Interview with Dr. Yasuharu Tokuda, Director of Muribushi Okinawa Center for Teaching Hospitals, Okinawa, Japan

The Outlook for the Pandemic

By *Japan SPOTLIGHT*

There is still a high-degree of uncertainty around the outlook for the pandemic at the beginning of March 2021 in spite of the significant increase in vaccinations. We are not sure yet if these vaccines will be effective for all the variants that have rapidly occurred in 2021. It is also unclear how quickly the vaccines can be made available around the world including developing nations.

We do not yet know when we can find effective therapeutics for the pandemic. What we do know at this stage is that the best policy to restore malfunctioning economies due to the pandemic is to contain the virus. For the good of the economy, we need medical experts' views on the outlook for the pandemic.

We interviewed Dr. Yasuharu Tokuda, a general practitioner, clinician-educator, and distinguished expert on clinical epidemiology on this issue.

(Interviewed on March 2, 2021)

Introduction

JS: First, could you please introduce yourself briefly? You have been working on a wide range of healthcare issues including local medical care and medical education, as well as public health policies as a member of a think tank named the Health and Global Policy Institute.

Tokuda: I was born in Okinawa and have been working as a general practitioner, tutoring medical residents and working on medical research since graduating from the Department of Medicine at Ryukyu University in Okinawa 32 years ago (https://sites.google.com/view/cv-yasuharu-tokuda-md-mph/home). I am currently working for Muribushi Okinawa, an alliance network of teaching hospitals in Okinawa, as its director. There are some hospitals accepting medical residents on junior residency programs. Our alliance consists of 28 hospitals among which eight are core hospitals, and 20 are cooperative hospitals or clinics. As director of the Alliance, my main responsibility in Okinawa is medical education.

In addition, I am doing outpatient consultation as a general practitioner and doing research on clinical epidemiology. I used to live in the Kanto district of Japan for 11 years and then worked for Tsukuba University for five years. Even now, I am a visiting professor of Tsukuba and frequently participate in education and research there.

Dr. Yasuharu Tokuda

Assessment of Public Health Policies to Counter the Pandemic

JS: How do you assess each nation's policies to deal with the pandemic so far?

Tokuda: A relevant assessment would need comparisons among nations. In this case, I believe that selecting nations properly to be compared would be important. The pandemic's impact on the human body is significantly different depending upon the infected people's genetic background and also their living climate and environment. Therefore, it would be appropriate to compare policy performance among nations ethnically close (meaning genetically close) to each other and also close geographically. In the case of Japan, thus I believe that we should compare the situation of infections with countries in Asia and the West Pacific area and not with either Europe or the United States. In comparison with Europe and the US, Japan has much fewer infection cases and less mortality. But in comparison with Asian or West Pacific nations, the situation in Japan is not necessarily good.

JS: The number of PCR tests in Japan was not enough to contain the pandemic at the beginning.

Tokuda: I think our target setting was not well placed. That would have a more negative impact upon performance than insufficient

PCR tests. Experts and policy makers in Japan thought at the beginning that it would be possible to achieve a growing economy with virus infections remaining flat, or not increasing much. Like the Europeans and Americans, Japan had a strategy for co-existence between economic activity and the pandemic. But I found that they were wrong. After having suffered significant increases of infections a few times, I found co-existence of our economy and the pandemic would be difficult.

JS: Containing the virus would be the first priority to restore our economy, since another big rise in infections and another possible lockdown policy could result in its destruction.

Tokuda: Yes. I would like to emphasize that pursuing zero infections would be a better strategy. All nations successful in containing the pandemic have been taking such strategies so far, such as China, Taiwan, and Asia-Pacific nations like Australia and New Zealand. On the other hand, the Philippines and Indonesia could not control significant increases in infections and mortality with the strategy of co-existence of the economy and the pandemic. New Zealand has been successful in having largely contained the pandemic with a zero infection strategy based on science and the prime minister's leadership. The economies of those nations with zero infection strategies have not been seriously damaged. For the economy's own sake, we would need to try to contain infections first. The WHO announced in March 2020 that it would be possible to fully contain the pandemic (https://www.npr.org/sections/goatsandsoda/2020/03/02/811271217/coronavirus-update-we-are-in-unchartered-territory-who-says). We should have set this as our goal at the beginning.

PCR Tests as Primary Means to Control Infections

JS: To contain the pandemic then, do you think enlarging PCR test capacity would be most important?

Tokuda: The WHO also mentioned the importance of PCR tests as a means to isolate as many infected people as possible to prevent widespread infections a year ago when they found that an infected person even before symptoms emerged could infect another and also an infected person without any symptoms could infect another. According to the latest data of the US Centers for Disease Control and Prevention (CDC), around 50% of infected people get infected from those without any symptoms.

So far, the policy of isolating infected people in past ordinary pandemic cases has been based on those people with obvious symptoms, but in the case of Covid-19 it is not valid anymore. We need to find who is infected before they start to have symptoms or even if they have no symptoms, and then isolate them. It would be difficult to do so without PCR tests. We did not have this test at the time of the so-called Spanish Flu over 100 years ago. We have it now. Thus we should have had more PCR tests at the beginning of the pandemic as well as other countermeasures, like requesting people to wash their hands, keep a social distance and wear a mask. A PCR test is a technology developed over the recent decades that has enabled us to find infections clearly. We should use this invaluable technology.

Science journals such as *Nature*, *Science* and *The New England Journal of Medicine* recommended large scale PCR tests, while the Japanese Ministry of Health, Labour and Welfare (MHLW) as well as some experts in the advisory group to the Japanese government were skeptical about its accuracy, which may still mislead people's understanding about it in my view. It is said that 1% of those tested would show false positive in PCR tests. But this is wrong. Because, PCR is originally a test to discover nucleic acid molecules with a specific nucleotide sequence, and in the case of Covid-19, this is an RNA (Ribonucleic Acid) virus and we try to discover RNA in the RT-PCR test. This RNA has an extremely specific nucleotide sequence, namely four kinds of bases – adenine, uracil, cytosine and guanine. SARS-CoV-2 has around 30,000 bases. A PCR test can identify very specific nucleotide sequences out of these bases. It is so specific that we cannot get the wrong result unless there is cross-contamination in which a different sample is mixed with the authentic one by human error. There should not be as much as 1% of false positive results in total.

Recently Developed Vaccines

JS: What do you think about the effect of the currently available vaccines?

Tokuda: Vaccines seem to be more effective than we assumed. But we have to add "at this moment" as a reservation. We have now four new-type vaccines developed – Pfizer, Moderna, AstraZeneca, and Johnson and Johnson. Among these, Pfizer is available now in Japan. Its clinical tests show rather positive outcomes, namely the preventive effect for symptomatic infection is more than 90%. In Israel, where

vaccine injections are most rapidly under progress, it has resulted in a significant decrease in infections. This truly shows the wonderful progress of medical science, as in the case of PCR tests.

JS: Vaccines are effective at this moment, but they may not last long and there is a concern that they may not work well against emerging variants. As most infections from now on will come from the variants, it is increasingly difficult to predict how the pandemic will develop.

Tokuda: Yes, certainly it is. From now on, most likely, how quickly we can achieve vaccinations against possible evolutions of the virus will be a key to containing the pandemic. We will need to repeat injections of vaccines in response to emerging variants. This was originally assumed, because RNA is a single helix and its bases are not protected as in DNA (Deoxyribonucleic Acid) with a double helix, where bases are preserved in a double helix structure. In transcription, errors in copy are unusual in DNA, but there could be errors often in RNA. Most of the variants are failed ones and useless for the survival of the virus and in many cases those viruses die on their own. However, there are some cases of survival of the fittest, the outcome of evolution. Such mutations could happen when the pandemic is spreading. At this moment, we have seen these variants of concern with strengthened functions in nations such as the United Kingdom, South Africa, Brazil and the US. In order to contain the epidemic, it is said that we would most likely need to give a booster injection of vaccines structurally adjusted to the variations of the molecular structure of a virus once a year or so, as in the case of flu.

Current Status of Therapeutics

JS: Another key to containment of the pandemic is therapeutics. How do you assess the current situation of the development of therapeutics?

Tokuda: So far, what has been known in the past year is that Dexamethasone could certainly lower mortality. Remdesivir used in the US could work well depending on the timing of the therapy or specific group of those infected. The cocktail therapy of monoclonal antibodies that former US President Donald Trump received would be effective at the early stage of the disease. However, both Remdesivir and monoclonal antibodies are so expensive and neither is recommended by the WHO. The WHO recommends only Dexamethasone. There have been many candidates for therapeutics such as Ivermectin. However, appropriate clinical trials for these have not been done so far in Japan. We should have done such clinical trials properly designed and played a leading role in the design of those tests under the leadership of the MHLW and the National Institute of Infectious Diseases.

As for PCR tests in Japan, collaboration between the MHLW and the Ministry of Education, Culture, Sports, Science and Technology should have achieved to ramp up capacity for PCR testing, since medical research organizations have more capacity. But except for departments of medicine at universities with their own hospitals which actively did PCR tests to prevent cluster infections at their university hospitals, the medical research organizations' capacity for PCR testing was not actively utilized – and this was very different from the US case.

On therapeutics as well, Japanese university hospitals have not succeeded in developing them so far. I think this is because collaboration between the two ministries I mentioned did not work well either. Therapeutics are possible only when clinical trial doctors for patients at hospitals and basic research scientists on virus structures at laboratories are well coordinated. I wish at least there had been a conclusion on the effectiveness of Ivermectin by clinical trials during this past year. We should have had a randomized controlled trial (RCT) for Ivermectin, simply comparing it with a placebo. It is actually used in Africa, but without an RCT, and though it looks effective that would not be enough evidence.

Anyway, laboratory researchers are working hard on developing therapeutics, so I believe it is possible for us to have more effective therapeutics than Dexamethasone, but we do not know yet exactly when.

Pandemic Making Us Innovative

JS: The pandemic has promoted medical innovation in a sense. For example, an RNA vaccine is an extremely remarkable innovation, isn't it?

Tokuda: Yes, it is. In the US, this vaccine development was achieved at so-called "warp speed" and what would take six years usually was done in six months. New types of vaccines were developed one after another such as a vaccine with a messenger RNA (mRNA) and the Adenovirus vector vaccine, as well as the ordinary inactivated vaccines developed by China. It is often said that mRNA would be an effective cure for a variety of diseases and at this moment it is considered to work well for preventing and curing tuberculosis and cancer. Though there is a BCG vaccine for tuberculosis, prevention of

it is difficult. Treatment for it is also difficult, in particular in the case of a tuberculosis virus with resistance. Thus it is still one of the three largest infectious diseases in the world.

Cancer is the primary cause of Japanese mortality, but also a challenge for the whole world. There is a treatment for it by eliminating cancer cells by an immune force called immune therapy developed by Prof. Tasuku Honjo, winner of the Nobel Prize in Physiology or Medicine. An mRNA vaccine could strengthen immunity and create immune cells specifically attacking cancer cells in large numbers within a patient's body. This is how this vaccine would have an extremely positive impact upon treatments for other diseases. That would lead to an unprecedentedly wonderful world which we have never dreamed about.

This vaccine would be ready to prevent possible new pandemics in the future, including the current one's variants that some experts even refer to as new infectious diseases, because new effective mRNA vaccines could be easily prepared only by changing bases. It would not take a long time to make them. Also, while in the case of a vaccine for flu we cannot make it without a chicken egg, an mRNA vaccine does not need a chicken egg as it is mechanically created in a factory like a laboratory. Thus massive production is easily done.

The Pandemic & Public Health Policy

JS: Have we Japanese learned a lot about public health policy to counteract the pandemic?

Tokuda: Japanese people have learned about their own weakness in public health policy. A virus is invisible, different from bacteria. We cannot find it even by an optical microscope. Therefore, without turning the invisible into the visible by PCR tests, we cannot have a public health policy intervention. In this regard, we should not have given up PCR tests at the initial stage.

There are only three public health policy interventions against infectious diseases – namely, countermeasures against infection sources; measures against routes of infection; and measures to enhance immunity among hosts. A vaccine is to enhance immunity and thus it is in the third category. Keeping a social distance, wearing a mask, keeping adequate ventilation in closed spaces, and washing hands are in the second category. Another important countermeasure against infections is to discover the sources of infection at an early stage and protect and isolate them.

Experts and policy makers of Japan should learn that these measures in the first category must have been exhausted on a large scale.

JS: We should examine and analyze the outcome of our public health policies on this occasion by an evidence-based approach and find out how we can improve our policies.

Tokuda: Yes, experts and policy makers of Japan should learn from the best practice cases such as in New Zealand, Taiwan and some Southeast Asian nations. Inside Japan, Wakayama Prefecture's case could be considered a successful one.

The Future of the Pandemic

JS: It is difficult to predict the future of this pandemic as we still see growing uncertainly around it. But predictions about the future of the pandemic are vital for economic forecasts. Most economists seem to see the end of this pandemic at the end of 2022. When do you think the pandemic will be contained?

Tokuda: The key question is to what extent effective vaccines prevail all over the world. Assuming the current speed of vaccinations goes on as it is now, it will be after 2022 when developing nations will have enough vaccine injections to contain the pandemic. That means the pandemic will not be contained until after 2023. It is also noteworthy that variants are evolving to make vaccines less effective even as vaccine injections are increasing.

According to the latest opinion poll organized by the science magazine *Nature*, a majority of experts worldwide think it will be difficult to eliminate this virus completely from the earth and assume this pandemic will become endemic.

For example, the Middle East Respiratory Syndrome (MERS) is similar to Covid-19 and is still now endemic in the Middle East with infections through camels. Covid-19 could infect an animal as well, though it is still unknown from what animal the infection comes. Since it is almost impossible to eradicate this virus completely, it would be endemic. The question is where this endemic will be. I hope it will not be in Japan or any countries in the world. JS

Written by Naoyuki Haraoka, editor-in-chief of *Japan SPOTLIGHT*, with the assistance of TapeRewrite Corporation.