**SURAJ KAPA:** All right, good morning, everybody. I know people are still coming in, but we'll go ahead and get started today. So this is the code up on the screen for everybody for receiving MOC and CME credit. Today, we have the pleasure of introducing somebody, a colleague from Singapore, who Nick Tan will be introducing shortly.

Just as a reminder, if everybody can keep their computers muted-- if you have any questions that arise over the course of the presentation, you can enter it into the Chat section on Zoom. And I will review those at the end, which will be about 30 minutes, with about 15 minutes for questions. Nick, I'll hand it over to you to introduce Paul.

**NICK TAN:** Good morning, everyone. I have the honor of introducing Dr. Paul Tambyah for today's Grand Rounds talk. Like me, he's from Singapore, and Singapore has been in the global media spotlight as an example for its initial response to the COVID-19 pandemic, as well as serve as bellwether for the aftershocks to come.

And so in this vein, Professor Tambyah has been in the forefront for developing strategies to combat the next wave of coronavirus infections within the community. Dr. Tambyah obtained his medical degree from the National University of Singapore, or NUS, and also completed additional training at the University of Chicago and the University of Wisconsin.

He's a professor of medicine at the National University of Singapore and a senior ID physician at National University Hospital. He's the current head of Infectious Diseases Research Coordinating Office at the National Centre for Infectious Disease and the chair at the IRB at NUS. Furthermore, he holds several international leadership positions, including president of the Asia Pacific Society of Clinical Microbiology and Infection, and Executive Committee member of the International Society for Infectious Diseases.

He has numerous publications in a multitude of prominent journals, including *Lancet, JAMA,* and *New England Journal of Medicine,* and also maintains several federal research grants as a principal investigator. He has received many accolades throughout his distinguished career, with the most recent being the John Forbes Fellow Award from the Melbourne Infectious Diseases Group.

And last, but not least, he has been a tireless servant to the public on multiple fronts, and his compassion and work ethic have been a privilege to witness in person. So everyone please join in welcoming him, at least virtually.

**PAUL TAMBYAH:** Thanks very much, Nick. Is my screen--

**PAUL FRIEDMAN:** Professor Tambyah, you're muted, and if you could unmute. And then we do see your screen. Thank you.

**SURAJ KAPA:** Yeah.

**PAUL FRIEDMAN:** And let me add my thanks to you for joining us.

**PAUL TAMBYAH:** Yeah, thanks very much. I think I've unmuted myself. Can you guys hear me?

**PAUL FRIEDMAN:** Yes.

**PAUL TAMBYAH:** Great. Well, thanks again for the invitation. It's a tremendous honor to be able to do this Grand Round. I have a huge amount of respect for the clinic and for our cardiology in the clinic in particular.

So I'm going to be talking to you about responding to successive waves of the coronavirus in Singapore and how we dealt with it. So this is a patient that we looked after. He's a 37-year-old man with a history of-- he had recently actually been in Wuhan, where he had an episode of diarrhea. And he went to the hospital, and there he was given IV fluids and discharged the same day-- happens a lot in China.

He flew to Singapore the following day, and he came with his family through Guangzhou, and he brought his father to the emergency department. He himself was not evaluated. Father was diagnosed as the first case of what was then known as the Wuhan coronavirus in Singapore.

The son presented the next day with fever, and, ultimately, both of them were admitted. The rest of the family went on to continue their tour in Malaysia, but thanks to good cooperation between the Singapore and Malaysian public health people, the rest of the family were quarantined in Malaysia, and four others were identified.

Of course, you know by now that there've been successive waves of what we now know as COVID-19, initially in China, followed by-- in Europe, and now in the United States and North America. So again, this virus first emerged in China in Wuhan, again, as we all know, in early December, maybe even November.

And then, there was a super-spreader event at the market in Wuhan [AUDIO OUT]. What is interesting is that Wuhan [AUDIO OUT] center of the international coronavirus, [AUDIO OUT] was thought to be very cutting edge. And it's being written up in many journals. [AUDIO OUT] a number of conspiracy theories that have been [AUDIO OUT] very comprehensively in this battle in major medicine by some of the leading experts in the field.

But we have the existing patterns, and there are three possible scenarios where it could have emerged. [AUDIO OUT] there was one cross from an animal, which subsequently spread to multiple humans, or [AUDIO OUT] in humen. And they say much less likely, there was multiple [AUDIO OUT] purposely infected at the laboratory.

And they say that the initial coronavirus [AUDIO OUT], but it is highly improbable to prove or disprove the theories of its origin. And, you know, it took years before we were able to [AUDIO OUT]. And then [INAUDIBLE].

**SURAJ KAPA:** Paul?

**PAUL TAMBYAH:** Yep?

**SURAJ KAPA:** Your voice is breaking up a little bit. I'm not sure if it's the connection. I think it's for a few people.

**PAUL TAMBYAH:** Yeah, OK, maybe--

**SURAJ KAPA:** Actually, it's better now.

**PAUL TAMBYAH:** Is that better?

**SURAJ KAPA:** That's better.

**PAUL TAMBYAH:** OK. Yeah, I'm moving a bit closer to the microphone.

**SURAJ KAPA:** Perfect.

**PAUL TAMBYAH:** OK. So again, as most of you know, the symptoms are very similar to most upper-respiratory infections, the fever, the cough. [AUDIO OUT] in my office. And the majority of cases, actually, are mild to moderate, and this is data from 72,000 cases [AUDIO OUT].

We showed that [AUDIO OUT] most cases are mild, meaning that no evidence of significantly [AUDIO OUT] disease. But 5% of them are fatal, and 2 and 1/2%-- sorry, 2 and 1/2% of them were, and 5% of them are critical.

So this is a fairly typical case that we looked after. 38-year-old administrative person, she was sick early in February, and this is about a week after a Chinese New Year dinner with her cousin, who later on was diagnosed with COVID-19 disease.

She went to see her family physician. She was treated with clarithromycin. She rested at home. She developed shortness of breath constantly for a day. She went back to see the GP over the weekend. He referred her to the emergency department, where she was seen and discharged.

She was on leave for a couple of days, and she wanted to come back to work because she worked in the hospital. She went to [INAUDIBLE] Health, and they made her do a PCR. And to everyone's surprise, the PCR came back positive. She was completely asymptomatic by that time, but she was kept in hospital because we keep all individuals who are PCR-positive. So she stayed in hospital for another eight days, until we finally discharged her.

So like I said, the symptoms are very similar to other respiratory tract infections. So a group from our National Center for Infectious Disease tried to see what predicts COVID-19 versus other upper-respiratory tract infections from their screening center.

And, ultimately, what they showed was high temperature, lack of sputum production. Gastrointestinal symptoms, interesting enough, were positive predictors. So were chest X-ray abnormalities, and normal neutrophil counts were also predictors of COVID-19 versus other upper-respiratory infections.

The other interesting thing which has had a lot of play in the media was the idea of anosmia, and this has been reported by a number, not just in Singapore, but elsewhere. This is one of my fellows. She went round asking our patients, and she found very quickly that 5 out of 13 of them did not have loss of smell, but actually 8 out of 13 did. So she's actually embarked on a little project to try and define that.

And there is a biological basis for this because the olfactory epithelium, which is right at the top of the nose, actually has the ACE receptor. So it is possible that the ACE receptor is damaged when the virus enters into the cell at the olfactory epithelium, and that's how the anosmia develops.

I don't know about the actual science of the thing, but somebody gave my wife a sachet of lavender, and we put that on the door. And so what I tell her is if either of us can't smell that, it's time to get ourselves quarantined.

So anyway, again, as you've heard, a small number of cases are fatal, and a significant number are severe. But the bulk of cases are mild or asymptomatic. And that is the question that a lot of people are asking is, what proportion of the disease is mild or asymptomatic?

And, again, Singapore investigators tried to find the answer to this question by looking at a flight, one of the evacuation flights that came out of Wuhan. And, basically, 97 people arrived for boarding. 3 of them were denied boarding because they had fever, so 94 of them came to Singapore.

And out of this 94, 2 of them had fever and were found positive for SARS-CoV-2. One of them-- and they tested them repeatedly, and one of them was found to be asymptomatic. So out of 94 people, you've got about 3, which means about 3% to 4%, and these were unselected Singaporean individuals living in Wuhan.

So we've had various surveillance systems in place, including contact tracing, which I'm going to talk about a little bit later, as well as influenza-like-illness surveillance. And in the early part of the outbreak in February, there were actually no cases amongst the influenza-like-illness surveillance or test positive for SARS-CoV-2. And that has changed. In fact, in the last week, we've heard from our local authorities that we have started seeing unlinked cases amongst the ILI surveillance.

So what is the-- the way we diagnose it, again, as you all know, is a PCR from a nasopharyngeal swab primarily, but also from a throat swab. The interesting thing about this virus is the virus-- viral load peaks early in the disease. In fact, there is some suggestion that the virus load is highest on day zero or maybe even in day minus one of the disease. We found this to be so amongst the patients in Singapore, where we see a gradual decline in viral load, although, in some individuals, they can be PCR-positive for weeks.

Now, this is in marked contrast to SARS. Now, in SARS, the viral load peaked about day 10 to day 14, when the patients were markedly ill in hospital. And this has huge implications for the epidemiology and transmission of the virus.

So SARS is primarily a health-care-associated virus. It infected doctors and nurses because patients are shedding virus when they were ill in hospital, as opposed to this virus, which is predominantly transmitted in the community. The other question that comes up with PCR positivity, like with our patient who was completely asymptomatic but continued to be PCR-positive for eight days after the admission, is how viable is the virus?

And this is data from Germany, where they showed that individuals after day eight didn't really have any positive viral cultures, whether it was from stool, throat, or nasopharyngeal swabs. So the suggestion is that PCR may be way too sensitive in terms of identifying virus for transmission.

The other issue, of course, is false negatives. Now, we've had cases where, based on the clinical suspicion, the patient looks like they might have COVID-19 disease, they've got strong epidemiological risk factors, but they're repeatedly negative. And, in fact, there was one individual who was only positive on the fifth nasopharyngeal swab, on the seventh day of illness. So that's another issue.

The other issue is we've tended to use respiratory swabs, but, again, some individuals who can present with GI symptoms, they may be negative in terms of respiratory swabs, even though they have abnormal CT scans. And this is a patient that we looked after who eventually turned positive on a stool sample.

Serologies are now being widely used. They're rapid-test. There are multiple manufacturers, predominantly coming out of China, also out of Korea, but I would caution individuals on this. They're only positive on day 10 onwards, and we've had false-positive dengue serologies in individuals with COVID-19 disease.

So there are many, many kits out there, molecular diagnostic tests, serology. I just heard that Mayo Lab offers an IgG, which-- Mayo Lab is actually our reference lab here at the University Hospital in Singapore. But I think we really need a good understanding of the sensitivity and specificity of these tests.

And what's more is we really need a rapid diagnostic test very quickly. This is a very unfortunate migrant worker. He showed up in the hospital. He was swabbed and discharged, and he died at home, and it turned out that he had a myocardial infarction at the age of 32, without any known risk factors. And this has been a major concern, the cardiac complications, sudden cardiac death, cardiac arrest occurring in individuals infected with COVID-19.

There have been relatively few post-mortem studies. This one from China shows predominantly a lung disease, but, again, the mechanism of the cardiopathology has yet to be elucidated, as far as I know. There are some suggestions that this is an immunopathology, and, again, this is researchers from Singapore showing a spike in various inflammatory mediators, in particular, IL6, which has led to some treatment considerations.

Now, moving on to treatment, this is another patient of ours. A 45-year-old man came with upper-respiratory symptoms. He works in a church. His initial chest X-ray was normal. He was sent home. He re-presented to the emergency department, was admitted to isolation, found to be positive for SARS-CoV-2.

He developed mild dyspnea a couple of days into his hospitalization, which was about a week into his symptoms. And he was treated with Kaletra, also ceftriaxone, azithromycin. He responded really quickly. In fact, he responded too quickly for this to be a drug-treatment response, and he was discharged within a couple of weeks.

So these are the Singapore Interim Treatment Guidelines, and we've included remdesivir as being part of the trial, Kaletra, interferon beta-1b, hydroxychloroquine, and tocilizumab. But all of these, the bottom line is that the efficacy is difficult to determine, and we encourage participation in a number of the clinical trials.

So there has been a lot of interest in hydroxychloroquine and azithromycin. And this is from the French study published in *IJAA,* which the society that sponsors the journal has expressed concern about because the analysis is very questionable. And, of course, there is this issue of the QT prolongation with both the combination of hydroxychloroquine and azithro.

Now, Kaletra, for lopinavir-ritonavir has been studied in a randomized controlled trial in China, and the response to this trial has been pretty dismal. But there has been a one-day improvement in clinical symptoms. Now, it may not seem like a lot, but, you know, that's the difference that people see with Tamiflu in the licensing study, and you know we've got millions of doses of Tamiflu stockpiled all over the world.

So Kaletra, I have used Kaletra in a number of patients. The benefits, though, are uncertain, and this is one of my patients. She said she-- she was actually-- both the husband and wife are our patients. And she said she had a long video call with her husband. He took the Kaletra in the evening, but had diarrhea, and they couldn't control it, so this really got him down. So the GI side effects of these drugs are not unsurmountable.

Lately, there's been intriguing data on ivermectin. Now, ivermectin, as you know, has been used for years as an antiparasitic drug, and this is an uncontrolled study-- or from a global international database where they suggested that there may be some benefit to ivermectin. And the Australians have shown in vitro benefit for the drug.

Ultimately, I think a lot of these trials have to be studied-- drugs have to be studied in clinical trials. The WHO has what they call the SOLIDARITY clinical trial, where you can enroll a patient really easily. And they get randomized to either local standard of care or local standard of care plus one of remdesivir, chloroquine, lopinavir-ritonavir, or lopinavir-ritonavir plus interferon beta-1b.

Now, again, these are the mild to moderate patients, but we've also had patients with severe disease. 53-year-old jeweler, no past medical history apart from hyperlipidemia, had a cough. He had a temperature of 38.5, was admitted to a regional hospital. He desaturated. He was intubated, was proned. Interferon beta was added, meropenem, levofloxacin, vancomycin.

He was eventually put on ECMO. He had a PEA collapse, developed a right-tension pneumothorax. He was initially on VV-ECMO, then VA-ECMO, and then he developed this north-south syndrome, which, I have to admit, I had to look up before this presentation. And, therefore, he got switched to VAV-ECMO.

He had other complications, including acute kidney injury, ischemic hepatitis, a hemothorax, segmental PE. He was anticoagulated, went on to get a GI bleed. His PCR testing from the ETTA aspirate was positive. He'd had a day of negative, then positive again, and then it became negative. When he was extubated, his nasopharyngeal aspirate was first a positive-- subsequently, low copy numbers, and, finally, last week, it turned negative.

So far, he's doing pretty well. He was decannulated on day 13, extubated on day 14. He had to be reintubated on day 18, but was extubated, and he's currently sitting in a general ward awaiting rehab placement, day 39.

So ultimately, I think, the bottom line is that treatment of patients with severe COVID-19 disease depends on good medicine. And the Asian Critical Care Group have put together guidelines which essentially is the management of ARDS and critically ill patients.

What about the vaccine? Now, there's a huge race to develop a vaccine, but, to be honest, I don't think that we're going to get a vaccine in time for the vast majority of individuals with the disease. So we're down to preventing transmission.

Now, again, as most of you all know, the SARS virus started to spread globally in 2003 when a single individual from China went to the Metropole Hotel, stayed in room 911, and individuals who had no contact with him whatsoever, but stayed in room 912, 910, 914, and 918 brought the virus all over the world, to Canada, to Ireland, to the United States, Singapore, Vietnam, and other parts of Hong Kong.

Now, I stayed at that hotel, and I don't know if you can see this sign, but it was on the elevator buttons. There's a film, and the sign here says, this film is cleaned and sterilized every hour. And it's true. They sincerely believe that the elevator button was how this virus was transmitted. And so every hour, there's a lady who comes by and cleans the elevator buttons.

So there was one individual that came to Singapore, and she spread the virus to a number of others, including some health care workers, who went on, and then we had fourth and fifth-generation transmission with SARS. Now, the interesting thing is, the vast majority of people with SARS didn't spread the virus to anyone else, and the same is true of COVID-19.

Now, this is not appreciated, but there's a very detailed epidemiologic analysis published in *The Lancet* by the Singapore public health group, where they showed that more than 80% of individuals did not spread the virus to anyone, but you had these super-spreaders who spread to 7, 8, 11 people. And that is the problem we had with SARS, and it's also the problem here.

So prevention begins with epidemiology, understanding how the chains of contact transmission occurred, and this is what we did very well in the first wave. When we had patients coming in from China, the team went down, questioned them, got their contacts. We even got the electronic surveillance put in place, and we were able to track down cases.

Unfortunately, with the second wave, when we had cases coming in from Europe and North America, we've had widespread transmission. And the biggest problem has been transmission in these migrant-worker dormitories. It's a bit like what's happening in meatpacking plants in South Dakota and in Iowa.

And so you've got these dormitories where dozens of individuals are staying in very close quarters, sometimes 10 to 20 people in a room. There are a hundred people who share a bathroom, and that's, of course, a recipe for spread for a viral infection.

What the authorities have done is they've tried to isolate these areas, and they're trying to identify individuals who are sick. But, you know, that's a little bit like the Diamond Princess. When you isolated the ship, you end up with the virus spreading throughout the ship over a period of time, and we're afraid that that's going to happen in these dormitories.

So although most of these people in the dormitories are young men, they do have risk of complications, including cardiac complications. And we had one of these workers who was in the ICU for more than two months. He didn't even know that his wife had given birth to a baby boy, and they're trying to find some way of getting that across to him.

So this virus has been harder to control than SARS. SARS came and went relatively quickly, and part of the reason for that is that it's believed to be transmissible from a presymptomatic stage. And this has been shown again by the Singapore public health authorities when they did this detailed epidemiologic analysis. And they defined presymptomatic transmission as individuals who are documented to have transmission the day-- up to 24 to 48 hours before the onset of symptoms.

An illustration of this was a case where we had two people who traveled to Singapore from Wuhan, headed to church service. They left immediately after the service, didn't have contact with anyone else. But based on closed-circuit camera findings in the church, they found that two-- an individual who occupied the same seat as these two people, didn't meet them, ended up getting infected.

Now, don't ask me why they have closed-circuit TV in the church. Maybe people are-- they're going after the offering bag, but, ultimately, they managed to track down the transmission. And this was confirmed by serological and molecular epidemiology testing.

So you know, there's a lot of talk about moss and airborne transmission, and to me, this is a little bit like harking back to the miasma theory that reigned from the time of Hippocrates to Pasteur. And it took a good epidemiologist, John Snow, to prove that cholera wasn't spread by a miasma, but rather by contaminated water.

So this letter published in the *New England Journal* raised this question about aerosol transmission of SARS-CoV-2. And I want you to read the fine print because the fine print actually shows that what they did was they used a jet nebulizer to generate high-pressure aerosols. And then they had it in a chamber, and this chamber was used to test bioweapons during the Cold War. And, in fact, it was designed for testing Klebsiella aerosolization.

When-- in the real world though, when researchers from Singapore looked at patients with SARS-CoV-2, they found that the air samples were negative, despite extensive environmental contamination. And the group from the University of Nebraska found the same thing. They found positive viral RNA in the air, but they did not find culturable virus.

So I am really skeptical about whether the virus can really be transmitted by aerosols under normal circumstances. I'm not talking about aerosol-generating procedures. And this group, which has looked-- you know, they produce these really pretty pictures of plumes of air when people cough or talk or sing. And they had also found that for influenza there was no transmission of actual virus because you generate the aerosol, but it tends to drop to the ground rather than go across.

And what is the implication of this? So if an infection is droplet-transmitted, it transmits about 3 feet. Now, our emergency department is built by evidence-based guidelines, so 3 feet is 0.9 meters, so the beds are 1.1 meter apart. So we had this unexpected SARS patient in this bed, and the patient in the next bed, which is 1.1 meters apart, did not get infected because it was just a droplet infection. Unfortunately, his wife, who was standing in between, she got infected, and that's the problem.

So with droplet infections, we tend to use surgical masks. There was a case of an intubation in Changi General Hospital in Singapore, where health care workers just wearing surgical masks did all right. And, in fact, more recently, in the United States, in California, where they looked at health care workers, they showed that those who were not wearing masks, either surgical or N95 masks, during aerosol-generating procedures were more likely to be infected. This is a small number. It's just three individuals. But routine clinical care did not appear to be significant as a risk factor for transmission.

In terms of contamination of PPE, in negative-pressure rooms, the contamination rates are very low. In our Children's Hospital, they've shown that-- this was the little baby-- no chance of the baby wandering around. But you find that hand hygiene by health care workers is critical because there were many areas around the room which were contaminated by the virus.

And, of course, this is also depending on the temperature. At high temperatures and high humidities, the virus doesn't survive very long, as compared to at 4 degrees or at 22 degrees centigrade. And this is data out of Hong Kong.

But health care workers need protection. When I show this slide, people ask me, why do you need a N95 to answer the phone? And the answer is, if you don't protect your health care workers, they're going to lose their trust and confidence in you. So we had N95 masks all over the place. We even had a bank robber using a N95 during SARS.

So I don't like N95 respirators. I find it hard to breathe through them, and we've documented that they reduce tidal volume and minute ventilation. They also have a psychological impact, and that's a concern. So again, I believe that if you do need to-- for routine care, you can use a surgical mask.

We've seen an explosion in Singapore, and that's mainly the migrant worker dormitories. The concern has been about children, where the children actually have the reservoir, or they shed virus without actually getting infected in themselves, and that question hasn't been answered.

So for a long time, Singapore resisted the lockdown, but, finally, at the beginning of this month, we've got a lockdown. It's a really strict lockdown, and in Singapore, they take the laws very seriously. We have this poor guy who was charged after breaching a stay-at-home notice because he went out to deliver newspapers, presumably because his livelihood depended on that.

And there's a lot of talk about flattening the curve, but Harvey Fineberg, who many of you know, is from the Institute of Medicine. He was the head of the Institute of Medicine. He published an editorial in the *New England Journal* where he talked about crushing the curve.

And I think that's what we should try and aim for because, ultimately, you know, there's talk about the end of globalization. But I think we do live in a globalized world, and no one is truly safe until everyone is truly safe. And that's the lesson that we have learned the painful way with the second wave in Singapore. Thank you.

**FEMALE SPEAKER:** [INAUDIBLE]

**SURAJ KAPA:** Thanks, Paul. That was excellent. So I think we have a couple of questions for you. So Tom Munger's asking, are the super-spreaders those who have a heavy viral load, those who are confined to kind of packed areas, people who are very extroverted, in other words, going to a lot of areas, restaurants, et cetera, people who travel excessively, or some combination thereof?

**PAUL TAMBYAH:** Right now, we don't know. And, in fact, this has been one of my biggest bugbears is that we haven't been able to pinpoint why somebody is a super-spreader and why somebody is not. We've had a quick look at the individuals who had been associated with multiple transmissions, and those with dead-end transmissions, and there's no difference in terms of their viral load, in terms of the cycle threshold level.

We're actually trying to explore-- and this is one of the sad things, as somebody who does epidemiology. I haven't seen a single case-control study out of China, out of Italy, out of Germany, or anywhere. So we're trying to get one going to try and determine what it is that actually makes someone a super-spreader. Over.

**SURAJ KAPA:** And so another question in from Paul Friedman was whether or not-- so when we-- think of somebody who's infected. How long after they're initially diagnosed as having an infection can someone be told they're safe, in other words, that they're not contagious anymore?

**PAUL TAMBYAH:** And this is like the million-dollar question because in Singapore what we do is we keep them until they're PCR-negative times two, 24 hours apart. And that's been a huge strain on the health care system. We've had to convert a huge convention center into kind of a holding place for people who are well, but they are still PCR-positive.

The data from the German study suggests that after day eight, nobody has culturable virus anymore. But there are these reports that are coming out of Korea, people who have tested negative, and then test positive again, and that's raised concerns.

So in practical terms, what I do is, if somebody has got two negatives, we discharge them, but I tell them stay at home for a week or so, just to make sure you don't have a recurrence of fever. And most of them need the time anyway to recuperate. Over.

**SURAJ KAPA:** OK. And do you see a role for prophylactic medication, you know, while waiting for a vaccine to-- for either people who you know might have been exposed or otherwise to prevent them from progressing?

**PAUL TAMBYAH:** Yes, and, like I mentioned, we have this epidemic, which is raging through the migrant worker dormitories in Singapore, and we're actually trying to start a clinical trial of hydroxychloroquine versus ivermectin versus zinc as a prophylaxis because when you've got 15, 20 people in a room, it's really impossible to isolate these people and practice social distancing. So I think that's the challenge. I do believe that we are going to see prophylaxis at some point in time. Over.

**SURAJ KAPA:** And a number of people ask questions just about overall societal response because, obviously, the first time around, it seemed like you didn't really have to lockdown much, but then, obviously, with this research, there's more so. So the question is how-- is, what's the Singaporean thought on how to open up society again? You know, because, obviously, as you release restrictions, early uptick of cases-- what's the overall thought on that?

**PAUL TAMBYAH:** I mean, I think people are in two minds about it because on the one hand, we do recognize that you have to-- you can't sustain a lockdown like this. People are losing their jobs. You know, all our research has been suspended. The PhD students are having to defer their PhD deadlines.

But on the other hand, there's a fear that if you release things too quickly, then you're going to be in trouble. And so we had the benefit of starting our lockdown late, so we're able to see what's happening to other places where they've released the lockdown, like, for example, in China, in certain parts of Europe.

But I personally think that what's critical is you've got to have good surveillance. You know, you've got to have your influenza-like-illness surveillance. You've got to have your pneumonia surveillance. And so you've got to be ready to pick up a signal, and you can't release your lockdown until you can be sure you either hit a plateau, or the numbers are on their way down. Over.

**SURAJ KAPA:** All right, and a couple of people have questions just about PCR and what you consider a real negative versus a real positive. So one question was, do you consider two consecutive PCRs as indicating lack of infection, especially given what you said about the false-negative rate? And the other question is, for patients, the GI symptoms, do you ever obtain fecal PCRs?

**PAUL TAMBYAH:** Yep. So I'll answer the second question first, and the answer is yes. We do fecal PCRs. Our microbiologists always tell us that the test is not validated for feces, but we have done that, and it has worked in individuals with GI symptoms.

And the first question, it goes back to this whole point about, ultimately, we've got to remember that it's the clinical diagnosis that's really important. So the woman who had four negative nasopharyngeal PCRs before she had a fifth that turned positive, she had a very strong pretest probability.

She was the daughter of someone who-- I mean, her whole-- both her parents were positive. She had persistent fever, and she had a CT chest which showed ground-glass changes. So you know, the pretest probability was extraordinarily high, whereas you've got individuals-- I know-- we've got worried well colleagues who keep getting themselves tested, and they're negative all the time. I tell them, look, time to stop. Over.

**SURAJ KAPA:** So I have another question now, and from Paul Friedman, is, with the decision to try and use hydroxychloroquine and whatnot, other QT-prolonging medications, in some patients, do you have a national institutional approach to ECG monitoring?

**PAUL TAMBYAH:** Yeah. We haven't quite got that down in a written guideline. We do a baseline ECG, so anyone who's got a QTc which is prolonged, or is on other drugs which might prolong the QTc, they're obviously not eligible for hydroxychloroquine. Over.

**SURAJ KAPA:** So you basically say if the QTc is prolonged at all, that you just won't use hydroxychloroquine at that juncture?

**PAUL TAMBYAH:** Yeah, we won't. We would switch to fully try something else. Over.

**SURAJ KAPA:** OK. And so there's a lot of discussion about contact tracing that was used in Singapore, and what are your thoughts on that? Has there been a high penetration of that, of GPS or Bluetooth contact tracing in Singapore? Have you experienced that?

**PAUL TAMBYAH:** Yeah. So there is an app called TraceTogether, but it's only got about 25% of the population who have signed on. And it's a Bluetooth kind of app, and the trouble is that you've got to have your Bluetooth turned on all the time. And not everybody does that because they're worried about running out of data and stuff like that, or battery.

So I think that's probably the future, but we may not be there just yet. Interestingly enough, actually, and this is public knowledge, that the police were involved in the contact tracing early on. And they didn't tell us all that they know, but they keep track of cell phone mobile data. They keep track of, like, in subways, with the stored-value cards that people use on the subway, credit card stuff. And so they're able to build these networks, and that helped a lot with some of the contact tracing. Over.

**SURAJ KAPA:** And there's another question because there's a lot of papers out there whether or not having the BCG vaccine is protective for some people against the more severe manifestations of COVID. I mean, do you have any thoughts on that or experienced that?

**PAUL TAMBYAH:** Well, you know, BCG vaccine is still used in Singapore, and we're still trying to figure out why such a few kids have COVID disease. We had an outbreak in a child care center where 16 out of 25 staff were infected, but none of the children were positive. And they screened a whole bunch of the kids, and these are four and five-year-old kids who had recently been BCG-vaccinated.

But, again, there are a whole lot of other reasons why the kids may not have been infected. And, again, some of our pediatricians are trying to explore that. There is a possibility-- because within the virus itself, there is some role of the interferon gamma IL-12 kind of pathway, but, I'll-- again, a lot of that is preliminary and needs to be elucidated. Over.

**SURAJ KAPA:** And another question is, there's been a lot of discussion about a variety of mutant strains, and how there's some strains that are more virulent than others, and whether that might be putting a factor or not. And do you have any thoughts on that overall?

**PAUL TAMBYAH:** Yeah. I mean, I'm not a molecular biologist, but I have good friends who are, and the indications are that the mutations are not really affecting the phenotype, as far as we can tell. There is a mutation which was described in Singapore, which is an ORF deletion, or-- which was originally believed to be associated with less virulence, but it hasn't really panned out in clinical studies. And, again, I think these are still early days yet. Over.

**SURAJ KAPA:** And overall, when you look at the population approach, what's your testing approach in the population? I mean, is it you only test people as they're becoming symptomatic, or are you trying to test everybody possible?

**PAUL TAMBYAH:** Yeah, right now, what we're doing is we only test those who are symptomatic, but the focus is on contact tracing. So we test contacts pretty aggressively, and then we do surveillance. So we do pneumonia surveillance, hospitalized pneumonia patients. We do ICU patients with severe pneumonia, and we do influenza-like illness.

So those give us sort of a feel as to what's going on in the general public, but we try to discourage the testing of asymptomatic individuals. And right now, part of the problem is the whole world running out of RNA-extraction kits and stuff like that. So that's been a challenge.

**SURAJ KAPA:** Mm-hmm. And so there was-- there's just a question about what-- given the concern of ACE-driven receptors and whatnot, do you ever discontinue ACE inhibitors or ARBs?

**PAUL TAMBYAH:** No, we don't, and I think, again, the professional societies have been pretty clear about that. There's no evidence that-- and there have been a couple of cohort studies looking at individuals on ACE inhibitors and ARBs, and it doesn't seem to be associated with more severe disease.

**SURAJ KAPA:** And there's one general question about, what are your thoughts on how do we get from where we are to the point where we have herd immunity? Is it that we mitigate the disease to such an extent that it dies out, or are we kind of stuck with this until we get a vaccine?

**PAUL TAMBYAH:** Well, you know, I'm kind of optimistic that the weather's going to make a difference. And what I think is that it's going to go down with the Northern Hemisphere summer, and the key has got to be if we can stop it spreading in the tropics.

And Australia and New Zealand have done a really good job in keeping the numbers down, and that is also critical, because, otherwise, it's going to be like the flu. It appears in the north. It moves down to the south, and then it goes back to the north again.

So the hope is that with the warm weather in the north, if it doesn't really get established in the tropics, and then it may die out. But, again, some people would say that's wishful thinking.

**SURAJ KAPA:** And two final questions, so first off, we're talking about the IgG test, but, obviously, there will be a delay. So while that's delayed, is there a role for IgM for acute diagnosis?

**PAUL TAMBYAH:** Again, IgM only turns positive on day seven or eight in the majority of cases, so it's probably not that useful. And bear in mind, the key with testing is that you want to get this person out of circulation so that they don't become a super-spreader, or they don't start spreading it to their family.

So if the test is only going to turn positive on day seven or eight, by which time they may not really be shedding viable virus, I don't see it as being that useful in terms of clinical use. But it obviously is going to be useful in terms of epidemiology, trying to know what's the prevalence.

And, in fact, when people are talking about how to release the lockdown, they're saying, like, you know, when health care workers have to demonstrate immunity to varicella or hepatitis B before they start work, maybe we're going to have to demand that people show that they're immune to COVID-19. But, again, that's kind of speculative.

**SURAJ KAPA:** Mm-hmm. And you know, another question is, a lot of people have either tweeted about or talked about using lung ultrasound to follow their clinical courses. I mean, is that a practice you have, in terms of clinical assessment, following patients' courses or even evaluate those with false-negative PCRs, like doing lung ultrasounds?

**PAUL TAMBYAH:** We haven't used lung ultrasounds a lot. In fact, in China, as you know, they use CT scans because CT scans are so widely available there. In fact, in the private sector in Singapore, you can walk in and get a cardiac CT.

So what they did, I think, in China, is they converted-- they used a lot of those machines and started CT scanning anybody who had symptoms. And, in fact, their comment was it was easier to do a CT scan than to get a PCR.

**SURAJ KAPA:** [INAUDIBLE]

**PAUL TAMBYAH:** So we haven't quite got there, but no, the answer is no. We don't use lung ultrasounds a lot.

**SURAJ KAPA:** OK. And I'll leave you with one final question of just your personal opinion. How long do you think the virus will really be a problem when you think about things? And I know Singapore's a different climate zone than we are here, but if you had to make an offshoot prediction, would you say months, half a year?

**PAUL TAMBYAH:** Yeah. [LAUGHS] Well, you know, I've kind of gone on record as saying that I think this is going to be done by the end of May. That's becoming increasingly difficult to see whether that's-- see if that's going to happen. But it is plateauing in Europe, and I think there are signs that the peak may have been hit in the United States.

So I think the impact of the weather is going to be critical because if it warms up and the numbers drop drastically, then there is a possibility that that might happen. But, of course, again, there's the possibility that it might reappear in November.

**SURAJ KAPA:** Right. Thanks so much for joining us during your evening, Paul. And--

**PAUL TAMBYAH:** Thank you.

**SURAJ KAPA:** --I think everybody really enjoyed it.

**PAUL TAMBYAH:** Thanks very much.

**SURAJ KAPA:** Thanks, everybody.

**PAUL FRIEDMAN:** Thank you. Fantastic lecture. Really appreciate your coming.

**PAUL TAMBYAH:** Thank you.