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CHUGAI PHARMACEUTICAL CO., LTD.

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CHUGAI PHARMACEUTICAL CO., LTD.

Information Meeting on RONAPREVE

August 26, 2021

Event Summary

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[Participants]	
[Number of Speakers]	3
	Dr. Osamu Okuda — President & CEO
	Satoshi Aida — Ph.D., RONAPREVE Lifecycle Leader
	Kazuhiro Tateda — M.D., Ph.D., Department of Microbiology and Infectious Disease
[Analyst Names]*	Seiji Wakao — JPMorgan Securities Japan Co., Ltd.
	Hidemaru Yamaguchi — Citigroup Global Markets Japan Inc.
	Shinichiro Muraoka — Morgan Stanley MUFG Securities Co., Ltd.
	Kazuaki Hashiguchi — Daiwa Securities Co., Ltd.

*Analysts that SCRIPTS Asia was able to identify from the audio who spoke during Q&A.

Presentation

Sasai: Thank you very much for taking time out of your busy schedule to join us today for the product presentation of Ronapreve, a new treatment for the novel coronavirus infection. My name is Sasai from the Corporate Communications Department, and I will be moderating today's session. I'd like to thank you for your cooperation.

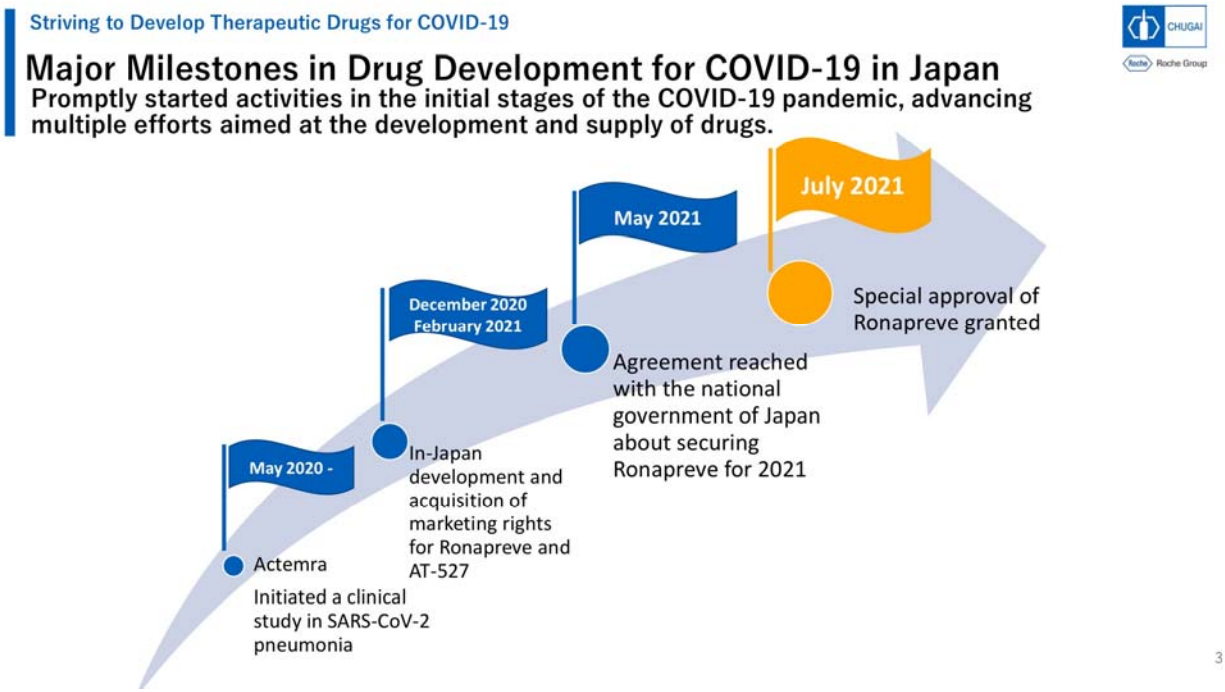
Today's session will be conducted in the form of a conference call due to the coronavirus pandemic.

The agenda for today's meeting can be found on our web page, and on the second page of the presentation materials. I will explain according to the contents here.

Today, we have invited Prof. Kazuhiro Tateda, Department of Microbiology and Infectious Disease, Toho University School of Medicine, as a special lecturer. A summary of Professor Tateda's work is included in today's presentation materials.

Questions will be taken after all presentations are completed.

Dr. Okuda, President and CEO of Chugai Pharmaceutical, will now discuss the Company's efforts to develop COVID-19 therapeutics.



Okuda: Hello, everyone. I'm Okuda, the Company President. Thank you very much for joining us today.

First of all, I would like to talk about the overall picture of Chugai Pharmaceutical's efforts to develop drugs for the treatment of the novel coronavirus infection.

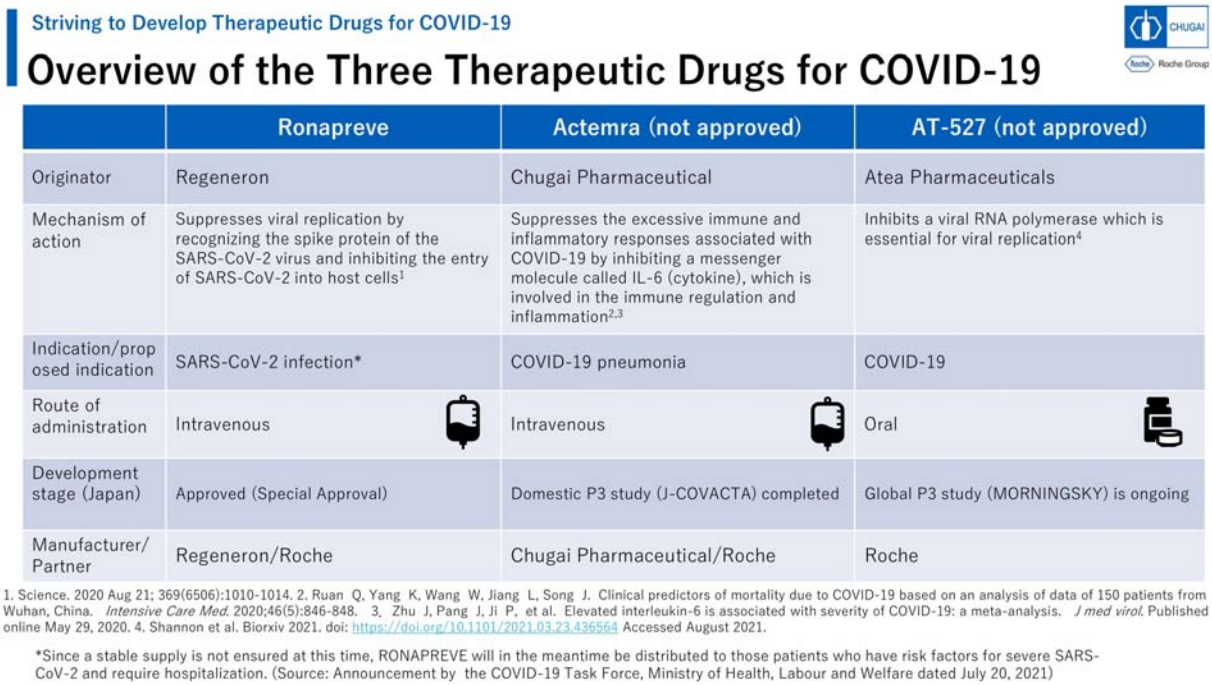
First, I would like to show you the major milestones in the development of products in Japan to date.

The first thing we started with was Actemra, a product created in-house. In March of last year, we began participation in the global COVACTA clinical trial led by Roche. At about the same time, in May, we started a Phase III trial in Japan called J-COVACTA.

In December of last year, the antibody cocktail therapy Ronapreve was introduced. In February of this year, the oral antiviral agent AT-527 was introduced. Under a strategic alliance with Roche, we have acquired the rights to develop and market this product in Japan.

Then, in May, we reached an agreement with the government on securing supplies for 2021 for Ronapreve. On June 29, we filed for special approval, which we received on July 19. This was after an exceptionally fast review period of 3 weeks.

We were able to deliver Ronapreve to patients in Japan very quickly after obtaining the domestic development and marketing rights. The time period was 6 months altogether.



I will now give you a brief overview of the 3 novel coronavirus drugs that Chugai is working on.

First of all, there is Ronapreve on the left, which is an antibody cocktail therapy created by Regeneron in the US and introduced by Roche. It recognizes the spike protein of the SARS-CoV-2 virus, preventing it from entering the host cell, thereby suppressing its multiplication. It is called an antibody cocktail therapy because 2 types of antibodies are administered intravenously at the same time. Roche and Regeneron are responsible for manufacturing.

In the US, we have already received an emergency use permit, and in Japan, as I mentioned earlier, we have received special approval.

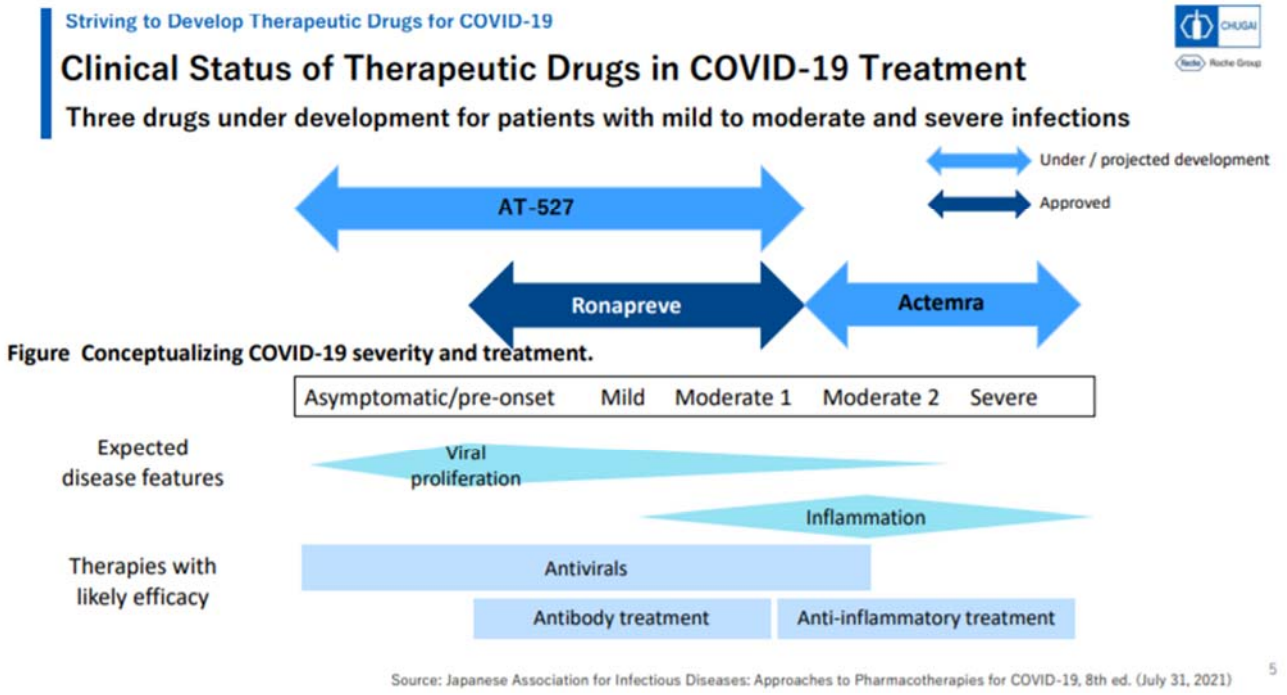
Actemra, discovered by Chugai, is an antibody drug that is approved and used in many countries for rheumatoid arthritis and other indications. This is the first product to be co-developed globally under our strategic alliance with Roche.

By inhibiting the cytokine IL-6 signaling pathway, which is involved in immune regulation and inflammation, it is expected to suppress the excessive immune response and inflammatory reaction caused by COVID-19.

Several clinical trials and investigator-initiated trials have been conducted in Japan and overseas. There is also an injectable preparation that is administered intravenously. In the US, an emergency use permit has just been issued.

The third drug, on the right, is AT-527. This is a virus-dependent RNA polymerase inhibitor discovered by an American company called Atea Pharmaceuticals. It is a small-molecule drug, and was initially developed for hepatitis C, but Atea started biological trials because it is expected to be effective for COVID-19. Roche has introduced this right, and is responsible for global production.

Currently, we are conducting a Phase III trial for patients with mild to moderate disease, called MORNINGSKY. This is shown on the right.



I would like to explain a little about the 3 drugs Chugai is working on and their position in the overall treatment of COVID-19 infection.

This figure shows a modified overview of drug treatment for COVID-19, and is taken from a July publication by the Infectious Disease Society of Japan.

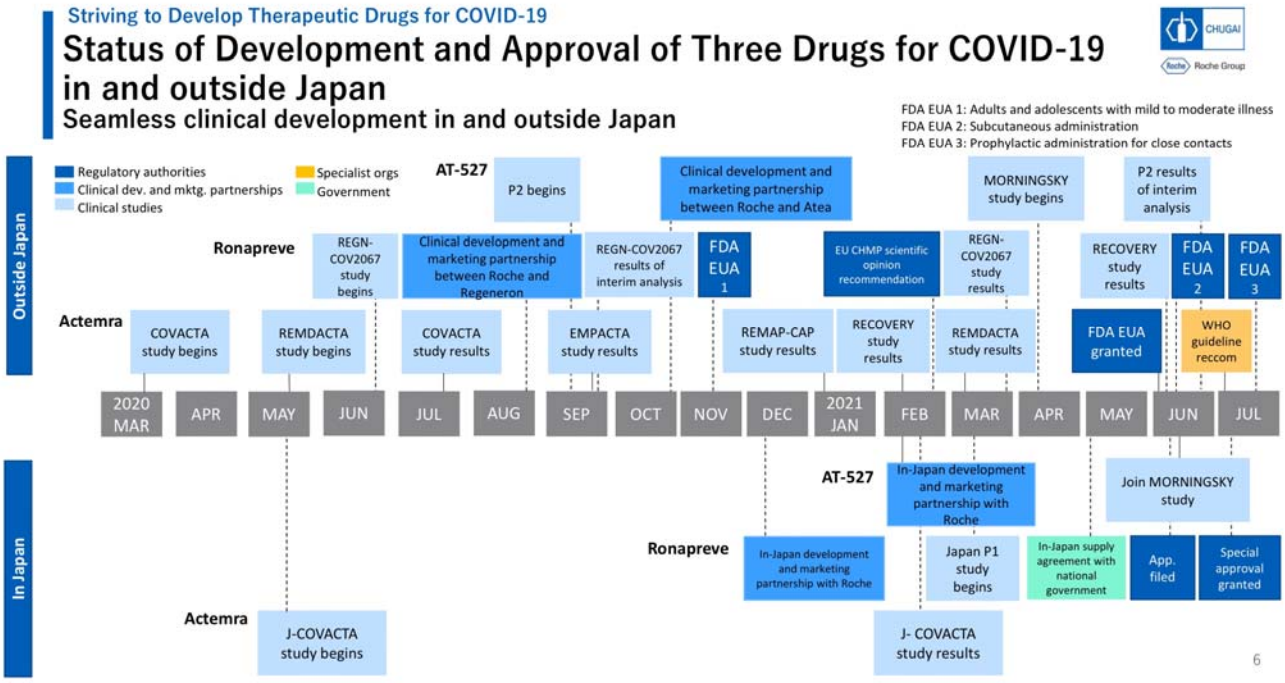
As you know, the coronavirus infection can develop from asymptomatic to mild, moderate, and severe as the virus multiplies. Here, the evolving condition and severity of the disease are said to define the drugs that are expected to be effective.

Antiviral drugs are expected to be effective during asymptomatic to mild disease, when the virus is still multiplying. This is where AT-527 may be applicable.

Then there is the mild to moderate range, where symptoms are a little more advanced, but before oxygen is needed. This is where antibody therapy is expected to be effective. In other words, Ronapreve falls into this category.

Anti-inflammatory treatment is expected to be effective with moderate disease and beyond. Actemra is expected to be effective here.

Looking at it this way, I believe that AT-527, Ronapreve, and Actemra, which Chugai is developing, can contribute to the treatment of COVID-19 in general, covering a wide range of cases from mild to moderate to severe.



Next, I would like to explain the development and approval status of these 3 drugs in Japan and overseas.

I would like to talk briefly about the situation overseas in the upper half of this slide. The bottom half shows the situation in Japan.

First, regarding Ronapreve, the originator, Regeneron, commenced multiple clinical trials in 2020. 1 of these is a study of high-risk COVID-19 patients who were not hospitalized. This is called the REGN-COV2067 study. Based on the interim analysis of this study, the FDA granted an emergency use permit last November.

Based on the results of the clinical trials conducted in parallel with this, the US subsequently granted an emergency use permit for subcutaneous injection and prophylactic administration to close contacts in June and July of this year.

In Japan, we did not participate in the global study, but we started a Phase I study in healthy Japanese subjects in March this year. Based on this and data from overseas, we filed an application for approval in June. This led to special approval in July, as I explained earlier.

Secondly, regarding Actemra. Last year, we conducted the COVACTA study, as well as the REMDACTA study, which assessed combination treatment with remdesivir. We have conducted several global comparative studies under the guidance of Roche. In parallel, a large-scale physician-led clinical trial was conducted in the UK, the RECOVERY trial. Other similar trials have also been conducted.

The results of the integrated analysis of these multiple trials have shown effectiveness in reducing the risk of severe COVID-19 disease, inpatient mortality, and reducing the time to discharge and the proportion of patients requiring ventilators.

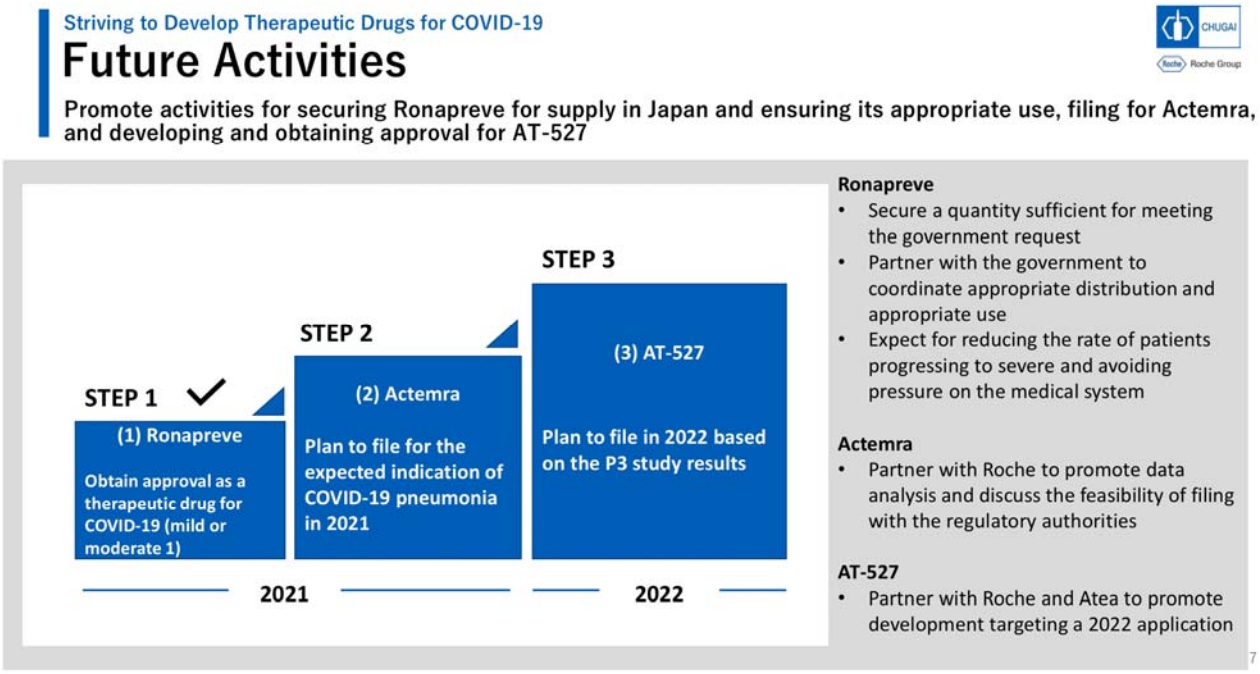
Based on these results, the FDA approved Actemra for emergency use in June of this year, and the WHO recommended it in its treatment guidelines in July.

Although it has not been officially approved by the regulatory authorities in many countries around the world, Actemra is widely prescribed in clinical practice for patients with severe COVID-19 infection.

Thirdly, AT-527. This is a Phase II study recently presented by Atea. It assesses effectiveness in patients with moderate disease, who are at risk of severe disease and are hospitalized or in need of hospitalization.

The results of the interim analysis showed that the AT-527 group had an average of 80% greater reduction in viral load on the second day of treatment compared to the placebo group. In this study, no new safety findings have been observed at the interim analysis stage.

Next, this is the MORNINGSKY study, which I mentioned earlier. It started in April of this year, and Chugai is participating within Japan. The results are expected to come out in the second half of this year, and we are aiming to file the application in 2022.



Finally, I would like to briefly introduce our future activities.

Firstly, Ronapreve. As the delta variant becomes more prevalent, the demand for therapeutic agents is increasing worldwide. In response to this, we will secure the necessary supply in response to requests from the Japanese government. We will also work with the government and other related parties to promote proper distribution and use.

We are hoping to reduce the number of cases of serious disease, and reduce the current load on the healthcare system. In addition, we will be looking to expand the indications for prophylactic administration to close contact individuals, and to file an application for additional subcutaneous administration.

For Actemra, we will proceed with data analysis and integration analysis, and continue to discuss with the authorities whether or not to file an application. We hope to improve the prognosis of patients with severe COVID-19 infection.

Thirdly, AT-527. As I mentioned earlier, the results of the current global Phase III trial will be available in the second half of the year, and we will be working with Roche and Atea to develop the drug for filing in 2022. Since this is an oral drug, we hope that early treatment of mild cases will help prevent severe disease.

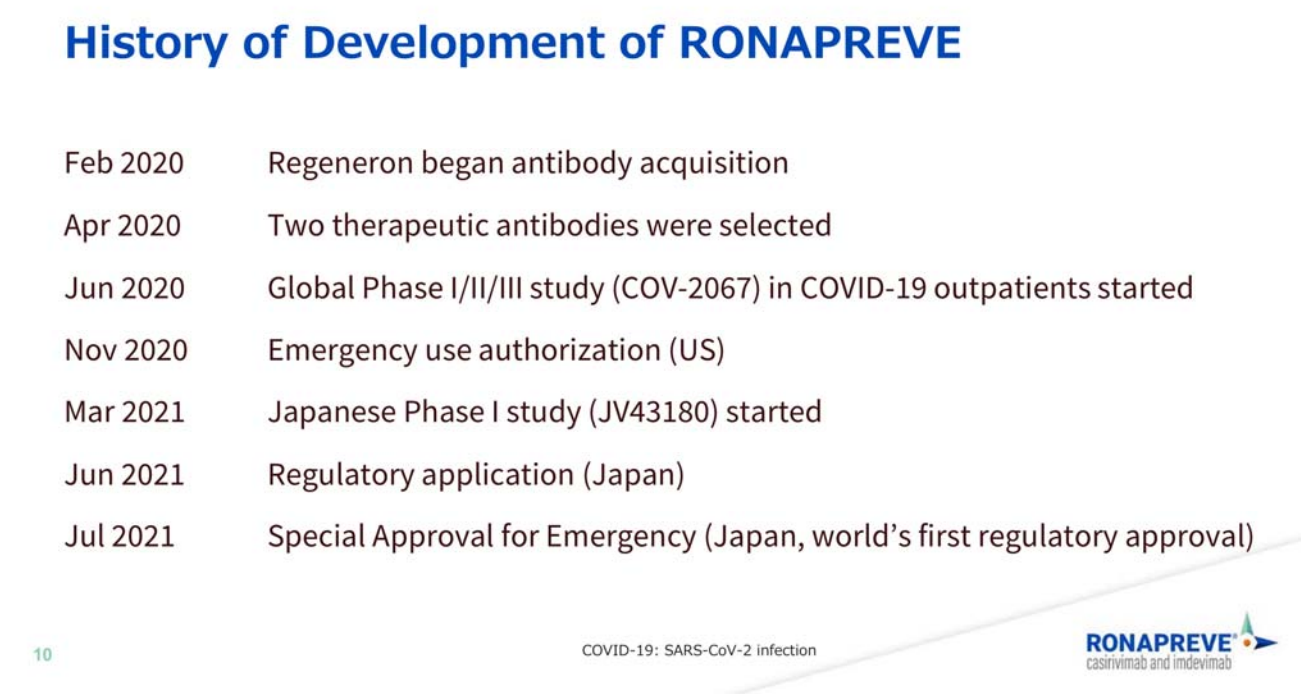
This concludes my brief introduction of the 3 drugs that Chugai is working on.

Sasai: Thank you. Next, Dr. Aida, Chugai's Ronapreve Lifecycle Leader, will give an overview of the status of Ronapreve.

Aida: This is Aida, Ronapreve Life Cycle Leader. Thank you.

This is Ronapreve. It is a combination of casirivimab and imdevimab. As you can see in the picture on the lower right, casirivimab and imdevimab are contained in vials, and they are mixed together. This is why it is called antibody cocktail therapy.

It is indicated for the treatment of SARS-CoV-2 infection, particularly in patients with risk factors for severe SARS-CoV-2 infection and who do not require oxygen.

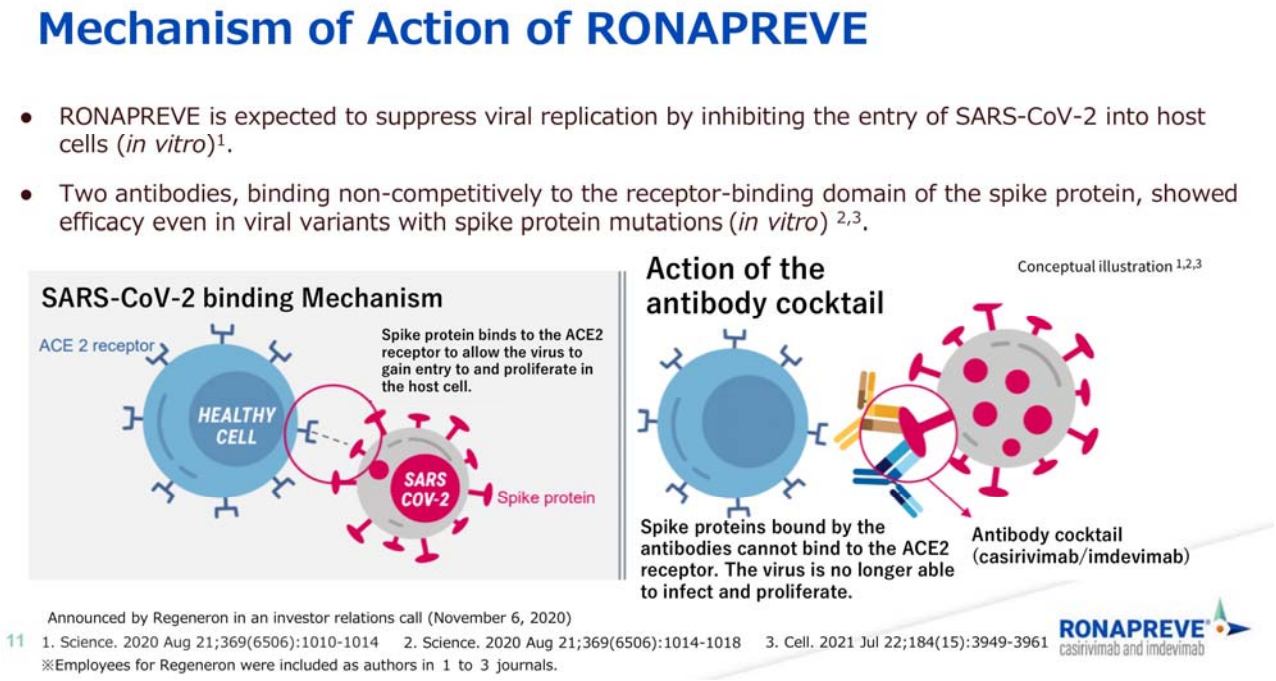


Let me show you how it was developed.

In February of last year, Regeneron began the process of acquiring antibodies. 2 months later, they selected 2 therapeutic antibodies. Another 2 months after that, they have started overseas Phase I/II/III trials.

Only 5 months later, they gained approval for emergency use in the US based on the results of the Phase I/II trials.

In Japan, we started Phase I trials in March of this year. At the end of June, we filed an application for domestic approval. 3 weeks later, on July 19, we received special domestic approval.



Here is a brief description of the mechanism of action of Ronapreve.

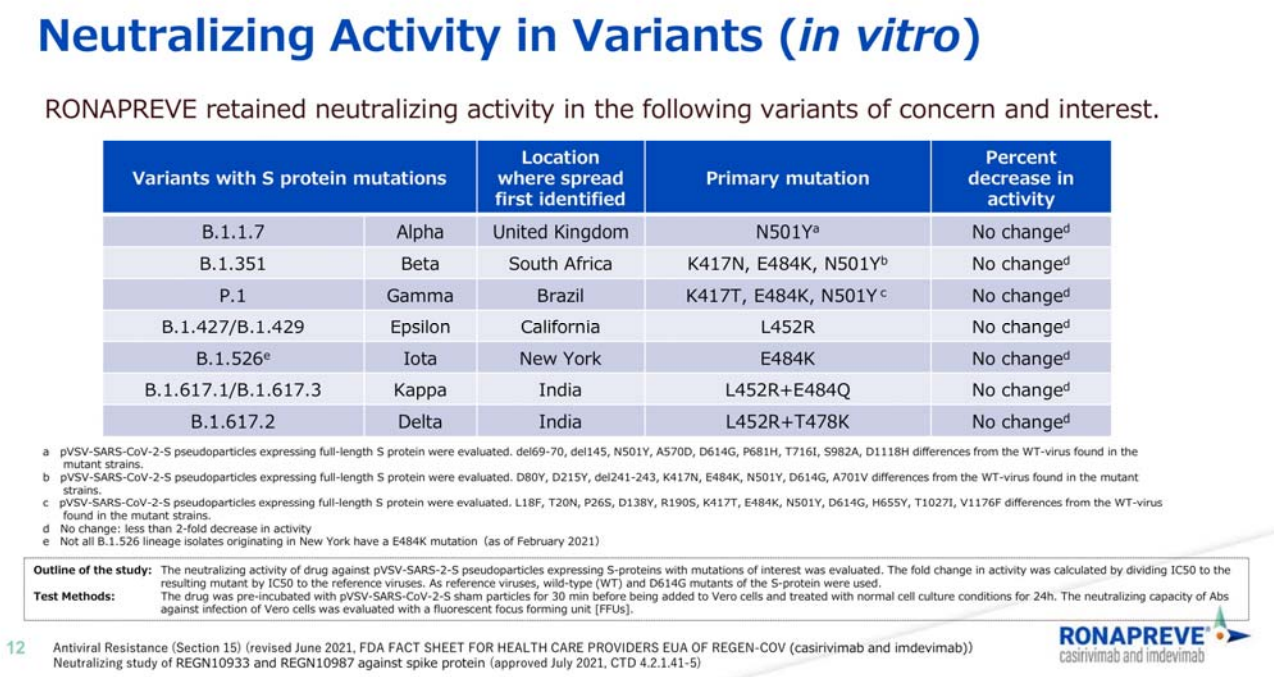
This figure on the left shows the binding mechanism of the SARS-CoV-2 virus. In the image here, we can see the SARS-CoV-2 virus interacting with human body cells.

The spike protein expressed on SARS-CoV-2 binds to the ACE2 protein expressed in our cells, allowing the SARS-CoV-2 virus to infect the cells. When the cells are infected, the virus multiplies. This process is well understood.

Where does Ronapreve fit into this? It binds to this spike protein and prevents the virus from entering the cell. This is thought to inhibit the multiplication of the virus.

In this cocktail therapy, 2 antibodies are used. Although each antibody alone can suppress this binding of spike protein and ACE2, administering these 2 antibodies at the same time means that they are effective against various viral variants. This is the basis for administering as a cocktail therapy.

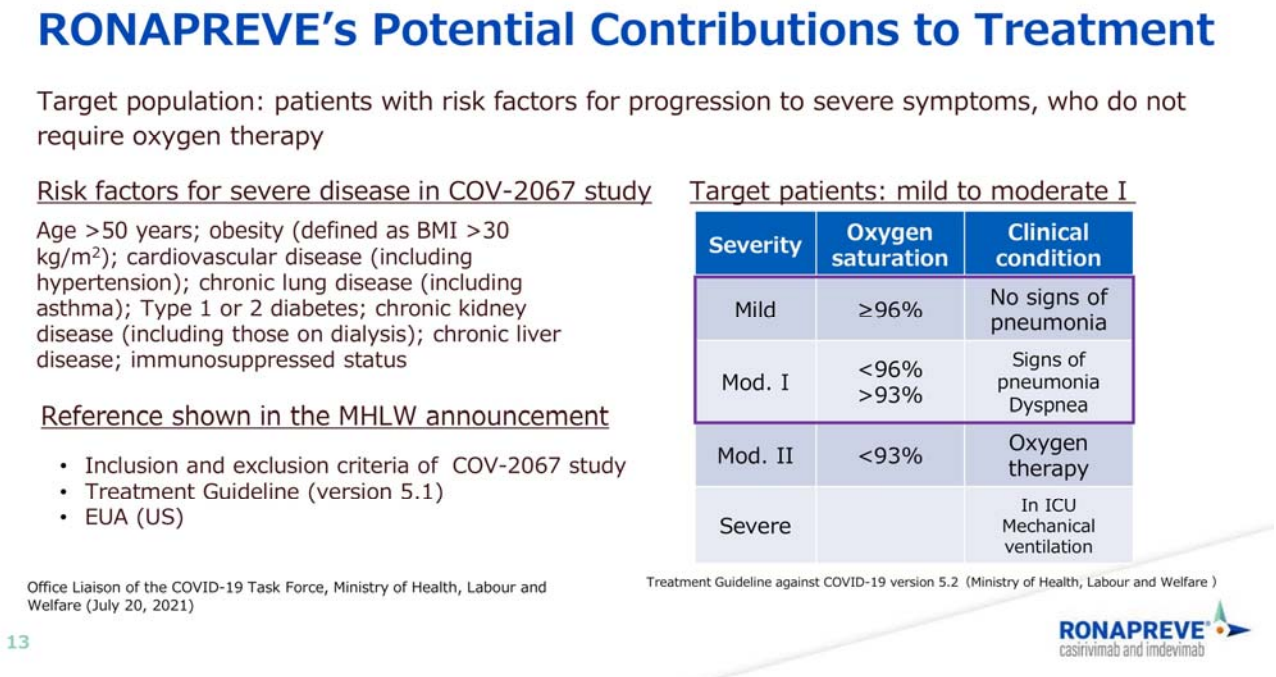
Mutations often occur in the binding site on the spike protein. If a mutation occurs, 1 of the antibodies may lose its binding ability. In such cases, the activity of the other antibody remains, and the overall effect is maintained.



This slide shows the actual effect on different variants.

Here, we show the effect on the alpha variant, the delta variant, which is currently spreading, and other variants.

It is shown here as a percentage change in activity. Although the results are in vitro, we have shown that the activity of the cocktail therapy does not decrease in any of these variants.



Next, I would like to talk about the therapeutic goals to which Ronapreve can contribute.

As I mentioned earlier, patients who have risk factors for severe disease and who do not require oxygen administration are eligible for treatment. I would like to begin by explaining these risk factors for severe disease.

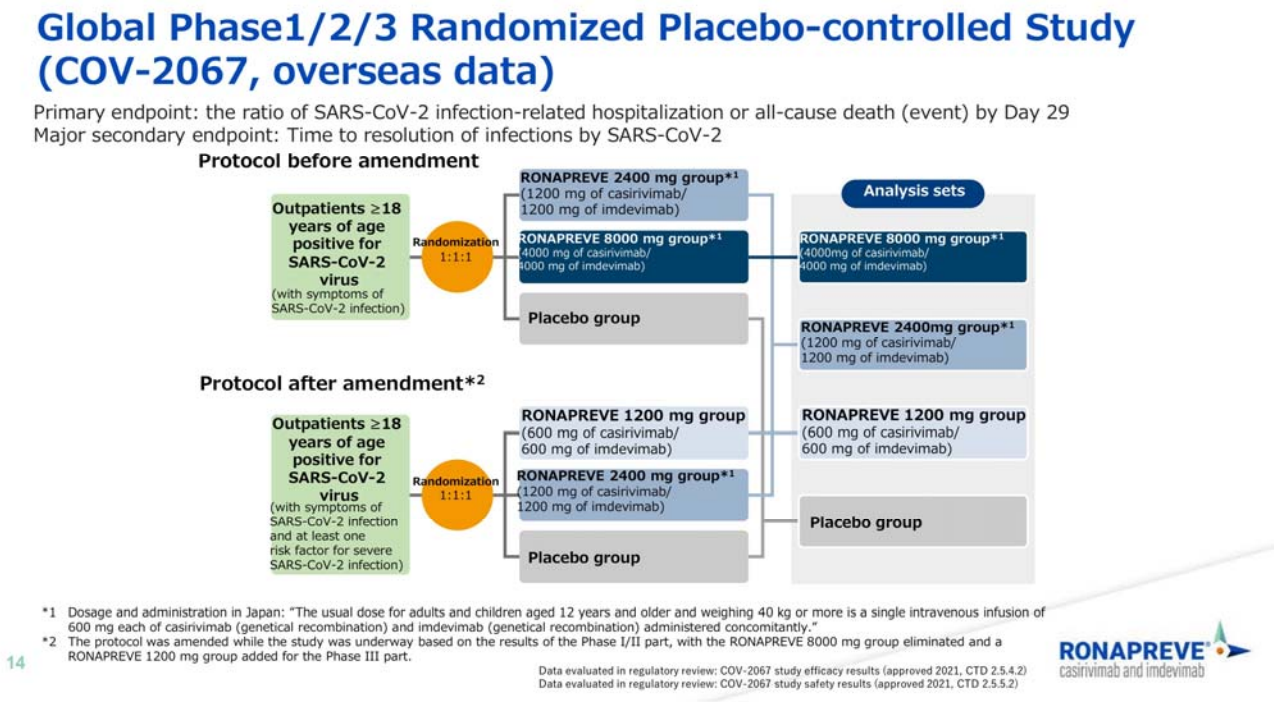
This is based on the COV-2067 study. The risk factors for severe disease are as shown here: age over 50, obesity, cardiovascular disease, chronic lung disease, diabetes, chronic kidney disease, chronic liver disease, and immunosuppression.

The Ministry of Health, Labour, and Welfare has issued an administrative communication, which includes these criteria, as well as treatment guideline version 5.1, which was issued at the time of approval. This guideline is now in version 5.2.

In the US, the dosing criteria for emergency use approval are based on these criteria to ensure that the drug is administered to the appropriate patients.

The table on the right deals with patients by requirement of oxygen administration. In order from top to bottom, patients are classified as mild, moderate, or severe. Oxygen administration is required for patients with moderate II disease and above. Since the drug is intended for patients who do not require oxygen administration, it is administered to patients with mild and moderate I level disease.

Ronapreve is the first drug to be approved for the treatment of patients with mild disease.

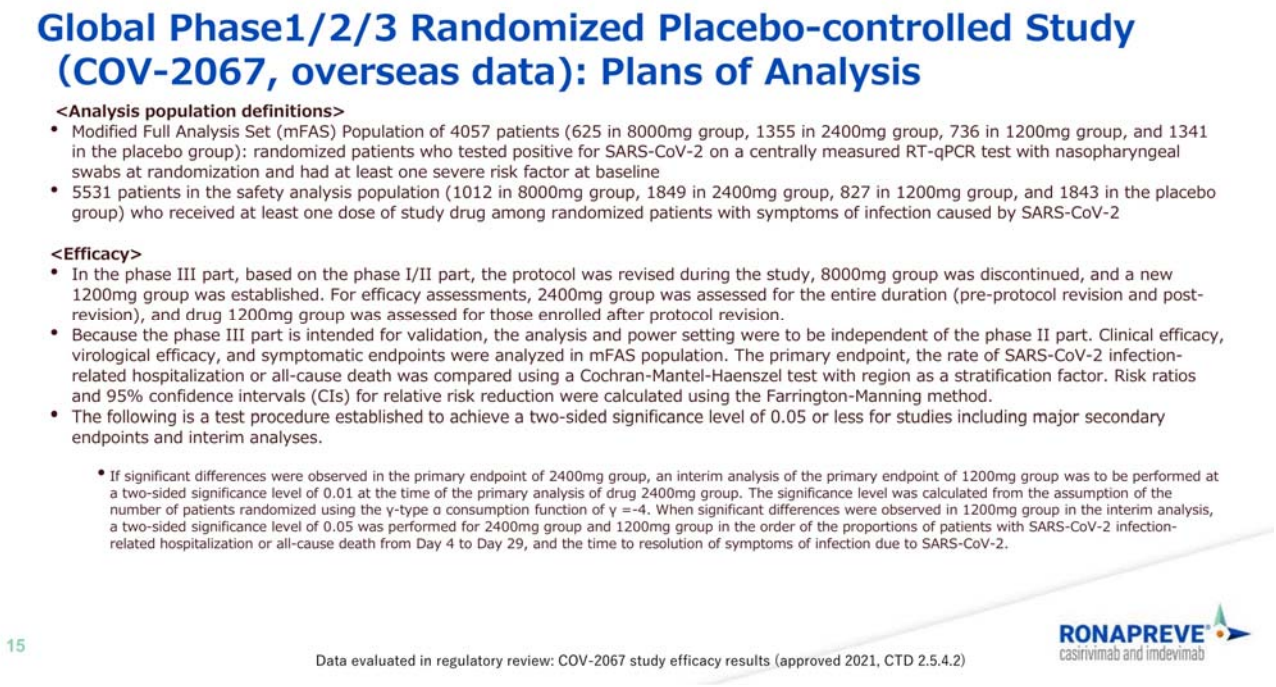


Next, I would like to show you the study design of the COV-2067 study that was mentioned earlier.

In this study, the protocol was changed in the middle of Phase III of the study. Before the revision, the protocol included a 2400 mg group and an 8000 mg group, but the results of Phase I/II showed that there was little difference in efficacy between the 2400 mg and 8000 mg groups.

Therefore, in the middle of the trial, we changed to 2 groups, 1 group receiving 1200 mg and the other receiving 2400 mg. We also stipulate that the patients have risk factors for severe disease when we make these changes.

I will show you the efficacy and safety data later, but I would like to focus on the data for the 1200 mg group, which is the approved dose shown here.



The first step is to plan the analysis.

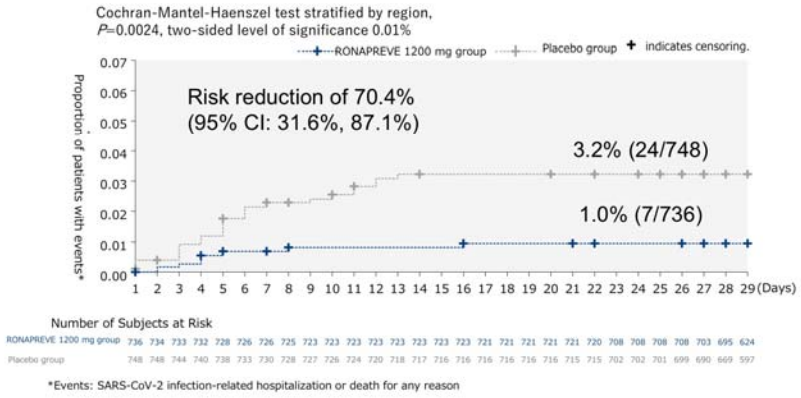
I apologize for the very busy slides. I would like to talk briefly about the content.

In terms of efficacy, we analyzed 736 patients in the treatment group and 748 patients in the placebo group. The safety data included 827 patients in the 1200-mg group and 1,843 patients in the placebo group.

The primary and secondary endpoints were subjected to statistical analysis. This is described in further detail here.

Global Phase1/2/3 Randomized Placebo-controlled Study (COV-2067, overseas data): Efficacy Data

Ratio of SARS-CoV-2 infection-related hospitalization or all-cause death by Day 29 (Primary endpoint)



Time to resolution of infections by SARS-CoV-2 (secondary endpoint)

	RONAPREVE 1200 mg	Placebo
Median	10.0 days (95.0% CI: 9.0, 12.0)	14.0 days (95.0% CI: 13.0, 16.0)

Log-rank test stratified by region, P<0.0001

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Data evaluated in regulatory review: COV-2067 study efficacy results (approved in 2021, CTD 2.5.4.2)

RONAPREVE casirivimab and imdevimab

Next, I would like to talk about the efficacy data.

The primary endpoint was the proportion of hospitalizations or deaths from SARS-CoV-2 infections for any reason by day 29 of treatment.

The vertical axis in the figure on the left shows the number of hospitalizations and deaths. The horizontal axis shows the number of days after administration. As events occur, the curve gradually moves upward.

In the placebo group, which is shown in gray, the event occurred in 3.2% of the patients. In the 1200-mg group, which is shown in blue, this event occurred in 1% of the patients. Therefore, the risk of hospitalization and death was reduced by 70%.

The table on the right shows the time to resolution of symptoms as a secondary endpoint.

In the placebo group, it took 14 days, whereas in the 1200-mg group, it took 10 days. As you can see, we have seen a reduction of 4 days.

Global Phase1/2/3 Randomized Placebo-controlled Study (COV-2067, overseas data): Overview of Adverse Events

Adverse events	RONAPREVE 1200 mg group (n=827)	Placebo group*1 (n=1843)
Adverse events occurring or worsening during observation period*1		
Adverse events	59 (7.1%)	189 (10.3%)
Grade 3 or 4 adverse events	11 (1.3%)	62 (3.4%)
Serious adverse events (severe hypersensitivity reactions, infusion reaction)	9 (1.1%)	74 (4.0%)
Adverse events leading to treatment discontinuation	1 (0.1%)	0
Adverse events leading to withdrawal from study	0	1 (<0.1%)
Death	1 (0.1%)	5 (0.3%)
Adverse events of special interest occurring or worsening during observation period*2		
Adverse events of special interest	17 (2.1%)	51 (2.8%)
Serious adverse events of special interest	1 (0.1%)	6 (0.3%)
Grade ≥ 2 infusion reactions through Day 4	2 (0.2%)	0
Grade ≥ 2 hypersensitivity reactions through Day 29	0	1 (<0.1%)
COVID-19-related adverse events leading to medical attention through Day 29	15 (1.8%)	47 (2.6%)
COVID-19-unrelated adverse events leading to medical attention through Day 29	0	5 (0.3%)

*1 Events absent at baseline or worsening of symptoms occurring during the observation period (from RONAPREVE or placebo administration to final visit)
*2 Adverse events of special interest: Grade ≥ 2 hypersensitivity reactions through Day 29, Grade ≥ 2 infusion reactions through Day 4, and adverse events either related or unrelated to COVID-19 that lead to medical attention through Day 29

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Data evaluated in regulatory review: COV-2067 study efficacy results (approved in 2021, CTD 2.5.5.2)

RONAPREVE casirivimab and imdevimab

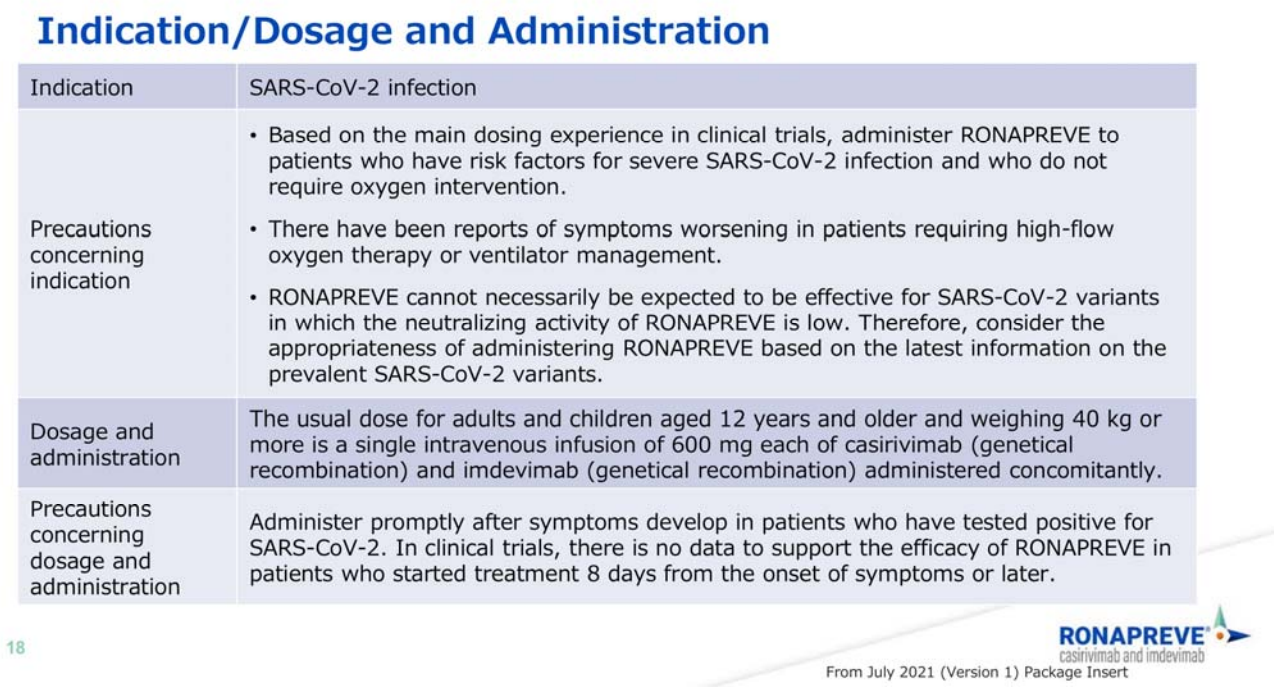
I would like to continue with the safety section, and discuss the data on adverse events.

On the left is the data for the 1200 mg group, and on the right is the data for the placebo group.

First of all, the incidence of adverse events was 7% in the treatment group and about 10% in the placebo group. We believe that the higher number of patients in the placebo group is due to worsening of disease caused by COVID-19.

In the bottom section, the most notable adverse events are grade 2 or higher infusion reactions up to day 4 of treatment, and grade 2 or higher hypersensitivity reactions up to day 29 of treatment. These are the adverse events that occurred up to day 29 of treatment. These notable adverse events occurred in 2.1% of cases in the treatment group, and 2.8% in the placebo group.

Especially noteworthy are infusion reactions and hypersensitivity reactions. The data for these is shown here.



I will talk about indications, effects, dosage, and administration.

I mentioned at the outset that we will be targeting patients who do not require oxygen for SARS-CoV-2 infection and who have risk factors for severe disease.

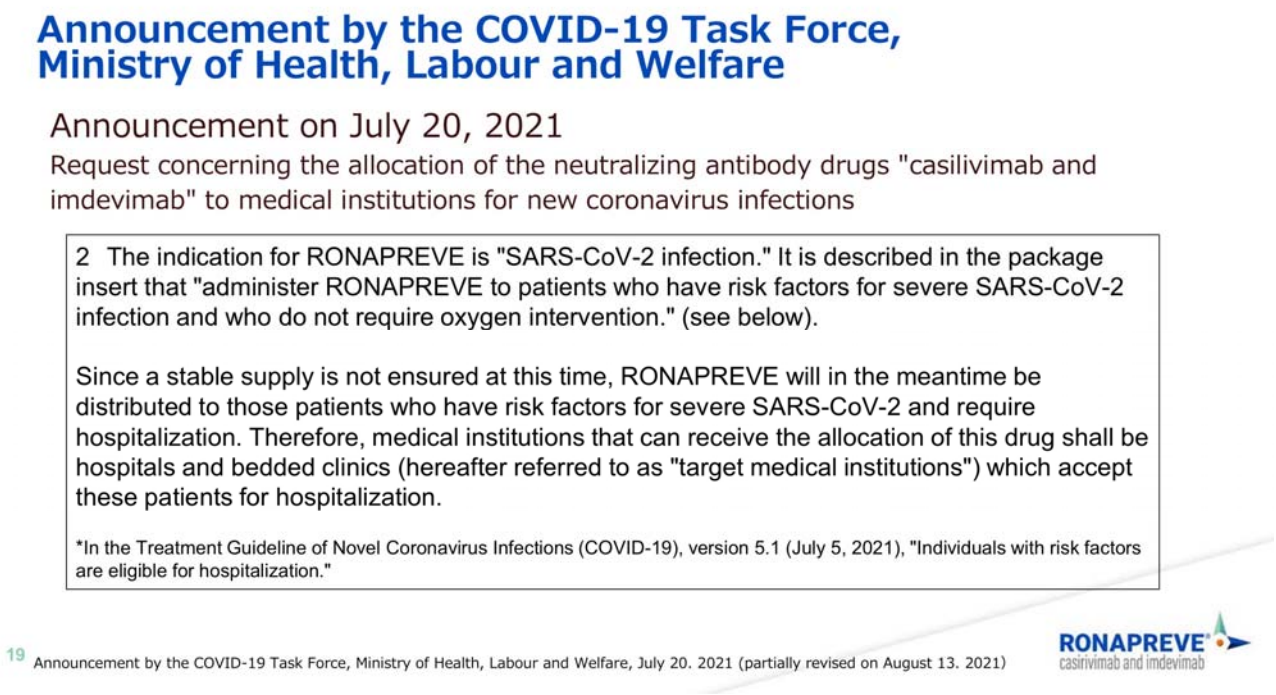
There have been reports of worsening of symptoms in patients requiring high-flow oxygen or ventilators. This is a different study, COV-2066, which was conducted in hospitalized patients. Although the causal relationship with the administration of this drug is unknown, we have been alerted to the fact that there were such patients.

In addition, since the efficacy of this product may not be expected for SARS-CoV-2 mutations with low neutralizing activity, we have issued a warning that the appropriateness of this product should be examined based on the latest information on the prevalent variants.

As shown in the previous slide, we have not yet identified any variants that would cause a loss of activity. However, we do not know what will happen in the future, and that is why we are issuing this warning.

The dosage and administration is 600 mg of each of casirivimab and imdevimab, for a total of 1200 mg.

As a precaution regarding dosage and administration, the drug should be administered as soon as the symptoms of SARS-CoV-2 infection appear. In the COV-2067 study, we recruited patients up to 7 days after the onset of symptoms. Therefore, we are issuing this warning because there is no data on the efficacy of the drug for patients 8 or more days after the onset of symptoms.



After the approval, the Ministry of Health, Labour, and Welfare issued an administrative notice. The target patients are defined as those who are infected with SARS-CoV-2, have risk factors for severe disease, and do not require oxygen administration.

The environment has been changing rapidly, and on August 13, we started administering the drug to patients who are hospitalized for a short period of time or are receiving treatment in residential treatment facilities. Yesterday an administrative notice was released stating that the drug can also be administered to outpatients.

I believe that the number of patients who will receive Ronapreve will increase in the future.

Approval Conditions

1. A risk management plan should be formulated and implemented appropriately.
2. Physicians should be requested to administer the drug only in cases where the administration of RONAPREVE is deemed appropriate, and to explain the efficacy and safety information in writing to the patient or their representative and to obtain their written consent before administering RONAPREVE.
3. The grace period for submission of materials based on Article 41 of the Ordinance for Enforcement of the Pharmaceutical and Medical Device Act (PMD Act) (Ministry of Health and Welfare Ordinance No. 1 of 1961) shall be 2 months from the date of approval. Moreover, when changing the approved items based on the submitted materials, etc., is deemed necessary, an order to change the approved items may be issued in accordance with Article 74-2, Paragraph 3 of the PMD Act.

20 From July 2021 (Version 1) Package Insert

RONAPREVE casirivimab and imdevimab

These are the conditions for approval.

On the next slide, I would like to briefly discuss the pharmaceutical risk management plan, which is to be formulated and implemented appropriately. In addition, 1 condition of approval is that the drug should be administered only after written consent has been obtained.

Overview of RONAPREVE Risk Management Plan

1.1 Safety Specification		
[Important identified risks]	[Important potential risks]	[Important missing information]
Anaphylaxis and other serious hypersensitivities	None	None
Infusion reaction		
1.2 Efficacy Considerations		
None		

2. Outline of Pharmacovigilance Plan
Regular pharmacovigilance activities
• Collection and evaluation of individual cases • Research reports: Collection and evaluation of publications, etc. • Reports of non-Japanese action plans: Collection and evaluation of information on measures taken outside Japan • Signal detection and evaluation using approaches including data mining techniques for adverse events (including deaths)
Additional pharmacovigilance activities
• Early post-marketing phase vigilance • Special drug use surveillance in patients with a SARS-CoV-2 infection with risk factors for severe SARS-CoV-2 infection
3. Outline of Plan for Efficacy Studies and Surveillance
None

4. Outline of Risk Minimization Plan
Normal risk minimization activities
• Create (revise) a package insert
Additional risk minimization activities
• Provide information through early post-marketing phase vigilance • Inform and reach understanding with patients to be treated (information sheet, patient handbook)

Sources: RONAPREVE for Intravenous Infusion Set 300
RONAPREVE for Intravenous Infusion Set 1332
Risk Management Plan (released July 2021)

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RONAPREVE casirivimab and imdevimab

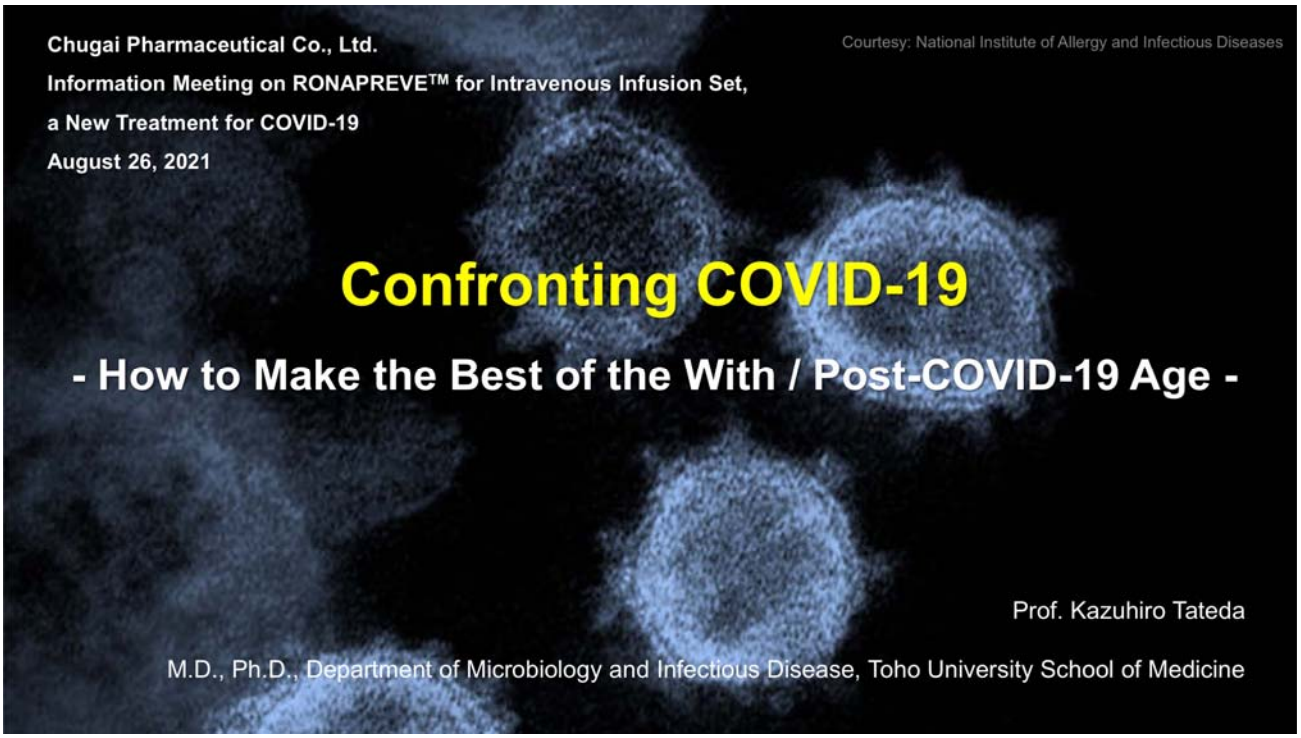
This slide shows more detail about the risk management plan.

Significant identified risks include anaphylaxis and other serious hypersensitivity reactions, as well as infusion reactions.

In addition, we will also collect information on side effects and other information through immediate post-marketing surveillance and specific use-results surveys.

In the current infection situation, which can be called a national crisis, we would like to contribute to medical care as much as possible with our Ronapreve treatment.

Thank you very much for your attention.



Sasai: Next, Prof. Tateda, from the Department of Microbiology and Infectious Diseases, Toho University School of Medicine, would like to explain the clinical positioning of Ronapreve in COVID-19 treatment.

Tateda: I am Tateda from Toho University.

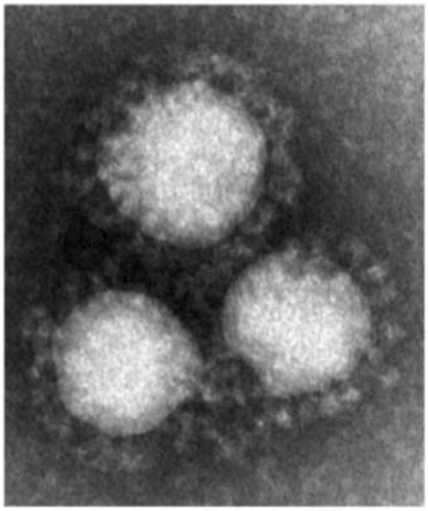
The coronavirus pandemic continues to be a difficult situation, with no end in sight. Recently, the fifth wave of infections, with more than 20,000 new patients per day, has been continuing. There are some areas where we are forced to provide disaster-level medical care.

In the midst of all this, there has been some bright news.

One of these is vaccines. This includes the world's first mRNA vaccine. The vaccines have been reported to be highly effective. In Japan, about 40% of the population has received 2 doses of vaccine. We need to ensure vaccination of those who want it as soon as possible.

The second piece of good news is the approval of Ronapreve, an antibody cocktail therapy, following the efficacy results we have seen. There is a great deal of expectation regarding this treatment among medical professionals and specialists. I would like to talk a little bit about its mechanism and how it is used.

Novel Coronavirus Disease (COVID-19)



- Four types of coronaviruses cause common cold
- Severe acute respiratory syndrome coronavirus (SARS-CoV), 2002
- Middle East respiratory syndrome coronavirus (MERS-CoV), 2012
- **Novel coronavirus (SARS-CoV-2), 2020**
- Infects and lives in bats, reptiles, camels, dogs, cats, etc.
- Crown-like structure on the virus surface (Corona = Crown)
- RNA virus (genome size: 30 kb)

What is coronavirus? (National Institute of Infectious Diseases, Japan)
(accessed August 23, 2021)

24

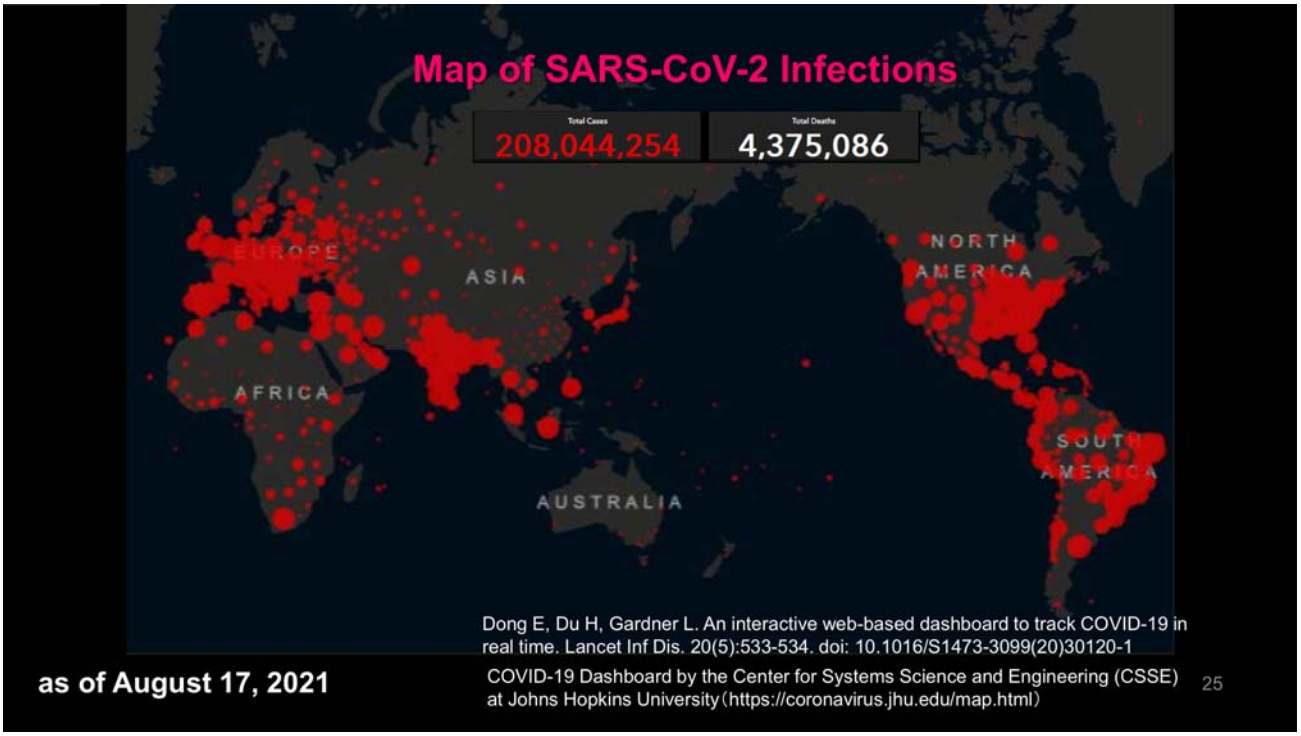
First, a few words about the coronavirus itself.

The coronavirus itself is similar to a cold virus. In addition to the 4 known to cause the common cold, we also saw the SARS infection in 2002, followed by MERS in 2012.

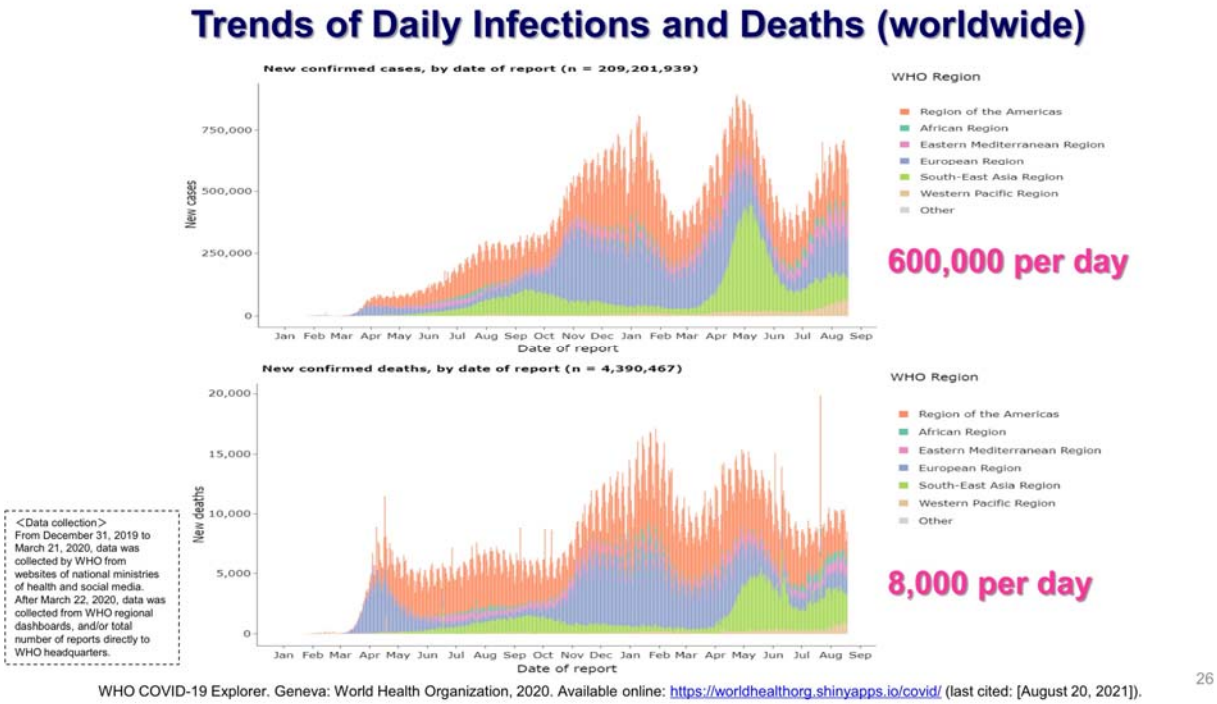
Against this background, the novel coronavirus infection began spreading in China and around the world at the end of 2019, and it has since become a major problem.

The coronavirus is known to infect bats, reptiles, camels, dogs, cats, and other animals, and also to infect humans.

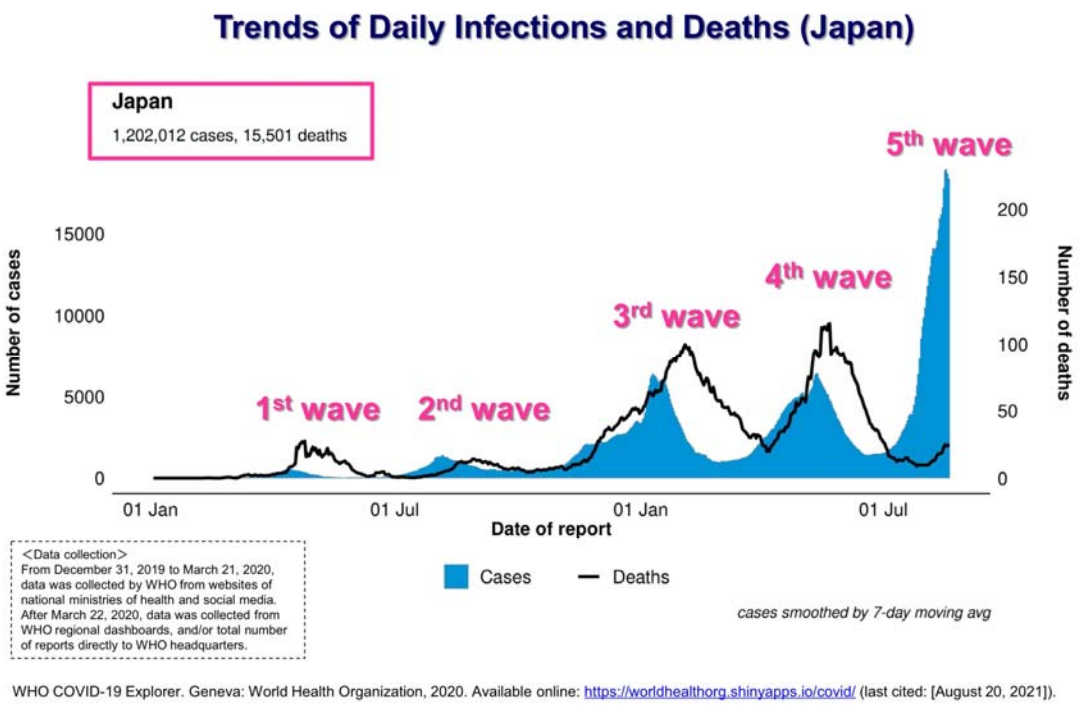
Morphologically, it is named the coronavirus because of its crown-like shape, as you can see from the image on the left.



It has been reported that more than 200 million people around the world have been infected with this disease, and unfortunately, more than 4 million people have died from it.

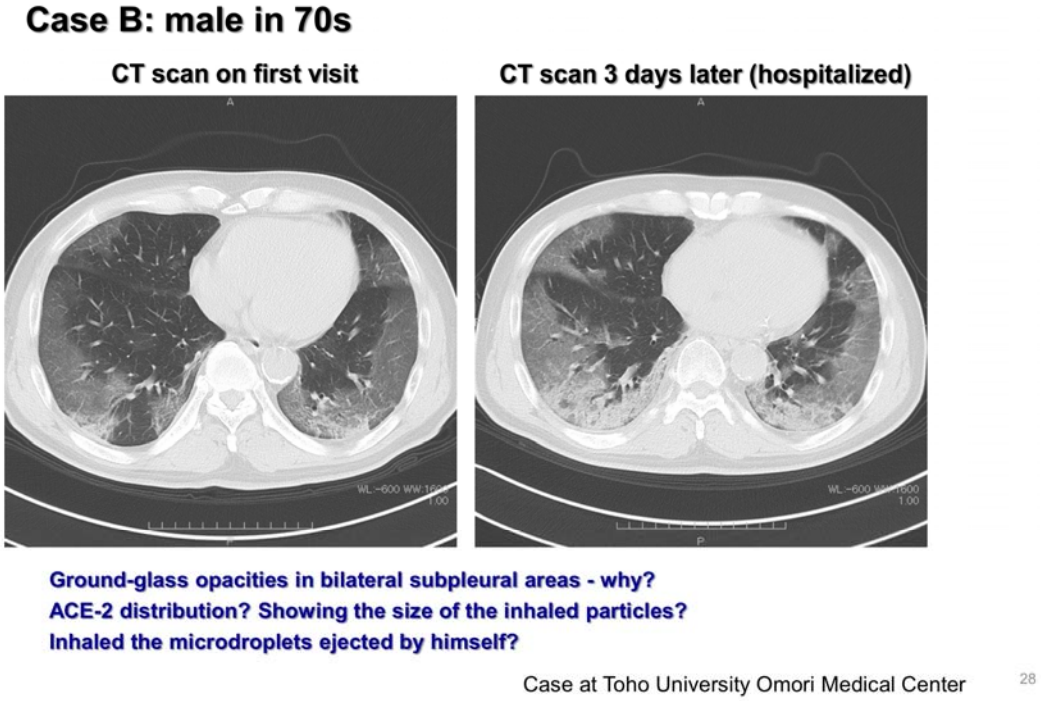


We are still seeing more than 600,000 cases per day, and more than 8,000 people are dying per day.



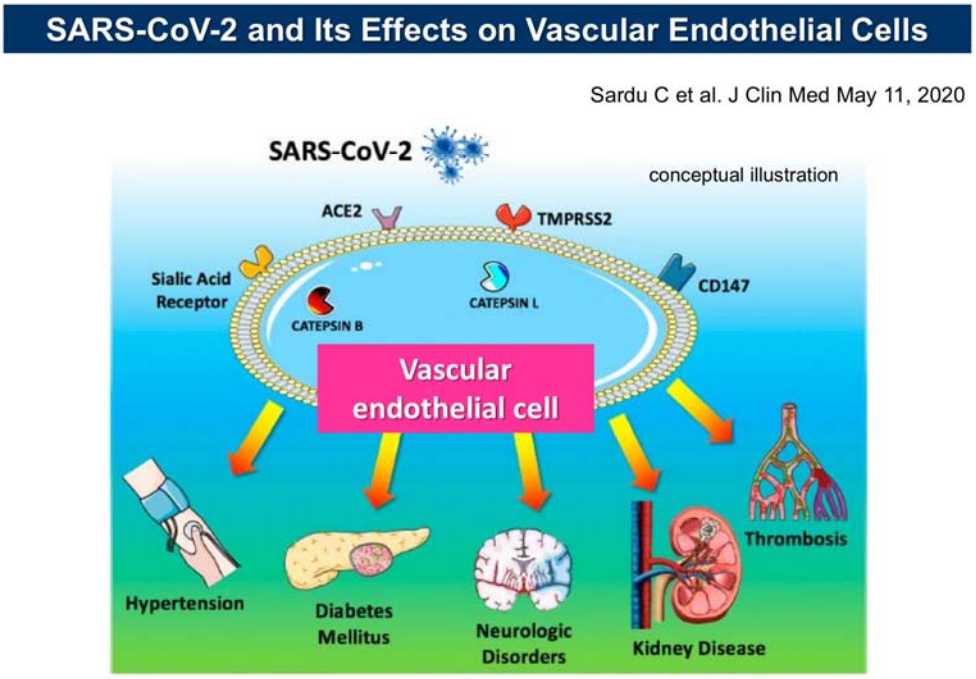
Japan is in the midst of the fifth wave of infection, and its peak is nowhere in sight. In the midst of this very confusing situation, it has been reported that more than 1.3 million people have been infected in Japan, and unfortunately more than 15,000 people have died.

As shown here, the black bar shows the trend of deaths, and the number of deaths is slightly delayed from the peak. With the peak of the fifth wave not in sight, I think we are all very concerned about how many people will die.



This is a CT image of the chest of a patient with coronavirus infection. This was the first case of coronavirus that we saw at Toho University, early last year. The ground-glass shadows bordering the chest wall, visible in the image on the left, are very typical. These features are easily recognizable to us now.

But why do we see such a characteristic pattern? Is it the receptor of this virus, ACE2, its localization, or the size of the particles inhaled? A recent theory is that this pneumonia pattern may be created by inhaling one's own saliva, which contains viral particles.



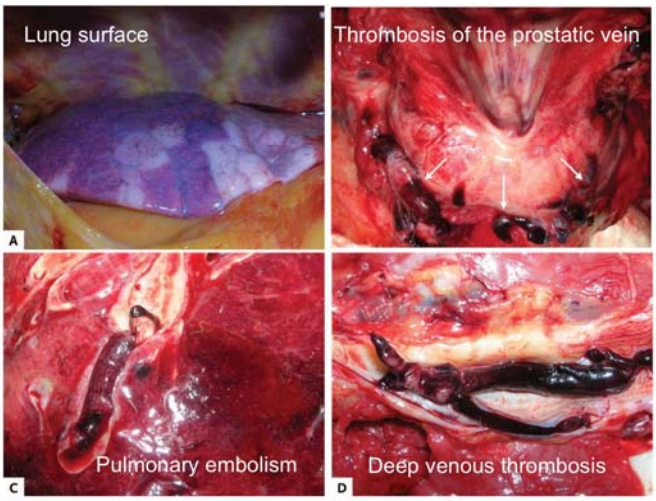
In addition, while pneumonia is 1 manifestation of disease, this infection infects the ACE2 receptors in the endothelial cells of blood vessels. This causes damage to the lining of blood vessels. It has been shown that it can cause damage to various organs, and is associated with severe or even permanent illness.

One of the contributors to severe disease is the development of blood clots. It has also been reported that this is a very important factor.

Thrombus Formation due to SARS-CoV-2 (overseas data)

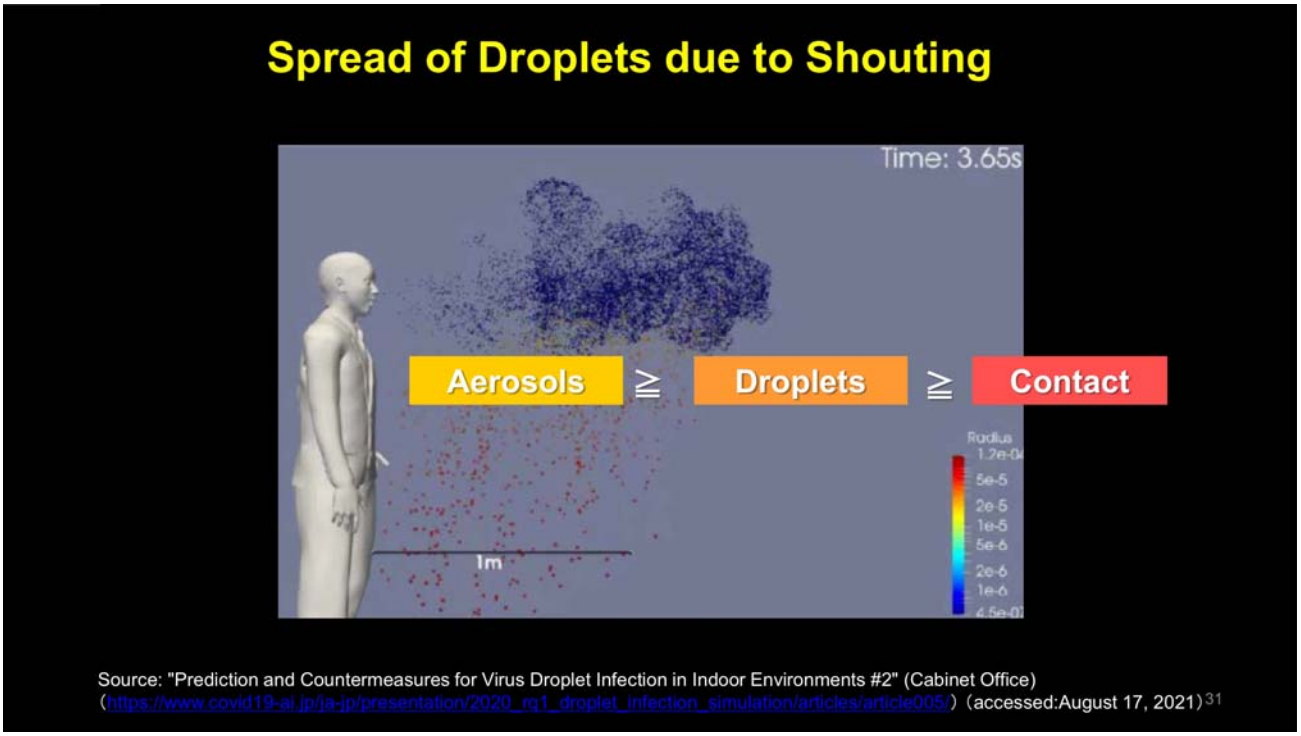
Wichmann D et al. Ann Internal Medicine 173: 268. 2020

- Deep venous thrombosis was found in 7 of 12 patients (58%), not suspected before death.
- Pulmonary embolism was presumed to be the direct cause of death in 4 patients.



30

On the top left, we can see the surface of a lung post-mortem. It looks like a mosaic. On the bottom left, we can see a blood clot in the lung, and on the top right, a blood clot in the prostate. On the bottom right, a deep vein thrombus can be seen. It has become apparent that the formation of this clot is more important in severe cases than we at first thought.

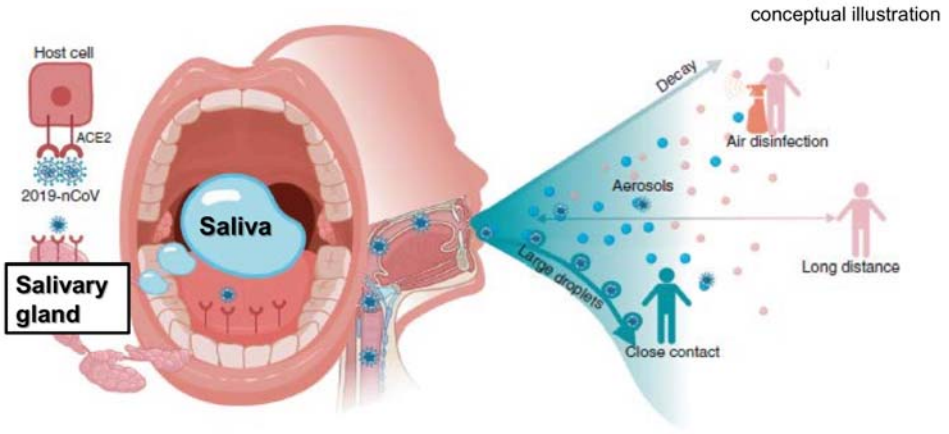


31

This was also a surprise to us. It has been thought that infectious diseases like influenza are spread mainly by droplet infection and contact infection.

What is becoming clear is that micro-droplets, such as from when people are speaking, cause infection in people nearby. This is micro-droplet infection. As you know, it has become clear that this is very important, and it has also become clear that non-woven masks are very effective against it.

Transmission of SARS-CoV-2 via Saliva, Diagnosis Using Saliva



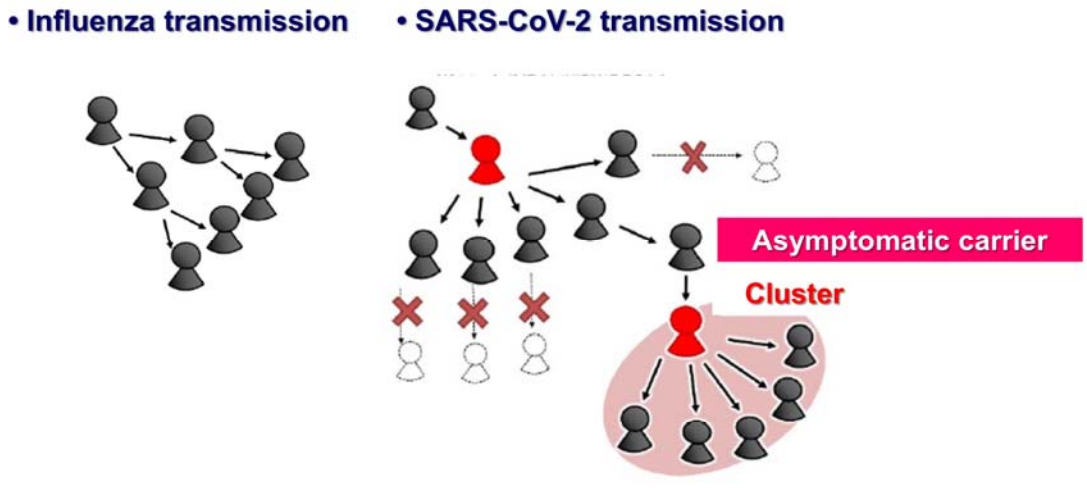
Xu R et al. Int J Oral Sci. Apr 17, 2020

32

Infection affects the salivary glands, resulting in high concentrations in the saliva. The virus is then released when people talk. Then, the infection is spread by inhaling the micro-droplets.

On the other hand, I am sure you are aware of the great progress that has been made in diagnostics with the introduction of saliva-based tests, PCR, and antigen tests.

Characteristics of SARS-CoV-2 Transmission



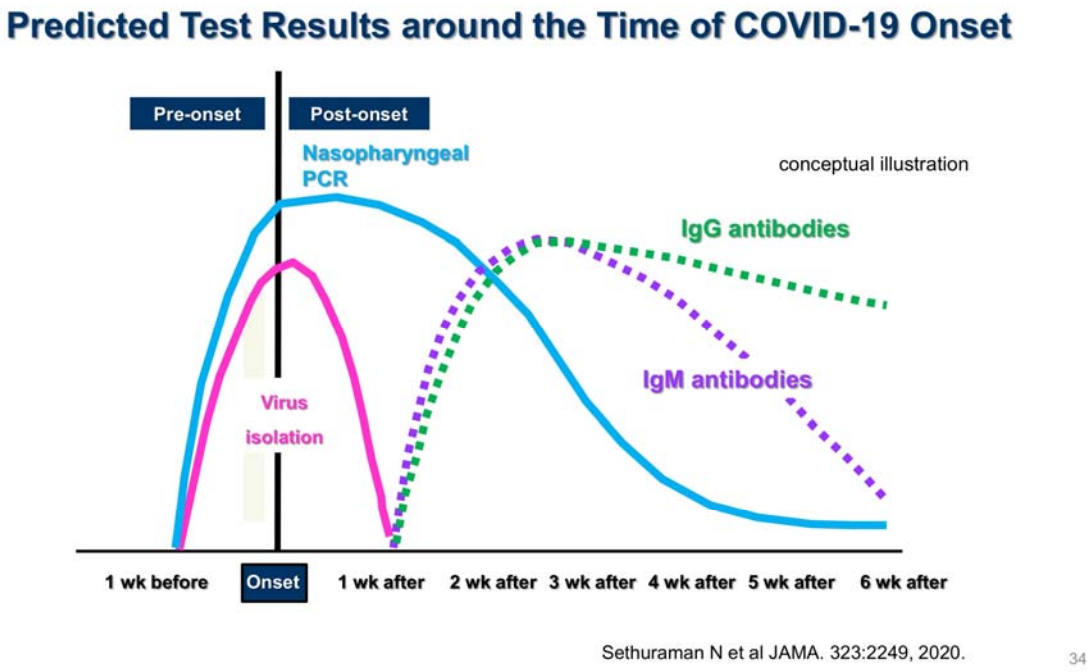
Ministry of Health, Labour and Welfare, Expert Committee on Countermeasures for New Coronavirus Infections
"Situation analysis and recommendations for COVID-19 countermeasures" (May 29, 2020)

33

This infectious disease is often compared to influenza, but influenza has an incubation period of 1 to 3 days. It can spread from 1 to 2, 2 to 4, 8 to 16 people, and can quickly cause closures of school classes, for example.

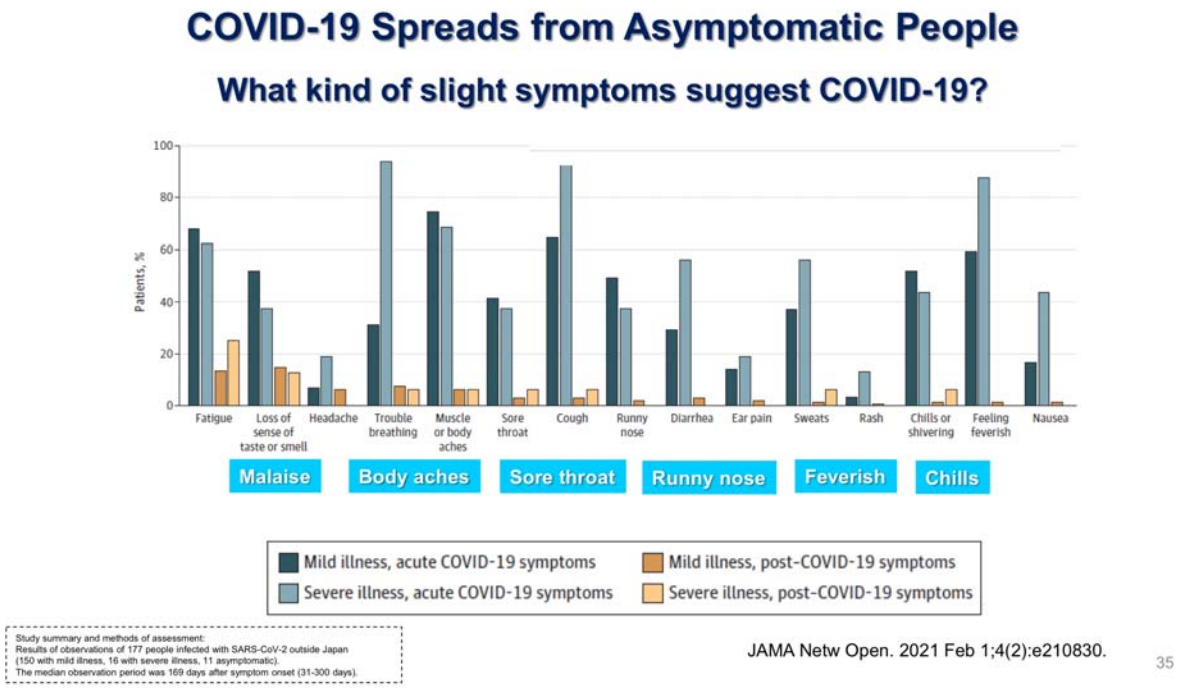
The novel coronavirus infection, on the other hand, may pass from 1 person to 5, but 4 of those people will not become infected. Suppose someone has the virus and is asymptomatic, and then that person happens to be in close contact with others. It is in such an environment that the infection spreads, and clusters of infection occur.

In other words, the risk of asymptomatic people spreading the infection is a very important feature of this infection and one of the reasons for the difficulty in managing it.



And the difficulty in diagnosing this infection is also shown here. In other words, even before the onset of symptoms, as I mentioned earlier, live virus particles are being exhaled. These live virus particles usually disappear within a week.

However, PCR tests have been shown to remain positive for many weeks afterwards. In other words, many of the PCR-positive people we see are PCR-positive without being infectious. How do we tell if they are infectious or not? One way is to check whether specific antibodies or neutralizing antibodies have been produced, which will be an important factor in diagnosing COVID-19 going forward.

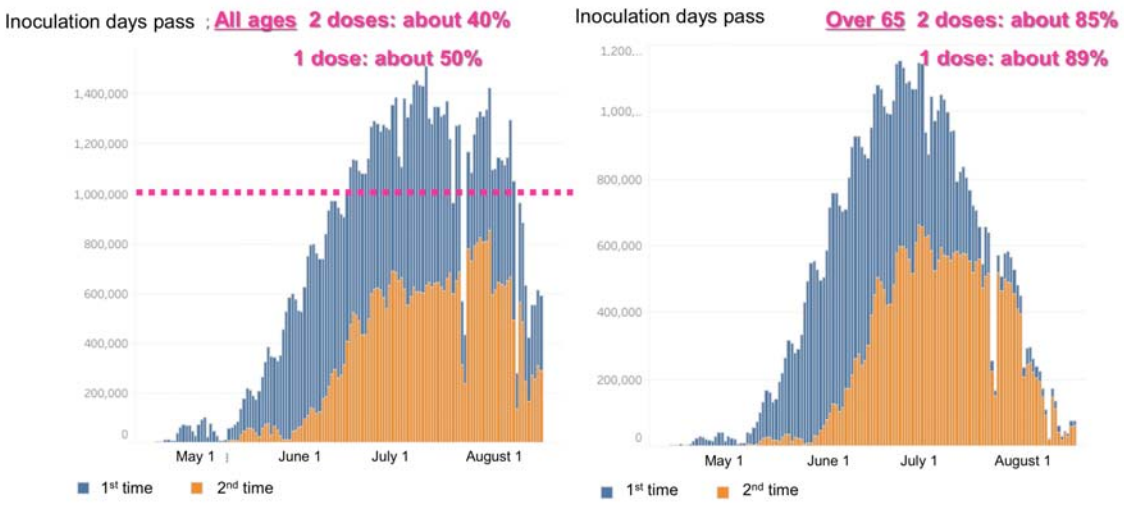


Furthermore, asymptomatic people can spread the infection. However, it is important to suspect coronavirus infection and test for it as early as possible in the course of the disease. At this stage, the symptoms are so minor that it is difficult to tell whether the patient has been exposed or not.

In those circumstances, symptoms could include a feeling of fatigue, body aches, a slightly sore throat, or a runny nose. When I see symptoms such as feverishness, chills, and mild colds, I cannot distinguish between them.

In that sense, we should test as soon as possible, and then rule out coronavirus. If someone tests positive, it is important to quarantine them.

COVID-19 Vaccination Status (August 17, 2021)



IT Strategy Office, Cabinet Secretariat 、https://cio.go.jp/c19vaccine_dashboard
Accessed August 18, 2021

36

Next, I'd like to say a few words about the efficacy of vaccines. The government is recommending a million vaccinations per day. At first it was thought to be impossible, but with the cooperation of Japanese medical professionals and the general public, we have been able to prove that it is possible.

Unfortunately, the number of vaccinations has been decreasing recently due to the difficulty in procuring vaccines, but if vaccines become available, the number of daily vaccinations will probably exceed 1 million again. Viewing all age groups as a whole, 40% of people have received 2 doses of vaccine, and 50% have received 1 dose. Among those aged 65 and older, 85% have received 2 doses. The figure is over 90% for 1 dose. I'm sure you're already aware of this.

Factors that may Affect Vaccine Effectiveness

1. Effectiveness differences attributable to vaccine type

   (e.g., mRNA, vector, DNA)

2. Prevention of onset, progression, or infection

3. Vaccine hesitancy

4. Breakthrough infections among vaccinated people

5. Duration and waning of vaccine effectiveness

6. Emergence of variants of concern (VOC)

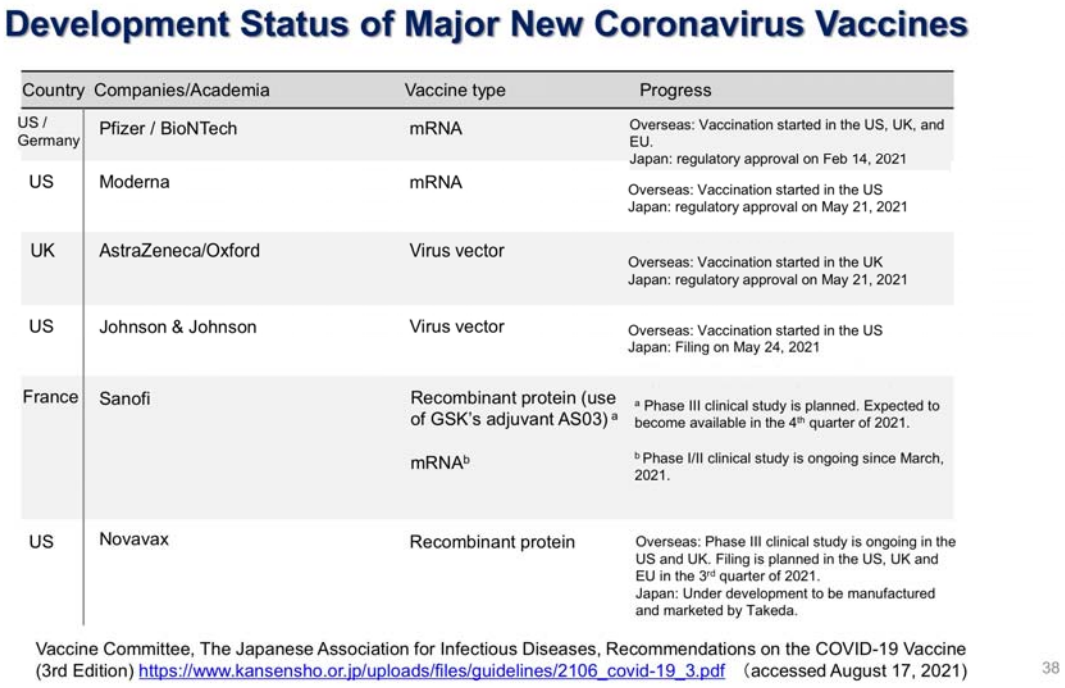
37

A little more about the effectiveness of vaccines. The vaccines have been proven to be highly effective, but one factor is the type of vaccine used. Messenger RNA vaccines and vector vaccines are used in Japan. In addition to preventing the onset and progression of the disease, vaccines have also been shown to suppress the infection itself.

However, there is the issue of vaccine hesitancy. It is true that there are people who do not want to be vaccinated or cannot be vaccinated. I am sure you are aware that so-called breakthrough infection, which is seen in vaccinated people, is now becoming a problem.

In addition, duration and waning of vaccine effectiveness related to antibodies, need to be monitored closely.

Then there is the emergence of variants of concern. You may know that the emergence and spread of the delta variant is now a cause for concern in Japan and around the world.



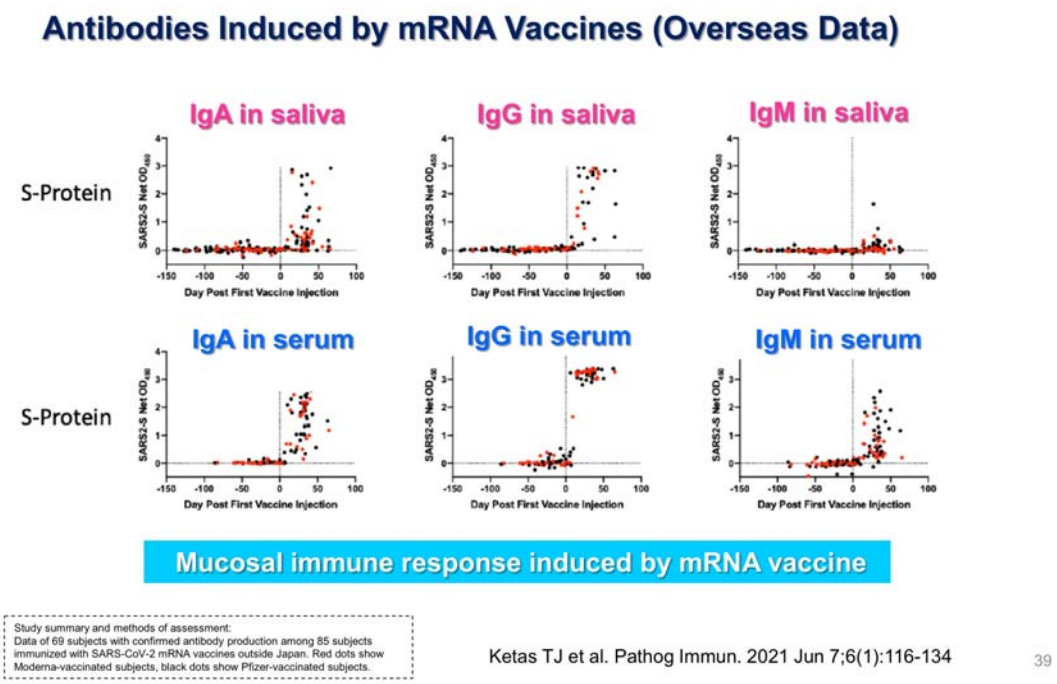
Development Status of Major New Coronavirus Vaccines

Country	Companies/Academia	Vaccine type	Progress
US / Germany	Pfizer / BioNTech	mRNA	Overseas: Vaccination started in the US, UK, and EU. Japan: regulatory approval on Feb 14, 2021
US	Moderna	mRNA	Overseas: Vaccination started in the US Japan: regulatory approval on May 21, 2021
UK	AstraZeneca/Oxford	Virus vector	Overseas: Vaccination started in the UK Japan: regulatory approval on May 21, 2021
US	Johnson & Johnson	Virus vector	Overseas: Vaccination started in the US Japan: Filing on May 24, 2021
France	Sanofi	Recombinant protein (use of GSK's adjuvant AS03) [a] mRNA[b]	[a] Phase III clinical study is planned. Expected to become available in the 4th quarter of 2021. [b] Phase I/II clinical study is ongoing since March, 2021.
US	Novavax	Recombinant protein	Overseas: Phase III clinical study is ongoing in the US and UK. Filing is planned in the US, UK and EU in the 3rd quarter of 2021. Japan: Under development to be manufactured and marketed by Takeda.

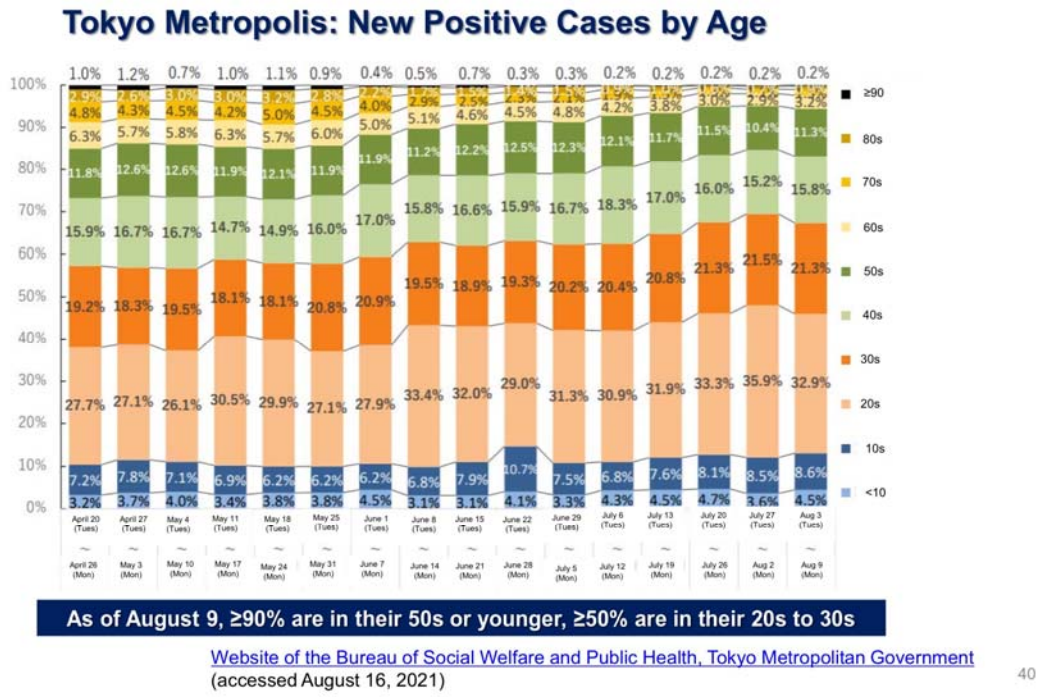
Vaccine Committee, The Japanese Association for Infectious Diseases, Recommendations on the COVID-19 Vaccine (3rd Edition) https://www.kansensho.or.jp/uploads/files/guidelines/2106_covid-19_3.pdf （accessed August 17, 2021)

38

This is a busy slide showing development status of major vaccines. We can see the mRNA vaccines from Pfizer and Moderna here. We can also see AstraZeneca's vector vaccine. These 3 are the main vaccinations used in Japan.

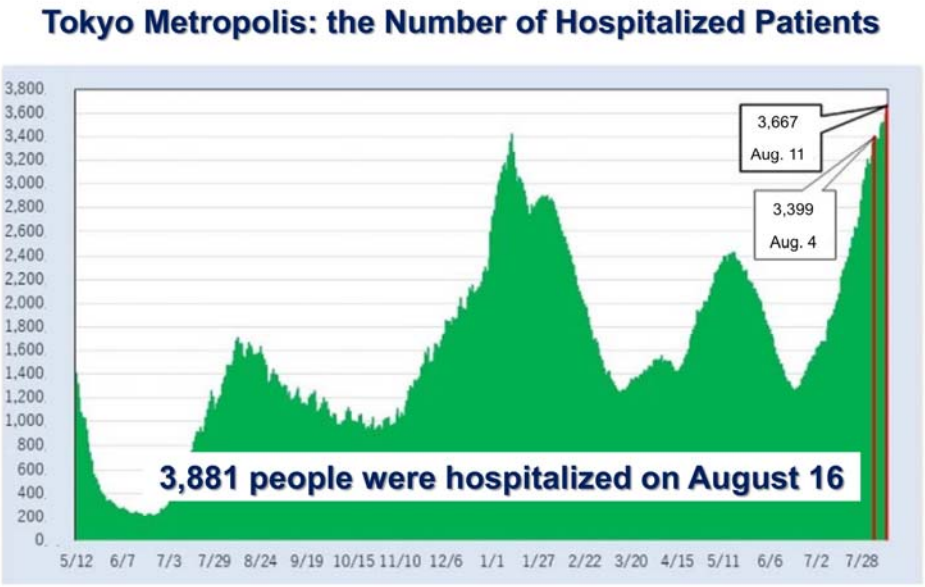


This vaccination induces not only IgA, IgG, and IgM in the blood, but also IgA in the saliva. In other words, salivary IgA is induced in a way that neutralizes the virus in the salivary glands or saliva. It has been shown that this mRNA vaccine has the potential to suppress the infection itself. In a way, it could be a game changer for vaccine development. I think that's one of the characteristics of this system.



As vaccination progresses, especially among the elderly, we can see the change in new positive tests in Tokyo. For example, the deep green color on this slide shows new positive tests in those in their 50s. Above that are those in their 60s and older. It is important to note that the number of elderly people infected with this disease

is decreasing significantly. More than 90% are in their 50s or younger, and more than 50% are in their 20s and 30s.

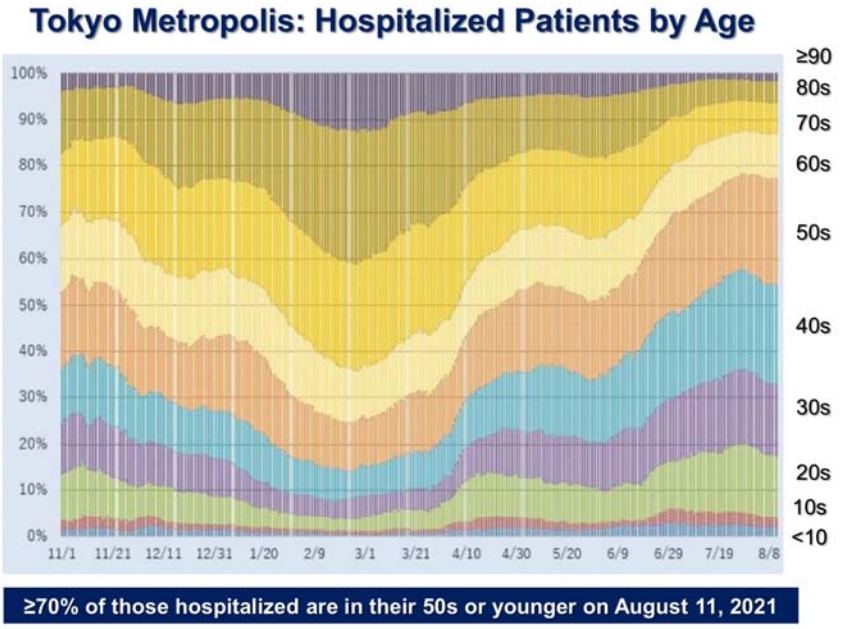


Website of the Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government (accessed on August 16, 2021)
Website of the Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government, Status of convalescents with new coronavirus infection (accessed Aug 17, 2021)

41

This is the number of inpatients in Tokyo.

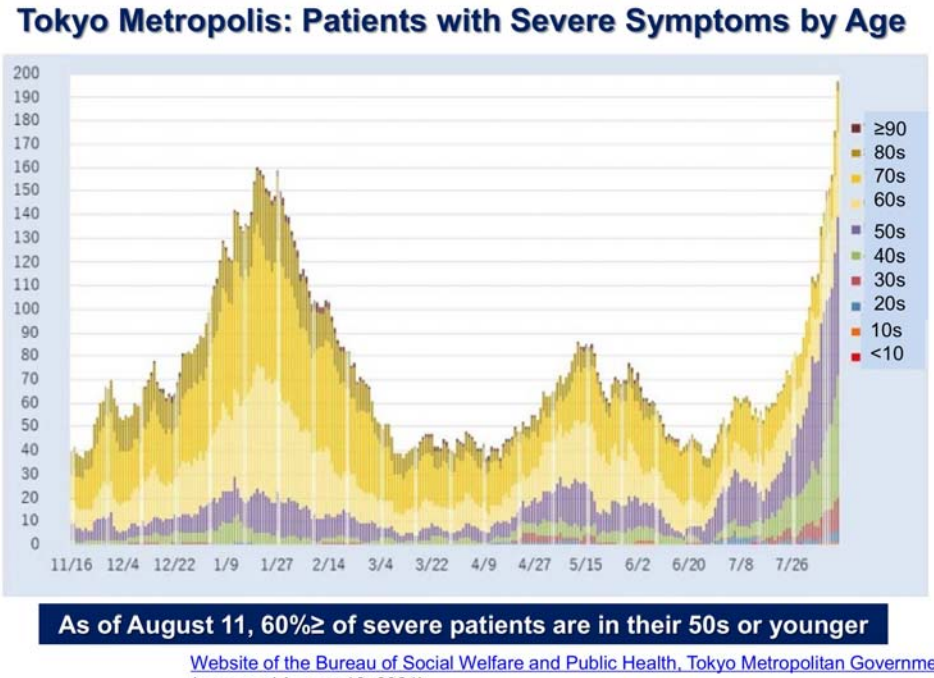
As of August 16th, the number of hospitalized patients was 3,800, but as of today, the number has exceeded 4,000. I'm sure you are aware of the difficult situation where some people who should be hospitalized are not being accommodated and need to standby at home.



Website of the Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government
(accessed August 16, 2021)

42

This is the number of hospitalized patients by age group. There are so many patients in their 50s, 40s, 30s and 20s who had to be hospitalized, according to this report.



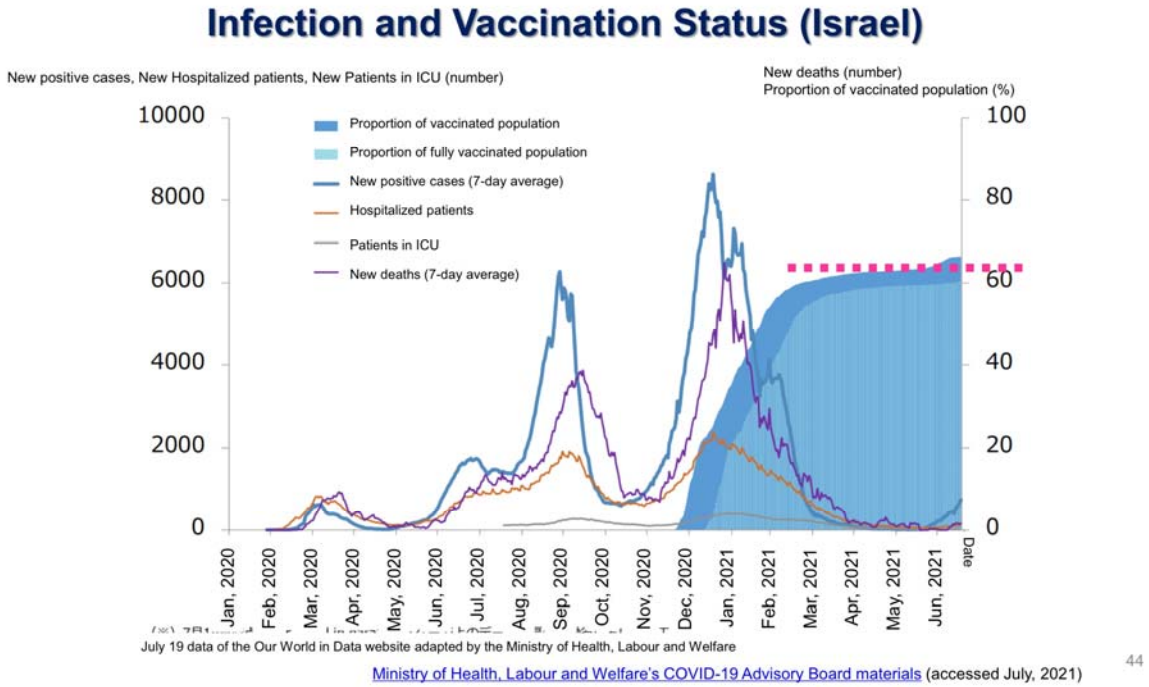
Website of the Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government
(accessed August 16, 2021)

43

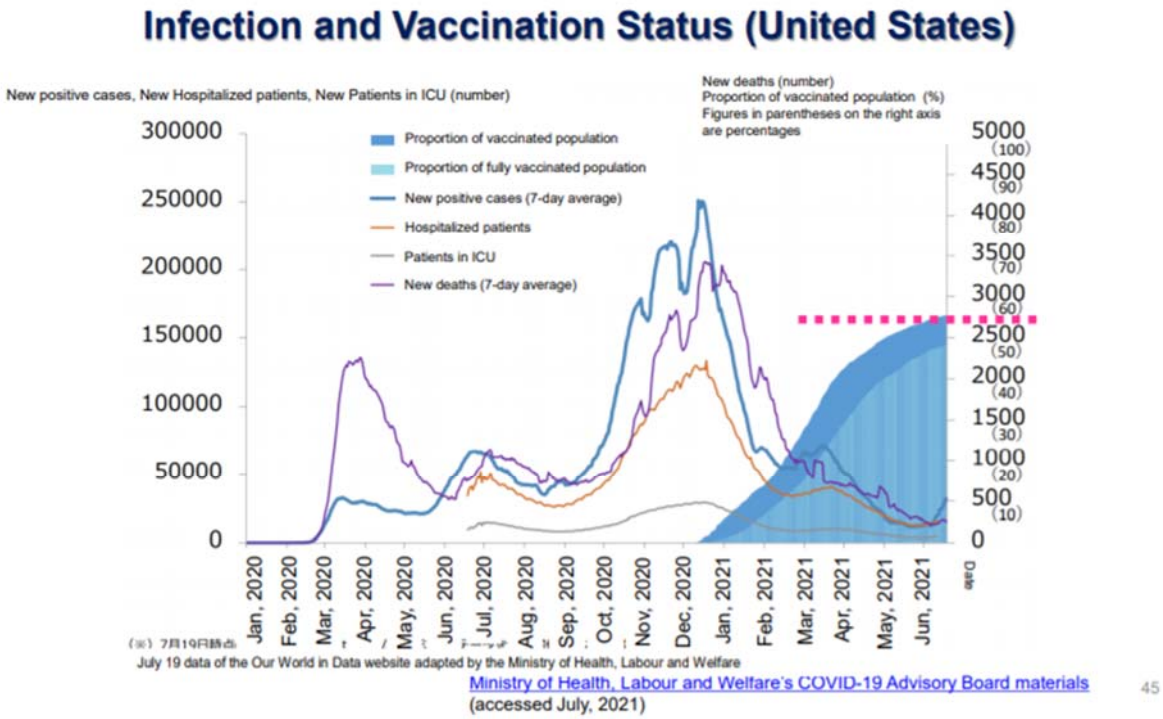
This slide shows the trend of number of severe cases. At present, more than 270 people in Tokyo are seriously ill.

This means that people in their 50s, 40s, and 30s are hospitalized as critically ill because they need a ventilator or ECMO. They could become fatal any time. Those in their 50s are shown in purple. Areas in purple and

below are patients in their 50s or younger: namely, those in their 50s, 40s and 30s are hospitalized with severe symptoms, as you can see here.

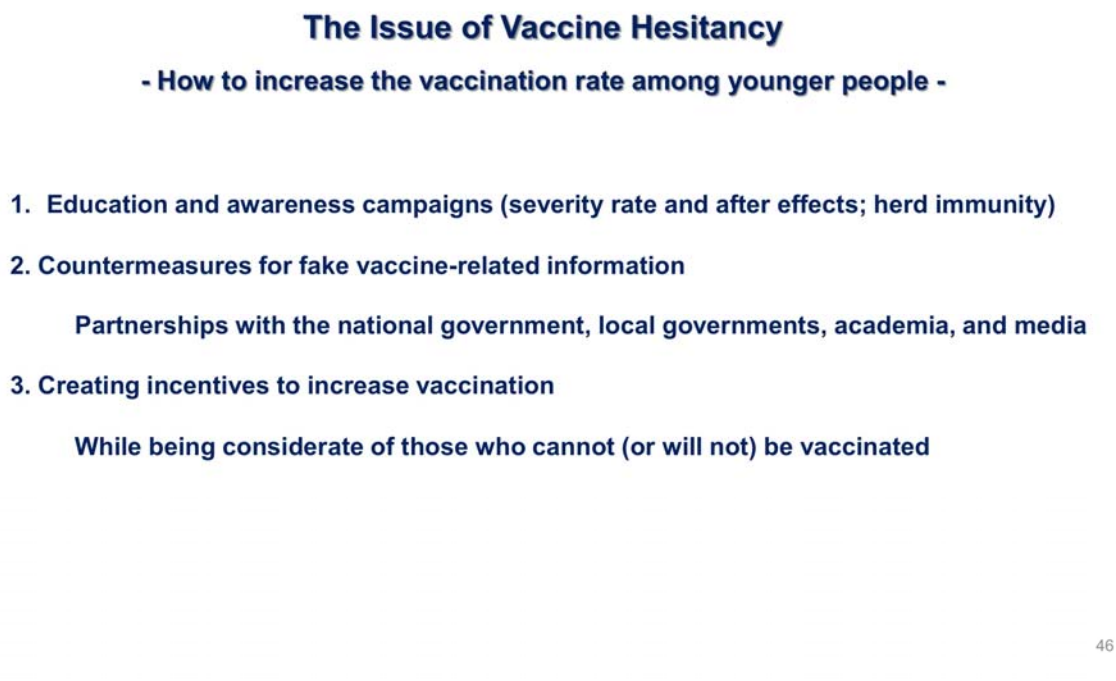


A further factor that affects the effectiveness of vaccines is the issue of vaccination coverage. In Israel, which is said to be a leading country in vaccination, unfortunately, it has been reported that the vaccination rate was hitting the ceiling of around 60%.



A similar phenomenon has occurred in the US, where the rate has reached the ceiling, leveling off at about 50% to 60%.

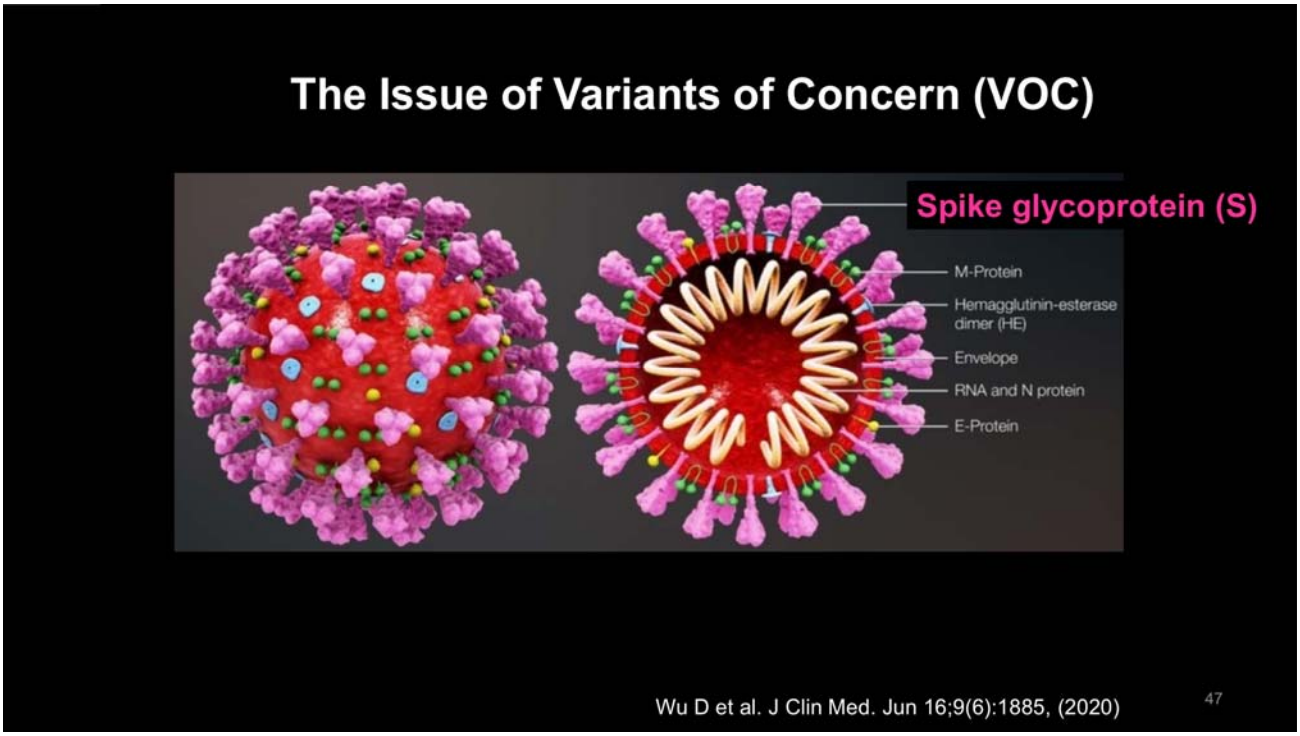
The question of how to increase the vaccination rate is a very important theme. I think that each country is working on this by creating incentives and making other efforts.



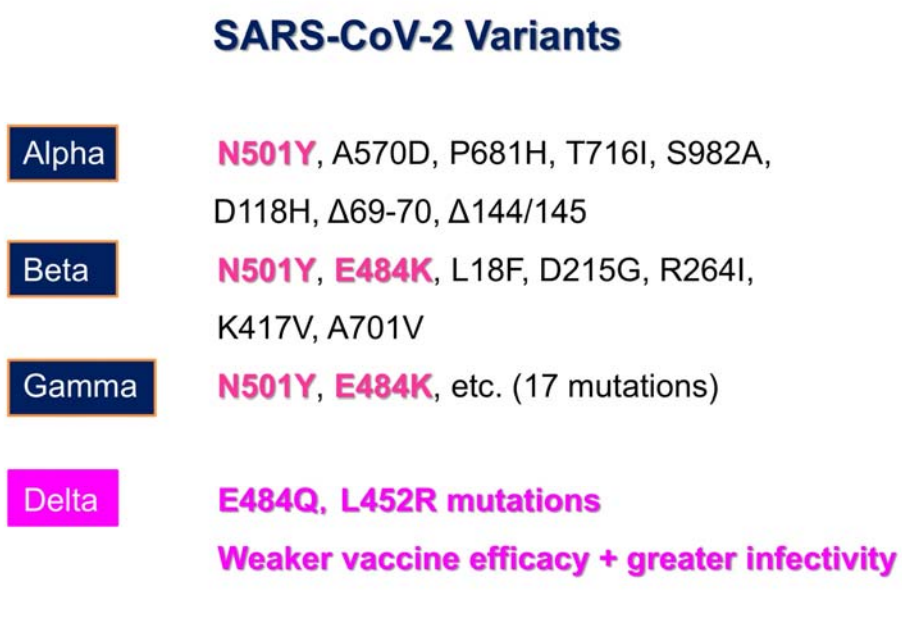
To address the issue of vaccine hesitancy, how can we increase vaccination rates, especially among the younger generation? Education and awareness campaigns are very important, as even young people can become seriously ill, or experience sequelae that are a major problem. Vaccination is also important from the perspective of mass protective immunity, protecting not only yourself but also your family and loved ones.

We also need countermeasures against fake vaccine-related information and false rumors. Not only the central government, local governments and academia but also members of the media who are joining today should cooperate to communicate the correct information and increase the vaccination rate. I think such initiatives are very important. We also need to create incentives such as certificates of vaccination to further promote vaccination. This is an important question going forward.

On the other hand, there are people who cannot be vaccinated, and there are people who choose not to be vaccinated. We have to also consider these people. I think it is important to take measures that do not lead to discrimination and bias.

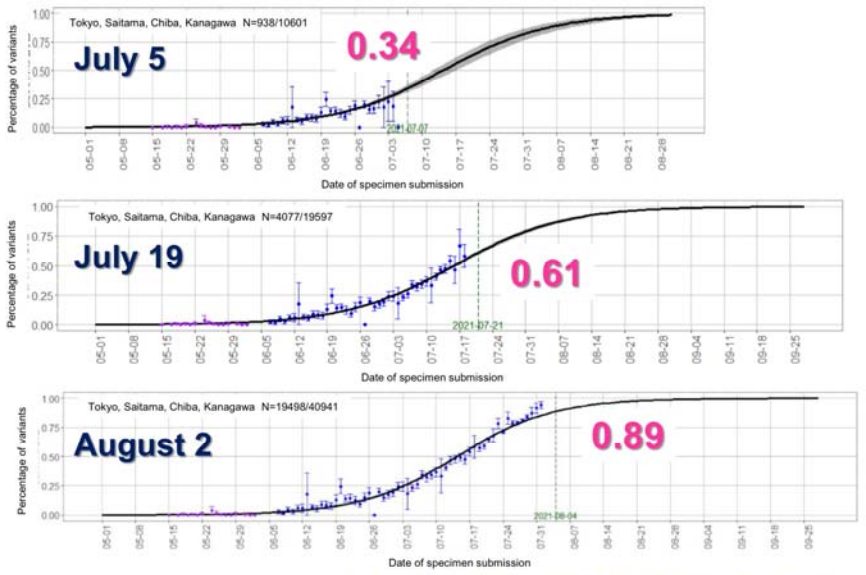


In addition, there is the issue of variants of concern, as was mentioned earlier. Infection is mediated by the virus spike protein in the body. Mutations there lead to variants of concern, changing the infectivity and virulence, according to the reports.



For example, the alpha, beta, and gamma types of mutant viruses, followed by the delta type, are now spreading in Japan and around the world. We all know that they are a major problem.

Proportion of L452R (Delta) Variant among Positive Cases (Greater Tokyo Area)

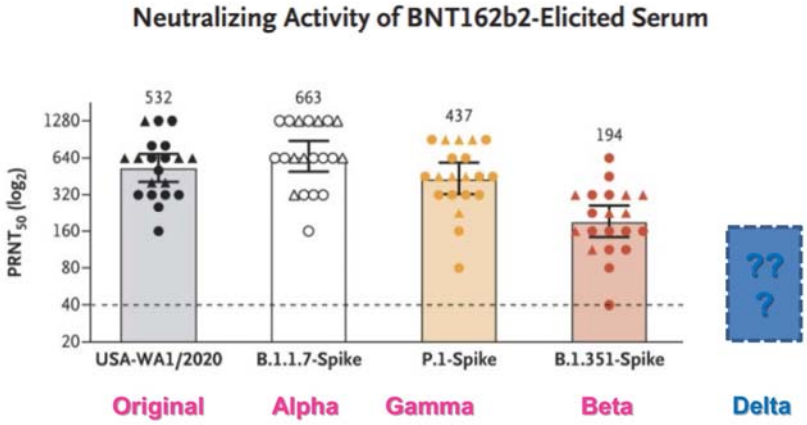


Ministry of Health, Labour and Welfare's COVID-19 Advisory Board materials
(42,44,46th meeting, accessed August 18, 2021)

49

The spread of the delta variant in Japan was about 34% on July 5th, exceeded 60% by the middle of the month, and was about 90% by the beginning of August. It has just been reported that most of the viruses have now changed to this delta variant.

Neutralizing Activity against Variants Antibodies Induced by the mRNA Vaccines



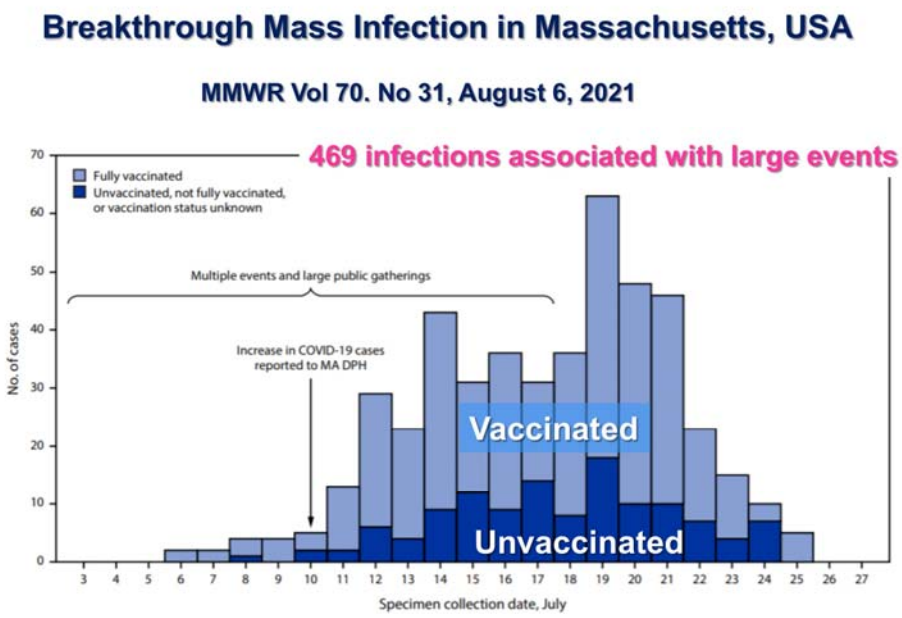
Study summary and methods of assessment:
Evaluation of the neutralizing activity of serum antibodies on SARS-CoV-2 variants using 20 samples obtained from 15 participants in the pivotal trial of the Pfizer mRNA vaccine

Liu Y et al. NEJM Apr 15, 1466-8 (2021)

50

Fortunately, the efficacy of vaccines against mutant variants has been reported to be consistent with that of conventional vaccines, although the efficacy of vaccines against alpha, gamma, and beta variants is slightly lower.

There are some reports that the efficacy of the vaccine for the delta variant has been slightly reduced, but I think it is an important fact that the vaccine is definitely effective.

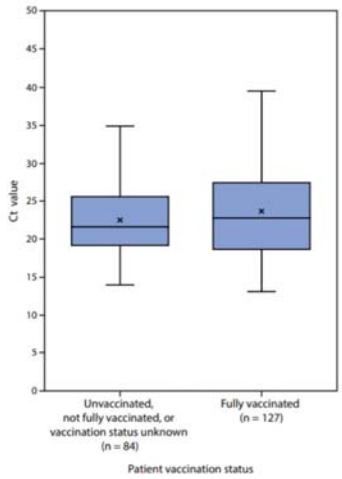


In the midst of all this, another worrying phenomenon has been reported.

It's called breakthrough infection, and it has occurred at large-scale events in the US that bring together vaccinated and unvaccinated people. This is for July. Then, in August, it was reported that more than 400 people were infected in connection with a large-scale event, and more than half of them were vaccinated. That was reported with a huge impact.

Breakthrough Mass Infection in Massachusetts, USA

MMWR Vol 70. No 31, August 6, 2021



- 469 infections associated with large events in July 2021
- 346 (74%) of those affected were vaccinated
- Genomic analysis revealed the Delta variant in 89% (119/133)
- 79% of those infected post-vaccination were asymptomatic
- Ct values did not differ between the vaccinated and unvaccinated people

The Delta variant is highly infectious and vaccine resistant

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The details at that time showed that 74% of the people had been vaccinated. Many had the delta variant. However, about 80% of the vaccinated patients were asymptomatic. On the other hand, as shown here, it has been reported that both vaccinated and unvaccinated individuals have the same viral load.

Vaccinated people may be infected, but are often asymptomatic. However, the viral load is just as high. In other words, there is a new risk that people with mild symptoms may become a driving force in spreading the infection. Such new risks are also emerging.

Viral Mutations and Course of Evolution

1. **Mutations occur once every 2 weeks**
2. **Mutations occur in random locations**
3. **There is a risk of change in infectivity when a mutation occurs in the receptor binding domain of the spike protein**
4. **Infectivity and virulence do not necessarily coincide**
5. **Evolution generally proceeds toward greater transmissivity and lower virulence**

1. National Institute of Infectious Diseases Genomic and epidemiological study of a novel coronavirus, SARS-CoV-2 https://www.niid.go.jp/niid/images/research_info/genome-2020_SARS-CoV-MolecularEpidemiology.pdf（accessed August 16, 2021）
3. Nat Commun. 2021 Feb 8;12(1):848

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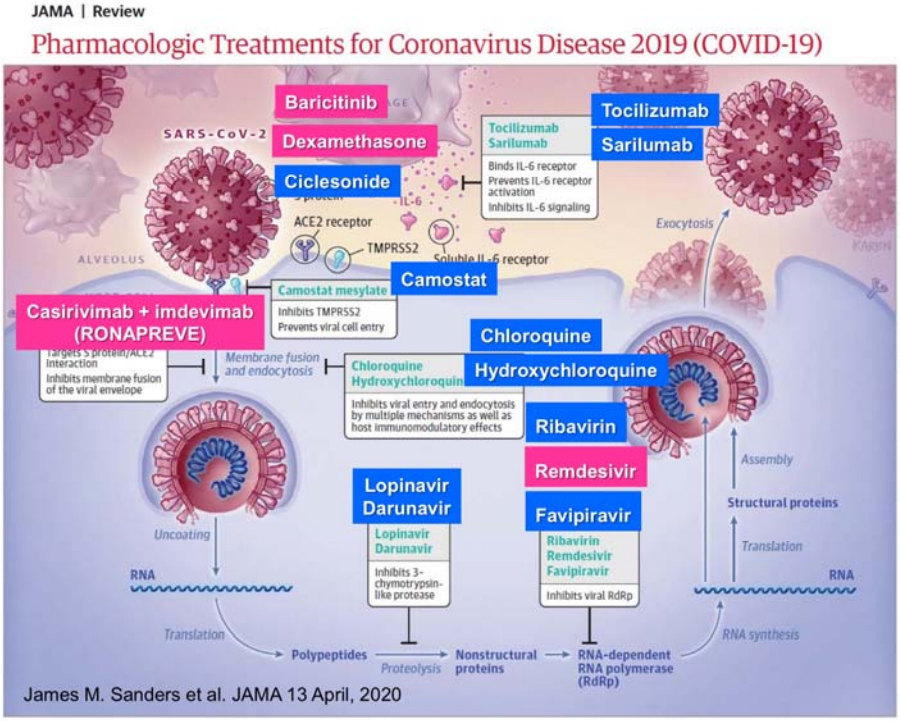
Regarding viral mutations and course of evolution, a lot of new facts are becoming clear. With regards to this virus, mutations occur once every two weeks. Mutations occur in random locations. There is a risk of change in infectivity when a mutation occurs in the receptor binding domain of the spike protein, but infectivity and virulence do not necessarily coincide. In the longer term, evolution generally proceeds toward greater transmissivity and lower virulence. But for COVID-19, it's difficult to predict how long it will take to reach such conditions.

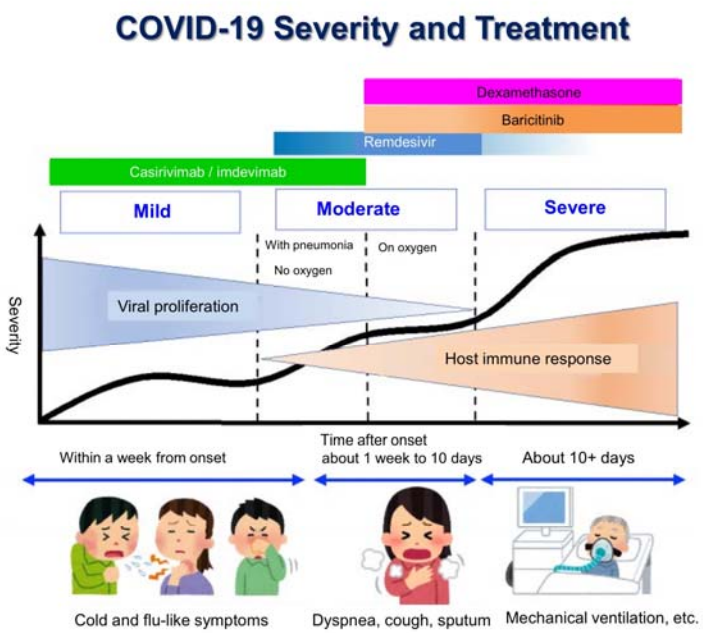


54

Let's move on to treatment. Various new directions in treatment have emerged.

Remdesivir was approved as a drug that suppresses gene replication after the virus has entered the body.

Then, after the virus is released, an excessive inflammatory response occurs, which is called a cytokine storm, and baricitinib and dexamethasone suppress this. Drugs that work on immunosuppression have been approved. Also, we now have Ronapreve, or casirivimab/imdevimab, which suppresses infection by binding antibodies to the spike proteins where the virus binds to the cells. This antibody cocktail therapy has been approved.

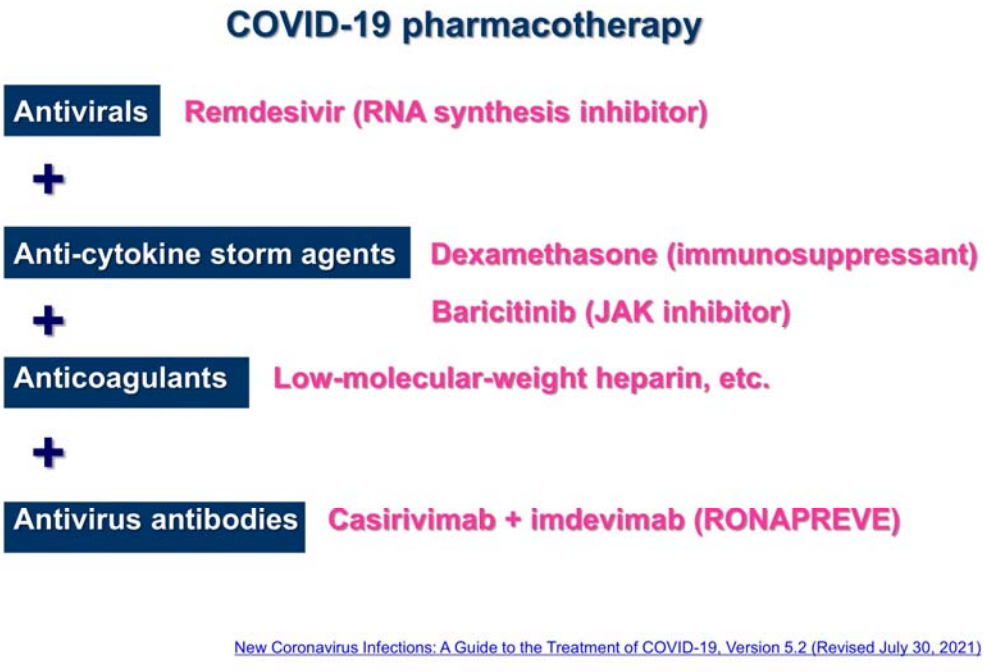


Japanese Association for Infectious Diseases: Approaches to Pharmacotherapies for COVID-19, 8th ed. (July 31, 2021) 55

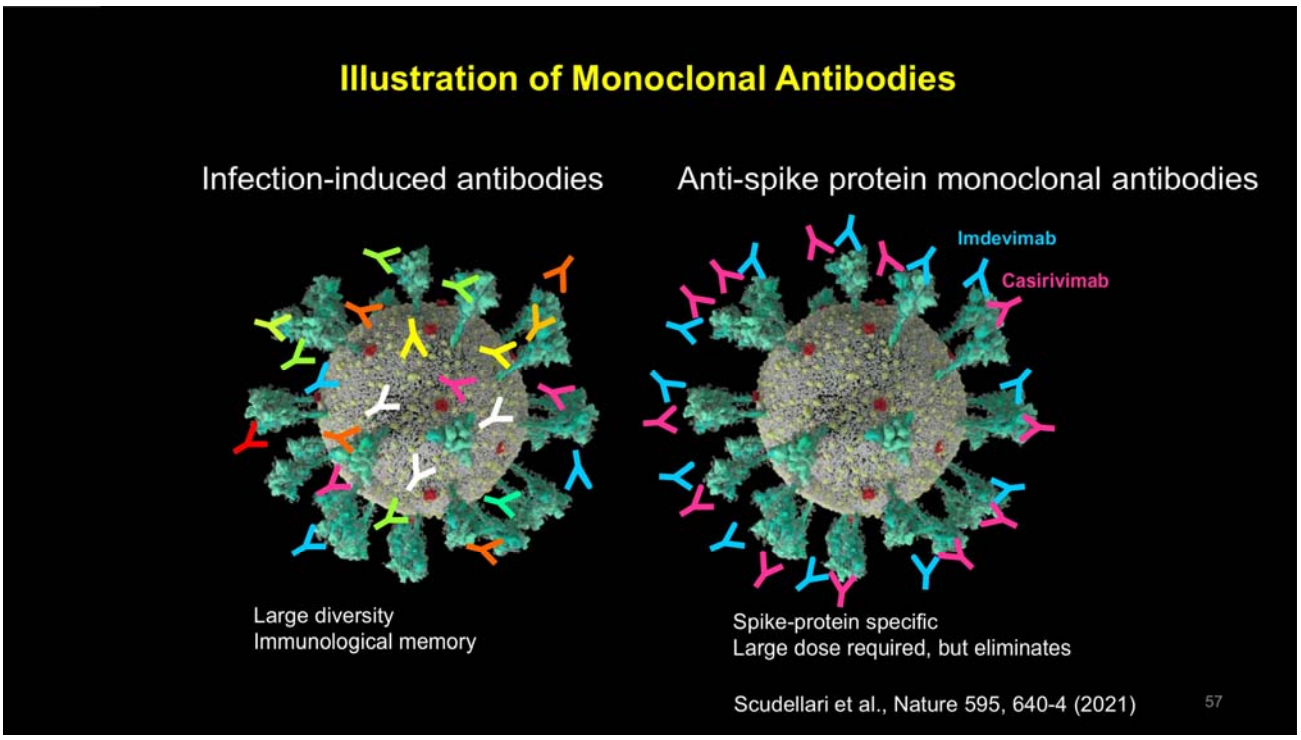
As I mentioned earlier, this is one of the main drug therapy themes on the website of the Japanese Association for Infectious Disease about the approaches to pharmacotherapies for COVID-19.. In the early stages of this infection, the main focus is on viral replication, but in the later stages, pathogenesis caused by the immune response, and the cytokine storm becomes more important.

Dexamethasone and baricitinib will be important in the terminal stages when the cytokine storm is strong. Remdesivir is important for viral suppression. It is also very important that Ronapreve has been approved. This is a drug that can be used from the early stage, suppressing the virus in the early and mild stages.

The fact that there are more and more drug options for mild to moderate infections is a big step forward.



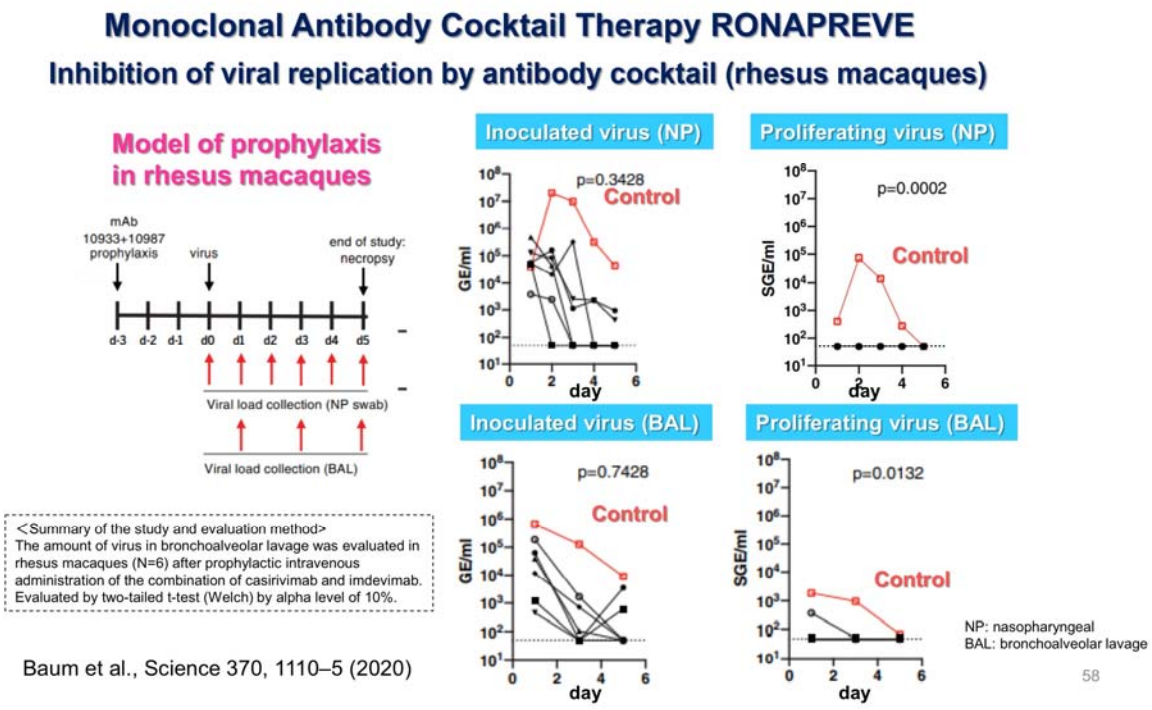
The principles of drug therapy for coronavirus nowadays are to use antiviral drugs, anti-cytokine storm therapy, anticoagulants, and antiviral antibodies. As a result, how to effectively administer and use them becomes important.



Firstly, Ronapreve. I've shown a simplified image of monoclonal antibodies here.

On the left, for example, are the antibodies that appear in the body of an infected person. The antibodies, which can be seen in red, yellow, and green, bind to the virus.

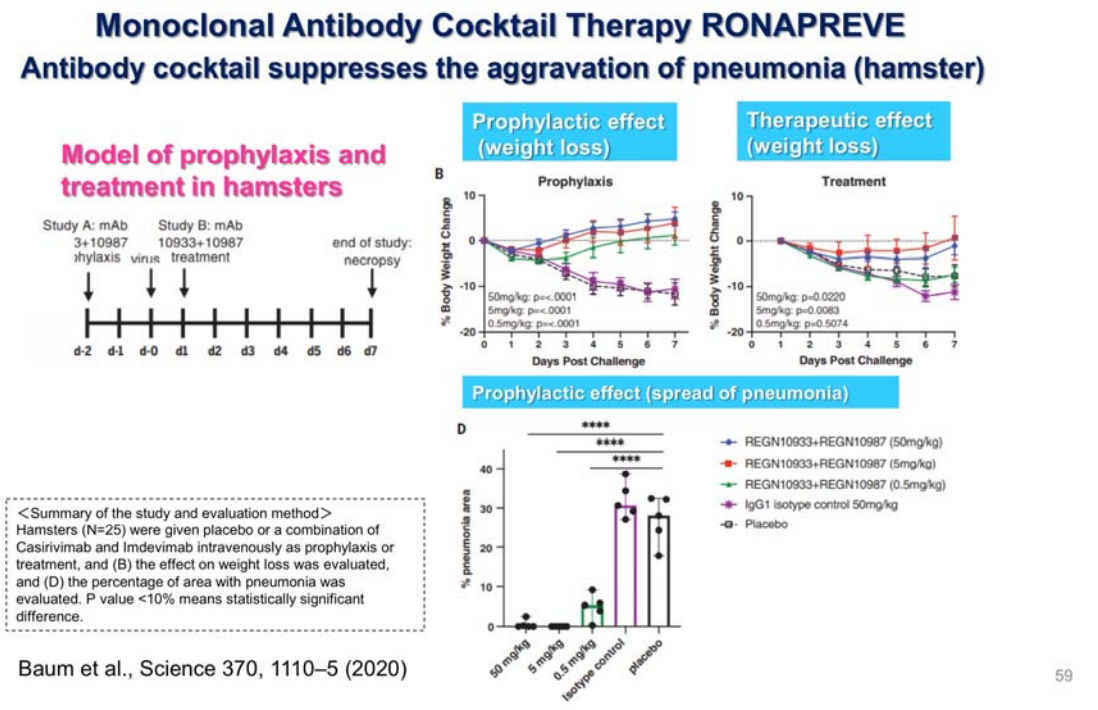
In the case of infection, antibodies that bind to various parts of the virus are produced. Monoclonal antibodies are artificially synthesized and produced to bind to specific parts of the S protein. By administering them, the virus can be prevented from infecting cells.



Clinical and trial data demonstrate the effectiveness of Ronapreve. This is a model of prophylaxis in rhesus macaques. The antibody cocktail was administered before viral infection, to see changes in the viral load.

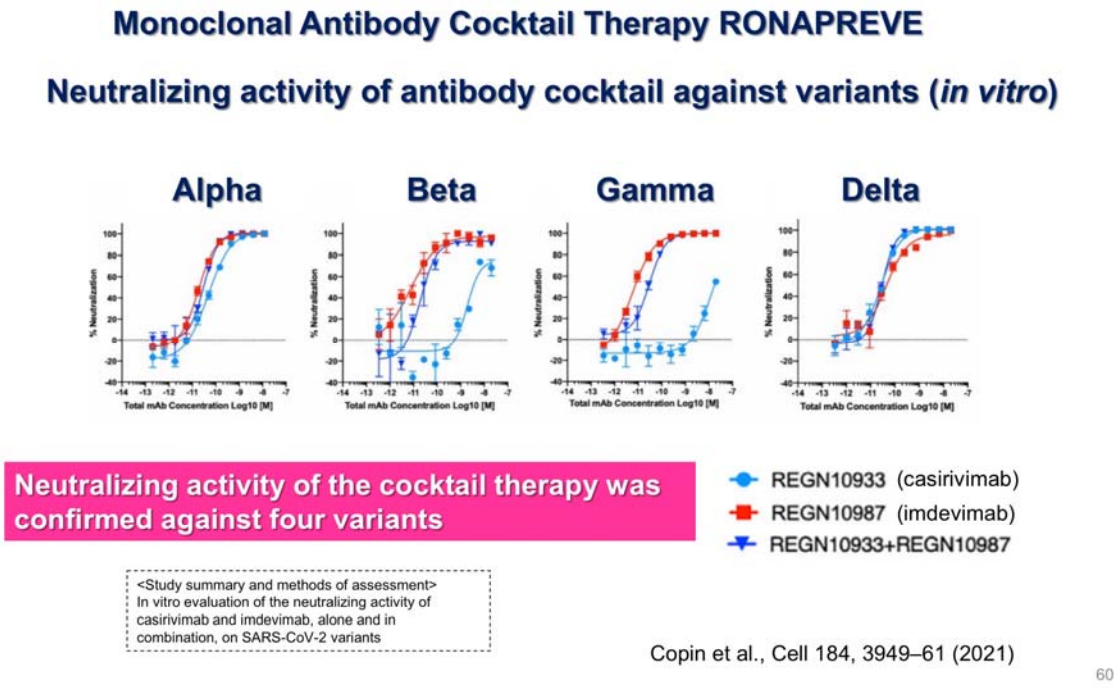
Here, we can see the viral load. What is the change in viral load in the nasopharynx after administration? Decrease in viral load is faster when Ronapreve is administered compared to controls.

What is even more interesting is that the antibody cocktail is very strong in inhibiting multiplication of the virus in the lungs and nasopharyngeal area. This antibody cocktail inhibited the viral proliferation very strongly. That was also reported in BAL, broncho-alveolar lavage.



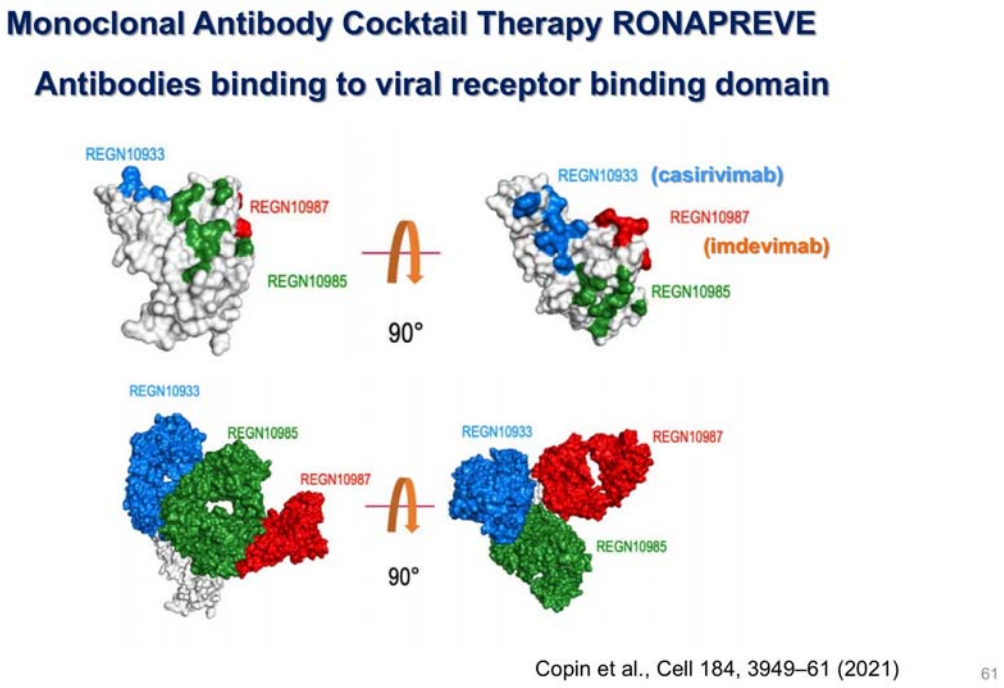
This is a model of prophylaxis and treatment in hamsters, to study the therapy before and after viral infection. Infections may reduce the body weight, but prophylaxis and treatment prevented weight loss.

It was confirmed that the spread of pneumonia decreased.



In addition, these results show how well the antibodies are able to neutralize variants in vitro. It is very strong against alpha strains, effectively neutralizing the virus.

Against the alpha variant, all the three, including each of the antibodies and the combination, had a very strong and effective neutralizing activity at a similar level. Against the beta variant, the neutralizing activity of casirivimab was a little lower. Also against the gamma variant, casirivimab's neutralizing activity was a little lower, but by using it in combination in the cocktail therapy, you can see recovery in the activity. As for the delta variant, good neutralizing activity was maintained, according to the report.



This shows where the antibodies bind to the spike protein.

The blue part is casirivimab. And the red part is imdevimab. Each antibody binds in a different place. However, it has been shown that by binding to different sites, strong neutralizing activity can be produced independently against the target region. This indicates a possibility that such efficacy can be expected.

Monoclonal Antibody Cocktail Therapy RONAPREVE

Emergence of resistant viruses by subculturing (*in vitro*)

Antibody type	Passage number										
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
REGN10933			Casirivimab								
REGN10985											
REGN10987			Imdevimab								
REGN10933+REGN10987								Casirivimab + Imdevimab			
REGN10933+REGN10987 +REGN10985											
CB6											
LY-CoV555											
CB6+LY-CoV555											
COV2-2130											
COV2-2196											
COV2-2130+COV2-2196											
VIR-7831											

Complete Escape
Partial Escape
No Escape

<Summary of the study and evaluation method>
When a model virus expressing the spike protein of SARS-CoV-2 was infected with a cell line, antibodies were added as a single agent or in combination. It was evaluated whether a resistant virus emerged by subculturing.

Copin et al., Cell 184, 3949–61 (2021)

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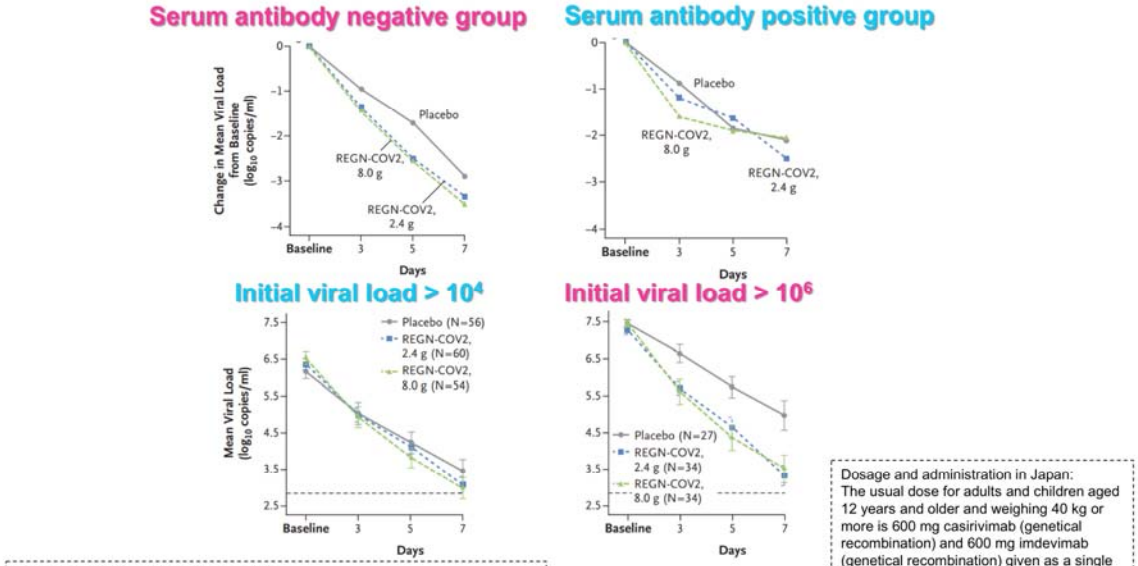
This is a summary of results.

It is true that when viruses are cultured in test tubes with cells, variants emerge and antibodies become less effective. With casirivimab alone, viruses that show this resistance emerge within 2 culture cycles. In the case of imdevimab, a variant appears in 2 culture cycles. When used in combination, a variant appears in 7 culture cycles.

It has been shown that variants and resistant viruses are less likely to appear. Furthermore, experimentally, in a triple antibody cocktail, it will be more difficult for resistant viruses to emerge.

Changes in Viral Load Following RONAPREVE Administration (Overseas Data)



<Study summary and methods of assessment>
Evaluation of changes over time in serum SARS-CoV-2 viral load based on baseline viral load and serum antibody status in participants in the Phase 1/2 part of non-Japanese Study COV-2067 in outpatients with COVID-19 (randomized to 3 groups: placebo group, REGN-COV2 2.4 g group, REGN-COV2 8.0 g group)

Dosage and administration in Japan:
The usual dose for adults and children aged 12 years and older and weighing 40 kg or more is 600 mg casirivimab (genetical recombination) and 600 mg imdevimab (genetical recombination) given as a single intravenous dose.

Weinreich et al., NEJM 384:238, 2021

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This was a study to see how much efficacy to reduce the virus load in human. As expected, the serum antibody titer shows a strong viral reduction effect in the negative group, and a strong viral reduction effect in those with high viral load.

Safety Evaluation for RONAPREVE (Overseas Data)

Event	REGN-COV2			Placebo (N=93)
	2.4 g (N=88)	8.0 g (N=88)	Combined (N=176)	
	number of patients (percent)			
Any serious adverse event	1 (1)	0	1 (1)	2 (2)
Any adverse event of special interest*	0	2 (2)	2 (1)	2 (2)
Any serious adverse event of special interest*	0	0	0	0
Grade ≥2 infusion-related reaction within 4 days	0	2 (2)	2 (1)	1 (1)
Grade ≥2 hypersensitivity reaction within 29 days	0	1 (1)	1 (1)	2 (2)
Adverse events that occurred or worsened during the observation period†				
Grade 3 or 4 event	1 (1)	0	1 (1)	1 (1)
Event that led to death	0	0	0	0
Event that led to withdrawal from the trial	0	0	0	0
Event that led to infusion interruption*	0	1 (1)	1 (1)	1 (1)

* Events were grade 2 or higher hypersensitivity reactions or infusion-related reactions.
† Events listed here were not present at baseline or were an exacerbation of a preexisting condition that occurred during the observation period, which is defined as the time from administration of REGN-COV2 or placebo to the last study visit.

Weinreich et al., NEJM 384:238, 2021

Monoclonal antibodies have been used in clinical practice

<Summary of the study and evaluation method>
Participants in part P1/2 of the COV-2067 study (overseas), conducted in COVID-19 outpatients was randomized to 3 arms (placebo, REGN-COV2 2.4g, or 8.0g) and were evaluated for AESI or serious adverse events.

Dosage and administration in Japan:
The usual dose for adults and children aged 12 years and older and weighing 40 kg or more is 600 mg casirivimab (genetical recombination) and 600 mg imdevimab (genetical recombination) given as a single intravenous dose.

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How about the safety of Ronapreve?

This slide is a little detailed, but essentially, this medication is a monoclonal antibody preparation, similar to Actemra and anti-TNFα inhibitors, applied to treating viral infections. I think it is important to note that there have been no reports of strong adverse reactions.

Efficacy of RONAPREVE and Expectation

Efficacy and safety reported to date[1]

- Reduction of hospitalization, serious symptoms and death (more than 70%)
- Shortened time to symptom improvement (about 4 days)
- Reduction in viral load (suppressive effect in high virus group)
- Safety profile (serious adverse events: 1.1% (9/827 patients),
  infusion reaction: 0.2% (2/827 patients), hypersensitivity: 0%)

Issues to be considered in the future

- Expansion of indications for outpatient administration
- Confirmation of further efficacy in combination with other treatment
- Triple combination?

1. Weinreich et al., NEJM 384:238, 2021
   Data evaluated in regulatory review: COV-2067 study efficacy results (approved 2021, CTD 2.5.4.2)

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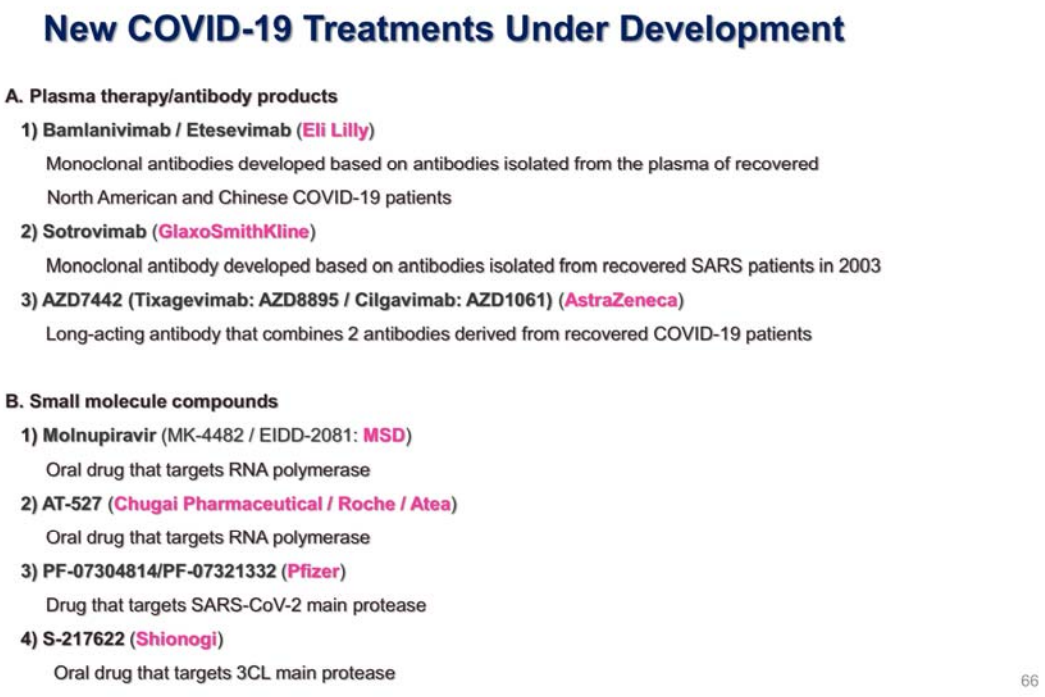
Now, a few words on the efficacy of Ronapreve and the expectations of healthcare professionals.

The reported efficacy and safety of the drug so far are as follows: over 70% reduction in hospitalization, serious illness, and death; reduction in time to symptom improvement by about 4 days; strong reduction in viral load, especially in the high viral load group; and no serious concerns reported in the safety profile, which is important.

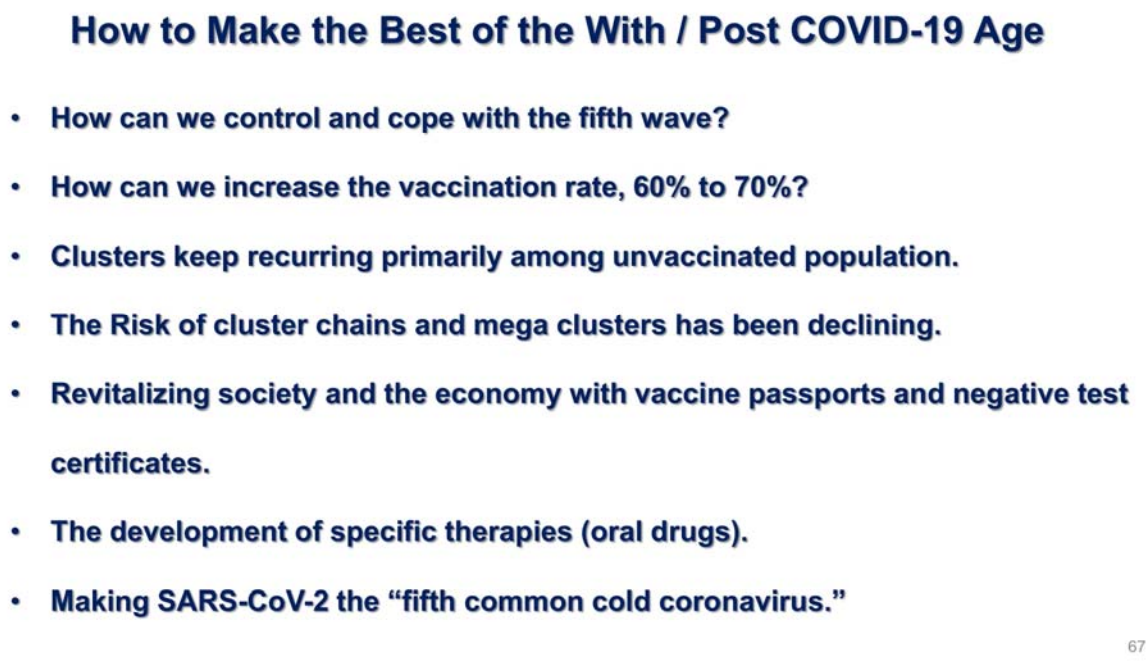
On the other hand, there are issues we need to consider for the future. I listed expansion of indications for outpatient administration, but this is going to be cleared. We are now on the way to be able to administer Ronapreve to outpatients and those who need to be watched while recuperating at home. Confirmation of further efficacy in combination with other treatments. We must consider the possibility of triple combination, etc., which I mentioned earlier, for the future.



I have outlined some of the new COVID drugs that are currently in development.

The upper half are antibody-related products such as those from Eli Lilly, GlaxoSmithKline, and AstraZeneca. The bottom half shows small-molecule compounds, including oral treatments by MSD and AT-527 by Chugai, as well as drugs by Pfizer and Shionogi. These oral small molecule treatments are now under development.

We are hoping that these treatments will be delivered to the clinical settings as soon as possible.



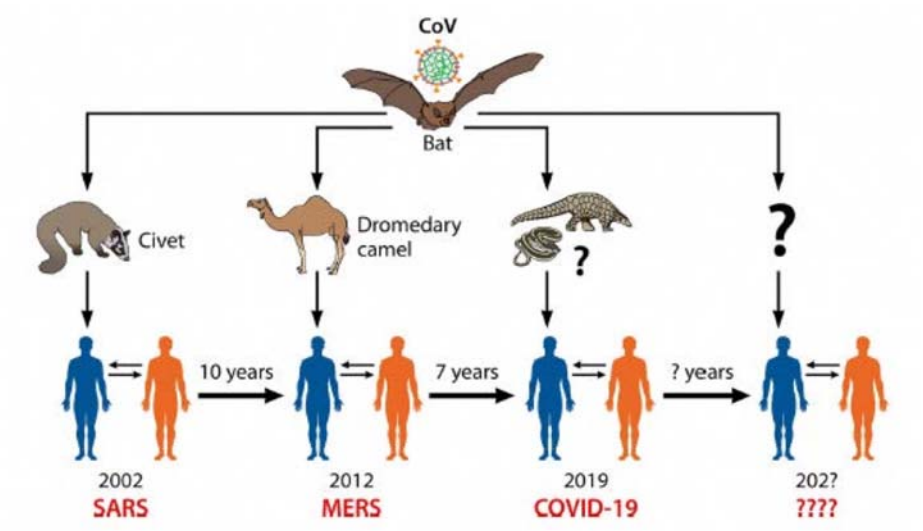
With regard to how to envision the future with coronavirus, the fifth wave is unfortunately quite large. It is important to find a way to bring this wave to an end, and also to increase the current vaccination rate in Japan. I am just hoping that we can exceed the 70% and 80% barriers that are so hard to break in Japan.

Clusters keep recurring primarily among unvaccinated population. 20 to 30% of the people cannot or will not to be vaccinated., and there is a possibility that clusters will develop among these people, but the risk of cluster chains or mega-clusters is expected to decrease.

At that time, it is important to use vaccine or negative test certification to quickly revitalize society and the economy.

As specific therapies, antibody medicine should be further advanced. In addition, if oral treatments become available, SARS-CoV-2 can be made the "fifth common cold corona virus." We should envision such a future.

Signs of the Emergence of COVID-19



Dhama K, Khan S, Tiwari R et al. Clin Microbiol Rev. 2020 Jun 24;33(4)

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The coronavirus pandemic, is the kind of pandemic that we should anticipate happening again in the future.

As I mentioned earlier, the SARS epidemic of 2002 and the MERS epidemic of 2012 have resulted in infection from animals to humans. On this occasion too, COVID-19 infection has come from animals. I think this is an important lesson for us to learn.

"Risk Management" for Pandemic Infections

(1) Control functions in emergencies (government, academia, etc.)

(2) Ensuring surge capacity (testing system, health centers, hospital beds)

(3) Developing and strategically placing regional leaders

(4) Continued investment in new technologies, therapies, and vaccine development

(5) Addressing discrimination and bias

Establish a Society Invulnerable to Infections

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This is the last slide.

The novel coronavirus has become a pandemic, and we are reminded of the importance of crisis management.

How to prepare for control functions in emergencies is an issue. Issues related to securing surge capacity, inspection systems, health centers, hospital beds, and so on are also important. We need to develop and strategically place regional leaders., and most importantly, continuous investment in the development of new technologies, therapeutics, and vaccines.

At the end of the day, when it comes to infectious diseases, discrimination and bias inevitably arise. It is a sad fact that this is still happening, but I believe that when we overcome this infection, we must build a society that is resistant to infectious diseases.

That's all. Thank you very much for your attention.

Question & Answer

Sasai: Thank you very much, Prof. Tateda.

We will now move on to the Q&A session. For the Q&A session, we are also joined by Mr. Seki, the Lifecyle Leader for Actemra and AT-527.

In order to allow as many people as possible to ask questions, we would like to limit the number of questions to 2 per person.

Please note that the audio of your questions will be posted on our website along with our presentation at a later date. If you have any questions, please let us know your company name and your name.

Now I would like to move on to the first question. Mr. Wakao of JPMorgan Securities Japan.

Wakao: This is Wakao from JP Morgan. Thank you very much for the clear explanation. There are 2 questions.

The first is about Ronapreve's approach to resistant strains. Also, what is your approach to resistant strains for small-molecule drugs?

As for strains resistant to Ronapreve, it was mentioned that resistant strains do not appear until 7 cycles in vitro. From that, can we assume that the probability of such mutant strains actually appearing is extremely low?

In addition, what do you think about the frequency of mutations in proteases and RNA polymerase inhibitors, which are the targets of small-molecule drugs, and the risk of the development of resistant strains?

As for both of them, since mutations are random, is the risk of a resistant strain developing something that we should be thinking about? Even if such mutations occur, such mutant strains often do not affect the virus in the first place, so do you think that there is a low risk of strains developing that are resistant to the small-molecule oral drugs currently being developed by Chugai and others?

Could you please answer this question, Prof. Tateda? Thank you.

Tateda: Thank you for your question. As you pointed out, according to the results I just showed you, resistant viruses emerge after 7 cycles in cell culture.

However, this was in a test tube. However, how virulent the virus is is another matter altogether, and I think the results show that the emergence of such resistant viruses is a very rare phenomenon.

Of course, we have to watch carefully what will happen in the real world, but I think it is quite a rare phenomenon that a virus can mutate so easily and become resistant to both antibodies at the same time. I think it is safe to assume that this is a very rare phenomenon.

Secondly, regarding RNA polymerase inhibitors, and the mutation of viruses resistant to them. Of course, living things mutate and evolve, so naturally there will be mutations.

However, as you mentioned, viruses that have mutated in such a way may become very weak and may not be able to survive.

So, while we must always consider mutations as a possibility, I don't think we need to think that they will immediately spread to the rest of the world and become a new problem.

Wakao: Thank you very much. Secondly, I think this question is for a representative from Chugai, but in the first presentation, you mentioned that you are preparing a supply system for Ronapreve in Japan.

Specifically, how much volume is the system ready to supply to Japan? Also, when will subcutaneous administration and prophylactic administration be available in Japan? What is the timeline for the development of the expanded indications? That's all. Thank you.

Okuda: Thank you for your question, Mr. Wakao. I'm Okuda from Chugai. You asked 2 questions.

The first is about the supply system of Ronapreve, and the second is the expansion of indications. Specifically, subcutaneous administration and prophylactic administration to close contacts.

For the first point, we will improve our supply system. I think it is important to work closely with the Japanese government to ensure that, to the greatest extent possible, we can secure the necessary amount of Ronapreve required.

We will provide a supply for 2021 through the agreement with the government that we announced in May. In light of the infection situation, we would like to work closely with the government to secure the necessary amount.

In response to the second question, we are preparing materials for the expansion of indications for subcutaneous or prophylactic administration. We are also discussing with the authorities about when to file the application. This is something that we are looking into in the future.

Wakao: Thank you very much. In terms of the supply volume, I think the current infection situation has changed drastically from the stage when your Company finalized the partnership with the government in May. Considering the current infection situation, is it safe to assume that the quantity requested by the government has increased since May?

Okuda: I can't give you a specific quantity because of the confidentiality requirement of the contract with the government. As I explained earlier, there are changes in the situation. We will secure the necessary amount for this.

Wakao: I understand. Thank you, that's all.

Sasai: Next, Mr. Hashiguchi from Daiwa Securities, please go ahead.

Hashiguchi: My name is Hashiguchi from Daiwa Securities. Thank you.

The first question is for Prof. Tateda. In your explanation on page 67, you mentioned the importance of developing oral therapeutic agents in order to make the novel coronavirus infection into a new type of common cold. Could you please explain a little more about the importance of those oral remedies?

Also, what do you think the position of the vaccine will be when such a treatment becomes available, and we start thinking of the novel coronavirus as a type of common cold?

Tateda: Thank you for your question.

Indeed, this so-called novel coronavirus may come to be treated as a new common cold. At that time, for example, diagnostic methods will probably become widespread. If you went to the hospital when you thought

you had a cold, you could immediately have your saliva tested for antigens and come out positive. You could be told then and there that you had a novel coronavirus infection. You could then be advised to take a medication for a few days in order to prevent the infection becoming serious. That's the kind of image I had in mind when I wrote that.

If the current direction of the development of oral therapeutics proves to be successful, there is a possibility that this will happen, although it is not yet clear how many years it will take.

At that time, are vaccines really necessary? Maybe when that happens, we won't need vaccines anymore. However, this is still not easy to assert. I think it is necessary to carefully monitor the situation over the next year or 2.

Hashiguchi: Thank you very much. 1 more question to someone from Chugai: I understand that 1 of the current bottlenecks in the supply of Ronapreve for the Japanese market is that production is quite difficult.

What are your thoughts on the possibility of having Chugai manufacture it in Japan in order to improve the supply constraints?

Is there a limitation on this in the contract with Regeneron, Roche, or other parties relating to this?

Okuda: Thank you for your question, Mr. Hashiguchi. Regarding the production or supply of Ronapreve, it is currently manufactured by Regeneron and Roche. Indeed, this points to the importance of how to secure supply in the face of rising global demand.

It is important to have a clear understanding of the amount required to be secured for Japan, and to discuss it with Roche and Regeneron, and co-operate in obtaining the necessary supply.

I would like to refrain from discussing the contractual terms or the substance of the contract, but for example, if we think about whether it is realistic for Chugai to produce Ronapreve, since it is an antibody drug, the first thing to consider is the capacity of the tanks necessary. Technology transfer is also a factor. Given the nature of these issues, you may be able to appreciate that it would take a long time to start production, and I think that you may understand the possibility of this. That's all.

Hashiguchi: Thank you very much. That's all.

Sasai: Next, Ms. Mitsutake of the Nihon Keizai Shimbun, please go ahead.

Mitsutake: Thank you very much. My name is Mitsutake from the Nihon Keizai Shimbun. This is a question for both Prof. Tateda and a representative of Chugai.

Prof. Tateda, how many cases have you treated with Ronapreve, and what was the clinical course of these cases?

Also, if there are any points that I should pay attention to in relation to administering the drug as an outpatient or at home, could you please let me know?

Tateda: Thank you for your question. Although the number of cases at our facility is still small, we had an infection control meeting this morning, and we received a report that 12 cases at our facility have been treated with the drug. There have been no major adverse reactions, and the progress is going well.

As I explained earlier, this antibody cocktail therapy was initially given with caution and was restricted to inpatients. However, now that its safety has been confirmed, it was authorized yesterday to be administered on an outpatient basis in facilities that are able to monitor the patient's progress.

In this sense, we have received quite good feedback from many clinicians regarding the effectiveness of the treatment. Although we can't show the results in terms of numbers yet, we have heard from quite a few clinicians that they feel the treatment is effective.

In this sense, it is probably important to focus on those who test positive at an early stage in the outpatient clinic, and to administer the drug to those who have risk factors and are over 50 years old, or to those who have any other risk factors, in order to reduce the severity of the disease. I think it will be important to use the drug in such a way as to reduce the severity of the disease.

Mitsutake: Thank you very much. To date, Ronapreve has been administered in the first 7 days of infection. However, there must be a larger number of people in outpatient clinics who will not be able to receive it within that time. Have you encountered any cases where a patient could not receive it because they presented outside the 7-day window?

Tateda: Fortunately, in our case, we were able to keep to the 7 days from onset restriction in selecting patients.

The important point is, as you pointed out, that the efficacy of the drug has only been confirmed within 7 days of onset. So we don't know how effective it will be after the 7th day.

However, the characteristic of this drug is that it is only for mild cases, not for severe cases. This drug is important in that it reduces the risk of hospitalization. I think it is important to have a good understanding of this point, and to use it at an early stage of onset and for people who do not need oxygen administration.

Mitsutake: Thank you very much. I also have 1 question for Chugai.

Genentech recently announced that they expect to run out of stock of Actemra for several weeks or several months. Is there any risk of this happening in Japan?

Also, in Japan, do you have any plans to increase production at the Utsunomiya Plant or further increase production, or any plans for investment?

Seki: Thank you very much for your question.

As for the global supply situation, with the spread of the delta variant, demand has been increasing greatly. The global supply has been unable to keep up.

As you pointed out, the supply situation will be difficult for a few months, as you know. Roche and Chugai are having some discussions to deal with this situation.

I cannot directly talk about specific plans related to points such as increased production, but we have already started working on some measures, and we are currently discussing ways to reduce the impact as much as possible.

Mitsutake: Thank you very much. In that case, is it correct to say that you are working to avoid any risk in terms of the impact in Japan?

Seki: Thank you. We believe that Japan will not be directly affected by the global supply shortage.

However, as the number of infected people in Japan is increasing, we would like to carefully monitor the demand for Actemra for intravenous infusion and consider how to respond.

Mitsutake: I understand. Thank you.

Sasai: Thank you very much. Ms. Kubota from Nikkei Business Publications, please go ahead.

Kubota: Thank you very much. I'd like to ask a representative from Chugai 2 questions.

The first question is about the use of Ronapreve. In Japan, Ronapreve has been authorized for use in outpatient clinics, and its use is becoming more widespread. However, since the EUA in the US last year, I believe we have not seen such a rapid increase in its use in the US, because of, for example, the time required for infusion.

Could you say something about levels of use of Ronapreve in other countries, like the US, compared to in Japan? This is the first question.

Aida: Thank you for your question. This question is about the usage situation overseas and in Japan.

In other countries, the drug is administered on an outpatient basis, and in the US, it can only be administered to outpatients under the EUA.

The process of intravenous infusion takes 20 to 30 minutes, and is followed by 1 hour of follow-up observation. At first, use was not progressing very well, but recently we have heard that administration of the drug is picking up.

We are not sure about the specific figures, so we cannot present them here, but we have heard that the volume of use is gradually increasing.

On the other hand, in Japan, the use of the drug was limited to inpatients. I have heard that intravenous administration has not been a bottleneck at all. Therefore, we are aware that use in Japan after its approval is quite high compared to other countries.

Kubota: Thank you very much. I would like to ask 1 more question.

I would like to ask you about AT-527. There are several other oral medications being developed for people with mild disease. Some of them are now moving on to late stage clinical trials.

If the primary endpoint is met in these clinical trials, how will they be used around the world? For example, anti-influenza drugs are covered by universal health insurance in Japan, but in the US and especially in Europe, they are not widely used.

Even if they are used widely in Japan, how do you imagine these drugs being used overseas?

Okuda: Thank you for your question. Now, you mentioned AT-527, or oral antiviral drugs, and you gave an example of influenza. You've asked about the outlook for use within and outside Japan. This is a very difficult question to answer. I would like to pass this question on to Mr. Seki.

Seki: Thank you for your question.

Globally, as you know, influenza is very well treated in Japan and not so well treated in the rest of the world.

How will oral medications, including AT-527, be used? Basically, I think the most important point is to prevent mild disease from becoming serious disease. Although I can't disclose a detailed outlook, we believe that the drug will be widely used worldwide for patients with mild disease.

It is important to address the issue of supply, and we hope that the drug will be used for patients with mild disease around the world as long as supply is possible.

Kubota: Thank you very much.

Sasai: Next, Mr. Muraoka from Morgan Stanley MUFG Securities. Please go ahead.

Muraoka: Hello, this is Muraoka from Morgan Stanley. Thank you.

First, I have a question for Prof. Tateda. Based on your personal clinical experience, how much Ronapreve and AT-527 do you think you will actually need?

First of all, for Ronapreve, I've seen the figure of 200 thousand peoples' worth in the press for 2021. Since it has become available in outpatient clinics, I'm curious as to whether this will be enough. How much demand do you anticipate this year, given the conditions on the ground?

Similarly, for oral drugs such as AT-527, what demand would you anticipate, say for next year? For Japan, would the figure be in the order of 1 million peoples' worth of doses, or do you think more would be necessary? It would be very helpful if you could give us some indication of what you feel based on the situation on the ground, and how much it is when you look at Japan as a whole.

Tateda: Thank you for your question. I think it is a very difficult estimation. First of all, I have high expectations for AT-527. Other oral drugs are also being developed, and I think there are very high expectations for these oral drugs.

With the current pandemic, we can now use various diagnostic methods, including genetic diagnosis and antigen testing, in a timely manner. In such a situation, as soon as a diagnosis is made, a specific treatment can be administered.

At the moment, the only option is this injectable drug, Ronapreve. If AT-527 comes out, and is shown to be effective, it could be very important. Until we see how effective it is, it's difficult to say.

However, if a specific treatment can be developed that eliminates the virus and settles the symptoms after 3 days of taking the drug, then I think the drug will be widely used.

Specifically, in the current situation, if this were to become available for use immediately with such efficacy, for example, 20,000 cases a day are reported in Japan. Therefore, I think the drug will soon be required to be used for millions or even tens of millions of people.

However, as for whether or not this will last forever, I am not sure. If many people become infected, herd immunity may develop. I think that if that happens, we probably won't see the kind of spread we're seeing now. That's all.

Muraoka: Thank you very much. What are your thoughts about the reported 200-thousand figure for Ronapreve?

Tateda: With regard to Ronapreve, the expectations of doctors in the field are very high. In cooperation with national and local governments, there are many doctors who would like to create a Ronapreve capability to treat patients with mild disease, reduce the severity of disease, and reduce hospitalization.

So, I think this will be used quite frequently from now on.

The only thing we have to be a little careful about is that it is at times like these that we have to proceed with caution and care. As I mentioned earlier, if we do this too drastically, for example, in cases where the onset of the disease exceeds 7 days, where a patient requires oxygen therapy, or where the disease is more severe, we have to consider the risk of unexpected side effects.

We have to proceed safely, and use this treatment as effectively as possible for as many people as possible.

Muraoka: Thank you very much. The second question is for a representative of Chugai.

I had also thought that oral treatment would be in the millions or tens of millions, as the Professor suggested. In the case of your Company, that would be AT-527. I wonder if manufacture might become a rate-limiting factor next year, for example, when such large-scale demand occurs.

Of course, raw materials or other intermediates could also be factors. Are you aware of any manufacturing problems, or problems at Roche, or any supply concerns, whether it is the number of tablet machines or anything else? I would appreciate it if you could let me know if there is one, and if you have any solutions.

Seki: Thank you for your question. As for bottlenecks in supply, it is difficult to be specific.

We are currently discussing with Roche to establish a system to produce as much as possible, so it is difficult to give a clear answer as to how much we can supply. We are now looking at ways to increase production by considering all of these areas.

Muraoka: I understand. That's all. Thank you very much.

Sasai: Next, Mr. Yamaguchi from Citigroup Global Markets Japan. Please go ahead.

Yamaguchi: This is Yamaguchi from Citi. Thank you. Thank you for the talk. I learned a lot.

The first question is about IV administration of Ronapreve. I see on the news that more and more patients cannot be admitted to hospital and are seen at home by a doctor on call.

Listening to what you have said, I think that such patients are the ones who need Ronapreve. Also, I think that those who can be hospitalized are already very sick and the time to use Ronapreve has passed.

In that case, the question becomes how to deliver Ronapreve to the patients who need it. Although there are outpatient clinics, I don't have a mental image of these patients being treated in outpatient clinics.

I wonder if there is a gap between the location of patients and how the drug is used. If so, how do you go about solving it?

Tateda: I'd like to answer. Thank you for your question.

I think it will be important to find a way to solve this problem. This is because there are now many people who are at home and cannot be hospitalized.

In this situation, for example, temporary medical institutions can be created. Not a field hospital, but something like that. We can also use oxygen stations or facilities for administering Ronapreve.

For example, the drug is administered in the presence of a medical professional who can monitor the patient's progress for a while, and after confirming that there are no adverse reactions, the patient returns home. After that, I think it is important to create a system that ensures follow up with medical professionals.

There have been a lot of developments yesterday and today, and I think it has been reported that some local governments are considering such a move.

Yamaguchi: Thank you very much. In that case, there is a possibility that we can create infusion centers, where patients can receive the drug, be monitored, and return home.

Tateda: Yes, indeed.

Yamaguchi: I understand. Also, 1 more question, please. When the SC comes out, it is generally thought that it will suddenly become much easier to use, but when the Ronapreve SC comes out, will it be possible to use it at home?

Aida: Thank you for your question. I understood that the question was about how the medical environment would change when SC administration became possible.

As for subcutaneous administration, we are currently working hard to file the application. We are preparing to do so as soon as possible.

On the other hand, whether or not SC administration can be extended to home care when it is established is another question. We believe that SC administration will improve the ease of administration in outpatient clinics, and we believe that it will increase the convenience of the current outpatient administration.

On the other hand, in terms of administration at home, I believe that there are still many issues to be addressed, such as follow-up observation. We would like to discuss this issue with the authorities.

Yamaguchi: Thank you very much.

Sasai: Next, Mr. Ando from TV Tokyo. Please go ahead.

Ando: Ando from TV Tokyo. Thank you.

I would like to ask another question about supply of Ronapreve.

You mentioned that you could not disclose the number of doses. When we look at the current situation, is it correct to say that you are moving toward an increase in imports? Thank you.

Okuda: Thank you for your question, Mr. Ando. I am Okuda.

I can't give you a specific number, but we will secure the necessary amount in consultation with the government.

Ando: So you are saying that you will negotiate with Roche. The reported figures are 70 thousand or 200 thousand.

Okuda: I can't explain the details of the negotiations or the contract, but I hope you will understand that we will secure the necessary amount through collaboration based on the Japanese government's request, and based on changes in the infection situation.

Ando: Thank you very much. 1 more question. I think the reason why the number is not disclosed is because it is a confidential matter with the government.

In fact, Chief Cabinet Secretary Kato said in his press conference yesterday that about 3,000 medical institutions nationwide have requested the use of the drug. As of the 20th, 1,200 medical institutions have already administered the drug to about 5,600 people.

The number of patients is very large, and now that treatment is available on an outpatient basis, a large number of patients will need to be treated. However, medical institutions are very concerned because they do not know what numbers will be available. There is concern about whether it will be possible to secure enough doses. What are your views on this issue?

Okuda: Thank you for your question. I am aware that Chief Cabinet Secretary Kato announced the figures you have just mentioned.

It is difficult to predict the future infection situation. Of course, as Prof. Tateda explained, vaccination will continue to progress. The number of infected people may be higher at this point than we had initially expected.

It is very difficult to predict how the number will change in the future.

In this context, we are continuing to make efforts to secure the necessary volume in cooperation with the government.

Ando: Given the anxiety that medical institutions feel because they don't know the number of doses available, do you have any plan to make the number public?

Okuda: This is part of our contract with the government. We are not able disclose the specific number of doses. We hope you will understand.

Ando: Understood. Thank you. That's all.

Sasai: Thank you very much. Due to time constraints, the next question will be the last. Apologies for any inconvenience.

Mr. Tsujita from the Yomiuri Shimbun. Please go ahead.

Tsujita: Hello. Thank you. My name is Tsujita from the Yomiuri Shimbun Medical Department.

I would like to ask both a representative from Chugai and Prof. Tateda about the future prospects of therapeutic drugs for people with mild disease.

How do you use antibody therapy and antiviral drugs in these cases? Are there plans to use the 2 therapies together?

If we disregard the distribution volume and cost, it may be possible to cover all patients with mild to moderate illnesses with antibody cocktails, but what should we think about that? I would appreciate it if you could tell me about that.

Tateda: Thank you very much, Mr. Tsujita. This is Tateda.

As I mentioned earlier, we don't know about the effectiveness of AT-527 at this time. If this drug really has the ability to be taken orally for 3 days, eliminate the virus, and reduce the symptoms of infection, and it can be used in a similar way to a cold medicine, then I think AT-527 will be the drug of choice.

It isn’t possible to say at this time, since I don't know the status of development. But at any rate, we are now able to use 1 important therapeutic agent, Ronapreve, which is a big step forward. And most importantly, I think it is a step forward that will help clinicians in the field feel a little more secure.

It is important to prevent an increase in the number of severe cases. This will reduce the necessity of hospitalization. That's all.

Tsujita: Putting aside the distribution volume and cost issues, at least Ronapreve can still be used. Of course, you will continue the development of AT-527, but what do you think about the possibility that Ronapreve can be used as a therapeutic agent for all patients with moderate or mild disease?

Okuda: Thank you for your question. I will answer first, and then Dr. Aida or Mr. Seki will provide additional explanation if there is anything to add.

COVID-19 is not a disease where 1 drug is enough to cover everything. As indicated by the Japanese Society of Infectious Diseases, several types of drugs are needed to match the severity of the disease, as well as the stage in disease development.

In this way, for example, within the category of oral RNA polymerase inhibitors, a number of drugs are being developed. When it comes to antibody cocktails, Ronapreve is ahead of the others, but there are other drugs in development.

As clinical trials progress, and as the drug is used in actual clinical practice, data on effectiveness, safety, and ease of use will gradually accumulate.

In these circumstances, the way in which these drugs are used in the treatment system is gradually determined. So in that sense, I think it is important for us to develop these 3 drugs and make them available.

Tsujita: Understood. Thank you very much.

Sasai: Thank you very much. This concludes the Information Meeting on Ronapreve, the new treatment for the novel coronavirus infection.

If you have any questions that we were unable to answer due to time constraints, please feel free to contact our Corporate Communications & Investor Relations Department. Contact details are listed on the last page of the presentation.

Thank you very much for taking time out of your busy schedule to join us today. Thank you for your time.

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