they become a little bit closer together and more similar in terms of the characteristics of the tests. So, well, I think there are limitations with the costs of home-based tests right now. I think they can provide a really important tool for giving people kind of the ability to have a little bit more ownership over understanding their infection status, and to take precautions. But I do think it's also important to keep in mind that, you know, if people do test positive, that there are resources to link them to care, if needed or to help support isolation, if that's the next step.

Shitij Arora: Thank you Rebecca. And this is a very interesting point which I would like to reiterate. So, the fact that an RT-PCR is positive, it is a very sensitive test but it could be the case that this positive RT-PCR does not mean that this individual is infectious or very capable of spreading infection. But this home-based testing when, although the sensitivity is less, they might be picking up disease at a level where the individual could actually be infectious. So, at a population or a community outbreak level, these tests would not be a compromise on RT-PCR. Is that fair to say?

Rebecca: Right, yeah. I think, you know, it depends on the specific characteristics of each test, but I do think, yeah, thinking about it in terms of sensitivity for infectiousness is important.

Shitij Arora: Thank you Rebecca. So now that home-based testing is available

Anu Acharya: Sorry, I just wanted to add one thing, the only challenge is, if it's an early infection, you would not pick it up with the antigen. So sometimes, in communities, if you are going to isolate based on just purely antigen, then it becomes a challenge because you might be leaving people out because within a day or two they might become infectious. So that's the challenge. Of course, it's okay in the later stage, but in the early stages that's a problem.

Shitij Arora: I see. And in terms of costs, so how much are these home based tests versus RT-PCR, how much, what is the price difference or how much do they cost?

Anu Acharya: So, the home based tests, there are three. I know the cost of one of them. So, one is priced at 250 rupees, which is barely three dollars something, so that's inexpensive. But I think RT-PCR is also not expensive, I think in most of the places, I think the cost is between 500 to 800, is the standard cost of an RT-PCR if you go to a lab. So, that's not too bad I think, if we look at where we are, you know, turning it around for the airport, for instance, I think then the turnaround is also not too bad. It's usually four to six hours, or maybe a little bit more. So, I think it depends on your, you know, one is the cost is not that much, but the point of care on the other hand, I think majority of them are expensive. And I think that is in some ways justified, because you do one test at a time, versus an RT-PCR, where you can do 96 at a time. So, I think that's probably the trade-off that you have, that if you had to do something in 15 minutes and someone was in an emergency situation for travel or wherever else, then you do a point of care. But if you wanted to do an RT-PCR, I think if you had at least let's say seven-eight hours, then that's a better option because you will probably get the best between value and the cost of these tests. So that would be, I think, approximately what I would look at. The point of care tests are probably around three thousand to five-six thousand rupees on average. So that is that would be approximately what you'll be seeing.

Shitij Arora: I see. So, thank you. With that, we'll move on to our next segment, which is on vaccines, and I know there's a lot of interest around it. So the first question is the very obvious question, "what vaccines are approved for use in India now or about to be?" Anu?

Anu Acharya: So, there are five that have been approved I think. There is the first two that are approved and mostly widely in circulation, the Covishield, which is the Astrazeneca vaccine, and then we have the Covaxin, which was developed by Bharat Biotech. Then the third to be approved was Sputnik, which is an adenovirus vaccine. And then, we had the Moderna vaccine, that was approved and then there was one more I think, and then there are many more in pipeline that are almost there. So, Zydus is one which is almost about to be approved. And then we have the Corbivax, that the government has ordered substantial quantities of vaccines from, and that's more subunit protein vaccines. So, there is a variety of different types of vaccines that are approved or some almost on the verge of approval. So

the last two are, I think, Zydus is, maybe today-tomorrow it should be out, and the Corbivax also should be out fairly soon, and the fact that the government has ordered it, I think, is a sign that it's ready for approval.

Shitij Arora: And, do we know if these vaccines remain effective against the variants?

Anu Acharya: So, it depends. I think they are there, so there are multiple aspects to whether they are effective against, you know, variants. If you're looking at it from hospitalization and death, I think they are effective. If you are looking at it from an infection perspective, not all the vaccines have been that effective. So we have found that, you know, several people that we find that come back are a little unhappy because they've taken their, you know, they've taken both their doses of vaccine, they come back and they find they are positive. The good news is that they usually are asymptomatic or very mild. So, I think what we are seeing is that the available vaccines in India, and I think the large majority so far have been the Covaxin and Covishield, and I think now we've started to see the others as well. They've been fairly effective at least in terms of the, you know, having a deadly disease that would need hospitalization and all of that, which I think is a huge thing, but of course I think many of them will probably need boosters as we go along, but for right now I think it is way better to be vaccinated than not. Yes, that is probably the conclusion of at least what all we can read about it.

Shitij Arora: Absolutely and, yeah, it's the vaccines, like you said, they remain very effective in preventing severe disease and hospitalizations. There is a notion which is now building that Pfizer has emerged, as you know, the champagne of all vaccines, or mRNA based vaccines are turning out to be really good. So, I guess the question comes that, in patients who are, who have received Covaxin or Covishield, should they receive an mRNA vaccine as the third dose if at all? And now, as I frame this question I realized that when the vaccines are so limited, and half of people are not vaccinated, and if you're talking about giving somebody a third dose of mRNA vaccine, but in terms of efficacy standpoint Priya, do you think that would change anything or make a difference ?

Priya: So there are some small studies, and these are, you know, measuring antibody levels that suggests that even in patients who've received two, or people who've received two doses of the of an mRNA vaccine, giving a third dose can boost antibody levels and these are very small studies primarily in immunosuppressed patients solid organ transplant recipients. So, yes, these vaccines or third dose do boost antibody levels, but whether that translates into real improved vaccine effectiveness remains to be seen. And i think the point you made about, you know, it's not half the world isn't vaccinated, it's more like 90% of the world isn't vaccinated, so talking about third doses or a booster with an mRNA vaccine when you've completed a vaccination with other types of vaccines does not seem to be the right thing to do. We know that the other types of vaccines other than the mRNA vaccine, the viral vector vaccines like the Astrazeneca, the Covishield vaccine and now the inactivated vaccines, now that Bharat Biotech has released their Covaxin data, that they do protect you against severe disease and hospitalization which is the most important thing for an individual. They have reduced effectiveness against overall disease with the rise of the variants, but they're still protecting you as an individual. So recommending a third dose is probably not the right thing to do. I think as time goes on and vaccine supplies increase that may become the norm

and Pfizer, as you know in the US, announced that they're going to apply for EUA for a third dose for people who previously received two doses. And the data that they presented doesn't seem to justify it and I'd be interested to hear what Rebecca has to say about that too, but I would say that at this point in time the goal should be to get everyone fully vaccinated with two doses of available vaccines, and not do third doses. For the vast majority of people there may be isolated instances where it may be appropriate.

Shitij Arora: Excellent, thank you. Another thing that has been happening a lot, is that the individuals have been checking their antibody titers after vaccination, probably as a proof of an immune response. Anu, what are your thoughts on that?

Anu: Well, I guess immune response is more than antibody response only, but let's assume that that is, you know, that's a good sign of at least finding out if your vaccine is working. I think there are people who can afford it, and there are people who can't afford it, and people who can access it. So I think people like me, have done this on myself several times to check, but I think that is not necessarily if someone was in the state government and had to decide on a budget and to see whether it made sense to vaccinate, you know, 'X' amount, versus checking the antibodies, I mean vaccinating and then checking antibodies, I think you're better off doing the first, vaccinate everybody and rather than spend that money on checking the antibodies, because the cost of doing an antibody test is higher than doing a vaccine, right. So I think that would be a challenge, that if you had just a resource crunch, then I think it made sense to not necessarily check, but at least vaccinate as crazily as possible, as quickly as possible, so that we'll find that, you know, statistically we have a much more vaccinated nation, and therefore less chances of replication, and variety of different reasons. But if you did have that, if you, let's say, if money was no constraint, then I think it would be a good idea to check, because it allows us to be able to test for neutralizing antibodies, that would be one. But then, if money was no constraint, I would also test for T-cells and a variety of other things as well. So, I think that's the challenge that, do we you know what are our restrictions, in terms of what we can do as a nation and can't do.

Shitij Arora: Absolutely. So, Priya, what about one dose of vaccine instead of two doses? How much protection does that offer?

Priya: So, before these variants came about, that was a very successful strategy. So, as you know, the UK decided that they would vaccinate as much of their population as they could, with one dose, before they moved on to second doses. And that worked really well for them initially, but now with the delta variant, we now have data that suggests that one dose simply is not enough, that the protection offered by one dose of both the mRNA vaccine - the Pfizer vaccine, and the Astrazeneca viral vector vaccine, was sub-optimal, in roughly 33 percent of people were protected. With two doses, protection improved significantly. It was still reduced for the variants for overall efficacy, but both of them had very good protection, over 90 percent, for the protection against hospitalization and death. So, short answer to your question is that one dose seemed to be very good before the delta variant became so widely prevalent. Against the delta variant, you do need two doses of vaccine for protection and so, you know, it just made life a little harder for India, especially where we need so many doses to get everybody vaccinated.

Shitij Arora: Thank you. And, you know, there have been so many cases of COVID now, and now that vaccines are becoming available, the question really is- how long should they wait after the infection before getting vaccinated? Thoughts on that, Priya?

Priya: Yeah, so we know that infection does give you protection for at least three months. So, it's okay to wait for three months to get up to get vaccinated, or if you were in the middle of a series, to wait three months to get your second dose. In terms of safety, there's no reason to wait though, so if your chance comes, you have access to vaccine, you can go ahead and get vaccinated before that three months. So, there's no hard and fast rule that there's a minimum waiting interval.

Shitij Arora: Thank you. So Rebecca, question for you. Who should not get vaccinated?

Rebecca: Yeah, so I think almost everyone should get the vaccine. These vaccines are very effective, especially at preventing the most severe outcomes. You know, I'm interested in what Priya has to say on this, but my understanding is that unless you know someone has a severe allergic reaction to the first dose, or is, in the rare case, allergic to an actual component of the vaccine, unless in those rare cases, everyone who's age eligible should get the vaccine.

Shitij: Excellent, thank you.

Priya: I just would want to add to that, I completely echo with that. So, you know, one thing that was very concerning was the high number of cases in pregnant women and the very poor outcomes in pregnant women in India during the horrific second wave. And in India, the government of India had recommended against vaccination of pregnant women, and just recently within the last two weeks they lifted that recommendation. So now, pregnant women are eligible for vaccination, and I just want to re-emphasize that to all the listeners that, you know, outcomes are much worse in pregnancy and so, getting pregnant women vaccinated is very important.

Shitij: That's an excellent point, thank you. Another area of vaccine reluctance is the age. So the notion is that if somebody is really young they might not get seriously ill and so, what do you think? If the vaccine becomes available for children in India, what are your thoughts on that? Should they go get vaccinated?

Priya: Is that question for me ?

Shitij: Yes, both Rebecca and you.

Priya: Yeah okay. So, I think if the vaccine is widely available, children should be vaccinated. We have been vaccinating children over the age of 12 in the United States, and the vaccine appears to be safe. We have data from studies that show it is very effective in this population. In India, given the vaccine supply, should we be prioritizing children over adults? I think no. When we have less than, at this point, 10 percent of the overall population vaccinated, I still think that we should be prioritizing adults, and adults with high risk

conditions over children. But if the vaccine were freely available, I would completely support vaccination of children.

Shitij: Yeah, excellent. Thank you. Rebecca?

Rebecca: Yeah, I completely agree with that. I think, you know, high-risk individuals should be prioritized for vaccination, but once vaccines are more widespread, children should absolutely get the vaccine. Children still contribute to transmission, so, in terms of reaching population level immunity, they're an important factor, and while children do get, you know, less sick in general, if they're infected, there are some severe outcomes that can occur and we also still don't know a lot about long-term side effects of COVID, and you know, we've seen even in people who are asymptotically infected, that they experience kind of this long COVID. So, I think it will be really important to vaccinate children.

Shitij: That's an excellent point, thank you. So, just to reiterate, Pfizer did apply for the booster dose, and CDC and FDA issued a joint statement yesterday saying that there is absolutely no clinical indication for a booster dose at this time. So, other than the vaccine distribution issue, even clinically it doesn't seem to be a strong indication for booster, at least today. With this, we're going to move on to the next segment, which is another very interesting segment, given where we are in the pandemic and that is- variants. And the first question is for Anu. What are the major variants in circulation, and what are the important differences to know? It is an open-ended question, Anu.

Anu: Okay, so the first important thing is that a variant can basically have multiple mutations or changes from the original sequence of the virus that occurred, and, you know, there are many different kinds of mutations that might occur, and the kind of mutations that we would see would be one where one letter is changed, but that change can cause a change in the amino acid, and therefore the structure of the protein that is there. And the other kind is where some part of the sequence is deleted and that can also cause a fairly significant change in terms of what we are looking at, on a from a protein structure, and so on perspective. Now, earlier, it was a little bit painful to sort of look at all these multiple types of names that were coming in circulation. There were the pango lineages, which had like the A-B-C classification, and they had like 1.1.7 and then p.1, then there were some that were in different letters. Then there was a separate code that came from next strain and so on. But I think what WHO did was, made it fairly simple to be able to understand the different variants of concern, and the ones that we find currently in circulation would be the Alpha, that was the one that became very popular, that everyone came to know as the UK variant. Then there was the Beta, Gamma and then the Delta, which was the one that was talked about as the India variant. So, these are the four that are currently what they call as the variants of concern, but there are also new, and I think everybody who's reading about the Lambda variant, it is another new variant that is there, that is a variant of interest by the WHO, but there are others like the Kappa, which was also found in India, that was the B.1.617.1, while B.1.617.2 is the one that is called as the Delta variant. And then there are the Eta and Iota variants. So, there are many different variants that are there in circulation. And the important thing to understand is that, there are two factors that can happen when they're looking at it from a variant's perspective. One is that- Does it increase the transmissibility of this virus? And the second is- Does it increase the infectiousness or the

severity of disease? And maybe, you know, in short, I think the important thing is that from the original strain that was there, to the UK strain, it became 50 percent more transmissible, and then when we looked at what came in the India variant or the Delta variant, we saw it became almost 100 more transmissible than the first. So, I think those are the things. There were also some Gamma and other variants, where we found that it actually was able to evade some of the antibodies. So those are the big issues that we saw, that in different variants of concern and interest, and all of these I think are made possible because of many genomic sequencing technologies.

Shitij: Wonderful. The prevailing Delta and Delta plus, like you said, they have increased transmissibility. Priya, do they also have increased mortality?

Priya: So, we don't know that for sure yet. So, during India's second wave, which was primarily fuelled by Delta, we did see very high mortalities, and it's not clear whether that was driven by the Delta variant itself, or just the fact that the healthcare system was so overwhelmed by cases. So we're gathering more data, now that the variant is so widespread in other parts, and from the UK data, it does appear that the disease is more severe, that patients are more likely to require hospitalization when they're infected by the Delta variant. But the mortality question has not been answered yet. We don't know whether more people are dying because they are infected with the Delta variant.

Shitij: Thank you. And speaking of transmissibility, there has been a lot of mention of R-nought (R_0) in various papers in the media. Rebecca, would you introduce R_0 to our audience?

Rebecca: Sure. So R_0 , or the basic reproduction number, is the number of people that one infected individual will infect on average, when they're in a population of entirely susceptible individuals. So, for the original virus that we saw first in China, the estimate was around 2.5. So, on average, each infected individual would infect two to three other people. As Anu has mentioned, you know, the new variants have become more transmissible. The virus that we saw and that caused Europe's first wave, had an R_0 estimated around three, the Alpha variant is estimated to be around four to five, and Delta is even higher at around five to eight. So, I think it's also important to distinguish between R_0 , which is the basic reproduction number, and then also the effective reproduction number. So that is often called R_t , and it takes into account the fact that there are interventions in place that are trying to reduce the number of contacts people have, or reduce infectiousness upon contact, and the fact that the entire population is no longer susceptible, even due to either past infection or due to vaccination. So, you know, the goal is always to get R_t to be below one, so that each person on average is infecting less than one other person and that's how the epidemic will stop.

Shitij: That's very helpful to know. So, as the virus has evolved from Alpha to Delta, actually from the Wuhan strain to Alpha to Delta, the R_0 has increased, is that right? So the same thing happened with measles, right? It settled around 12 to 18. And one of the issues, like you mentioned, with R_0 , is that the vaccine coverage needs to be much higher to attain herd immunity, if the R_0 is higher. So, I know it's a very open discussion, but do you think that the R_0 for COVID-19 might change further for SARS-COVID too ?

Rebecca: Yeah, So, I think we've seen this in a trend, as variants emerge, that the R0 has been increasing, you know. The viruses mutate, become more transmissible, R0 increases, So, I think, you know, there's definitely a possibility that new variants could have higher levels of transmissibility and higher R0, which, as you mentioned, requires higher levels of vaccination to reach herd immunity. So, I think just underscoring the importance of getting this under control and increasing vaccination as quickly as possible.

Shitij: Yes, the vaccination drive becomes critical. Do these variants, Delta in particular, do they have the potential to escape the conventional testing methods that we have?

Anu: I think it's unlikely, because you usually use multiple targets on the gene, right. So, I think, if you use only one, then it's a possibility of missing it, but I think if it's a carefully designed test, then typically, you would use two to three targets, and you try to find the one which is not falling in that mutation, and I think, in most cases, we have found that majority of the tests did not escape that. So, we found we didn't have any issue in terms of the actual testing. But there is a possibility, if somebody has done only one, and then it's always better which is why, I think Priya was also mentioning that in the second wave, we had people just assuming it to be COVID, but I think also we found, in Hyderabad, luckily, we didn't have such issues, but at least I think a lot of times, if there was a negative test result for whatever reason depending on the kit they used, I think the doctors also recommended additional blood tests to be sure that it was COVID, rather than just relying on RTPCR.

Priya: So, I just want to speak to that. So, the blood tests, you know, are indirect measures and I know you've talked about testing in another session, but one of the things that doctors were doing in India, was ordering a high resolution CT scan to confirm COVID, and I just want to say that that is a mistake, that no CT scan can confirm or rule out COVID. And the CT scans are expensive, and there's really no correlation between the appearance on CT and severity of disease. So people were getting CT scans, serial CTs, getting multiple CTs, which was really a drain on resources at a time when, you know, hospital beds were not available. So, I just want to re-emphasize that no blood test or a CT scan can definitely confirm or rule out COVID, and these are mostly unnecessary. The reason to do the blood test should be to assess need for certain types of treatment, and for the most part, no blood tests are really needed, no CT scan is needed.

Shitij: So that's a very important point you make, Priya. So, would you also agree that doing CRPs and D dimers to try and confirm diagnosis which are supposedly negative, is a wrong strategy?

Priya: It's absolutely the wrong strategy. So, if your COVID PCR is negative and you are short of breath or hypoxic, you need admission. If your COVID PCR is positive and you're not short of breath, you go home and stay home and isolate, so the CRP and CT scans add nothing, it really doesn't add any value at that point in time. So in a hospitalized patient, a CRP may be helpful in deciding whether you need to use certain advanced therapies, but for the average outpatient they're completely unnecessary.

Shitij: Thank you Priya. I think one of the questions which we have addressed already in our talks, but I think it's a more direct question, because it's a very common question that comes and that is- "What is the risk of being infected by the Delta variant for persons who are completely vaccinated?". Priya, I think any numbers that we know on this?

Priya: So that's a tough question. I'll rephrase the question and see whether that makes sense. So, what are the chances that you're protected if you've had two doses of vaccine? What are the chances you could still get COVID if you were exposed? Is that what you're asking ?

Shitij: Yes, because we know that the vaccines are very effective in preventing severe disease and hospitalizations. But here we are talking about overall infections.

Priya: So, I think the answer to that is that- it depends. It depends on- A) the type of vaccine you got and- B) the degree of exposure. So, if you're a household contact of someone with Covid, and you have had two doses of Covishield, for example, if you're not taking any precautions, if you are not wearing a mask around the infected person, if the infected person isn't wearing a mask and you're having close contact, even if you're fully vaccinated, there's still a 30 percent chance you could get, a 30 to 40 percent chance you could get Covid, because of that high degree of exposure. The effectiveness of the vaccine at preventing infection, as I said, even with two doses, has been reduced in the Delta variant, because people who are infected have higher viral loads, the virus has changed enough that it's more transmissible and more likely to cause infection in those who are exposed. But the chances that you will get very sick from the infection are significantly lowered by the vaccine. So, I don't want to sell vaccines short. I think it's very important that you get vaccinated, and the fact that the vaccine effectiveness has been reduced, is why the WHO is now recommending masking even of vaccinated individuals, in contrast to the U.S., where the CDC has said you don't have to be, you don't have to continue to mask if you're vaccinated.

Shitij: Now, as variants have emerged, one of the start several studies have now shown that in patients who are immunocompromised, who harbour the virus for a long time, you know the viruses tend to change and a lot of the variants could potentially be emerging from there. So, should the vaccination campaigns be more directed at, of course, there should be massive vaccination drives, but should it be more focused on those patients who are potentially immunocompromised and just to control the pandemic and probably the variants from emerging?

Priya: The variants emerge whenever the virus is replicating. So yes, immunosuppressed patients can have a more prolonged infection, more prolonged replication, but the other factor to consider is also that every time the virus passes from one person to another, it is replicating in that individual. So, anytime the virus is replicating, you run the risk of mutants. So, at the population level, vaccinating everybody and reducing the number of infected individuals will help to control the pandemic. For an individual who is immunosuppressed, vaccination is important. But if you just vaccinated all the immunosuppressed people, you still wouldn't be controlling the pandemic. So, you need to do both, vaccinating the immunosuppressed for their own protection because their risk of dying from infection is

higher, but the virus can still mutate even if it infects healthy individuals, if it infects enough healthy individuals. So viruses mutate just every time they replicate.

Shitij: Excellent, thank you. This was a wonderful discussion. There are many questions now in the Q&A, so we're going to wrap up our session and open up the Q&A. Satchit, do you wanna lead that? i don't see the questions.

Satchit: I'm happy to, yeah. I will ask some questions, some of which have been covered in your discussion. So, I'll uh club them together. Dr Satav from Mahan, which is an NGO that works in rural tribal belts in India, asks 'Which antibody based tests are good, which antibody tests will differentiate between an old infection and vaccine?' and 'Do we need permission from ICMR for antibody testing as part of the community study?'. So, maybe break that into two, the second question can be answered separately, 'Do we need permission from the ICMR ', but the first question is 'Will the antibody test differentiate between an old infection and vaccine?'. Would any of you like to take that?

Priya: I'll take it. I can't answer the question about the ICMR permission, but I can answer the question about what the antibody test detects. So, there are a lot of different antibody tests and they test for different targets, different types of antibodies. So, if you have antibodies to this spike protein, you cannot tell whether that antibody came from vaccination or from a past infection. If you have antibodies that detect the nucleocapsid and if there are antibodies to the nucleocapsid antigen, those indicate previous infection, because you can't develop those antibodies from vaccination. So, that's just the overall, you know, big picture question. So, it depends on the antibody assays, and some people, I don't know if this is particularly helpful other than in research settings when you're looking at zero surveys trying to see how many people in the community have been infected. For practical purposes, it probably doesn't have any value and I don't think there are any restrictions from the ICMR on doing antibody testing, but I don't know if Anu has more information on that.

Anu: Yeah, so the ICMR doesn't have restrictions for labs doing these testing for individuals, but there is if you're doing it for a research study or a community based testing, then you do need permissions. If you're doing it in a state, then from the state government. If you're doing it, you also need permissions from ICMR or a national body that has allowed you to be able to do that. So, we were involved in a couple of surveys in Karnataka, so we had to get a couple of, multiple permissions to be able to conduct that study. But you're right, on a normal, like, when we offer an antibody test to our customers that is perfectly fine.

Rebecca: Just quickly. I think understanding whether someone has antibodies from a vaccine, or previous infection, or both, can be helpful in studies of vaccine effectiveness over time, if you want to stratify it by people who have been previously infected or not. So that can be helpful in evaluating vaccines over time.

Shitij: Excellent. One of the questions we have for all the panelists is- 'what happens when antibody response is zero after both doses of vaccine? should they be revaccinated?'. Start with Rebecca.

Rebecca: That's a good question, but I'm not sure if I'm the best one to answer that though.

Anu: I'll tell you what happened with me. I think different people will develop antibodies differently, right. So, I think you know I was testing mine every week, just to check for me, it took six weeks for me to get my antibodies and neutralizing antibodies. But I think some people developed it much sooner. So, I think it depends on individuals. So, I think people shouldn't get worried if they didn't get antibodies when they expected it to, and also had they tested it with the right kit, I think that's an important thing. Because many times what happens is that an average person doesn't know the difference between how you would test for a vaccine-related antibody, and I think that's what Priya was mentioning, that if you did one on the end gene, then you'll probably not get it, and you'll feel sad about it. But you could do a neutralizing antibody, but you have to make sure that you wait the appropriate time before which you will get a response. So you shouldn't be in a hurry to actually, you know, jump into a conclusion that the vaccine is not working.

Shitij: Yeah, I think there's a big, and I think I'll go to Priya next, but I think that the bigger question here is that are we just looking at b-cell responses or just the antibody responses to get a certificate of immunity, or should we really rely on an entire immune system like memory b-cells and t-cells and everything? So Priya, your thoughts on this question?

Priya: So, I would say that the antibody tests, again, I don't know that the commercially available antibody tests are reliable enough to ever give you a certificate of immunity. I think so much depends on type of exposure at the setting, and I would not take a positive or a negative antibody test to mean I'm immune or non-immune. I think that science still doesn't have the answers to that. Over time we might have better tests, but at this time there's no way you can do a certificate of immunity. And then you had a second question, I'm sorry, did you have another? So, should we be looking at other, but right now again looking at, you know, your cell mediated immunity, still is only in a research setting. It isn't again a commercially available test. So it's tests that need to happen, these studies need to happen, but not for an individual. I think that if you got two doses of an approved vaccine, you can be reasonably sure you're protected and you shouldn't be doing, or seeking out these tests outside of a research setting.

Shitij: Excellent. Yes, that is a very important point to make. I think that's probably what the question addresses here also, that if the antibodies are negative should they then be worried that they don't have the necessary immunity, and the answer to that based on what you say is, probably no, they should not worry, if they have received the vaccines, they have, the immune repertoire is pretty big, so it's not just the antibodies, there are other mediators of immunity. So be rest assured if you have received the two doses, you are probably immune . Any other questions?

Satchit: There was another question about dosing intervals, which we covered earlier, but if you just want to sort of summarize again. How much after infection should you wait to start getting the vaccines, and what is the third dose interval? It says 'how do you think the certificate of vaccine afterwards variants are increasing?'. We touched upon these, given that we're at the end of the hour, probably just a quick summary of the various intervals after infection, how much do you wait for the first one, and what sense do you make out of

these very different recommendations around the world of what the right interval should be between the first and second vaccine depending on the type of vaccine? Thoughts?

Priya: So, I think that based on the trial data, the vaccine intervals are fairly clear for the mRNA vaccines. The minimum interval between doses is important, you should not get your second dose before that minimal interval. So for the mRNA vaccine for Pfizer, it's three weeks; for Moderna, four weeks; for Covaxin, it's four weeks. So, all of these are the minimum intervals, and I think it's really important to stay within those parameters. There is no maximum interval between doses, so if you miss your date to get your second dose, you can go ahead and get the second dose of the vaccine, it will still be effective. You may not be protected for a period of time, but you don't need to restart the series, there's no, you know, time at which the first dose no longer works, you need to get the second dose. As far as infection and getting the second dose, the infection itself, you know, gives you immunity. So it doesn't give you enough immunity that you don't need to get vaccinated, but you are safe to wait three months to get vaccinated. That being said, there's no minimum interval between infection and getting vaccinated, so if you happen to have the chance and you may not get it later on, it's perfectly safe to get the vaccine within the six months after infection. The only time I would recommend against getting vaccine is while you're still ill, you should not get the vaccine while you're still recovering. So if you happen to be afebrile, you also should not be infectious so that you're not infecting others at the vaccination site.

Shitij: Thank you, thank you. Any more questions?

Satchit: No we are at the end, on the hour. I'm going to take this opportunity to thank everyone, Dr Arora, for moderating this really compelling panel, which we could have used a year ago, six months ago hopefully, unfortunately, we'll continue to use. For all participants and panellists, the material is live on several websites, it is mirrored at the Mittal Institute, and at the Swasth foundation. We'll share with each of you to mirror it on your respective institutions, but we will also splice the content into manageable bits around smaller questions, and hope that both attendees and panellists can help disseminate this information. Unfortunately, we are likely to continue this exercise for a long time or so, seems the writing on the wall. This was the third in the first series of three panels, over the last two weeks, jointly hosted by the Harvard Mittal institute and the Swasth Community Science Alliance. I thank all of you for participating, and for joining the discussion. Thank you kindly everyone.