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Responses to COVID-19: Considering the Evidence
-How should we prepare for a second wave?-

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The spread of the COVID-19 has had a tremendous impact on the global economy and societies throughout the world. Why is the coronavirus causing such severe problems? Why has Japan suffered less severely from the virus than other countries? Is there a realistic possibility of the development of a vaccine? Discussions based on sound medical findings will be essential to preparing for a second wave and beyond. NIRA therefore invited Dr. Tai Takahashi, an expert on public health and the Japanese medical system, and Dr. Mitsuyoshi Urashima, an epidemiologist, to discuss the relevant issues. Dr. Yuri Okina, one of NIRA's Executive Vice Presidents, acted as moderator.

The discussion ranged over the following topics: (1) The mechanism of the "cytokine storm" (a "runaway immune system") that causes COVID-19 to become severe in certain patients; (2) The progress of a range of research, including into the question as to whether the relatively low mortality rate from the infection in Japan is due to an innate immunity peculiar to the Japanese or potentially to BCG vaccinations ; (3) Evaluation of the current status of development of drugs and vaccines; and (4) The importance of exit strategies tailored to risk factors such as age.

In order to prepare for the future, it will be important to verify the appropriateness of the response to the first wave of infections based on up-to-date findings, to establish a system that makes it possible to grasp the status of infections at the national level and in real time, and to establish a system enabling hospital beds to be assigned separately to patients with mild symptoms and patients with severe symptoms in each of the nation's regions. It will also be necessary to analyze data concerning infections in Japan and make the results of this research known overseas.

The spread of the COVID-19 from China throughout the world has caused enormous damage in the United States and Europe, and the virus is now spreading to developing countries. Japan's situation, however, is less severe than that of the western nations. Why is this the case? And if we halt the spread of the virus, how should we prepare for possible second and third waves, which it is thought will come after autumn?

On May 17, NIRA invited Dr. Tai Takahashi, an expert on public health and Japan's medical system, and Dr. Mitsuyoshi Urashima, an epidemiologist, to discuss issues including the evaluation of efforts to halt the spread of the infection and the best direction for Japan's medical system in the future. Dr. Yuri Okina, one of NIRA's Executive Vice Presidents, acted as moderator.

During the discussion, all participants wore masks; other efforts were made to respond to COVID-19, including ensuring adequate ventilation.

This paper was edited by Kozue Sekijima (NIRA Research Coordinator, Researcher), Maiko Sakaki (NIRA Research Coordinator, Researcher), and Tatsuya Yamaji.

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Part 1

Why has the Rate of COVID-19 Infection been lower in Japan?

Differences between COVID-19 and influenza

Okina: To begin, would you please explain the characteristics of COVID-19 as compared to influenza?

Takahashi: A variety of recent research has clarified the characteristics of COVID-19. While many of the findings are still at the hypothetical stage, we can compare the mechanism of infection and onset for influenza and COVID-19 as follows: (1) Level of virulence (Influenza: Strong; COVID-19: Weak); (2) Cause of death (Influenza: The virus itself; COVID-19: Cytokine storm), (3) Mode of recovery: (Influenza: Acquired immunity; COVID-19: Significant involvement of innate immunity); and (4) Duration of presence in the body (Influenza: About 1 week; COVID-19: 1 month to several months).

In the case of influenza, because of the virulence of the virus itself, the time from exposure to the virus until symptoms appear is short, and antibodies that protect the body appear quickly. Death may result from influenza pneumonia. When the body is attempting to eliminate a highly virulent virus, the "acquired immunity" function takes effect. This is a specific immune mechanism targeting the virus, and antibodies appear immediately. The action of these antibodies will cause the symptoms to subside in about a week. By contrast, in the case of COVID-19, the time from exposure to the appearance of symptoms is long, from several days to two weeks. Initially, the body tries to respond to the virus with "innate immunity," the body's natural immune mechanism. It takes about two weeks to develop antibodies by means of acquired immunity after being infected with the virus. This means that the virulence of the virus itself is low. Even with PCR tests, when a swab is taken from the nasopharyngeal region, the tests read positive about three weeks after symptoms appear, and become negative after that, but in many cases, the tests remain positive for a long time after the appearance of symptoms when the test is conducted via the pulmonary alveoli or feces.

Unlike influenza, the virulence of COVID-19 is extremely low, but this is precisely the problem. The major cause of the confusion throughout the world today is that the virus itself does not cause death, but when it spreads throughout the body, it can suddenly become severe due to a mechanism known as a "cytokine storm," which is different to the virus itself.

Okina: A "cytokine storm" is a runaway immune response. Could you explain this in a way that makes it easier to understand?

Takahashi: Normally, when a virus enters the body, cells release proteins called cytokines, which activate the immune system. However, when excess cytokines are released, a "cytokine storm" occurs and the immune system goes out of control and causes severe pneumonia.

In the case of influenza, severe pneumonia is caused by the highly virulent influenza virus itself. However, it is hypothesized that the severity of COVID-19 pneumonia is caused not by the virulence of the virus itself, but by virus-induced cytokine storms. Judging from the clinical pattern of the sudden worsening of symptoms, I believe that there is no doubt that a phenomenon like a cytokine storm is occurring in the body. When a cytokine storm occurs, symptoms rapidly worsen to the point that the patient dies. In addition, COVID-19 displays a rapid rate of transmission. Although the mortality rate from COVID-19 is much lower than the rate of death from influenza in Japan, the number of deaths in the entire population exceeded 740 by May 17 (last year there were 3000 deaths resulting from influenza). It is also assumed that some medical facilities were temporarily put under a severe and intense burden because the infected patients had to be isolated. And that caused a panic.

Figure 1 : Differences in Seriousness and Cause of Death between COVID-19 and Influenza

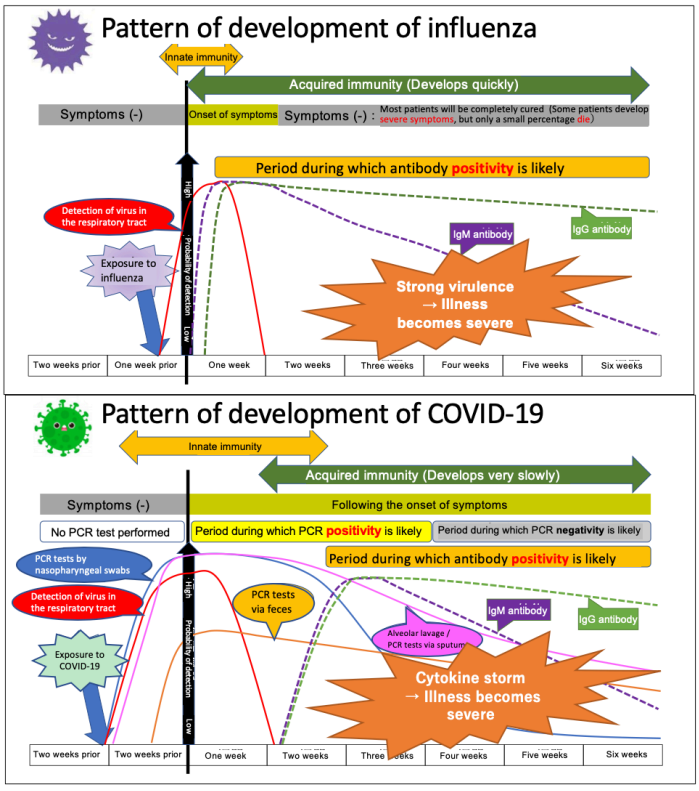
- Influenza

A deadly form of pneumonia caused by highly virulent influenza

- COVID-19

Disease increases in severity due to a different mechanism

Increase in severity leading to death due to cytokine storm



(Source) Formulated by Dr. Tai Takahashi

Four reasons that the coronavirus mortality rate is lower in Japan

Okina: We have seen that there are significant differences between influenza and COVID-19. The initial limit for the state of emergency declared in Japan was May 6, but this was extended to May 31 in eight prefectures. Following this, the state of emergency began to be lifted depending on the situation in each of the nation's regions. Japan has conducted a much lower number of PCR tests than other countries, so it is said that the actual number of infections is higher than the statistics.

However, the actual status of the damage caused by the virus in Japan should be seen in the number of deaths. How do you evaluate the status of COVID-19 infections in Japan?

Urashima: We may have underestimated the number of people infected. It is better to look at the number of deaths in order to grasp the actual status of the spread of the virus.

Looking at the number of deaths per 1 million people in different countries, the figure is between 500 and 600 in Italy, Spain and England, and 271 in the United States. By contrast, the figure is 5.88 in Japan (as of May 17, 2020; European Centre for Disease Prevention and Control data). The mortality rate in Japan is only about 1/10 to 1/100 of the rates in Europe and the United States, and the mortality rate among those infected is a fraction of the rates in those countries.

Of course, there is a possibility that the number of deaths has been underestimated, but it is difficult to believe that the Japanese medical system is not studying the status of coronavirus infection in deaths suspected of being due to the virus. Compared to other countries, I don't think the number of deaths has been significantly underestimated, for example by several tenths.

Okina: The mortality rate in Japan is certainly much lower than in the West, and there seems to be a lot of discussion about this. What do you think is the reason for the lower COVID-19 mortality rate in Japan?

Takahashi: I think there are four reasons why the mortality rate is lower in Japan than in the West. First, the Japanese have a strong "innate immunity" against COVID-19. The difference in the mortality rate between Japan and the West is more than 100 times, and this cannot be explained as a result of lifestyle and the medical system alone.

Urashima: Usually when people talk about infectious diseases, they tend to focus on "acquired immunity" and not on innate immunity. However, in many cases, COVID-19 is suppressed by this innate immunity.

For example, if we get measles or have a measles vaccination, antibodies are produced in the body. When the measles virus enters the body, the antibodies block it. This type of immunity that acts against a specific virus is acquired immunity.

But the human body also has an innate immune mechanism that goes into action at the initial stage when a potentially harmful antigen enters the body. This mechanism is precisely why human history has lasted so long.

It has become clear that this innate immunity can be further enhanced. One cytokine that has attracted particular attention recently is interleukin-1 ß (IL-1 ß). When produced in high quantities, IL -1 ß is a potent weapon against viruses. In some people, it is easy to trigger the “switch” for the production of IL-1 ß, while in others it is difficult. In the case of people in whom innate immunity has become further enhanced, when the virus enters the body, IL-1 ß production is switched on immediately; in a person for whom triggering the switch is difficult, however, the amount of bad cytokines increases, producing a cytokine storm and leading to pneumonia. It seems that the Japanese are somehow developing trained innate immunity. The hypothesis that this might be related to BCG vaccinations is attracting attention. We will discuss this later.

Takahashi: The second reason is that the level of isolation of elderly people is high in Japan. COVID-19 represents an overwhelmingly high risk for the elderly. There is a significant difference in the probability of the illness becoming serious and the patient dying between young people and the elderly. In Japan, there is a 1000-fold difference in the probability of death from serious illness between people aged 0-29 and those aged 70 and over. Ensuring that the elderly do not become infected has a major impact on the number of deaths.

Chart 2 : Differences in Seriousness and Cause of Death between COVID-19 and Influenza

Total PCR-positive patients		
	Severity	Mortality rate
Under 10 years old	0.40%	0.00%
10s	0.28%	0.00%
20s	0.16%	0.00%
30s	0.40%	0.09%
40s	1.47%	0.33%
50s	2.47%	0.63%
60s	7.63%	2.52%
70s	12.23%	6.82%
Over 80 years old	16.80%	14.84%
Aggregate for all age cohorts	4.5%	2.6%

Estimates based on 3.3% antibody positivity in Kobe city		
	Estimated severity	Estimated mortality rate
0 -29 years old	0.00122%	0.00000%
30 -59 years old	0.00927%	0.00223%
60 -69 years old	0.04783%	0.01582%
Over 70 years old	0.09190%	0.06877%

(Note) As of May 5, 2020. The rates at which the illness becomes serious and leads to death are a proportion of the total number of PCR-positive individuals; the estimated rates at which the illness will become serious and lead to death in Kobe City represent proportions of the population.

(Source) Formulated by Dr. Tai Takahashi based on Ministry of Health, Labour and Welfare and Kobe City data.

In Japan, facilities for the elderly are well prepared for viruses due to the spread of norovirus and the influenza virus. From the point of view of a virus, I think that it would be very hard to get into facilities for the elderly in Japan today, which are virtually like fortresses. And if you talk to people of 80 and above, you will find that they are very afraid of dying of the coronavirus. If it was reported that someone had died of the coronavirus, it would cause trouble to people around them. Therefore, they voluntarily live in isolation and reduce their contact with people. I believe that the "fortress-like" quality of facilities for the elderly and the voluntary isolation of elderly people have contributed greatly to the fact that the number of deaths of elderly people in Japan is much lower than in the West.

The third factor is lifestyle. Japanese have the custom of washing their hands frequently and wearing masks, and they take off their shoes indoors. They also don't hug or kiss excessively.

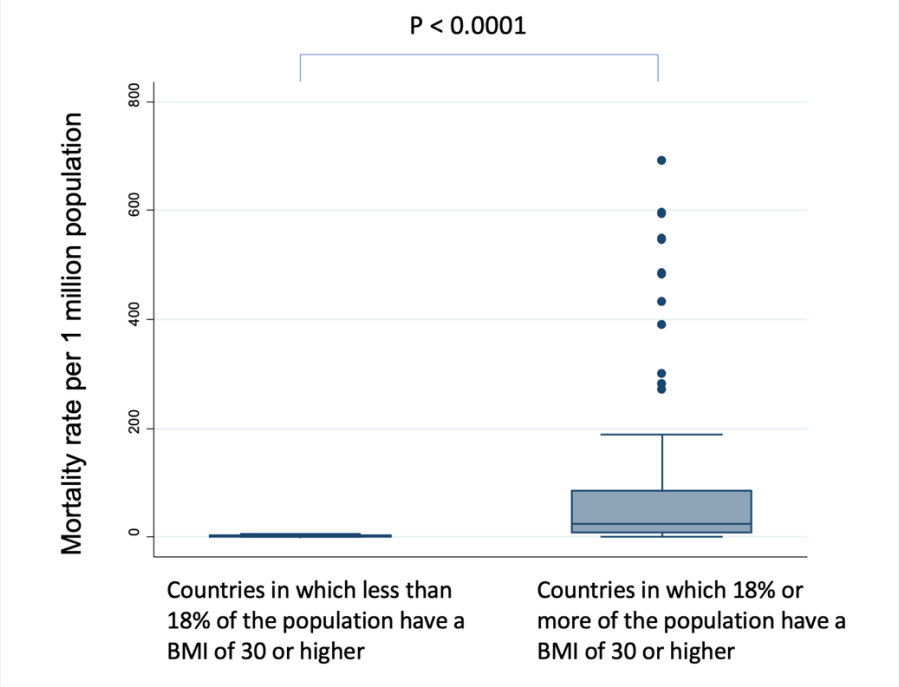
Takahashi: The fourth factor is the medical system. I think cluster task forces, which identify clusters (small groups of infected individuals) and trace the source of the infection, have also been effective. And if someone is hospitalized in Japan, they are able to receive the appropriate

treatment.

Urashima: This is because Japan and Korea have an overwhelmingly high number of beds per population. There are about 40 beds per 10,000 people in many countries, but there are 130 in Japan. The number of beds in intensive care units (ICU) is low, however.

Another reason is possibly the level of obesity. Obesity is expressed as a score called the body mass index (BMI=body weight [kg] / height [m]^2).

Figure 3 : Obesity (BMI) and COVID-19 Mortality Rate



(Note) Body mass index (BMI) is an indicator that expresses obesity. At a BMI of 22, a person is considered to be at a normal weight, and is the least likely to get sick. The World Health Organization (WHO) defines obesity as a BMI of 30 or more. The figure compares the COVID-19 mortality rate per 1 million people in countries in which obese people with a BMI of 30 or higher make up less than 18% of the population (for example, Japan, where the figure is 4%) and countries in which they make up 18% or more (for example, the US, where the figure is 37%). p < 0.0001 indicates a significant difference, with a median difference of 9 times.

(Source) Formulated by Dr. Mitsuyoshi Urashima from WHO data (https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-obesity-among-adults-bmi-=-30-(crude-estimate)-(-))

The normal range is 18.5 ~ 25. Japanese rarely have a BMI over 30, but 37% of Americans do. Comparing countries in which 18% of the population or more is obese to those in which the figure is less than 18%, we find that obesity has a significant impact on the mortality rate for COVID-19 (Figure 3).

However, it appears that it is high blood pressure rather than obesity itself that is affecting the severity of COVID-19. And it seems that high blood pressure is a negative factor whether or not the patient is taking medication to lower their blood pressure. The surfaces of human cells possess a mechanism for the regulation of blood pressure via angiotensin-converting enzymes (ACE). As ACE increases, blood pressure increases, and ACE2 increases to try to lower blood

pressure. ACE2 is present not only in the lung epithelium and the mucosal epithelium of the gastrointestinal tract, but also in the endothelium of blood vessels and the surface of the myocardium. The new coronavirus uses this ACE2 to infect the patient.

This is conjecture on my part, but ACE2 expression presumably increases in the bodies of people with high blood pressure in order to lower blood pressure. Both diabetic and obese people tend to have high blood pressure, and so there is a possibility that they produce high quantities of ACE2. Since COVID-19 infects cells using ACE2 as a foothold, high blood pressure and obesity may be risk factors. It is not possible to be certain about this, because at this point there is no data. If this hypothesis is correct, it could be a factor in the increased risk of COVID-19 becoming severe and the increased mortality rate in countries with high rates of obesity.

Part 2 International Competition for Vaccine Development?

Does BCG vaccination enhance innate immunity?

Okina: You mentioned earlier that the natural immunity of Japanese people may have been enhanced. This is thought to be an effect of BCG vaccination, isn't it?

Urashima: Yes. BCG, a vaccine developed to prevent tuberculosis, has recently become a subject of interest. It has been hypothesized that BCG vaccination may strengthen and train innate immunity.

This is based, in part, on a paper published in 2018 by a research team at Radboud University in the Netherlands[i]. BCG vaccination has never been conducted in the Netherlands. The researchers randomly assigned test subjects to a group that would receive BCG vaccination and one that would not. One month later, the test subjects were vaccinated against yellow fever. Because this is a live vaccine, the possibility of subjects developing viremia (a condition in which a virus enters the bloodstream) was high. Blood samples showed that only 29% as many of those who had received BCG vaccinations developed viremia compared with those who had not. A study of the participants' cytokines showed that interleukin-1ß was functioning particularly strongly, and this may have suppressed the yellow fever virus.

The Netherlands is currently conducting a randomized controlled trial of BCG vaccination among healthcare workers[ii]. Participants were divided into a group given BCG vaccinations and a group given a placebo, and the rate of infection with COVID-19 was compared. In addition to the Netherlands, clinical trials of BCG have also started at the Children's Medical Research Institute in Australia and at Harvard University.

Okina: The impact of BCG vaccination on COVID-19 is in fact also attracting interest in the field

of economics, but some studies have reached negative conclusions about the effect of the vaccinations. The percentage of people infected with COVID-19 is lower in the former East Germany than in the former West Germany. BCG vaccinations were conducted in the former East Germany, and it has been hypothesized that this fact might be related to the phenomenon. However, economists at the Federal Reserve Bank of New York have concluded that while there is clearly a difference between figures for the former East and West Germany, a comparison of the difference between infection rates in residents of the former West Germany who received BCG vaccination and those who did not indicated that the vaccinations are not significant.[iii].

Takahashi: The effect of BCG is probably more pronounced in terms of the mortality rate than the infection rate, and so we have to look at the number of deaths. However, because the mortality rate is low, it may not be possible to verify the effectiveness of BCG without a comparative study of several hundreds of thousands of people.

Okina: Your comments are very interesting, because they suggest the necessity for analysis based on the opinions of medical professionals.

Urashima: The number of new infections in Russia has recently been increasing at a rapid pace, and is now approaching that of the United States. However, the mortality rate per 1 million people is not increasing significantly, and is only a little higher than Japan's. BCG vaccination has been conducted in Russia since the era of the former Soviet Union. In Italy, the Netherlands, Belgium and the USA, where BCG vaccinations were not conducted, the COVID-19 mortality rate is high (Figure 4).

Takahashi: Simply put, with regard to BCG, there are different strains of tuberculosis bacilli. There are strains from Japan, the Soviet Union, Denmark, etc.

Urashima: It is possible that differences among these strains may also have an effect. However, it is not easy to measure the effect of BCG vaccination. For example, not every member of the population in countries in which BCG vaccinations were conducted were actually vaccinated; it is also possible that immigrants who were not fully covered by national systems are present in the nation.

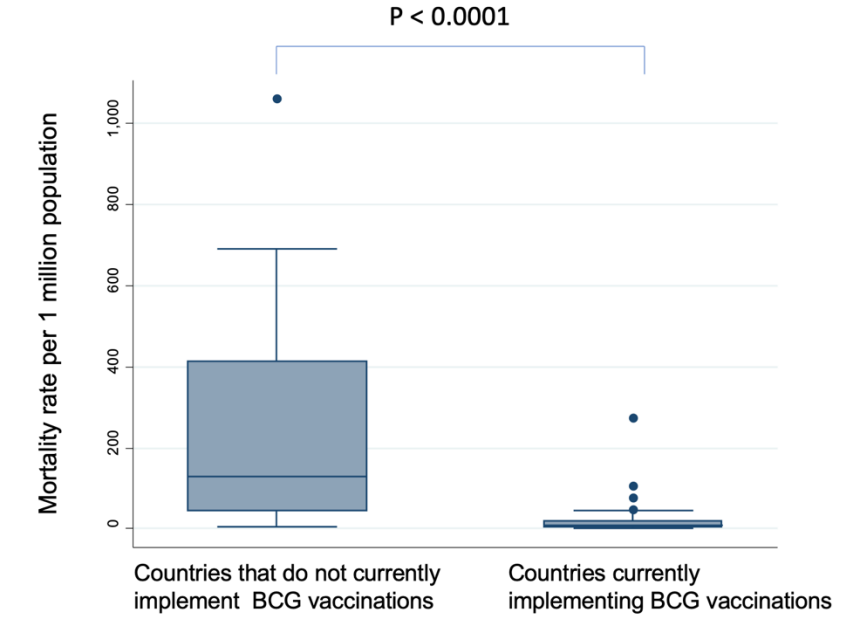
Also, the method employed for BCG vaccination varies greatly depending on the era. Until recently, children in Japan received BCG vaccinations when they were infants, and their tuberculin reaction was monitored when they entered elementary school. If the tuberculin reaction was negative, they received a further BCG vaccination. If the tuberculin reaction was positive, chest X-rays were taken to diagnose tuberculosis. However, since 2005, the tuberculin test has not been performed following BCG vaccination as an infant. BCG is basically a stamp injection of weakened tuberculosis bacilli. If only one shot is given to an infant, the bacilli may be eliminated by the infant's own immune system. Many young people in Japan may have negative tuberculin test results even if they have received a BCG vaccination. This presents in basically exactly the same way as them not having received a BCG vaccination.

Takahashi: It has also been indicated that intestinal bacteria may have an effect on the differences

in the Japanese reaction to COVID-19. In Europe, it has been reported that when COVID-19 enters intestinal bacteria belonging to the genus Prevotella, it causes a cytokine storm, resulting in serious pneumonia. There is a view that using a drug called azithromycin to regulate intestinal bacteria could be effective in preventing COVID-19 infections from becoming more serious, and research is being conducted in this area worldwide.

Okina: There are differences in intestinal bacteria among countries and individuals. The diversity of the bacteria is attracting attention from the perspectives of both health and longevity.

Figure 4 : Implementation of BCG vaccinations and COVID-19 mortality rate



(Note) The category "Countries that do not currently implement BCG vaccinations" includes countries that have never implemented a BCG vaccination program as part of their national vaccine program in the past (Italy, the Netherlands, Belgium, the United States, Canada, and Lebanon; in these countries, vaccination is recommended only for certain individuals), and countries that have implemented BCG vaccinations at some point in the past but have discontinued their program. The main reason for termination is a low incidence of TB; this is more common in comparatively dry areas such as Europe and the United States. $p < 0.0001$ indicates a significant difference, with a median difference of 18 times.

(Source) Formulated by Dr. Mitsuyoshi Urashima from data in The BCG World Atlas (http://bcgatlas.org/index.php) and WHO Situation Reports (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/)

We still have no drugs or vaccines with evidence behind them

Okina: The Council of Experts on COVID-19 Countermeasures have indicated their belief that there is no evidence for the effect of BCG vaccinations.

Urashima: When there is an announcement stating that there is no evidence, the general public and even doctors tend to think that it means that BCG vaccinations have no effect at all. But there are still almost no drugs or vaccines with evidence behind them. So far (as of May 17), the only agent for which evidence exists in relation to COVID-19 is interferon 1ß, which was just released in May. In a randomized clinical trial in patients with mild COVID-19 infections, interferon-1ß

showed the fastest viral clearance. Almost all other drugs and vaccines are at the stage of observational study. Even if you can say that a drug seems to be effective when used, no randomized clinical trials have yet been performed that clearly prove that a patient has actually been cured or that the drug has no side effects.

Okina: Gilead Sciences' antiviral drug Remdesivir has been approved in the United States and Japan at an accelerated pace. What are your views on this?

Urashima: The United States was one of the first countries to approve the use of Remdesivir, and Japan followed suit. (Following this three-way talk[iv], on May 22, the New England Journal of Medicine reported that patients treated with Remdesivir were able to leave hospital four days earlier than the comparison group[v]. Remdesivir, however, was only effective in patients with moderate pneumonia who required oxygen, but had no effect in severe cases which required the use of a ventilator or ECMO. There was also no significant difference in the mortality rate between the two groups. On May 7, with the approval of the United States, Japan placed a priority on speed and gave special approval for the use of the drug prior to the publication of the NEJM paper, without fully examining the data. According to the paper published on the 22nd, the drug was not effective in severe cases, but Health, Labor and Welfare Minister Katsunobu Kato stated that Japan would make an effort to ensure a reliable supply of the drug for people who are critically ill and regarded as being in need of it.

What Japan should do in the competition to develop vaccines

Okina: Countries around the world are working very hard to develop vaccines and therapeutic drugs. How do you view the current status of these developments?

Urashima: Whatever it takes, the United States will lead the world in developing therapeutic drugs and vaccines. I may be mistaken, but I see it as a manifestation of the will of the nation to achieve its goals, if need be disregarding academic orthodoxies and breaking the rules of the past. This is really a war. I think that the winner of this war will be the country that is the first in the world to develop an effective vaccine. Therapeutic drugs will not dramatically reduce the mortality rate, but the development of a vaccine may not only reduce the incidence of the disease but also the mortality rate.

If we can entirely prevent the disease or cut its incidence in half, we can reduce the number of deaths by nearly half. The country that is the first to develop a vaccine can lead the world in this.

The United States has invested a huge amount of money towards the development of a vaccine by the end of the year. The budget will be the largest since the Manhattan Project, the project that developed the atomic bomb in World War II.

Okina: Having invested an enormous amount of money, how do you think a country that has successfully developed a vaccine will be able to secure a global political advantage?

Urashima: Currently, in order to enter certain countries in Africa, you need to obtain a certificate

stating that you have been vaccinated against yellow fever – a "yellow passport". In the same way, there has been a suggestion that we might create a passport indicating immunity from COVID-19. If we do start to use such immune passports, the country that first developed the vaccine would have a huge advantage. If immune passports become the global mainstream, countries that do not have a vaccination program will suffer a considerable socioeconomic disadvantage.

Okina: How do you view the vaccine development process from the perspective of a doctor?

Urashima: When severe acute respiratory syndrome (SARS) broke out in 2003, the United States and China worked together to develop a vaccine. By the time that the vaccine was developed, the SARS outbreak had already stopped. So China and the United States have an advantage in developing a vaccine for COVID-19. There are rumors that China is launching a cyberattack against the United States, but the two countries are currently in a dead heat.

Okina: How is the situation in Japan? We hear reports of activity at Osaka University and a variety of pharmaceutical companies.

Urashima: Unlike the United States and China, which are competing for supremacy, Japan's stance is that it will be fortunate if a vaccine is developed, and so Japan can be seen to be lagging behind. This is because fewer deaths are caused in Japan by COVID-19 than by the seasonal flu.

Takahashi: I previously discussed the hypothesis of innate immunity in the Japanese, but in the case of vaccines, the question is whether or not antibodies are present.

Urashima: According to the Japanese Red Cross Society, a blood stock survey conducted two years ago showed a 0.5% positive rate for antibodies, and a 500 person survey following the coronavirus outbreak showed a 0.5% positive rate. The fact that the positive rate did not change before and after the COVID-19 outbreak indicates that very few Japanese who donated blood have antibodies to the virus. However, if people have innate immunity and are not affected by COVID-19, I think the presence or absence of antibodies is medically meaningless.

On the other hand, if there is a movement to issue an immune passport and use the presence or absence of antibodies politically, Japan may be rejected by the international community. Even if we claim that the presence or absence of antibodies has no scientific meaning, Japan will be treated as a non-conforming country, and we will be excluded from the community. We need to find a way of displaying Japan's advantage and winning global recognition.

My other concern is that when I look at foreign journals, there are few papers published by Japanese researchers. Although Japan was the next nation following China to note coronavirus infections, there has been no adequate publication in high-impact journals, for example regarding the Diamond Princess experience. I think that the reason why Japan's efforts in this area are not adequately appreciated by other countries is that we are not communicating scientifically within an international framework. Because there is no system that can properly survey big data on patients all over the country, only a few cases experienced by doctors are published in Japanese. If we can publish papers containing detailed data overseas, it will be useful for countries that will experience the epidemic later on. Being able to see our situation based on real-time data will also

be important in terms of deciding our next policy measures.

Okina: The future investment strategy which I have been working on with Professor Takahashi advocates data collaboration and data utilization. In response to the COVID-19, the importance of linking and storing real-time data has been reaffirmed. In addition, as you have indicated, understanding of the situation in Japan has not progressed overseas. I would like to hope that we will be able to promote the accumulation and analysis of data and ensure that it is communicated overseas by Japan's scientific community.

Part 3 Potential Exit Strategies

Strategies based on the characteristics of COVID-19

Okina: At first, there was a great deal of confusion about PCR testing and the isolation of infected people.

Takahashi: I think that the fact that COVID-19 is defined as both a Category 1 and Category 2 infection under the Law concerning the Prevention of Infections and Medical Care for Patients of Infections (the law classifies infectious diseases by virulence and mortality rate; Category 1 represents the most serious infectious diseases) is a major factor here. Despite the fact that the majority of cases are mild, patients with confirmed infections must be isolated. If a large number of PCR tests had been carried out as was the case in Korea, and all the people who tested positive were isolated, hospitals would be flooded and it would not be possible to treat severe cases. I think that under the current law, PCR testing had to be restrained in order to protect the Japanese medical system.

Because COVID-19 is completely different from influenza, a new classification, "Category 2.5," should be created to remove it from the list of designated infectious diseases and provide new protocols for dealing with mild cases without hospitalization.

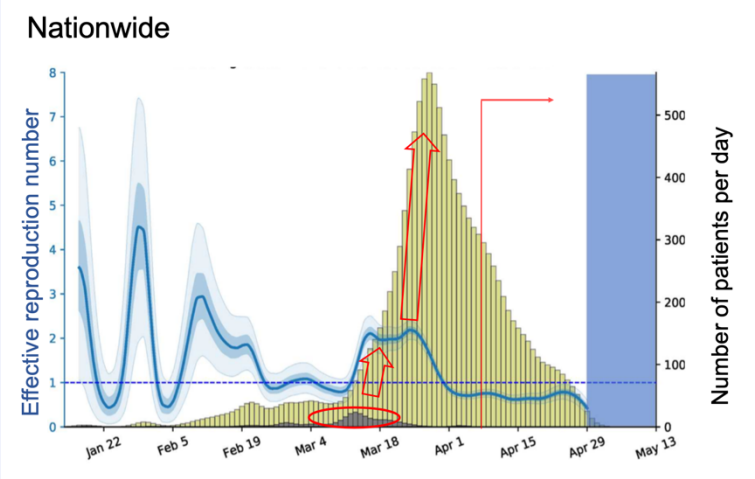
Okina: While we might question whether an adequate number of PCR tests are being performed, at the same time I think it would have been better if issues such as the effect of blanket PCR testing on the medical system, the fact that PCR tests do not provide an ideal basis for judgment as to who is negative, and the statistical problem of the probability of "false negatives" (the recording of a negative test result while the person tested is actually infected), had been more clearly known.

Urashima: Even if PCR results are negative, SARS-CoV-2 may proliferate deep in the lungs. We don't know the exact false negative rate for the PCR test, but one theory points to a rate of 50%, given the fact that while a throat swab might produce a negative result, the virus may be

proliferating deep in the lungs, or swabs may be taken during the incubation period. In other words, false negatives occur once in every two tests, which is a low level of reliability from the viewpoint of doctors working in the field. The diagnosis must be supplemented by consideration of the patient's symptoms and the judgment of the doctor.

Okina: That is because irrespective of whether we can expect sufficient accuracy from the PCR test, a person who is judged to be negative while they are actually positive will feel that they are able to go out, and as a result will spread the infection.

Figure 5 : Epidemic Curve for Japan by Day of Onset



(Note) The gold bars indicate the estimated number of infected persons using date of onset data, and the solid blue line indicates the estimated effective reproduction number. The effective reproduction number is defined as the average number of people who are directly infected during the period of infection when one person infected with the disease joins a population (which does not only contain uninfected people). The grey bars show cases of infections imported from overseas. The red line indicates April 7, when the state of emergency was declared.

(Source) Formulated by Dr. Mitsuyoshi Urashima based on data published on the Ministry of Health, Labour and Welfare website

Advance the removal of restrictions by age and location

Urashima: There are also problems with media reports. There have been reports of people infected by PCR testing, but this is based on the date of the report, and epidemiologically it is meaningless unless it is based on the date of onset. By date of onset, the number of infected people peaked at the end of March, and began to decline before April 7, when the state of emergency was declared (Figure 5). It is not necessarily the case that the decline in infections was sped up by the declaration of the state of emergency.

Okina: While the number of infections has ultimately subsided, do you think the government was late to declare a state of emergency?

Urashima: No, given that the number of patients began to decrease before the declaration was made, not after it was made, I can say in hindsight that I think the declaration need not have been made. I think that this kind of evaluation needs to be performed somewhere. In addition, the

number of imported infectious diseases increased in March, and the government stopped allowing foreign nationals to enter the country. Thorough PCR tests were also performed at airports. I see this as the biggest factor in producing a decline in infections. Of course, I also think that news reports prior to the declaration indicating that the number of infected people was increasing, prompting people not to go out drinking, for example, also had an effect. Given this, the lifting of the border closures needs to be implemented more carefully than the lifting of the state of emergency.

Okina: You believe that measures to prevent infections imported from overseas and voluntary changes in behavior have been epidemiologically successful in Japan. However, from an economic perspective, a declaration of a state of emergency raises the possibility of compensation for absence from work, so even if we are asking the same people to refrain from going out, the situation is very different for companies, which the declaration of a state of emergency forces to take time off.

Takahashi: At that point in time, I think that the declaration of a state of emergency was unavoidable. At first, predictions regarding COVID-19 were based on the conventional infectious disease model, which is predicated on the assumption that an epidemic will come in one wave like influenza, that a large number of people will be infected, that antibodies will be produced, and that the epidemic will then peter out. On this basis, it was estimated that up to 420,000 people would die. At that time, we did not know the actual characteristics of COVID-19, and I believe that it was appropriate to adopt measures based on the figures we had at the time. However, we now understand the characteristics of the virus much better than we did at that time, and we are now at the stage at which we should review the prediction model. I believe that the use of a model that takes into account the facts that the virus displays a low level of virulence and that innate immunity is effective against it will enable us to make predictions that accord more closely with the actual situation.

Urashima: The estimates do not match the reality of approximately 740 deaths in Japan as of May 17. The predictions and the results diverge widely. If things continue as they are, no one will believe what the government says, and we will not be able to respond when a second wave comes.

Okina: Somewhat similarly to Japan's response, many Western countries imposed lockdowns, but Sweden is known for not doing so. While some people point out that Sweden's mortality rate is higher than that of any other Scandinavian country, others praise the fact that the country did not adopt compulsory measures.

Urashima: I think that was the right answer. At one point, Sweden was criticized for the rapid rise in its death toll, but recently the per capita death toll has reached almost the same level as Spain, Italy and France. On the other hand, GDP dropped by 0.3% in Sweden, while it dropped by 4.7% in Italy, 5.2% in Spain and 5.8% in France. Even without lockdown, the death toll per capita is about the same in Sweden, but the decline in GDP is lower. The mortality rate in Sweden is higher than it is in Norway. Considering the possibility that BCG vaccinations are effective in preventing COVID-19 deaths, it is interesting to note that Sweden terminated its BCG program in 1975,

whereas Norway stopped its program in 2009.

Takahashi: Lockdowns clearly reduce the number of deaths, but I think the damage that they cause is too great, and they do not accord with the characteristics of the disease. Of course, it also has to do with the exit strategy that is implemented. As I mentioned earlier, people who are aged 70 and above have a more than 1000 times higher chance of the illness becoming serious and leading to death than people who are 0-29 years old (Figure 2). Easing lockdowns will definitely increase the rate of infection in cities and the mortality rate in nursing homes. So, I think we should proceed with the easing by age. This is an exit strategy that considers risks by generation. In particular, I believe that maintaining the current isolated situation of the elderly for a few more months will be effective in preventing the collapse of the medical system.

Okina: Dr. Daron Acemoglu, an economist at the Massachusetts Institute of Technology (MIT), published an analysis based on a multi-risk Susceptible-Infectious-Recovered (SIR) model that takes into account the differences in risk by age. He concluded that lockdown by age can reduce both mortality and economic damage.[vi] This way of thinking may be somewhat similar to Dr. Takahashi's exit strategy.

Takahashi: Restrictions should be removed beginning with the people at the lowest risk. The point in the case of COVID-19 is, rather than reducing the overall number of infected people, to protect those who are at risk of the disease becoming more serious.

Urashima: Based on domestic data up to the present, we will closely examine elements such as what triggered the increase in the number of patients and what factors reduced the number of deaths. We will also fully examine the effects of lockdown in other countries. We will then identify the places that can be reopened and the places that should not be reopened. I think it is important to find the best way to revitalize our society and economy quickly, without spreading the infection.

Takahashi: We should establish a hierarchy of places such as baseball stadiums and live music venues according to the expected risk of infection, take into consideration the fact that the risk of infection differs greatly depending on the age group, and create matrices of the type (Location: Infection risk level) × (Age group) to decide the order of reopening. From this point of view, I don't think it will be a problem to let young people actively participate in sports like the Koshien (the national high school baseball tournament) and inter-high school championships.

Based on the status of the disease in specific regions, I think it would be a good idea to commence with the reopening of outdoor stadiums in Sendai city and Hiroshima city, where there is little incidence of the disease, on a trial basis. If no clusters occur, the process could be gradually expanded.

Preparation for second and third waves

Okina: At the same time, it is necessary to respond with caution in the areas where there are many elderly people and poor medical system.

Takahashi: The elderly represent a high percentage of the population in areas that have become depopulated, and so it is necessary to proceed with caution even if there is currently no COVID-19 infection in the area. It is quite possible that the virus could spread throughout a village centering on the elderly, and some of them might die.

Urashima: In some rural areas, many people seem to have foregone PCR testing. I think it is very important to spread the message that PCR testing is not omnipotent, but that it is very important to visualize the situation via PCR testing. In particular, we need to change the mindset that a positive test is a bad thing, and create an atmosphere in which people are properly tested. As it is, people might stay inside their homes without receiving a check-up.

Also, as Dr. Takahashi says, using the concept of a Category 2.5, hospitalization could be limited to only those with moderate symptoms and above, and who need a ventilator. It will also be necessary to establish a triage (determination of treatment priority) system for patients with mild symptoms, by isolating them in hotels, etc.

In preparation for the second wave, we must also establish a large-scale examination system after securing sufficient beds to accommodate seriously ill patients and space to accommodate even mildly ill patients in each of the nation's regions.

In the United States, every region is provided with a system called an incident command system that makes it possible to grasp the number of available beds and the amount of medical supplies such as masks and protective clothing in real time. Furthermore, all the regional systems are agglomerated in a central system, and the entire system is managed by the government; if there is a shortage of materials, they are distributed as appropriate. Health care professionals are able to concentrate on patients without having to worry about masks.

Takahashi: In the future, the SARS-CoV-2 may become more virulent due to mutations and other factors. At the same time, it may be further suppressed by innate immunity. I think that it will be necessary to first formulate these two exit strategies and then formulate "comprehensive measures" to enable us to respond to either of them. We should direct our efforts towards improving the medical system in accordance with that.

Okina: To summarize your common points, first of all, we should review our response to the first wave based on new findings, create a system that makes it possible to obtain data concerning the status of infections at the regional and national levels in real time, and establish a hospital bed system that can accept patients with mild symptoms and those with severe symptoms separately in each region. In order to prepare for second and third waves, while proceeding with these measures, we should comprehensively analyze Japanese infection data, accumulate further evidence through research, and use it in our next response. During this period, the ban on online medical care has been lifted, and the medical care system that supports patients with other diseases has evolved while attempting to prevent the risk of infection. Although the number of medical examinations has been reduced, I believe that it will be very important to firmly establish this system in order to enable the continuation of essential necessary medical care. Thank you for sharing your insights in our discussion today.

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[iv] This information was not available when the discussion was held; this section was revised based on the information available at the time of publication of this paper.

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