Eminent clinical scientist and vaccine expert Dr Gagandeep Kang, who headed the committee looking into indigenous Covid-19 vaccines and drugs, believes that the fight against SARS CoV-2 needs a mix of vaccines and antivirals, while the focus has largely been on vaccines. In an interview, with Ishaan Gera, Dr Kang talked about the need to indemnify vaccine developers, and how vaccination won't be a route to eradicating the virus. Edited excerpts:

India hasn't seen a resurgence of Covid-19 infections, the second wave some countries have seen…

I think the disease is behaving a little differently in India than in other parts of the world. It seems to be behaving similarly in other South Asian countries and also in Africa—other than South Africa.

So, why is it behaving differently? I don't really have an explanation. I would be more comfortable proposing a hypothesis: If there was the availability of better sero-survey data from India, we could combine that with other data sources to try and understand why we are in this situation. We know the numbers of tests that were done and the tests that were positive. We know how many people were in hospital and died, but without serological data, we don't know how many were infected. We do have sero survey data that ICMR published at two time-points, but my understanding is that they excluded containment zones. But, when we've had surveys in the areas that have had high incidence, these have shown infection rates much higher than reported by ICMR. So, trying to make sense of those numbers probably can only come from having more granular sero-survey information. It would be very valuable if we could understand from the test positives, why the tests were done: Was the test done to screen contact, or to make a diagnosis? We have such information in some states, but not country-wide. And, it's not easily accessible for people to be able to analyze this information. And finding an explanation for India's situation is hard in the absence of data.

Has India had a highly infective variant, like the UK one? Have we seen genomic variations in SARS CoV-2?

Of course, we have. SARS coronavirus evolves all the time—but it's actually a pretty slow virus to evolve compared to other RNA viruses. But my understanding is that out of 30,000 base-pair genome, there are at least 4,000-plus documented mutations. Now, whether these

mutations are relevant or not depends on where they are located. You can have synonymous mutations where even though the mutation has occurred, the amino acid has not changed, or non-synonymous mutations that result in a change in the amino acid. Now, when we hear about in N501Y, that just means that this is a non synonymous mutation where there has been a change in the amino acid and therefore you expect a change in the way that the protein is likely to function.

In this case, it appears that many of these mutations promote better binding to the ACE 2 receptor, and this results in an ability of the virus to be transmitted more easily.

What is success for a virus? Success is its ability to spread and its ability to replicate. If you have a virus that kills its host, is that a successful virus? From the human point of view, it is a dangerous virus. From the virus's point of view, there is no gain in killing off your host because you are not going to be able to move on from there unless you're like an Ebola virus that can spread from dead people. What a virus is looking for is increased transmissibility.

So, the virus will continue to evolve to become more and more transmissible, so that it can spread easily. It's very unlikely to continue to evolve in the direction of becoming more dangerous because that's creating a dead-end for itself.

The other way that viruses can evolve is depending on the pressure that is put on them. So, if you were able to treat an infection with antivirals, then the virus might try to evolve in a way where it would make sure that the antiviral would not work. It would evolve towards an antiviral resistance.

Similarly, if we have a situation where there is a vaccine that works, then the virus will try to evolve so that the vaccine does not prevent it from getting in. So, this now becomes an immune-escape mechanism. You could have an antiviral-escape, you could have an immune-escape.

Now, if the virus sits around for a long time in a situation where there is immune pressure—and this can happen at the individual level and at the population level. At the population level, if lots and lots of people are vaccinated, then the virus is not going to be able to spread easily in that vaccinated population. So, what it will try to do is to evolve in a way

where the antibodies induced by the vaccination are no longer effective.

Now, if it gets into a person who is immuno-compromised in some way, who makes an immune response, but the immune response is not enough to shut the virus down entirely like what happens in an immuno-competent person, then the virus can evolve in an individual as well. And with the UK variant, one of the hypotheses is that this may have gotten into somebody who was in some form of immuno-compromise. So, the virus replicated in this person for a long time. And because this person's immune system was trying to get rid of the virus, the virus was constantly evolving to try and escape that immune response. So, the variant may have arisen in that fashion. And it is possible that if you have, in the future, other people with immuno-compromise where you can have chronic replication of the virus, we will see new mutations. It is not unusual at all.

Is eradication of SARS CoV-2 possible with vaccines?

With vaccines alone, I don't think so. Now, if we really went after any virus, the virus needs to have certain characteristics that allow it to be eradicated. So let's go back to smallpox. Why were we able to eradicate smallpox? We were able to eradicate smallpox because it was a purely human disease. It did not spread in animals. It had no reservoirs whatsoever. It was a disease that was very visible and very identifiable. You could tell that this person had smallpox without needing to do any laboratory test. Whenever a person got smallpox, there was no question of asymptomatic infection—you got it or you didn't get it.

And there was a good vaccine for smallpox. You took one dose of the vaccine and you would never get smallpox. So, this combination of four factors led to smallpox being something that was easily eradicable with vaccination. You could easily identify people who had the disease and you made sure you did a ring vaccination strategy, which made sure that everybody that this person had come in contact with got the vaccine so the disease could spread to anybody anymore.

So, all of these characteristics made smallpox a relatively easy disease to eradicate. Now, we look at polio, which is the next one we are trying to eradicate from humans. We have been able to eradicate one other viral disease called rinderpest, which is related to measles, but it's in animals. We are trying to eradicate polio. Why is it so hard—polio is a purely human disease, we have great vaccines for polio?

But polio can occur as an asymptomatic infection. When you cannot identify cases, unless you vaccinate the whole world and know that the vaccine has worked on the whole world, you are not going to be able to get rid of polio. That's what we are trying to do right now: We are trying to switch from the oral polio vaccine, which is not that great, to an injectable polio vaccine, which is somewhat better. And there are still pockets of disease in some parts of the world. Even with all that, we've managed to get rid of two types of the three polio viruses. But now, of course, we have the problem of wild polio virus 1 persisting as well as having vaccine derived polio virus because we've continued to use oral vaccines. They have their advantages, but they have their disadvantages of reverting to causing polio also. So, one of the most exciting advances in 2020 was that we got new polio vaccine—a new oral polio vaccine—which is actually safer than the old ones. And we hope that this will be a tool that will help us to go after polio. But polio had all the features—human pathogen, no reservoir in animals, good vaccines—but it had the problem of asymptomatic infections where you don't know in the community who is being infected.

We know that it causes asymptomatic infections. We know that it can go into animals and come back from animals. So in terms of thinking through eradication, it would take a humongous effort for us to think about being able to eradicate this virus. I don't think we are ready for that strategy right now. It's potentially feasible.

Some countries have shown us that they can do it for certain kinds of settings. China was able to manage it for quite a long time. But now, China has local transmission again—and they have much better resources than many other parts of the world to try and achieve control. So, I think we have a long way away from that. Theoretically feasible. But it would require an incredible amount of testing and isolation and also vaccines, not just vaccines alone.

Why haven't antivirals received as much focus? Can they be used instead of vaccines to control the pandemic?

I think not 'instead', but 'along with', because you are doing two different things with vaccines, you are trying to prevent people getting sick. Antivirals cannot be used for prophylaxis, for prevention. Vaccines are not going to work 100% of the time. So, if we can come up with better treatments, we absolutely should. I actually think that we've invested too much in vaccines and too little in antivirals. Do we need two hundred vaccines for coronavirus? We've got three hundred plus programmes that are going on. So, what's the right number? Should we stop at 10? Should we stop at 15? 20?

Vaccine manufacturers are asking for indemnity. Your thoughts?

At this stage, absolutely. And the reason I say that is because what we are trying to do is solve a public health issue here. It's not about vaccine companies making a profit. There used to be many companies in the past that made vaccines. Why do we have only four major manufacturers? Because you have to make enough money off your vaccines to protect yourself in case there are lawsuits. So, in the US, they have a programme called the National Childhood Vaccine Injury Act, where essentially they charge a small tax on every dose of vaccine that is sold with the idea that when a determination is made that a child has a vaccine related injury, then this group pays for that child's medical costs. The compensation is paid through this programme and this is called a no-faults compensation. Other countries have healthcare systems that actually provide universal health coverage and services so that if children are injured in Northern Europe, Australia and the UK, they will be looked after. I actually don't think that this is an unreasonable demand. It really is this issue of liability that has driven vaccine manufacturers out of business, because remember that vaccines are given to healthy people. …When vaccine companies start to make a profit out of these vaccines, if you've gotten to a stage where it's no longer part of a public health programme, it is an individual choice to get this vaccine or that, at that stage, you might not need indemnity, you might want to make this, you know, a private market approach. But within the public system, anything that is bought by the government, I think the government should indemnify the companies. They're doing it as a service. They may make some profit out of these later. And maybe we can think about it then. But at least some level or indemnification needs to happen. Otherwise, we're not going to have access to vaccines. And that's a very serious issue.

If vaccine protection, all possible immune stimulation considered, is short-lived, what, to your mind, will be the outlook for the world?

Booster doses. This vaccine is working incredibly well for a mucosal pathogen. Having looked at vaccines for a long time, I'm surprised by the levels of efficacy that we were seeing. I was expecting really good vaccines with 70-75% efficacy, and that would have been great. But that also leads me to think that I don't think these are going to be like influenza vaccines where you will need to take a shot every year. But whether it will wind up being every two years or every five years, we'll need to wait and see. It's feasible that we might not need new vaccine shots unless the virus changes a lot. But I don't think that it's going to be an annual shot based on what we currently know.

How do you rate the government strategy as of now as far as immunisation is concerned?

I think for vaccines, we are doing a better job. So even though this will be the largest immunisation programme in the world, even though that this is adults, which the government has never handled before, at least what I'm seeing and hearing about the planning is that it is being very well done. My worry is we're not involving the private sector at all. At least I'm not hearing about the private sector being involved. This is entirely being designed and delivered by government. And it would be nice to see what their plans are, given that for at least 30% of the population, even preventive services are provided by the private sector. So it would be nice to hear that. I'm really pleased that they are planning to do dry runs, it would have been even better if they had actually used a vaccine, like influenza in their dry run. So then we would have figured out even more issues of transport and delivery of vaccines, communication strategy, etc. But one thing that we need to remember is that with all the infrastructure, all the planning, everything that we have done for childhood immunisation, we reached only 90% of Indian children, 10% of children were not reached and 90% was our best possible performance at the beginning of 2020. Usually, it's been well below that. Now, we are talking about a population that is much more than the children we currently reach. So, you're really looking at a very tiny group, which is less than one 10th of the population that you are now planning to immunise. Will you get to 90%? Do you want to get to 90%, you're going to do this in phases, you're going to balance your prioritised population with your supply. It's hugely more complicated than anything we have done in the past, I'm really pleased to see that the government is doing detailed planning. But I think there are going to be glitches, that will happen. And that's inevitable in a programme. So what I'm hoping will happen is a lot of iteration and rapid iteration, to ensure that coverage is maintained. What I'd really like to see is independent monitoring. How well is this performing? And, you know, have indicators, but don't have the people who are delivering the service monitoring themselves, which is what happens at the moment.

The Health Secretary said we don't need to vaccinate everybody…

I understand the rationale of saving doses and making doses available to people who need them the most, at that point in time. But this is not a problem that is going to go away and it's not like the virus will magically stop circulating the minute you get 60% of the population infected or vaccinated. I've also heard that the government was thinking about potentially not vaccinating people who had been previously infected or who have an antibody test that shows that they are antibody positive. But if you don't know how long infection protects you, then on what basis are you saying we will not vaccinate people who have been infected before. And, if you look at the goals of controlling disease, disease control, disease transmission, reduction is going to come from vaccinating young people. It's not going to come from vaccinating the elderly, who are more likely to stay at home and interact less. Vaccinating them is for preventing severe morbidity and mortality, it is not for prevention of transmission. It will require young

people to be vaccinated in order to keep society functional and reduce transmission. So, I think the goal should be to vaccinate everybody over time. So, protect the most vulnerable most at risk of severe disease first, but then you need to switch your goals to prevention of transmission and ultimately to protecting everybody. I've also heard that the government, you know, at least some people have said that the government should not pay for all doses of vaccine. I think the government should offer to pay for all doses of vaccine. But we should think about whether if there are people who can afford it and want to, can they access vaccine in the private sector that is not available in the public sector. I don't think there should be any diversion of doses of what is meant for a public immunisation programme. But if you look at some vaccines are never going to be available in the public programme–the public programme will not have more than two or three vaccines in it–so if you have five vaccines or 10 vaccines that are licensed in the country, which are not going to be used for public immunisation, could you tell people who can afford it go take those vaccines so that it lowers the burden on the public system. But it should not be mandated that you know, X will get the vaccine because they are paying taxes or not paying taxes or below poverty line. And anybody who pays income tax, for example, does not get the vaccine because we think you can buy it yourself.

Can it happen that you get a vaccine and you lose antibodies within six months?

Absolutely. Yes. Okay, so with many vaccines, you will make an initial very powerful immune response, and then over time, it'll die down. Now, the question is, are you still protected or not? The detection of antibodies and then is an initial signal to show that you responded to the vaccine. And if the vaccines persist for a really long time, over a certain threshold, you say that that person is protected. But, for many vaccines, even when antibodies become undetectable, people continue to be protected. So, we don't know at the moment how long protection lasts, we don't know the correlation with antibody levels. We will know this in the future. And that will be the time to begin to think about when do we need to be considering a booster dose? Or is one necessary at all.

There is a Rand study which says that $119 billion will be lost if the poorer countries don't get the vaccine. What is the best strategy going forward?

Vaccines really are a global good, and access to vaccines should not be based on your ability to pay when you are dealing with what is a global public health problem. The problem so far has been that the COVAX facility, which is going to be the main source of vaccines for developing countries, has been very dependent on overseas development aid for the funding that will support the purchase of vaccines. We should be thinking about this from the point of views of ministries of finance and economics to make the case that it's good business sense to protect

yourself by protecting people who are not your citizens. This is not a large scale investment, given the kind of economic losses that the world has suffered over the last one year. And the faster we can get vaccines to the entire planet, the faster we will be able to look at businesses being able to recover. COVAX has enough vaccine or is planning to have enough vaccine to cover 20% of the world's population. What happens to the other 80% in terms of time and the doses available to them? World Bank, the Asian Development Bank are thinking about that.

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