Information Meeting on Ronapreve

Agenda

Moderator: Toshiya Sasai, Head of Corporate Communcations Dept.,
Chugai Pharmaceutical Co., Ltd.

1. **Striving to Develop Therapeutic Drugs for COVID-19**

   Dr. Osamu Okuda, Presidend & CEO, Chugai Pharmaceutical Co., Ltd.

2. **Product Overview of Ronapreve**

   Dr. Sathoshi Aida, RONAPREVE Lifecycle Leader, Chugai Pharmaceutical Co., Ltd.

3. **Confronting COVID-19 - How to Make the Best of the With / Post-COVID-19 Age -**

   Prof. Kazuhiro Tateda, M.D., Ph.D., Department of Microbiology and Infectious Disease,
   Toho University School of Medicine

4. **Q&A Session**

Striving to Develop Therapeutic Drugs for COVID-19

Dr. Osamu Okuda

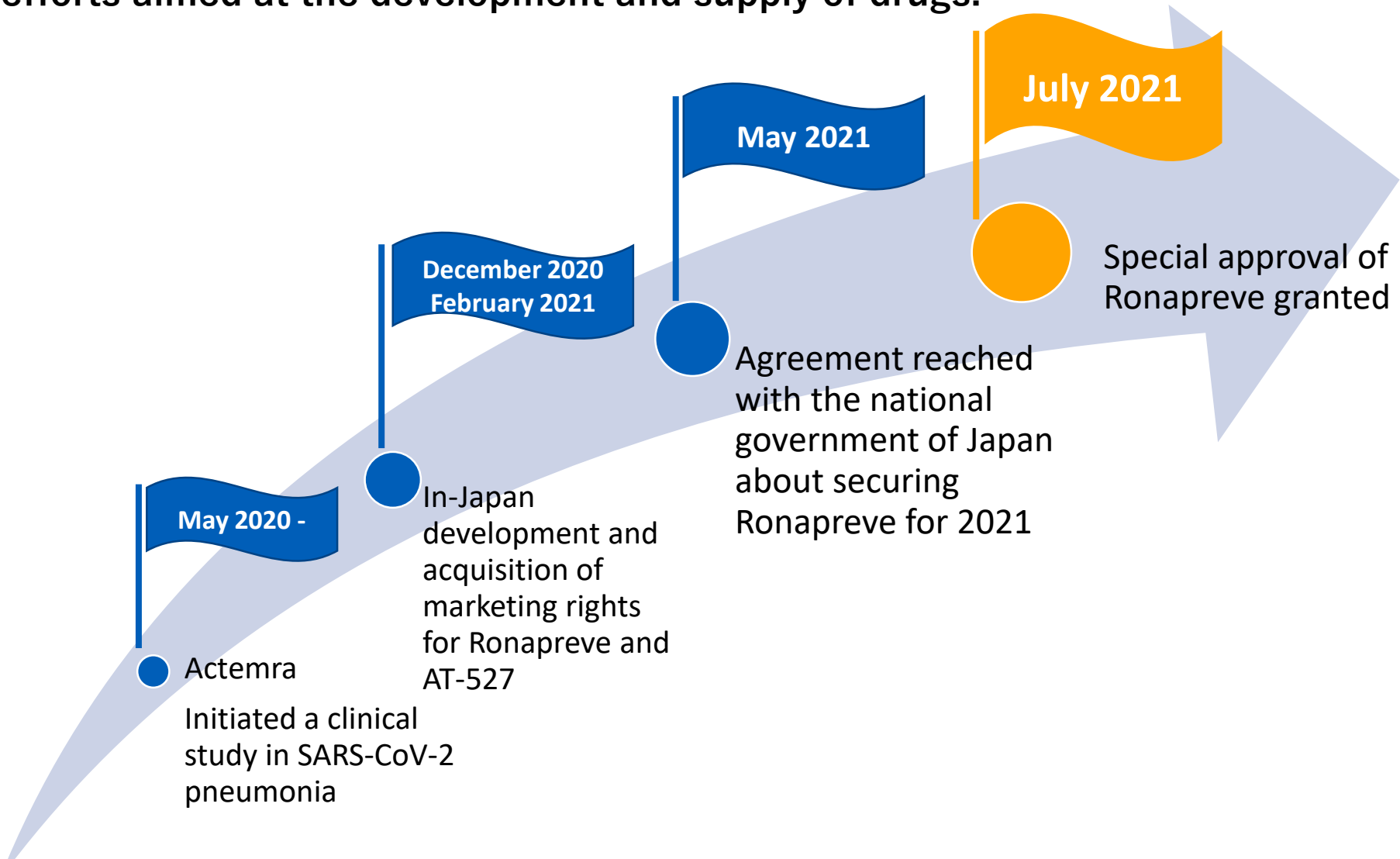
Representative Director, President & CEO

Chugai Pharmaceutical Co., Ltd.

26 August 2021

Major Milestones in Drug Development for COVID-19 in Japan

Promptly started activities in the initial stages of the COVID-19 pandemic, advancing multiple efforts aimed at the development and supply of drugs.



Overview of the Three Therapeutic Drugs for COVID-19

	Ronapreve	Actemra (not approved)	AT-527 (not approved)
Originator	Regeneron	Chugai Pharmaceutical	Atea Pharmaceuticals
Mechanism of action	Suppresses viral replication by recognizing the spike protein of the SARS-CoV-2 virus and inhibiting the entry of SARS-CoV-2 into host cells[1]	Suppresses the excessive immune and inflammatory responses associated with COVID-19 by inhibiting a messenger molecule called IL-6 (cytokine), which is involved in the immune regulation and inflammation[2,3]	Inhibits a viral RNA polymerase which is essential for viral replication[4]
Indication/proposed indication	SARS-CoV-2 infection*	COVID-19 pneumonia	COVID-19
Route of administration	Intravenous 	Intravenous 	Oral 
Development stage (Japan)	Approved (Special Approval)	Domestic P3 study (J-COVACTA) completed	Global P3 study (MORNINGSKY) is ongoing
Manufacturer/ Partner	Regeneron/Roche	Chugai Pharmaceutical/Roche	Roche

1. Science. 2020 Aug 21; 369(6506):1010-1014. 2. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46(5):846-848. 3. Zhu J, Pang J, Ji P, et al. Elevated interleukin-6 is associated with severity of COVID-19: a meta-analysis. *J med virol*. Published online May 29, 2020. 4. Shannon et al. Biorxiv 2021. doi: https://doi.org/10.1101/2021.03.23.436564 Accessed August 2021.

*Since a stable supply is not ensured at this time, RONAPREVE will in the meantime be distributed to those patients who have risk factors for severe SARS-CoV-2 and require hospitalization. (Source: Announcement by the COVID-19 Task Force, Ministry of Health, Labour and Welfare dated July 20, 2021)

Clinical Status of Therapeutic Drugs in COVID-19 Treatment

Three drugs under development for patients with mild to moderate and severe infections

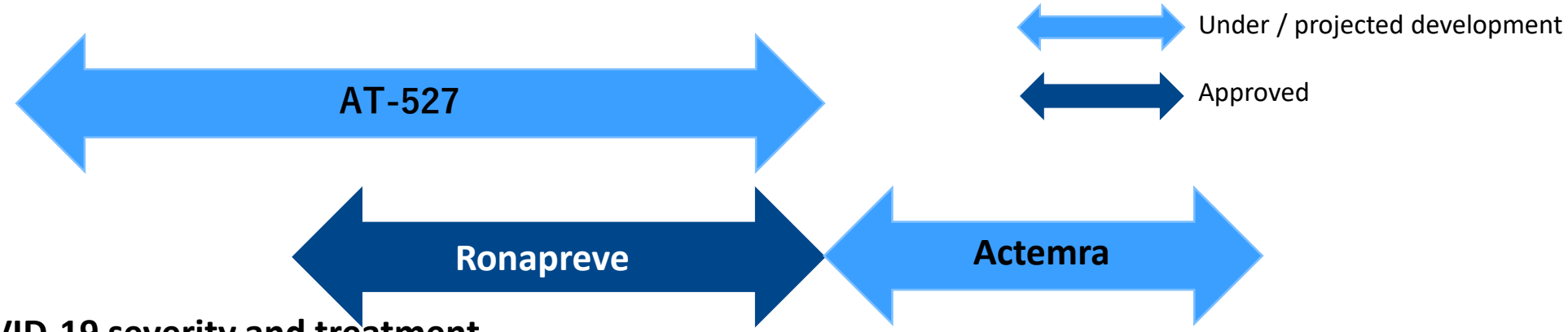
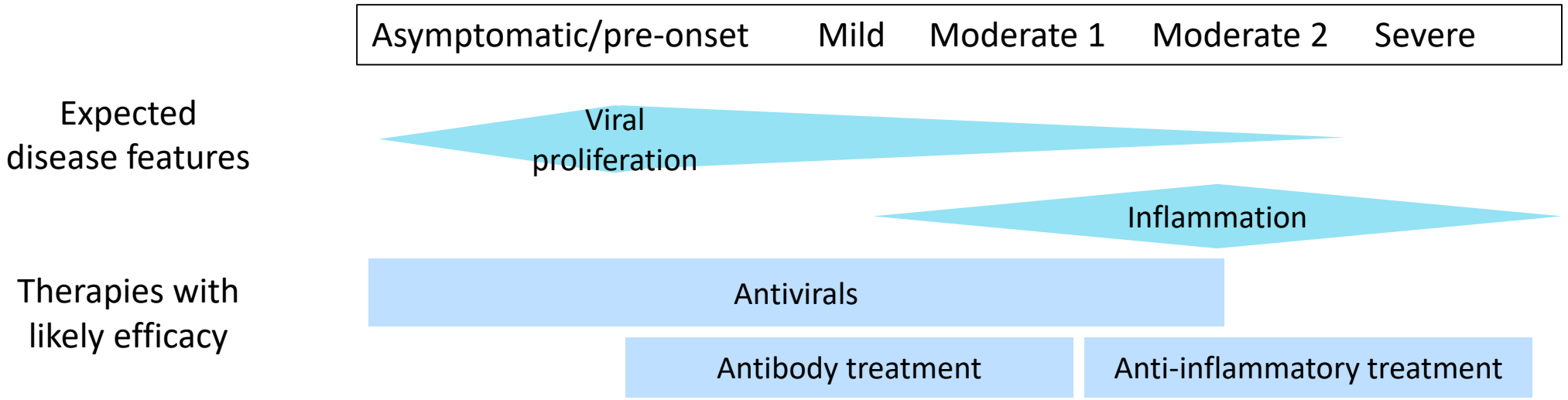


Figure Conceptualizing COVID-19 severity and treatment.



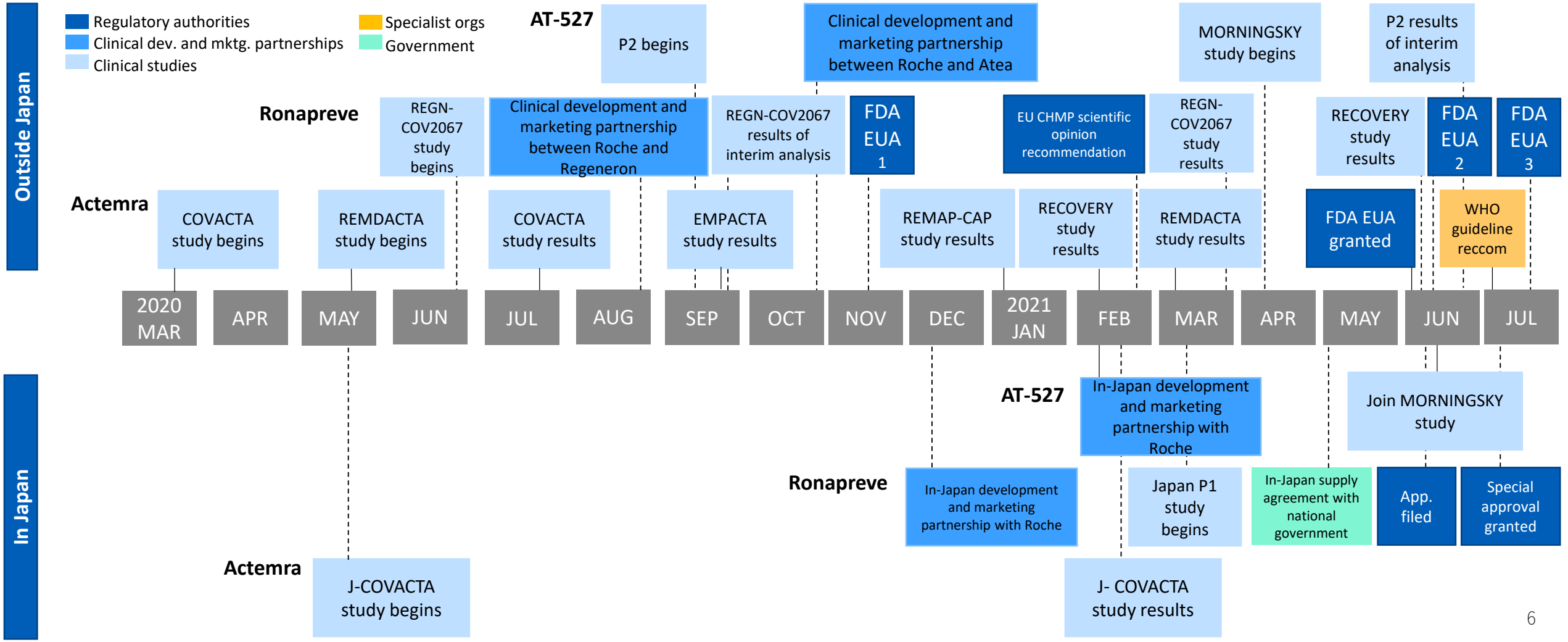
Source: Japanese Association for Infectious Diseases: Approaches to Pharmacotherapies for COVID-19, 8th ed. (July 31, 2021)

Striving to Develop Therapeutic Drugs for COVID-19

Status of Development and Approval of Three Drugs for COVID-19 in and outside Japan

Seamless clinical development in and outside Japan

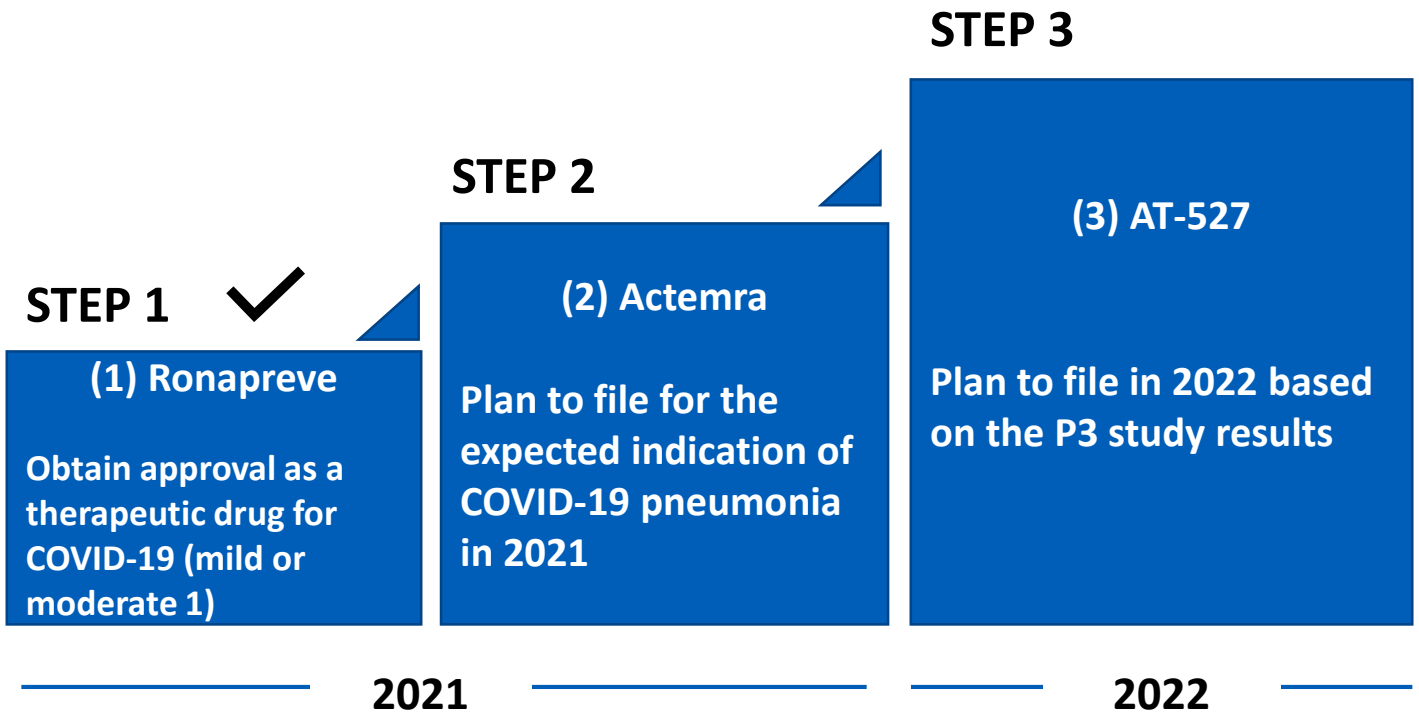
FDA EUA 1: Adults and adolescents with mild to moderate illness
FDA EUA 2: Subcutaneous administration
FDA EUA 3: Prophylactic administration for close contacts



Striving to Develop Therapeutic Drugs for COVID-19

Future Activities

Promote activities for securing Ronapreve for supply in Japan and ensuring its appropriate use, filing for Actemra, and developing and obtaining approval for AT-527



Ronapreve

- Secure a quantity sufficient for meeting the government request
- Partner with the government to coordinate appropriate distribution and appropriate use
- Expect for reducing the rate of patients progressing to severe and avoiding pressure on the medical system

Actemra

- Partner with Roche to promote data analysis and discuss the feasibility of filing with the regulatory authorities

AT-527

- Partner with Roche and Atea to promote development targeting a 2022 application

Information Meeting RONAPREVE™ for Intravenous Infusion Sets 300 and 1332

August 26, 2021

Satoshi Aida, Ph.D.,
RONAPREVE Lifecycle Leader
Chugai Pharmaceutical Co., Ltd.

RONAPREVE®
casirivimab and imdevimab

Product Outline

注意－特例承認医薬品

日本標準商品分類番号　87625

抗SARS-CoV-2モノクローナル抗体

生物由来製品、処方箋医薬品注)

薬価基準未収載

ロナプリーブ™点滴静注セット300、1332

RONAPREVE®

カシリビマブ(遺伝子組換え)注／イムデビマブ(遺伝子組換え)注

注)注意－医師等の処方箋により使用すること

Indication: SARS-CoV-2 infection

Precautions concerning indication:

- Based on the main dosing experience in clinical trials, administer RONAPREVE to patients who have risk factors for severe SARS-CoV-2 infection and who do not require oxygen intervention.
- There have been reports of symptoms worsening in patients requiring high-flow oxygen therapy or ventilator management.
- RONAPREVE cannot necessarily be expected to be effective for for SARS-CoV-2 variants in which the neutralizing activity of RONAPREVE is low. Therefore, consider the appropriateness of administering RONAPREVE based on the latest information on the prevalent SARS-CoV-2 variants.

RONAPREVE®
casirivimab and imdevimab

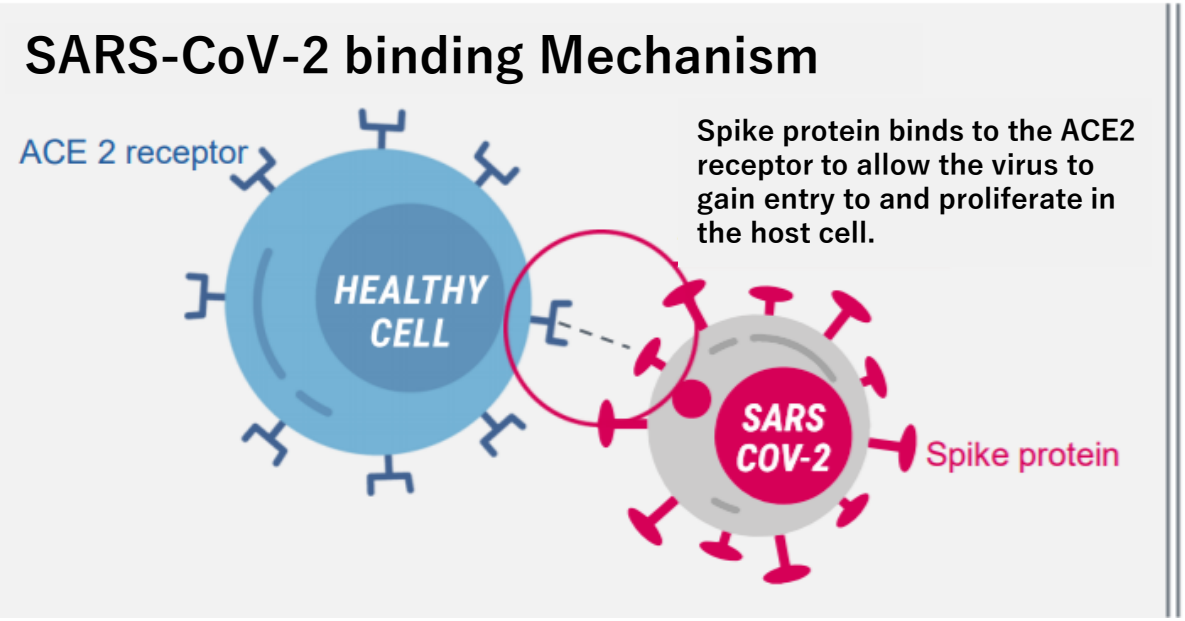
History of Development of RONAPREVE

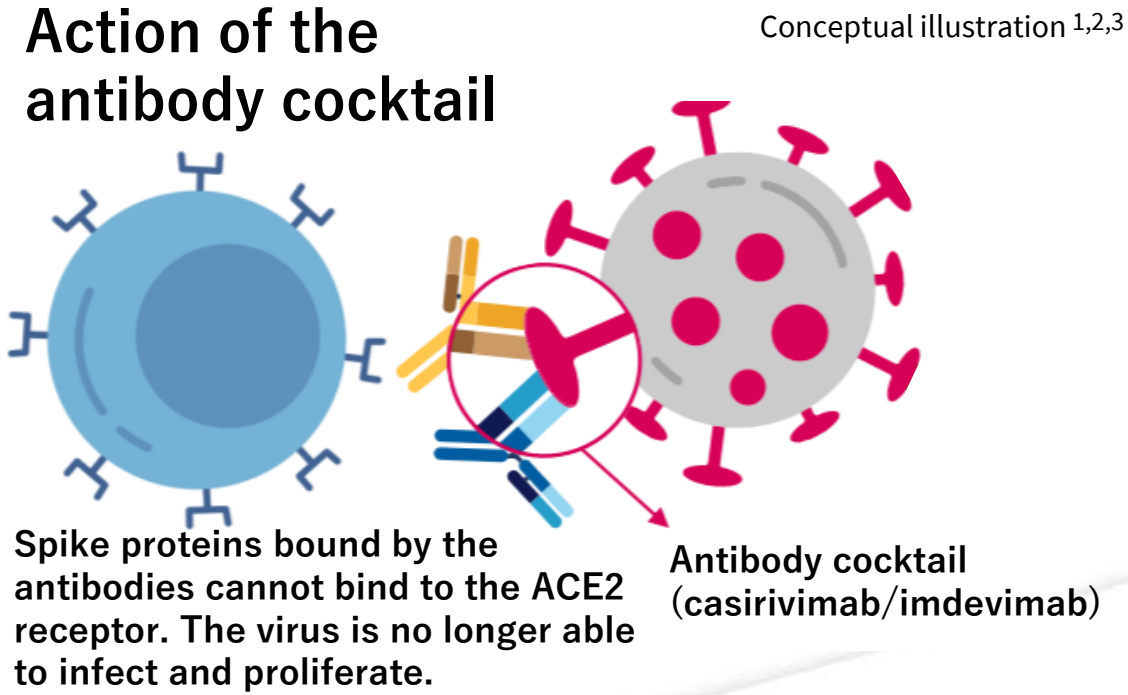
Feb 2020	Regeneron began antibody acquisition
Apr 2020	Two therapeutic antibodies were selected
Jun 2020	Global Phase I/II/III study (COV-2067) in COVID-19 outpatients started
Nov 2020	Emergency use authorization (US)
Mar 2021	Japanese Phase I study (JV43180) started
Jun 2021	Regulatory application (Japan)
Jul 2021	Special Approval for Emergency (Japan, world's first regulatory approval)

COVID-19: SARS-CoV-2 infection

Mechanism of Action of RONAPREVE

- RONAPREVE is expected to suppress viral replication by inhibiting the entry of SARS-CoV-2 into host cells (*in vitro*)[1].
- Two antibodies, binding non-competitively to the receptor-binding domain of the spike protein, showed efficacy even in viral variants with spike protein mutations (*in vitro*) [2,3].





Announced by Regeneron in an investor relations call (November 6, 2020)

1. Science. 2020 Aug 21;369(6506):1010-1014 2. Science. 2020 Aug 21;369(6506):1014-1018 3. Cell. 2021 Jul 22;184(15):3949-3961

※Employees for Regeneron were included as authors in 1 to 3 journals.

RONAPREVE® casirivimab and imdevimab

Neutralizing Activity in Variants (*in vitro*)

RONAPREVE retained neutralizing activity in the following variants of concern and interest.

Variants with S protein mutations		Location where spread first identified	Primary mutation	Percent decrease in activity
B.1.1.7	Alpha	United Kingdom	N501Y[a]	No change[d]
B.1.351	Beta	South Africa	K417N, E484K, N501Y[b]	No change[d]
P.1	Gamma	Brazil	K417T, E484K, N501Y[c]	No change[d]
B.1.427/B.1.429	Epsilon	California	L452R	No change[d]
B.1.526[e]	Iota	New York	E484K	No change[d]
B.1.617.1/B.1.617.3	Kappa	India	L452R+E484Q	No change[d]
B.1.617.2	Delta	India	L452R+T478K	No change[d]

a pVSV-SARS-CoV-2-S pseudoparticles expressing full-length S protein were evaluated. del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H differences from the WT-virus found in the mutant strains.
b pVSV-SARS-CoV-2-S pseudoparticles expressing full-length S protein were evaluated. D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V differences from the WT-virus found in the mutant strains.
c pVSV-SARS-CoV-2-S pseudoparticles expressing full-length S protein were evaluated. L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F differences from the WT-virus found in the mutant strains.
d No change: less than 2-fold decrease in activity
e Not all B.1.526 lineage isolates originating in New York have a E484K mutation（as of February 2021）

Outline of the study: The neutralizing activity of drug against pVSV-SARS-2-S pseudoparticles expressing S-proteins with mutations of interest was evaluated. The fold change in activity was calculated by dividing IC50 to the resulting mutant by IC50 to the reference viruses. As reference viruses, wild-type (WT) and D614G mutants of the S-protein were used.

Test Methods: The drug was pre-incubated with pVSV-SARS-CoV-2-S sham particles for 30 min before being added to Vero cells and treated with normal cell culture conditions for 24h. The neutralizing capacity of Abs against infection of Vero cells was evaluated with a fluorescent focus forming unit [FFUs].

Antiviral Resistance (Section 15) (revised June 2021, FDA FACT SHEET FOR HEALTH CARE PROVIDERS EUA OF REGEN-COV (casirivimab and imdevimab))
Neutralizing study of REGN10933 and REGN10987 against spike protein（approved July 2021, CTD 4.2.1.41-5）

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RONAPREVE's Potential Contributions to Treatment

Target population: patients with risk factors for progression to severe symptoms, who do not require oxygen therapy

Risk factors for severe disease in COV-2067 study

Age >50 years; obesity (defined as BMI >30 kg/m^2); cardiovascular disease (including hypertension); chronic lung disease (including asthma); Type 1 or 2 diabetes; chronic kidney disease (including those on dialysis); chronic liver disease; immunosuppressed status

Reference shown in the MHLW announcement

- Inclusion and exclusion criteria of COV-2067 study
- Treatment Guideline (version 5.1)
- EUA (US)

Target patients: mild to moderate I

Severity	Oxygen saturation	Clinical condition
Mild	≥96%	No signs of pneumonia
Mod. I	<96% >93%	Signs of pneumonia Dyspnea
Mod. II	<93%	Oxygen therapy
Severe		In ICU Mechanical ventilation

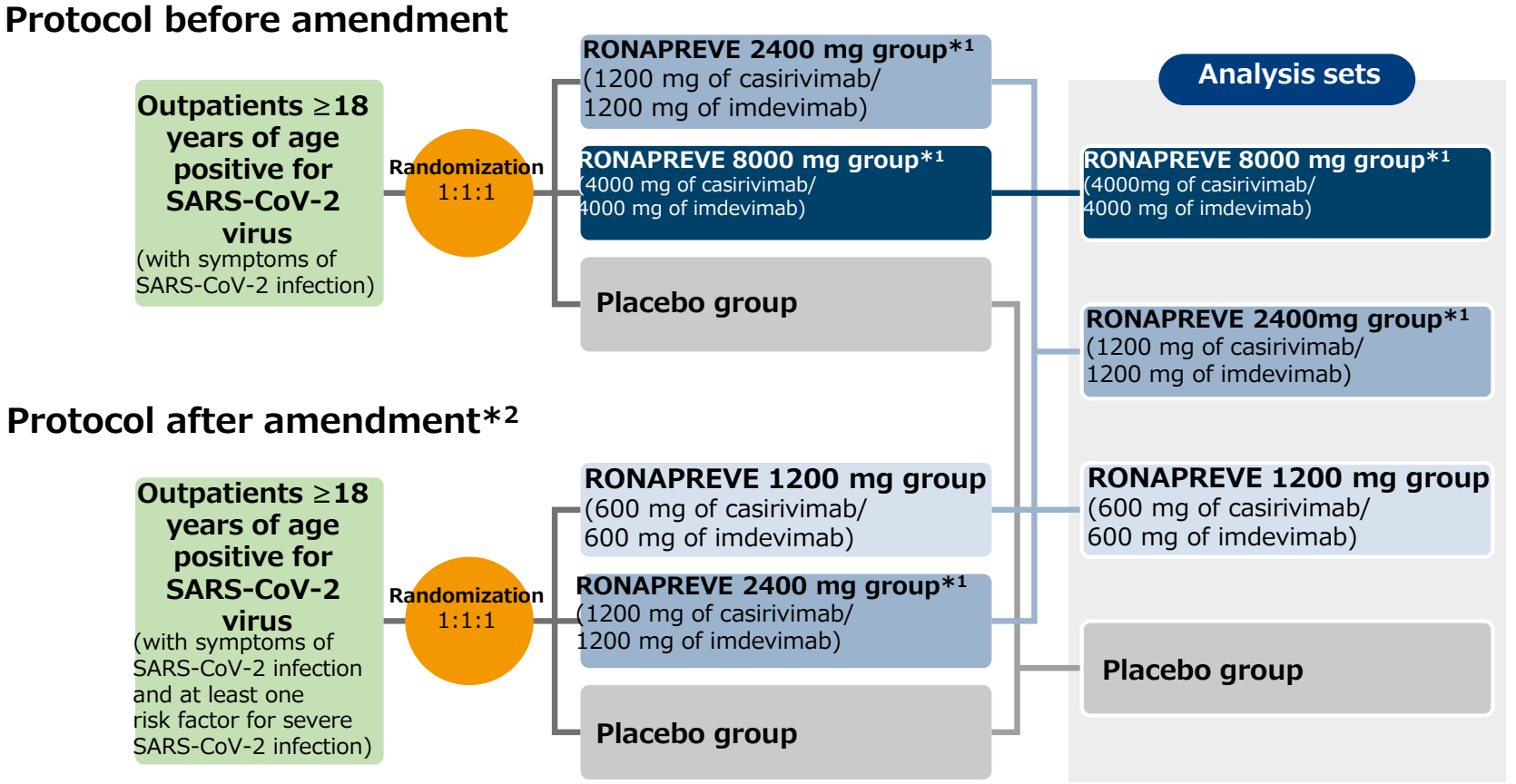
Office Liaison of the COVID-19 Task Force, Ministry of Health, Labour and Welfare (July 20, 2021)

Treatment Guideline against COVID-19 version 5.2 (Ministry of Health, Labour and Welfare)

RONAPREVE® casirivimab and imdevimab

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

Primary endpoint: the ratio of SARS-CoV-2 infection-related hospitalization or all-cause death (event) by Day 29
Major secondary endpoint: Time to resolution of infections by SARS-CoV-2



*1 Dosage and administration in Japan: “The usual dose for adults and children aged 12 years and older and weighing 40 kg or more is a single intravenous infusion of 600 mg each of casirivimab (genetical recombination) and imdevimab (genetical recombination) administered concomitantly.”
*2 The protocol was amended while the study was underway based on the results of the Phase I/II part, with the RONAPREVE 8000 mg group eliminated and a RONAPREVE 1200 mg group added for the Phase III part.

Data evaluated in regulatory review: COV-2067 study efficacy results (approved 2021, CTD 2.5.4.2)
Data evaluated in regulatory review: COV-2067 study safety results (approved 2021, CTD 2.5.5.2)

RONAPREVE® casirivimab and imdevimab

Global Phase1/2/3 Randomized Placebo-controlled Study (COV-2067, overseas data): Plans of Analysis

<Analysis population definitions>

- Modified Full Analysis Set (mFAS) Population of 4057 patients (625 in 8000mg group, 1355 in 2400mg group, 736 in 1200mg group, and 1341 in the placebo group): randomized patients who tested positive for SARS-CoV-2 on a centrally measured RT-qPCR test with nasopharyngeal swabs at randomization and had at least one severe risk factor at baseline
- 5531 patients in the safety analysis population (1012 in 8000mg group, 1849 in 2400mg group, 827 in 1200mg group, and 1843 in the placebo group) who received at least one dose of study drug among randomized patients with symptoms of infection caused by SARS-CoV-2

<Efficacy>

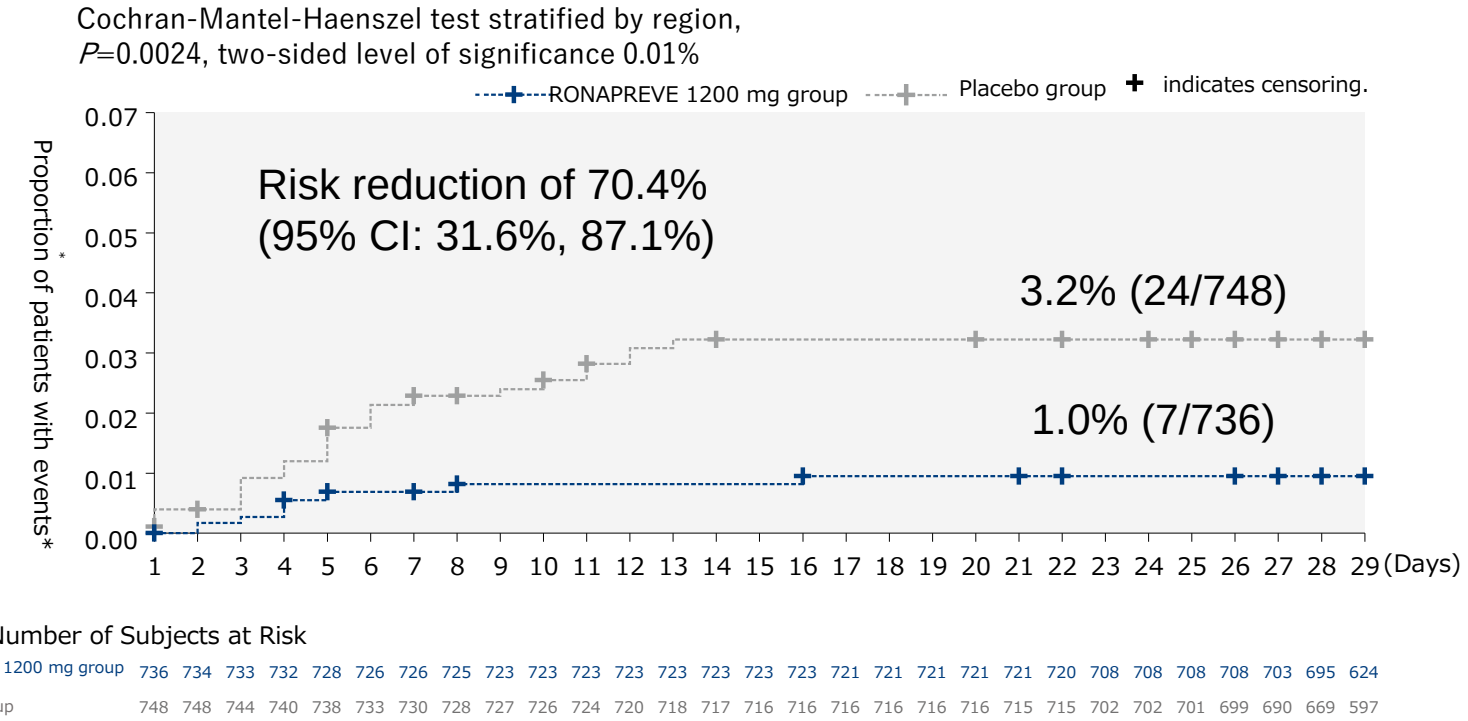
- In the phase III part, based on the phase I/II part, the protocol was revised during the study, 8000mg group was discontinued, and a new 1200mg group was established. For efficacy assessments, 2400mg group was assessed for the entire duration (pre-protocol revision and post-revision), and drug 1200mg group was assessed for those enrolled after protocol revision.
- Because the phase III part is intended for validation, the analysis and power setting were to be independent of the phase II part. Clinical efficacy, virological efficacy, and symptomatic endpoints were analyzed in mFAS population. The primary endpoint, the rate of SARS-CoV-2 infection-related hospitalization or all-cause death was compared using a Cochran-Mantel-Haenszel test with region as a stratification factor. Risk ratios and 95% confidence intervals (CIs) for relative risk reduction were calculated using the Farrington-Manning method.
- The following is a test procedure established to achieve a two-sided significance level of 0.05 or less for studies including major secondary endpoints and interim analyses.
    - If significant differences were observed in the primary endpoint of 2400mg group, an interim analysis of the primary endpoint of 1200mg group was to be performed at a two-sided significance level of 0.01 at the time of the primary analysis of drug 2400mg group. The significance level was calculated from the assumption of the number of patients randomized using the γ-type α consumption function of γ =-4. When significant differences were observed in 1200mg group in the interim analysis, a two-sided significance level of 0.05 was performed for 2400mg group and 1200mg group in the order of the proportions of patients with SARS-CoV-2 infection-related hospitalization or all-cause death from Day 4 to Day 29, and the time to resolution of symptoms of infection due to SARS-CoV-2.

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

RONAPREVE® casirivimab and imdevimab

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)



Number of Subjects at Risk

RONAPREVE 1200 mg group	736	734	733	732	728	726	726	725	723	723	723	723	723	723	723	723	721	721	721	721	721	720	708	708	708	708	703	695	624
Placebo group	748	748	744	740	738	733	730	728	727	726	724	720	718	717	716	716	716	716	716	716	715	715	702	702	701	699	690	669	597

*Events: SARS-CoV-2 infection-related hospitalization or death for any reason

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

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

RONAPREVE® casirivimab and imdevimab

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

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

RONAPREVE® casirivimab and imdevimab

Indication/Dosage and Administration

Indication	SARS-CoV-2 infection
Precautions concerning indication	• Based on the main dosing experience in clinical trials, administer RONAPREVE to patients who have risk factors for severe SARS-CoV-2 infection and who do not require oxygen intervention. • There have been reports of symptoms worsening in patients requiring high-flow oxygen therapy or ventilator management. • RONAPREVE cannot necessarily be expected to be effective for SARS-CoV-2 variants in which the neutralizing activity of RONAPREVE is low. Therefore, consider the appropriateness of administering RONAPREVE based on the latest information on the prevalent SARS-CoV-2 variants.
Dosage and administration	The usual dose for adults and children aged 12 years and older and weighing 40 kg or more is a single intravenous infusion of 600 mg each of casirivimab (genetical recombination) and imdevimab (genetical recombination) administered concomitantly.
Precautions concerning dosage and administration	Administer promptly after symptoms develop in patients who have tested positive for SARS-CoV-2. In clinical trials, there is no data to support the efficacy of RONAPREVE in patients who started treatment 8 days from the onset of symptoms or later.

RONAPREVE® casirivimab and imdevimab

From July 2021 (Version 1) Package Insert

Announcement by the COVID-19 Task Force, Ministry of Health, Labour and Welfare

Announcement on July 20, 2021

Request concerning the allocation of the neutralizing antibody drugs "casilivimab and imdevimab" to medical institutions for new coronavirus infections

2　The indication for RONAPREVE is "SARS-CoV-2 infection." It is described in the package insert that "administer RONAPREVE to patients who have risk factors for severe SARS-CoV-2 infection and who do not require oxygen intervention." (see below).

Since a stable supply is not ensured at this time, RONAPREVE will in the meantime be distributed to those patients who have risk factors for severe SARS-CoV-2 and require hospitalization. Therefore, medical institutions that can receive the allocation of this drug shall be hospitals and bedded clinics (hereafter referred to as "target medical institutions") which accept these patients for hospitalization.

*In the Treatment Guideline of Novel Coronavirus Infections (COVID-19), version 5.1 (July 5, 2021), "Individuals with risk factors are eligible for hospitalization."

Announcement by the COVID-19 Task Force, Ministry of Health, Labour and Welfare, July 20. 2021 (partially revised on August 13. 2021)

RONAPREVE® casirivimab and imdevimab

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.

From July 2021 (Version 1) Package Insert

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)

RONAPREVE® casirivimab and imdevimab

Chugai Pharmaceutical Co., Ltd.

Information Meeting on RONAPREVE™ for Intravenous Infusion Set,
a New Treatment for COVID-19

August 26, 2021

Courtesy: National Institute of Allergy and Infectious Diseases

Confronting COVID-19

- How to Make the Best of the With / Post-COVID-19 Age -

Prof. Kazuhiro Tateda

M.D., Ph.D., Department of Microbiology and Infectious Disease, Toho University School of Medicine

COI disclosure

Department of Microbiology and Infectious Disease, Toho University School of Medicine

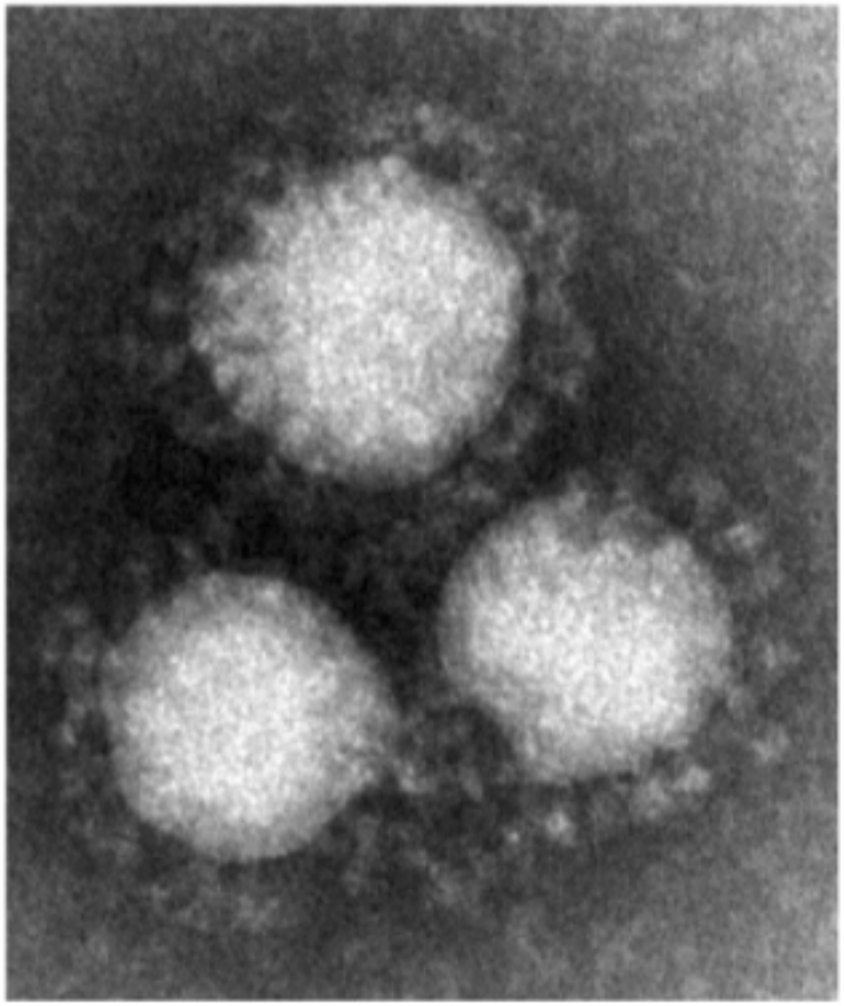
Prof. Kazuhiro Tateda

The companies that the presenter has COI relationships to be disclosed are as follows:

Chugai Pharmaceutical, Pfizer, Roche Diagnostics, Abbott Japan,

Denka Seiken, FUJIREBIO, Gilead Sciences

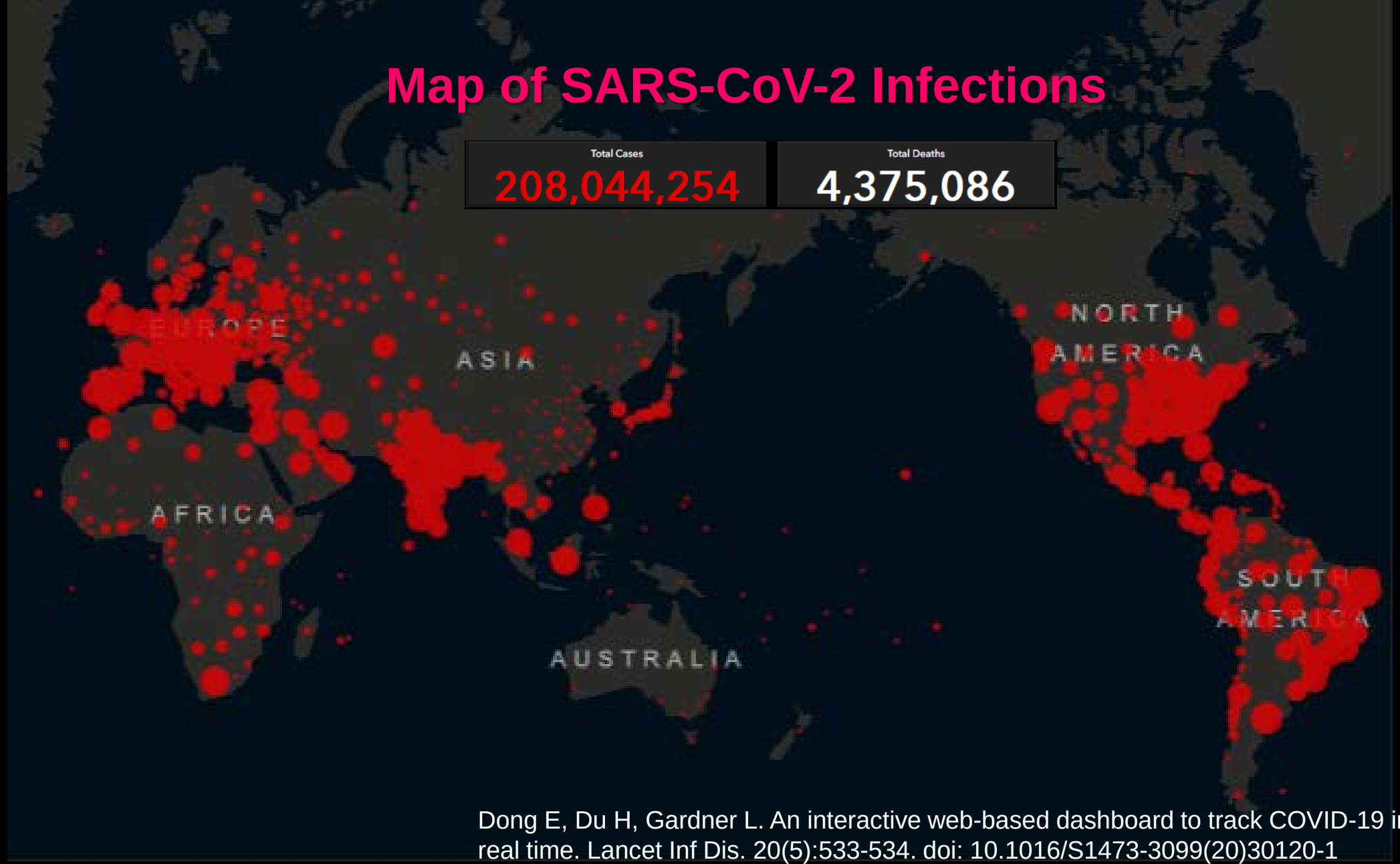
Novel Coronavirus Disease (COVID-19)



- 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)

Map of SARS-CoV-2 Infections

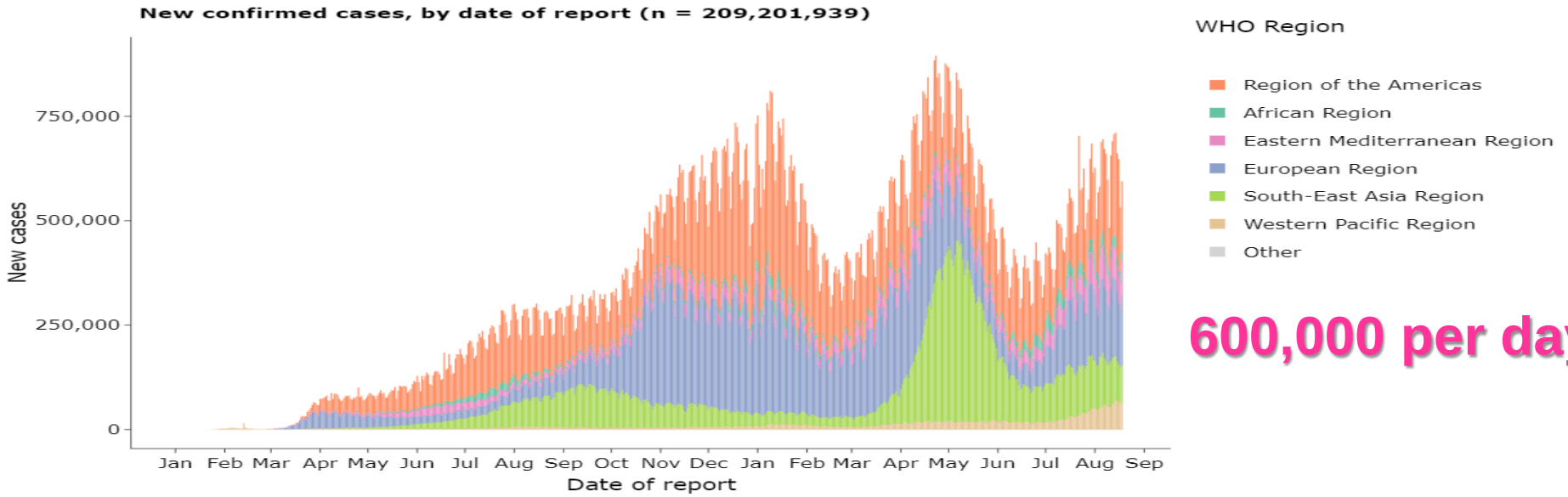


Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Inf Dis. 20(5):533-534. doi: 10.1016/S1473-3099(20)30120-1

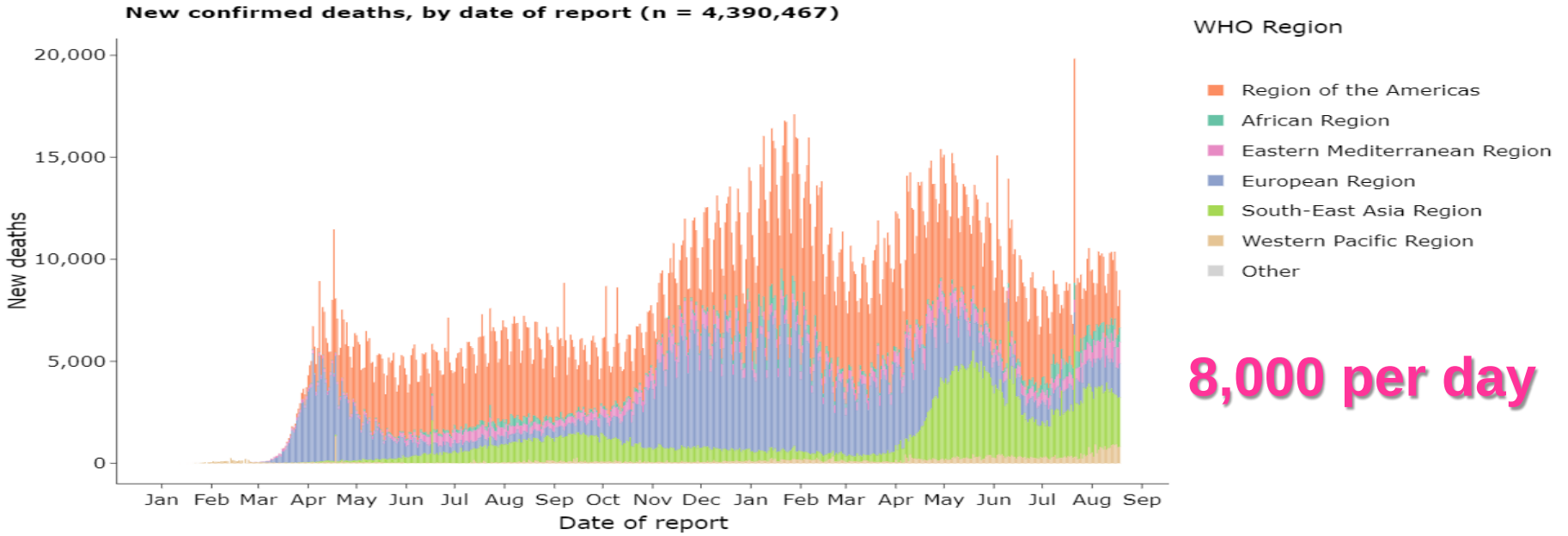
as of August 17, 2021

COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University（https://coronavirus.jhu.edu/map.html）

Trends of Daily Infections and Deaths (worldwide)



600,000 per day

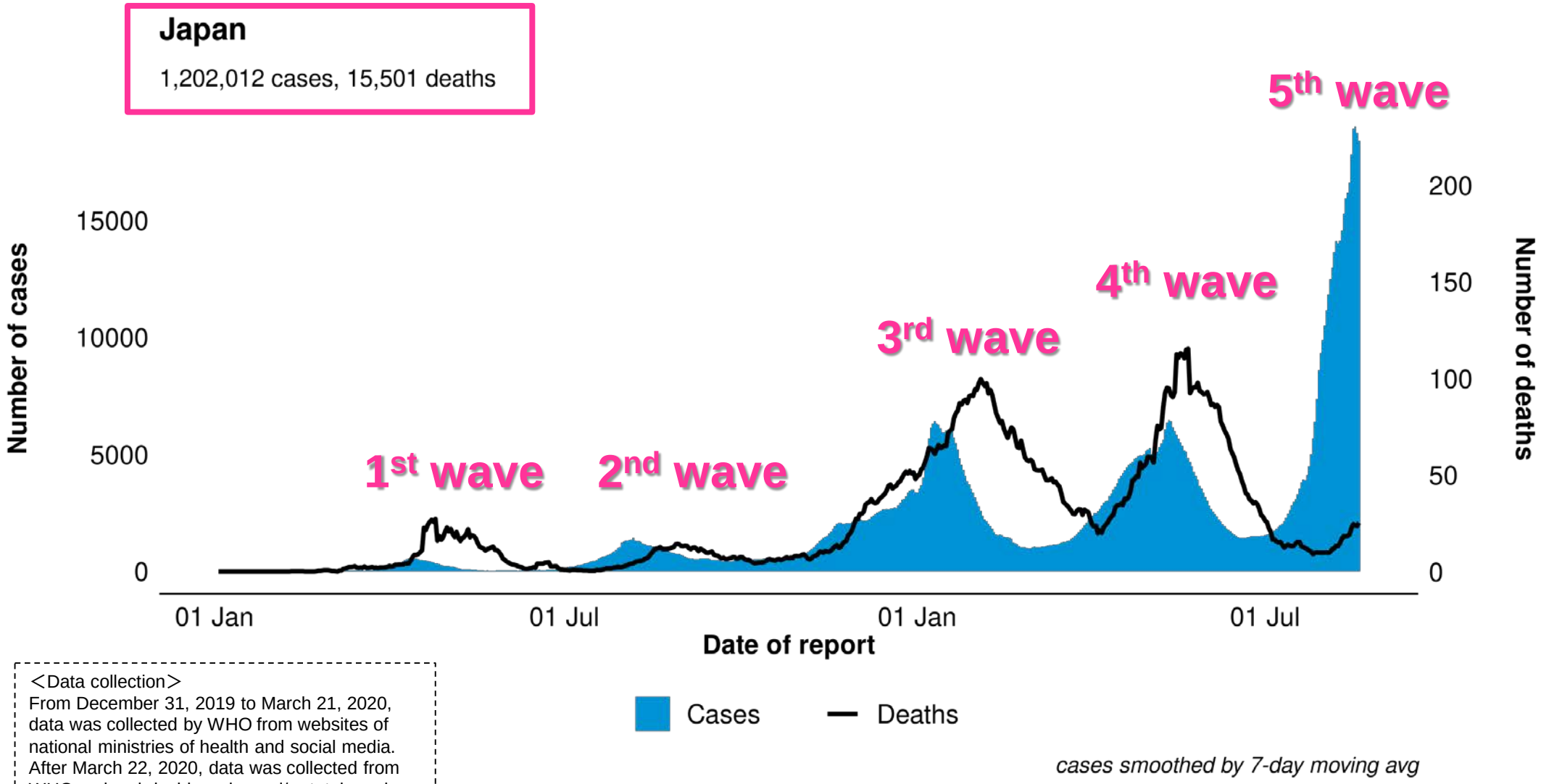


8,000 per day

＜Data collection＞
From December 31, 2019 to March 21, 2020, data was collected by WHO from websites of national ministries of health and social media. After March 22, 2020, data was collected from WHO regional dashboards, and/or total number of reports directly to WHO headquarters.

WHO COVID-19 Explorer. Geneva: World Health Organization, 2020. Available online: https://worldhealthorg.shinyapps.io/covid/ (last cited: [August 20, 2021]).

Trends of Daily Infections and Deaths (Japan)

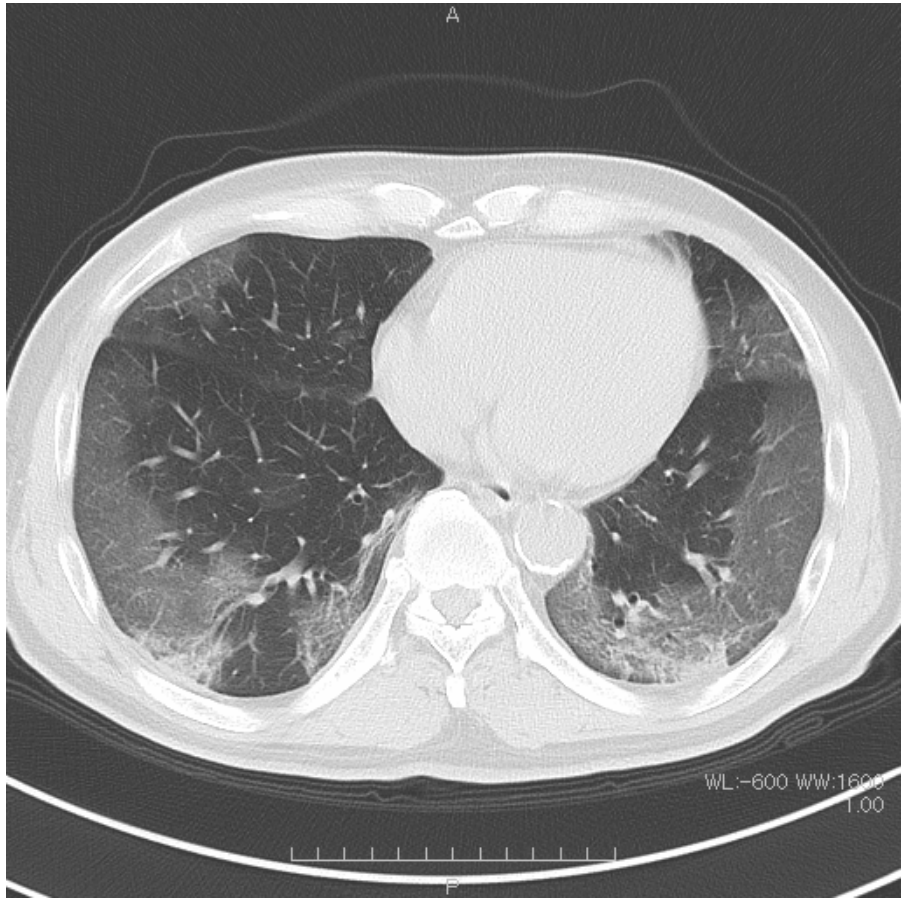


＜Data collection＞
From December 31, 2019 to March 21, 2020, data was collected by WHO from websites of national ministries of health and social media. After March 22, 2020, data was collected from WHO regional dashboards, and/or total number of reports directly to WHO headquarters.

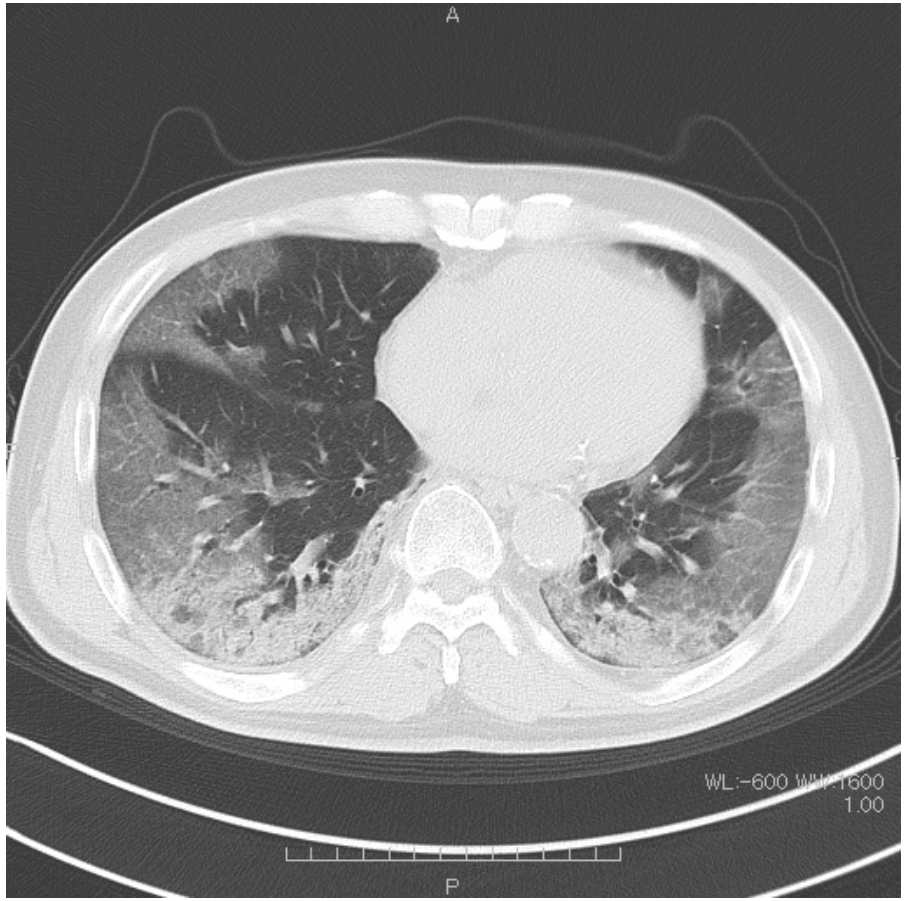
WHO COVID-19 Explorer. Geneva: World Health Organization, 2020. Available online: https://worldhealthorg.shinyapps.io/covid/ (last cited: [August 20, 2021]).

Case B: male in 70s

CT scan on first visit



CT scan 3 days later (hospitalized)



Ground-glass opacities in bilateral subpleural areas - why?

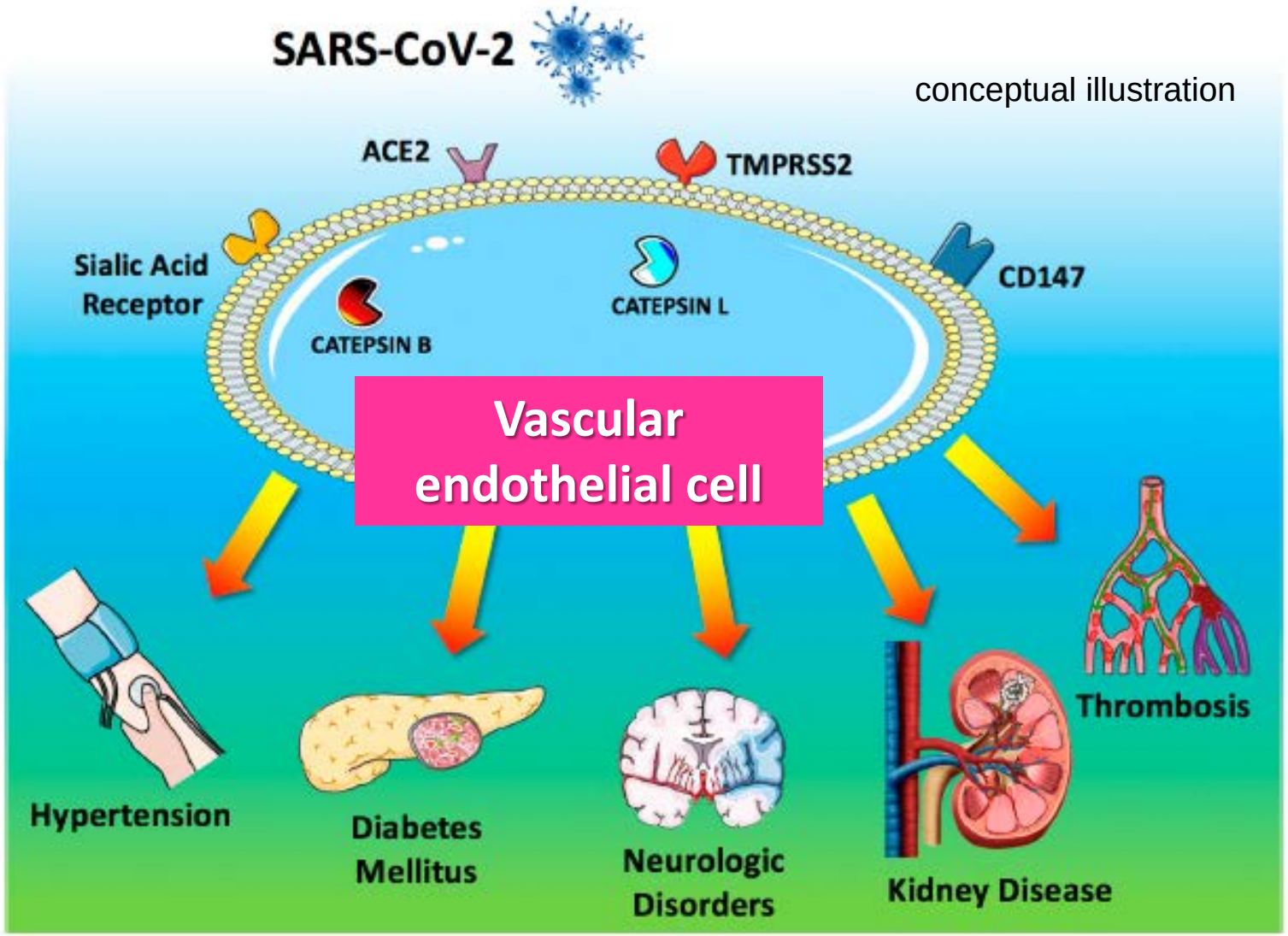
ACE-2 distribution? Showing the size of the inhaled particles?

Inhaled the microdroplets ejected by himself?

Case at Toho University Omori Medical Center

SARS-CoV-2 and Its Effects on Vascular Endothelial Cells

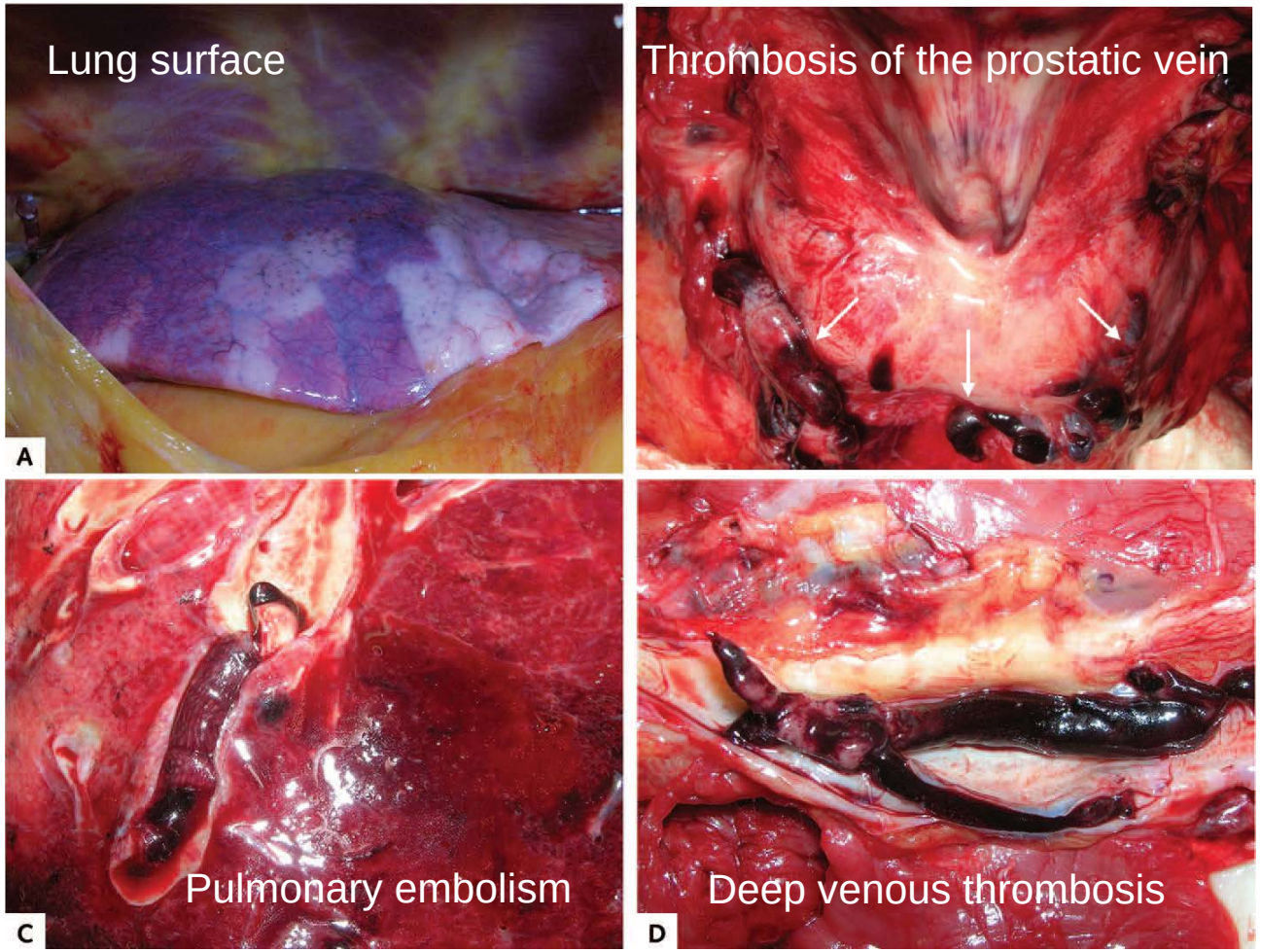
Sardu C et al. J Clin Med May 11, 2020



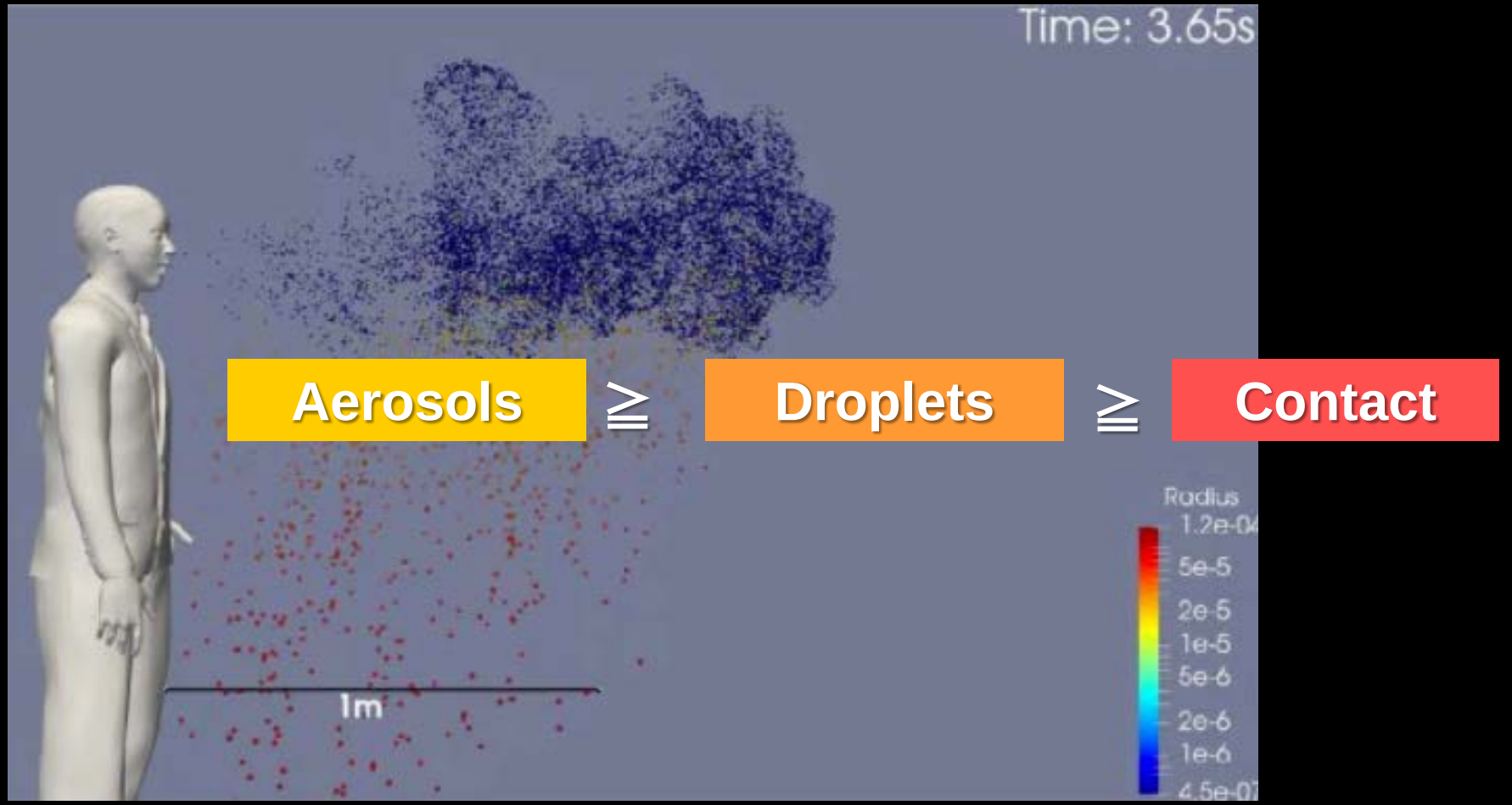
Thrombus Formation due to SARS-CoV-2 (overseas data)

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.



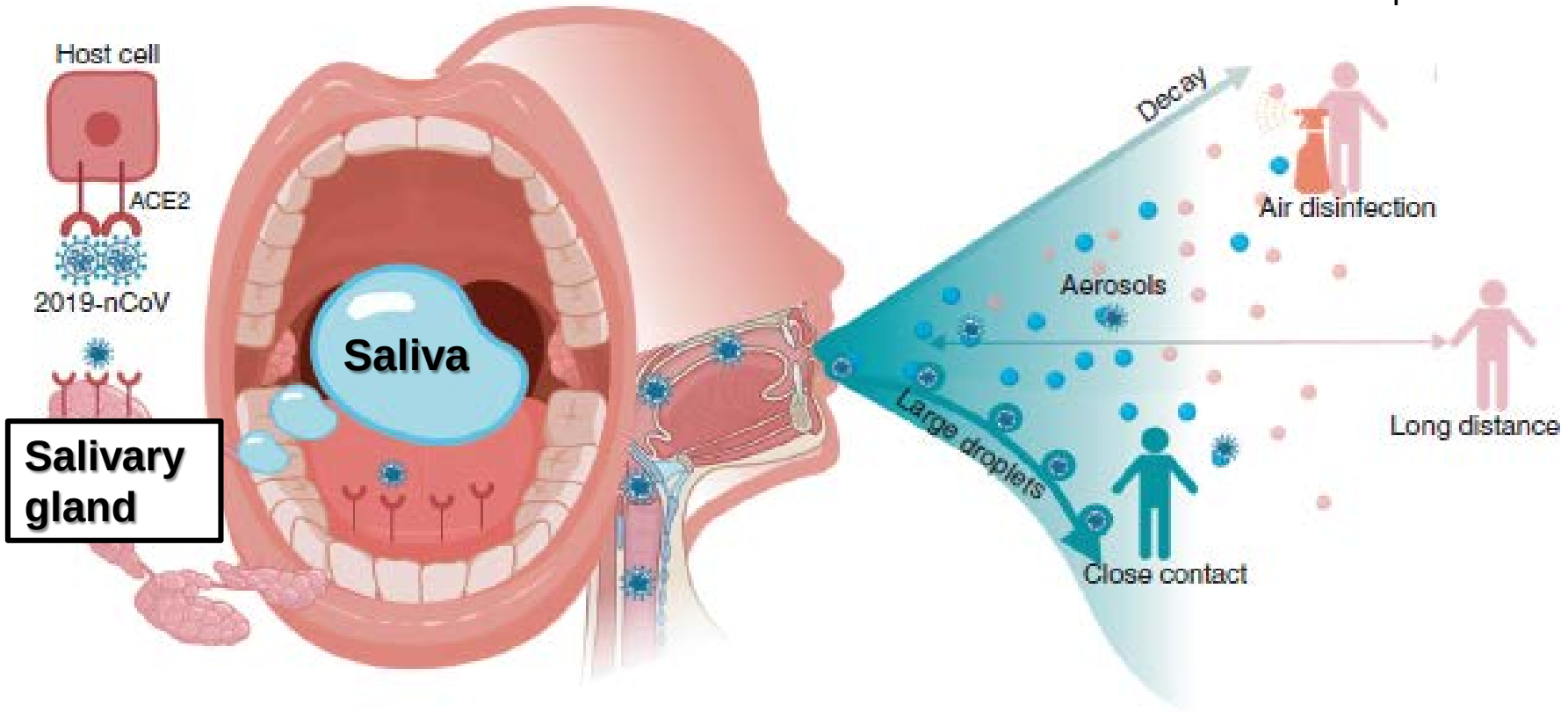
Spread of Droplets due to Shouting



Source: "Prediction and Countermeasures for Virus Droplet Infection in Indoor Environments #2" (Cabinet Office)
（https://www.covid19-ai.jp/ja-jp/presentation/2020_rq1_droplet_infection_simulation/articles/article005/）（accessed:August 17, 2021）

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

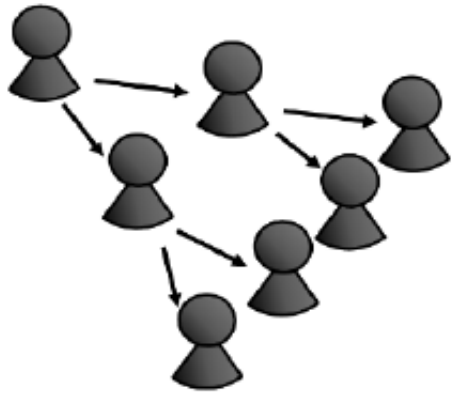
conceptual illustration

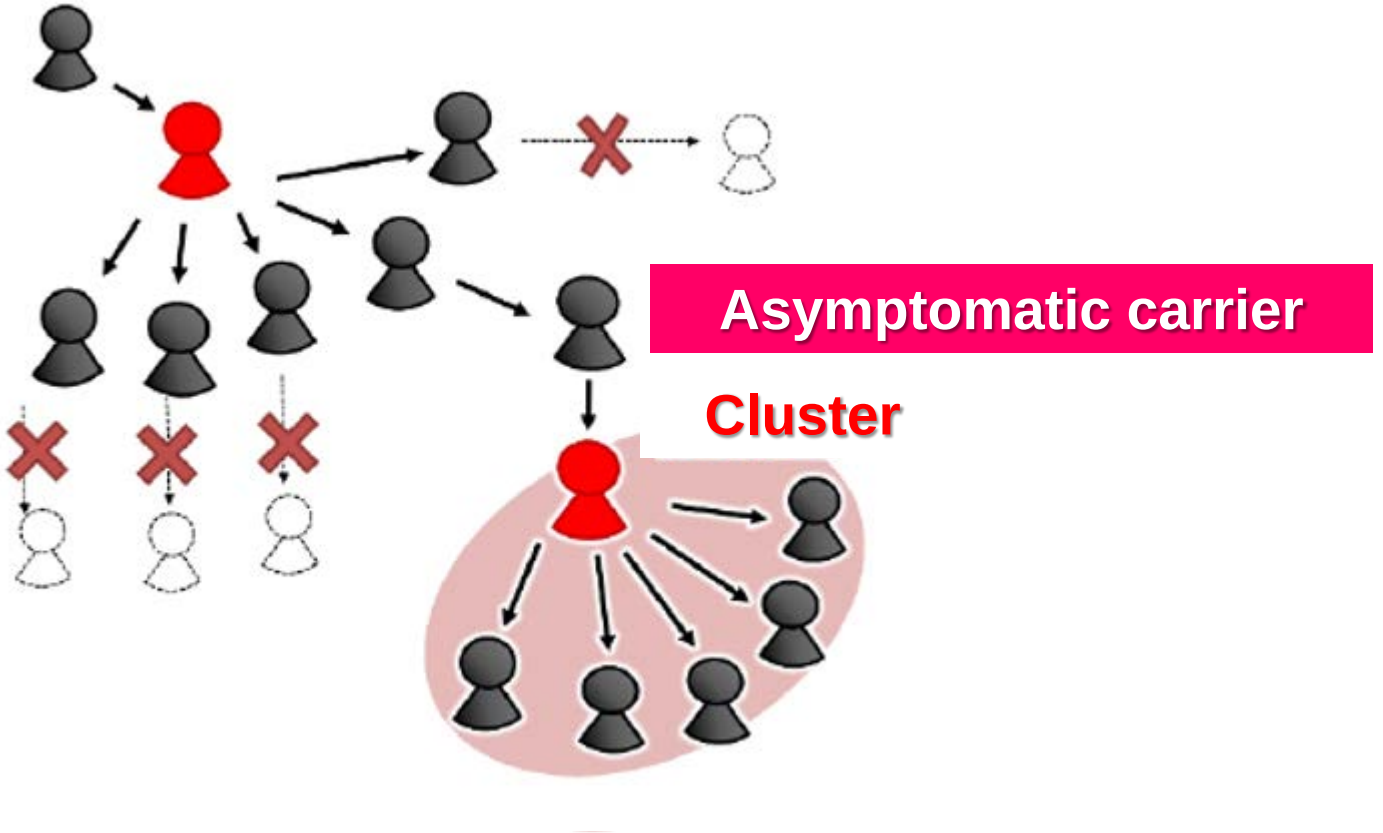


Xu R et al. Int J Oral Sci. Apr 17, 2020

Characteristics of SARS-CoV-2 Transmission

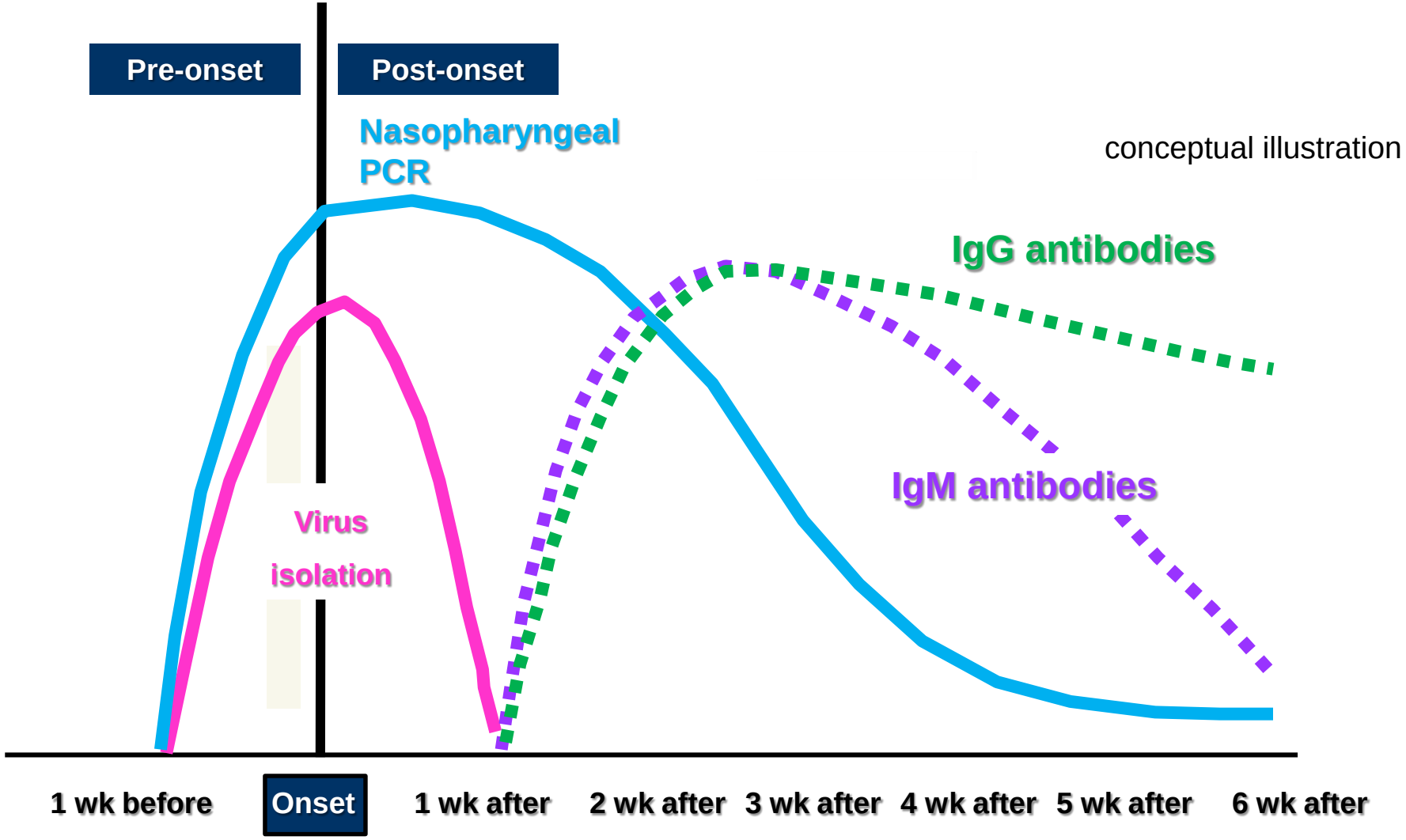
- **Influenza transmission**
- **SARS-CoV-2 transmission**





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)

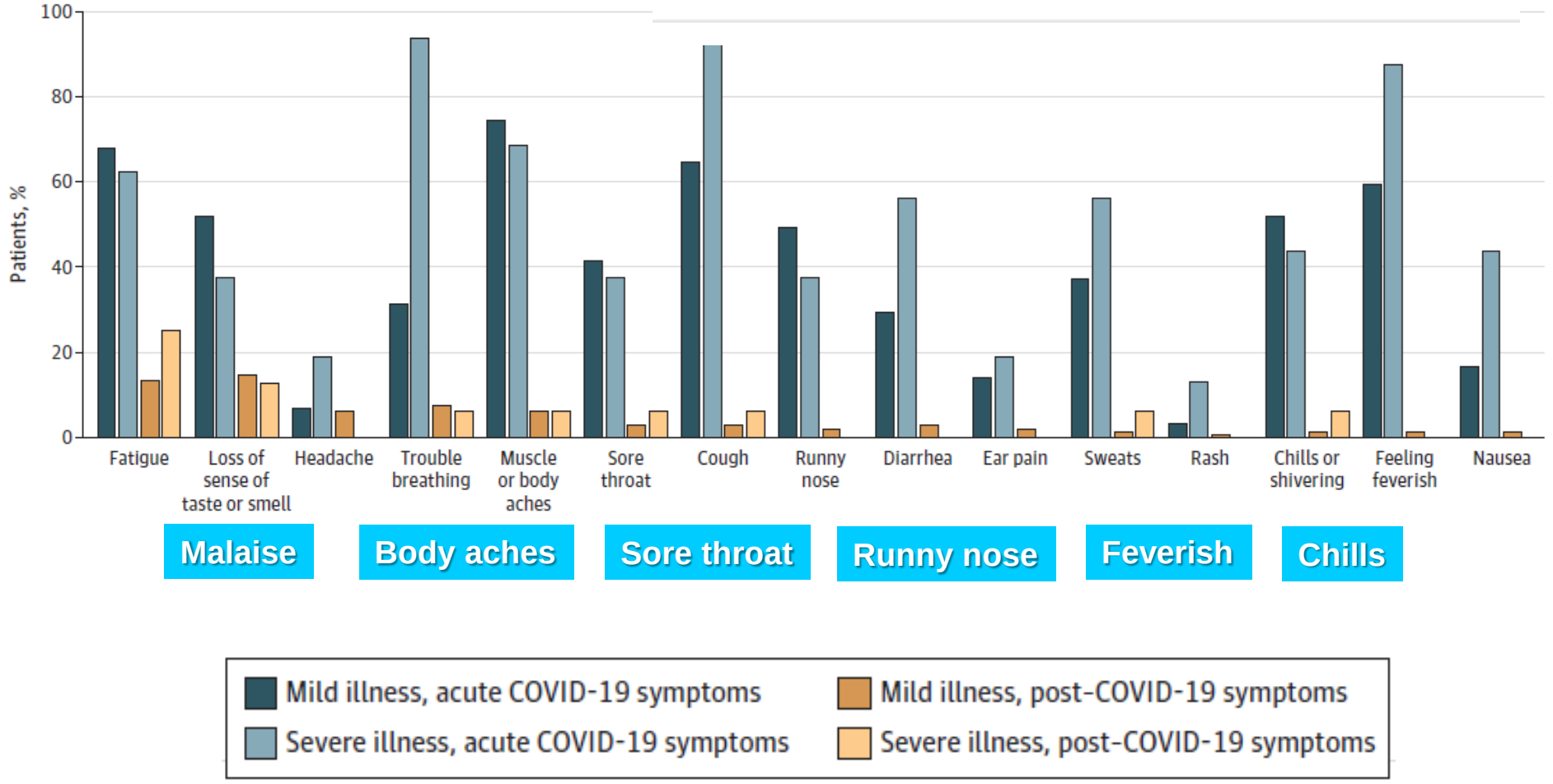
Predicted Test Results around the Time of COVID-19 Onset



Sethuraman N et al JAMA. 323:2249, 2020.

COVID-19 Spreads from Asymptomatic People

What kind of slight symptoms suggest COVID-19?



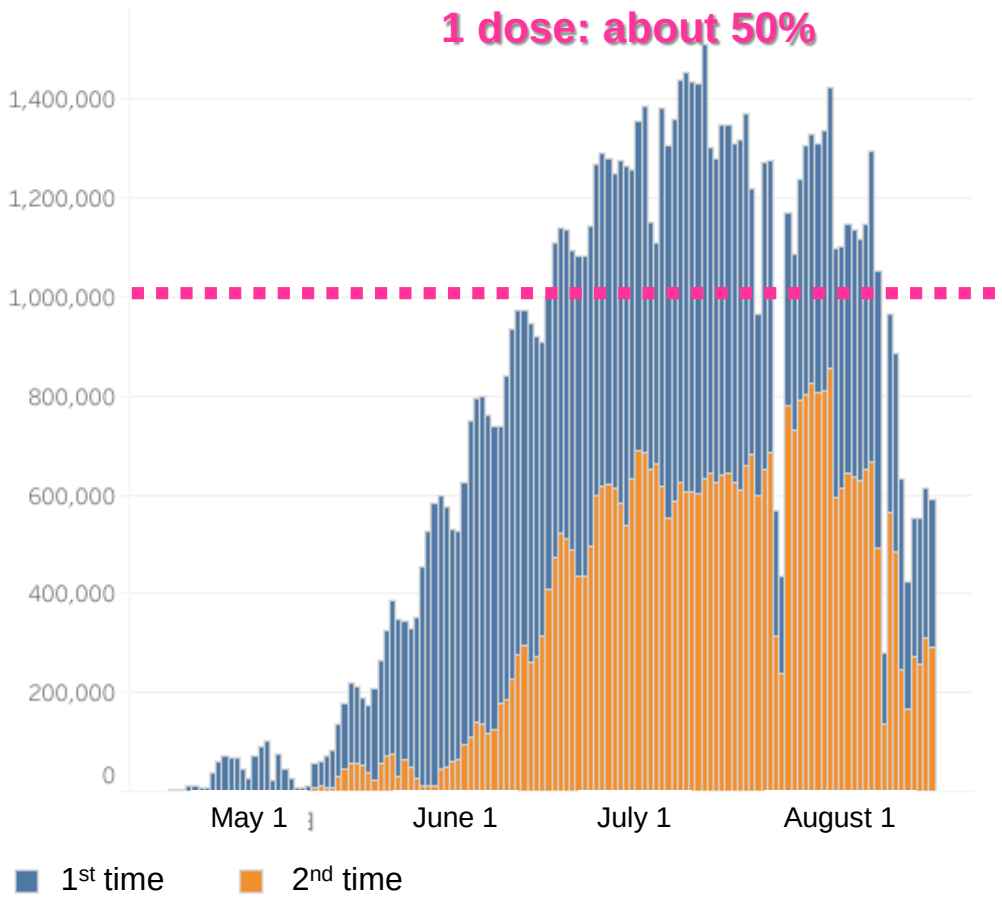
Study summary and methods of assessment:
Results of observations of 177 people infected with SARS-CoV-2 outside Japan (150 with mild illness, 16 with severe illness, 11 asymptomatic).
The median observation period was 169 days after symptom onset (31-300 days).

JAMA Netw Open. 2021 Feb 1;4(2):e210830.

COVID-19 Vaccination Status (August 17, 2021)

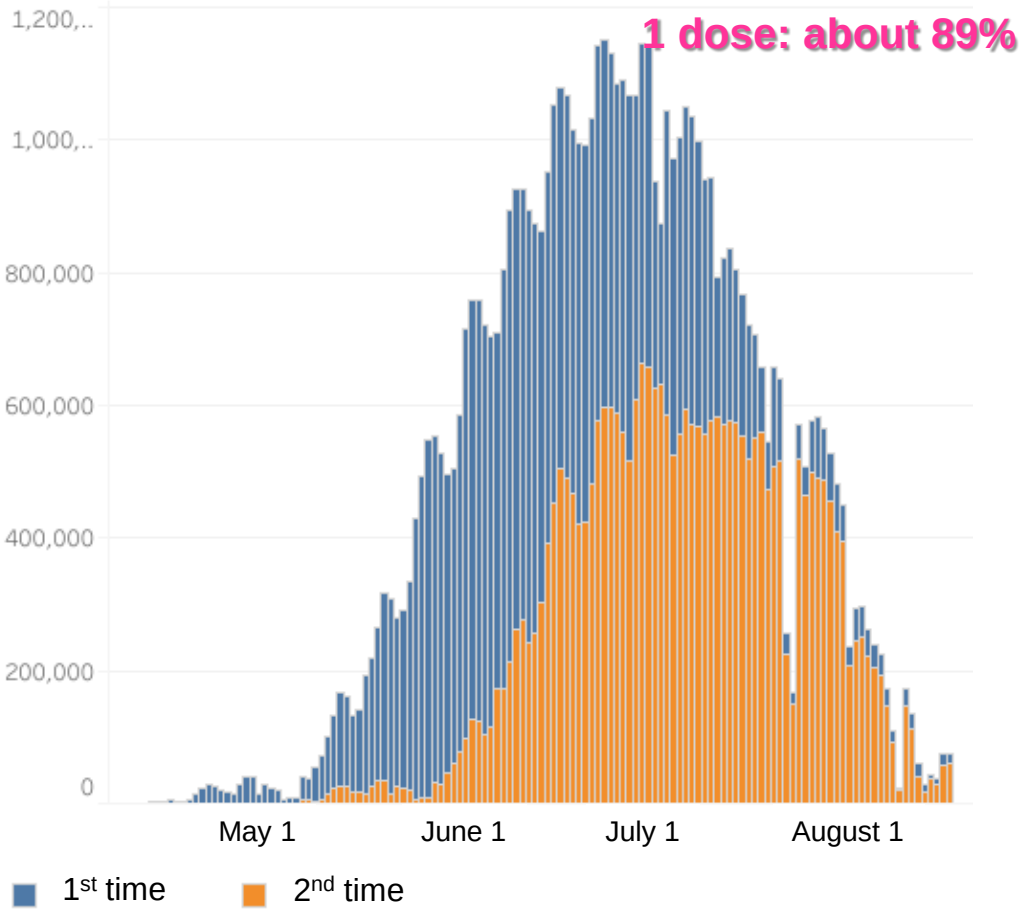
Inoculation days pass ; **All ages 2 doses: about 40%**

1 dose: about 50%



Inoculation days pass **Over 65 2 doses: about 85%**

1 dose: about 89%



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

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)

Development Status of Major New Coronavirus Vaccines

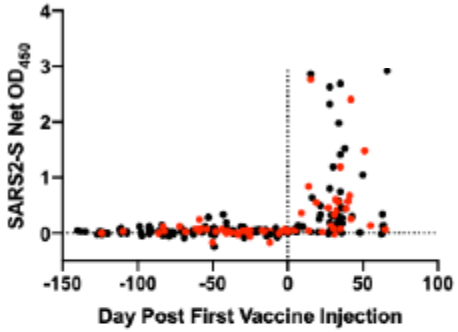
Country	Companies/Academia	Vaccine type	Progress
US / Germany	Pfizer / BioNTech	mRNA	Overseas: Vaccination started in the US, UK, and EU. Japan: regulatory approval on Feb 14, 2021
US	Moderna	mRNA	Overseas: Vaccination started in the US Japan: regulatory approval on May 21, 2021
UK	AstraZeneca/Oxford	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)

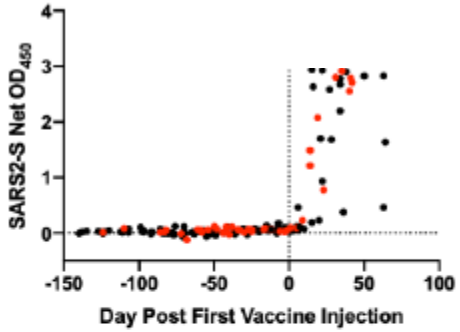
Antibodies Induced by mRNA Vaccines (Overseas Data)

S-Protein

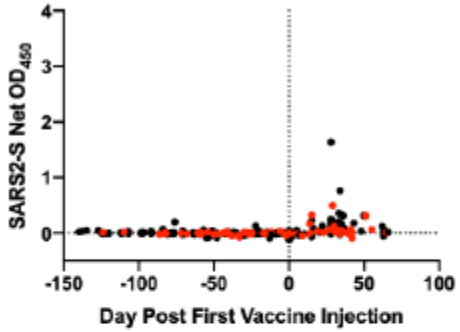
IgA in saliva



IgG in saliva

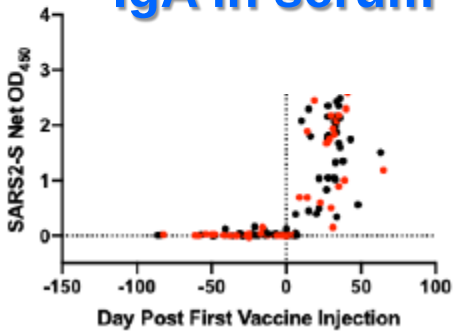


IgM in saliva

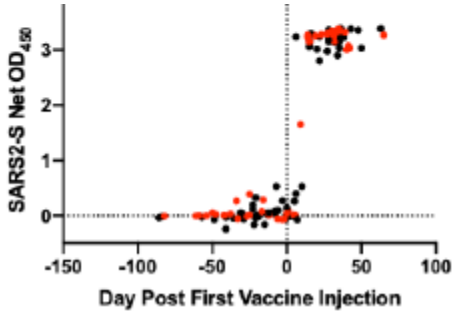


S-Protein

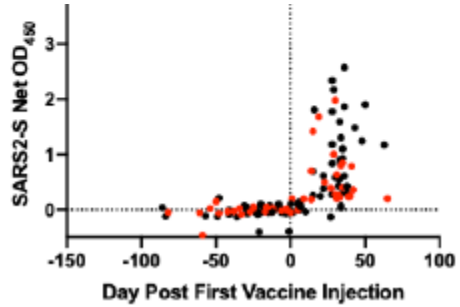
IgA in serum



IgG in serum



IgM in serum

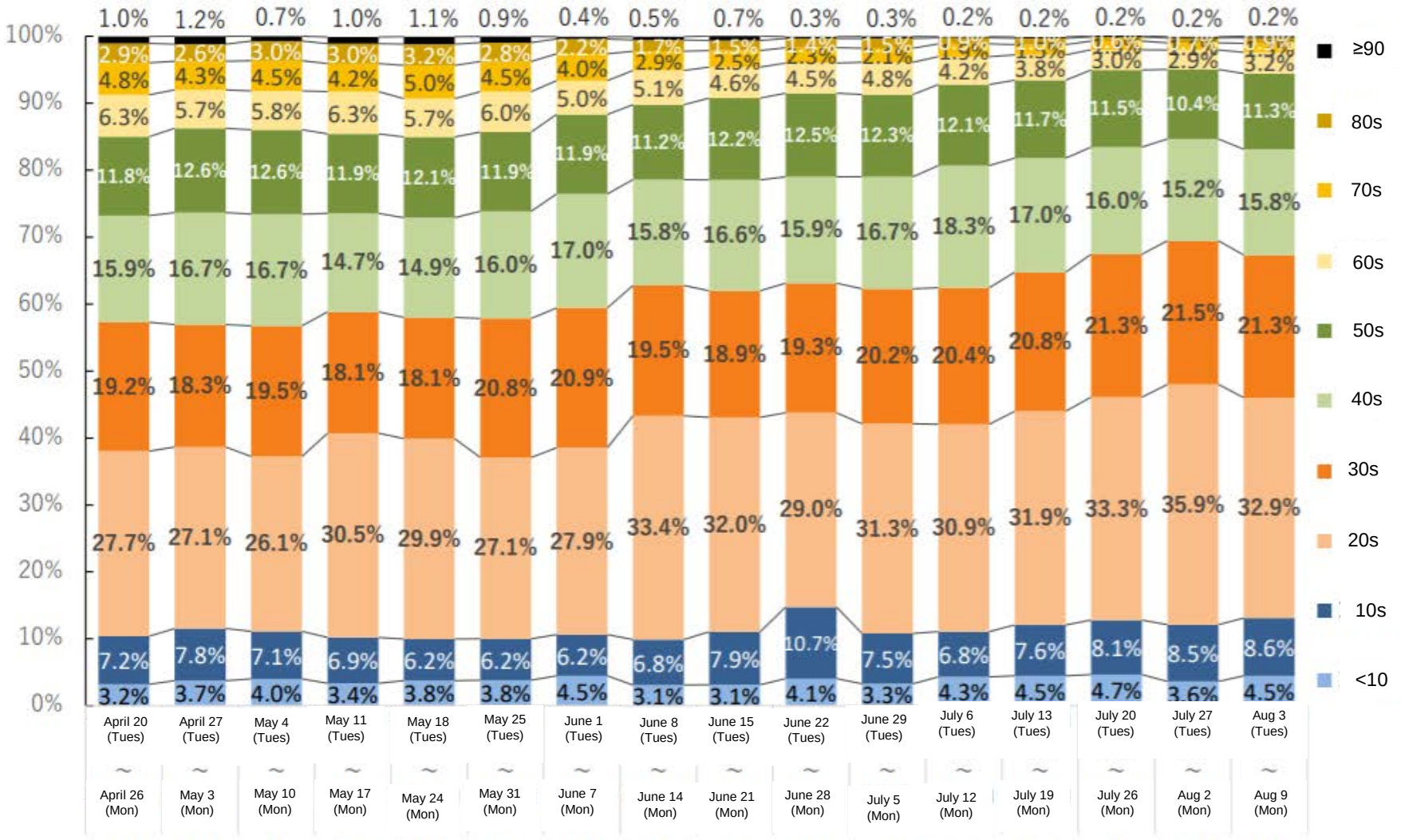


Mucosal immune response induced by mRNA vaccine

Study summary and methods of assessment:
Data of 69 subjects with confirmed antibody production among 85 subjects immunized with SARS-CoV-2 mRNA vaccines outside Japan. Red dots show Moderna-vaccinated subjects, black dots show Pfizer-vaccinated subjects.

Ketas TJ et al. Pathog Immun. 2021 Jun 7;6(1):116-134

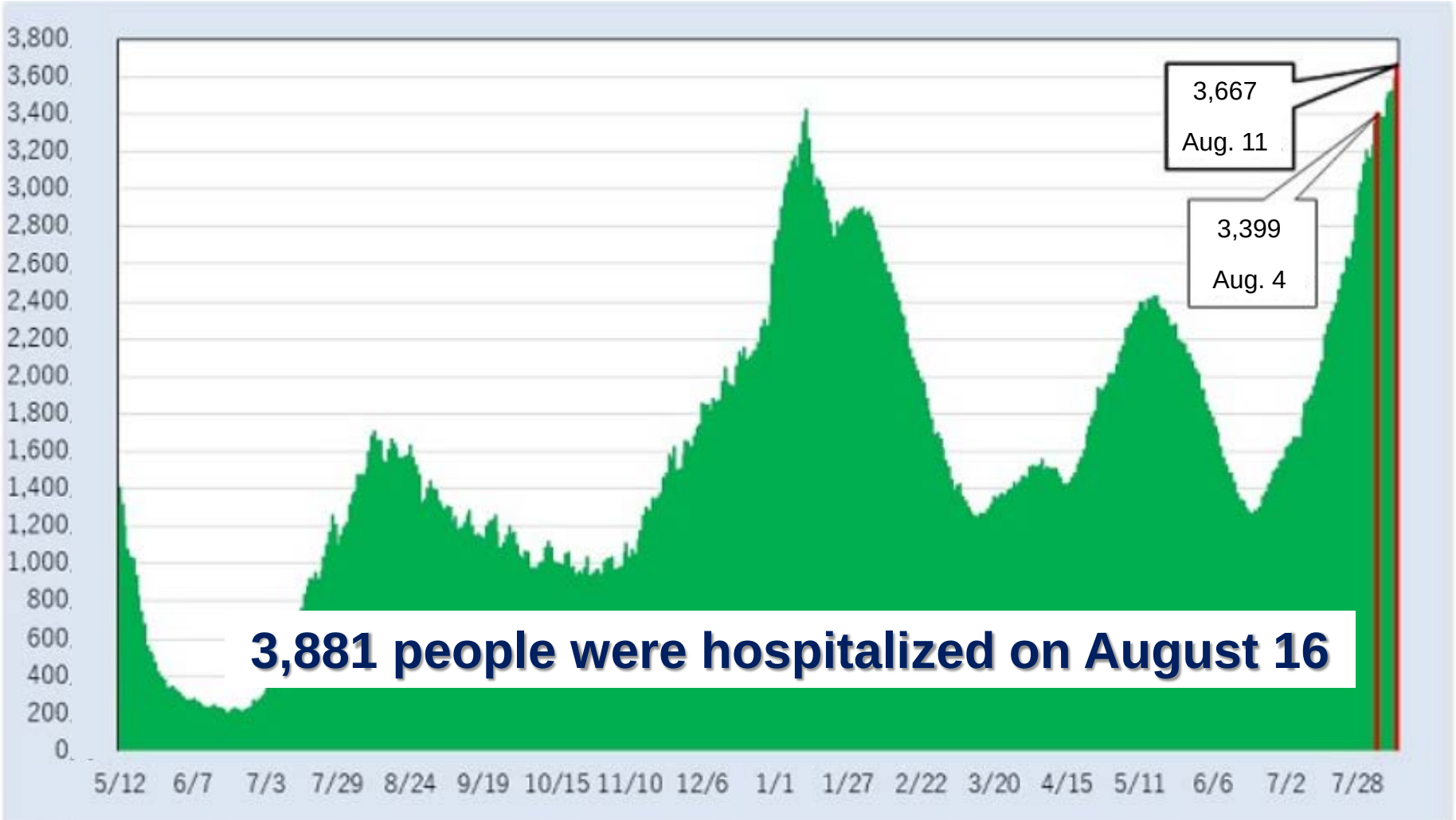
Tokyo Metropolis: New Positive Cases by Age



As of August 9, ≥90% are in their 50s or younger, ≥50% are in their 20s to 30s

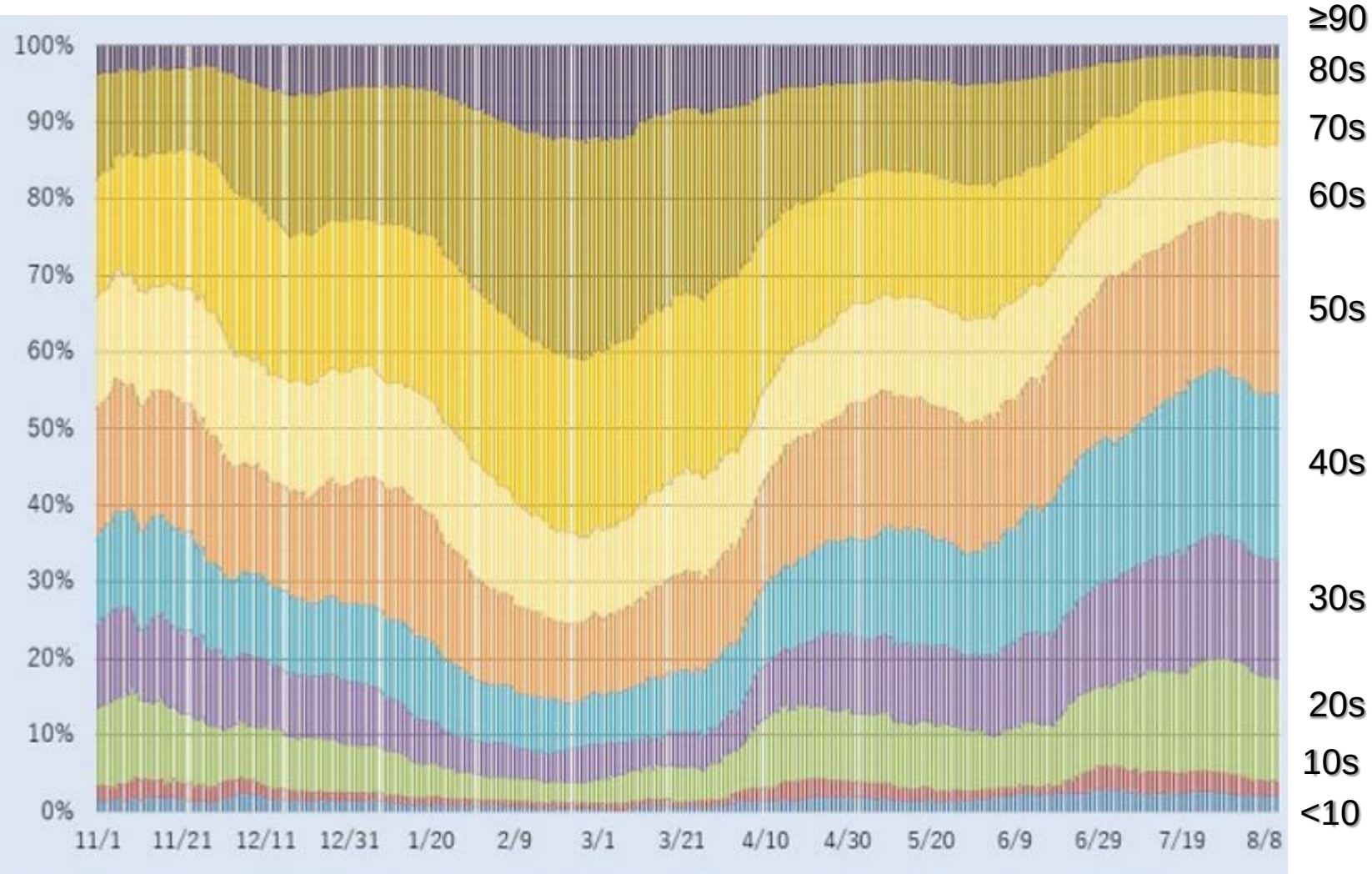
Website of the Bureau of Social Welfare and Public Health, Tokyo Metropolitan Government
(accessed August 16, 2021)

Tokyo Metropolis: the Number of Hospitalized Patients



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)

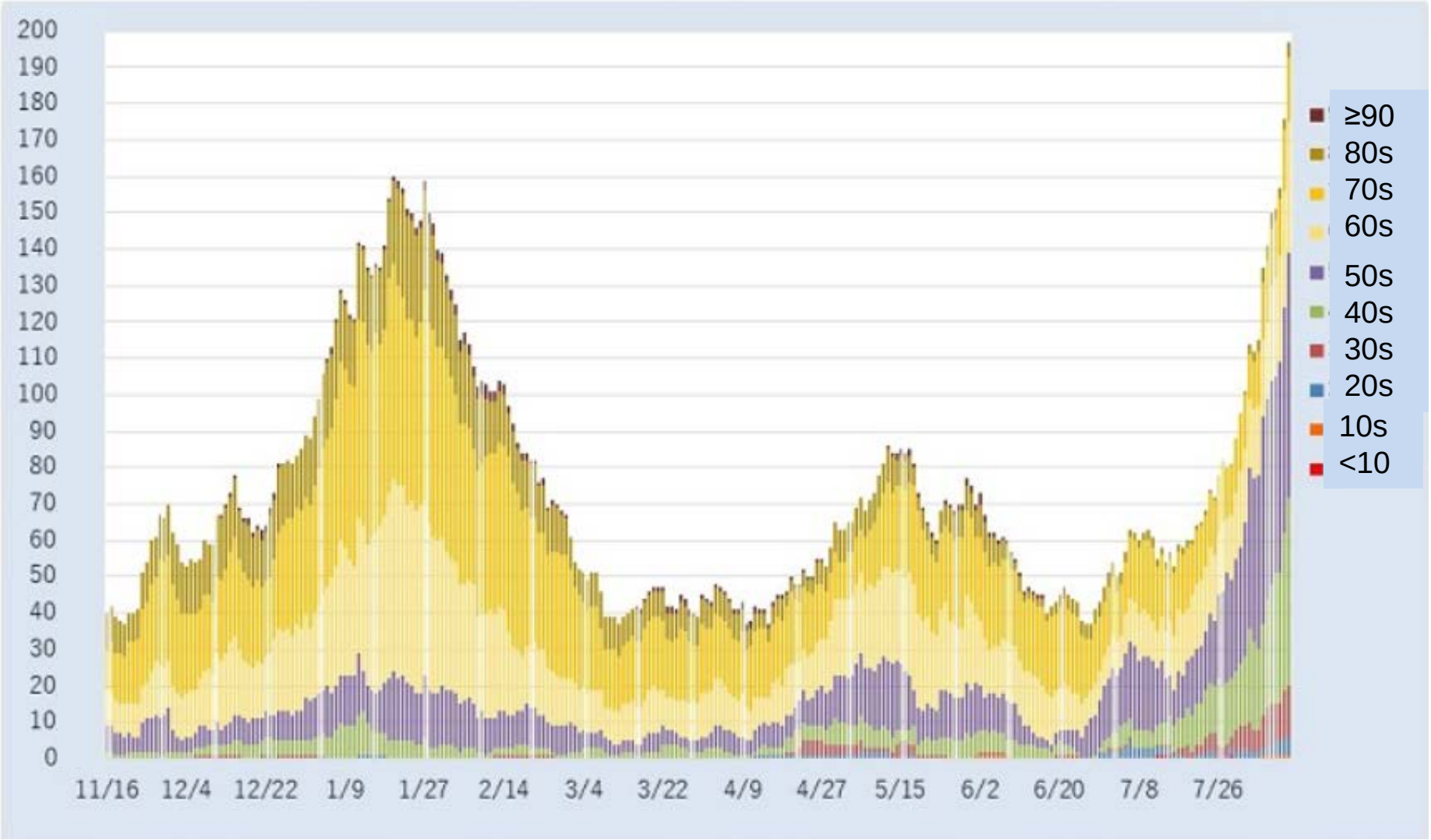
Tokyo Metropolis: Hospitalized Patients by Age



≥70% of those hospitalized are in their 50s or younger on August 11, 2021

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

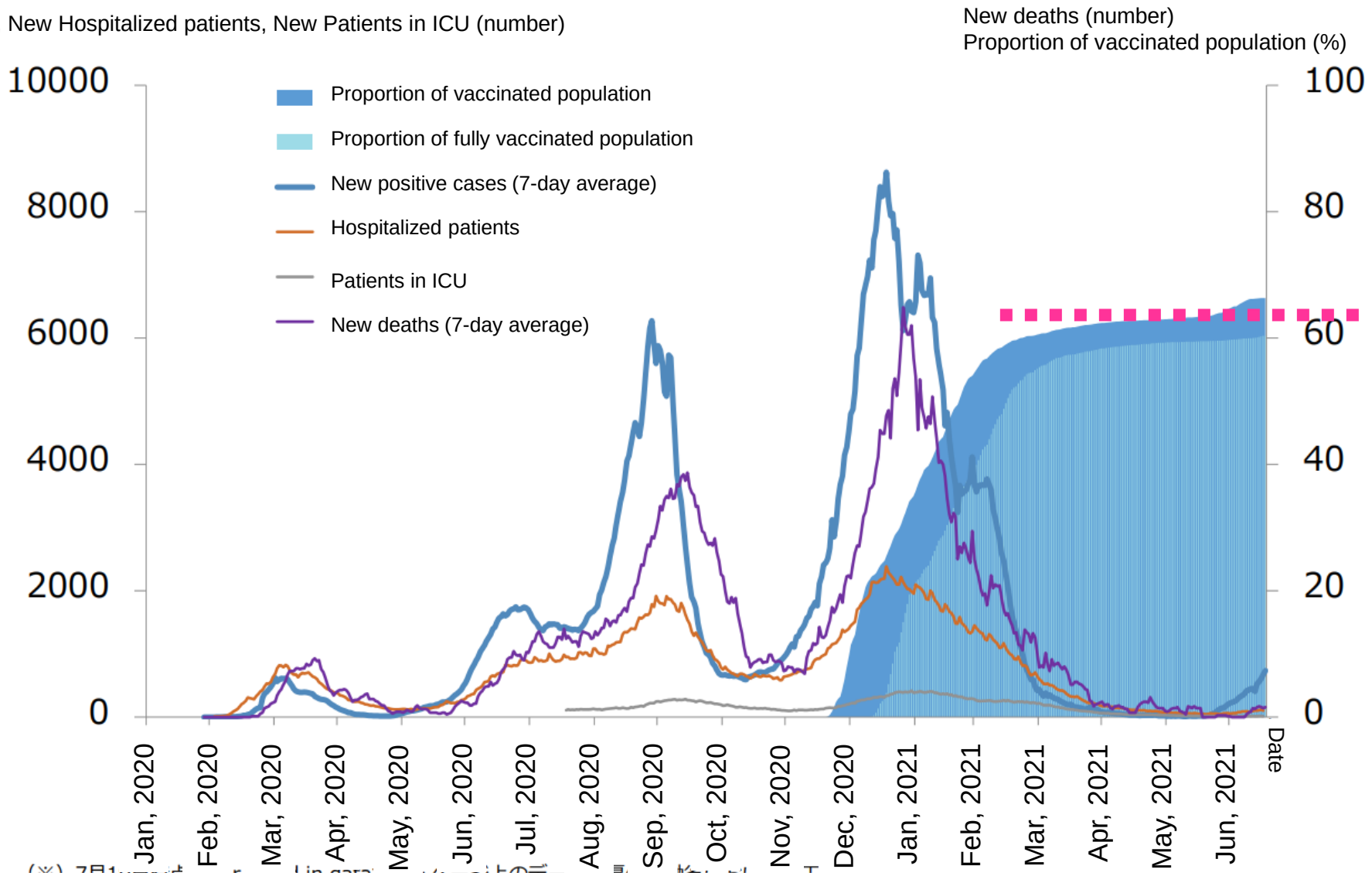
Tokyo Metropolis: Patients with Severe Symptoms by Age



As of August 11, 60%≥ of severe patients are in their 50s or younger

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

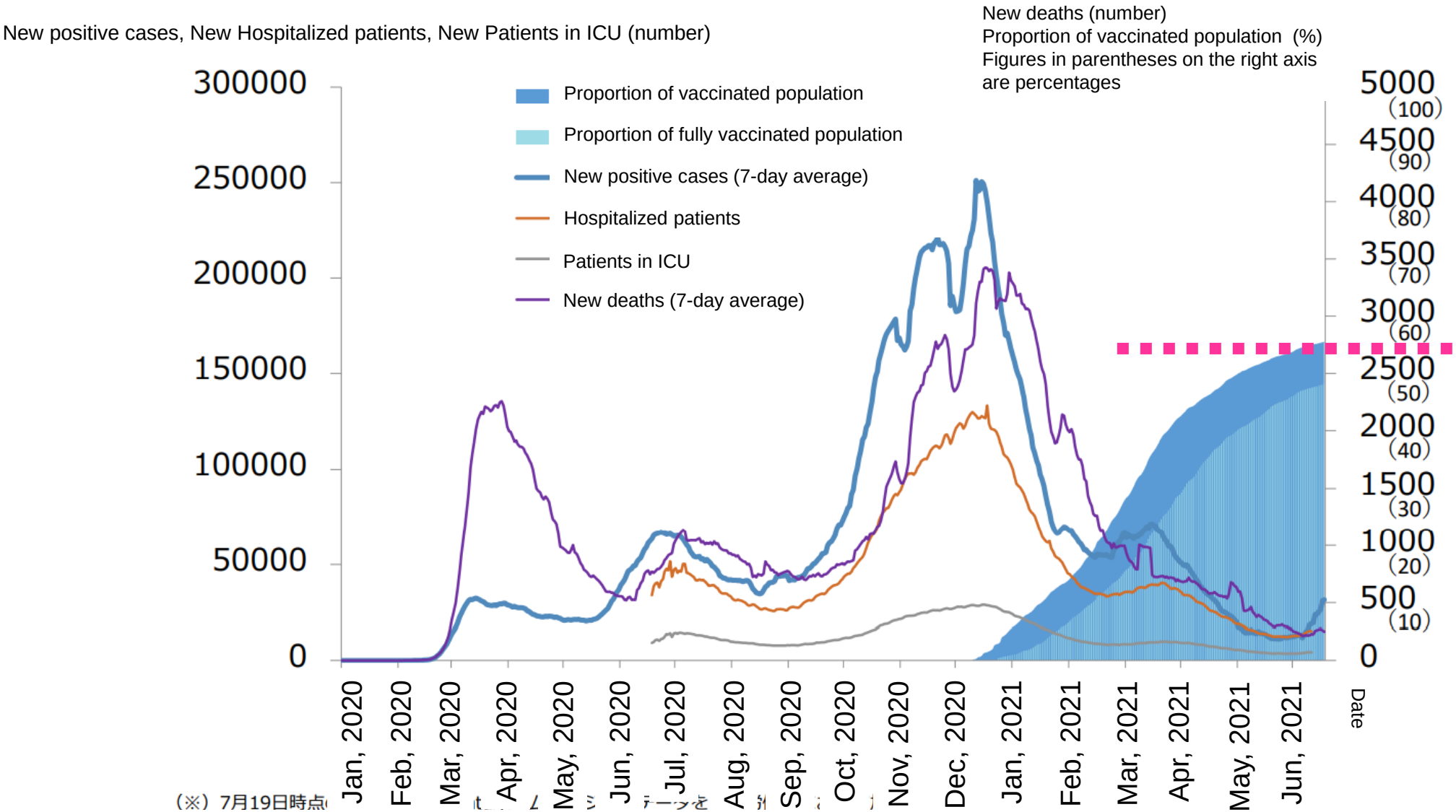
Infection and Vaccination Status (Israel)



July 19 data of the Our World in Data website adapted by the Ministry of Health, Labour and Welfare

Ministry of Health, Labour and Welfare's COVID-19 Advisory Board materials (accessed July, 2021)

Infection and Vaccination Status (United States)



July 19 data of the Our World in Data website adapted by the Ministry of Health, Labour and Welfare

Ministry of Health, Labour and Welfare's COVID-19 Advisory Board materials
(accessed July, 2021)

The Issue of Vaccine Hesitancy

- How to increase the vaccination rate among younger people -

1. Education and awareness campaigns (severity rate and after effects; herd immunity)

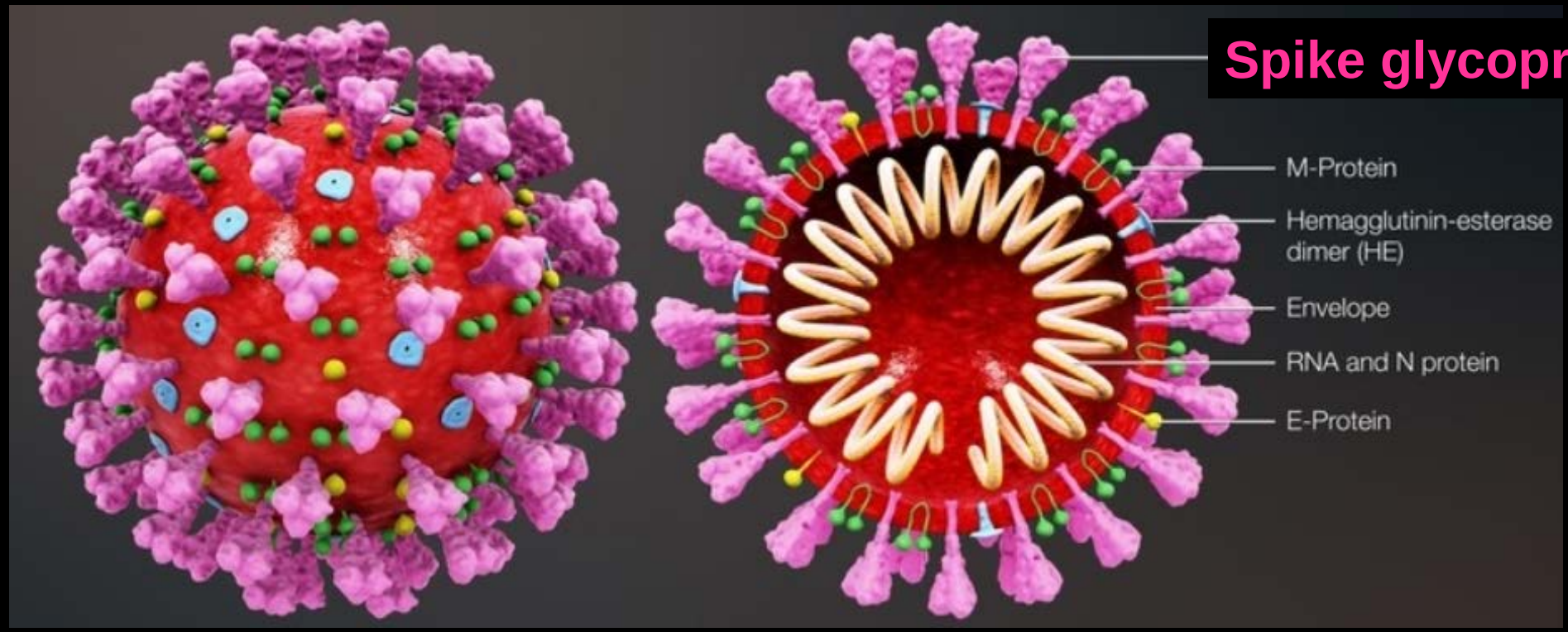
2. Countermeasures for fake vaccine-related information

    Partnerships with the national government, local governments, academia, and media

3. Creating incentives to increase vaccination

    While being considerate of those who cannot (or will not) be vaccinated

The Issue of Variants of Concern (VOC)



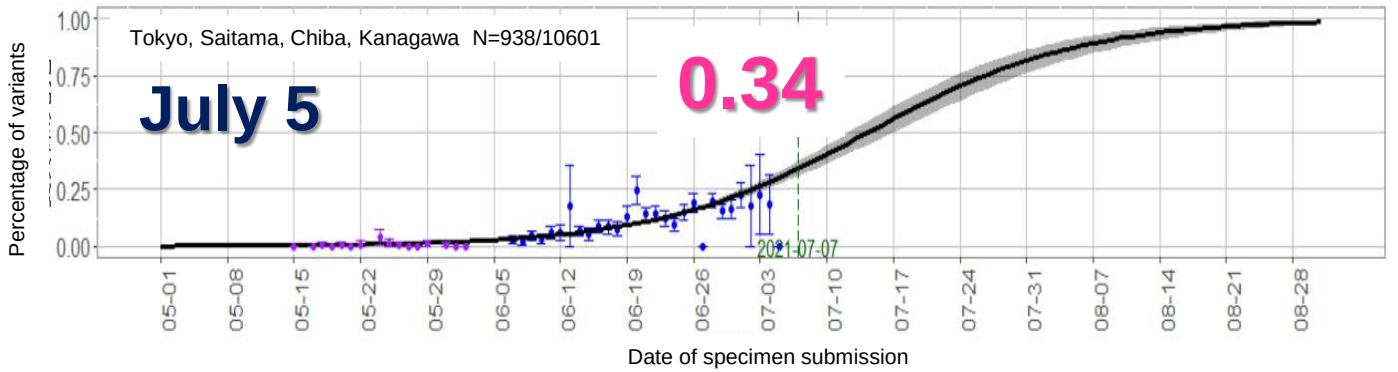
Wu D et al. J Clin Med. Jun 16;9(6):1885, (2020)

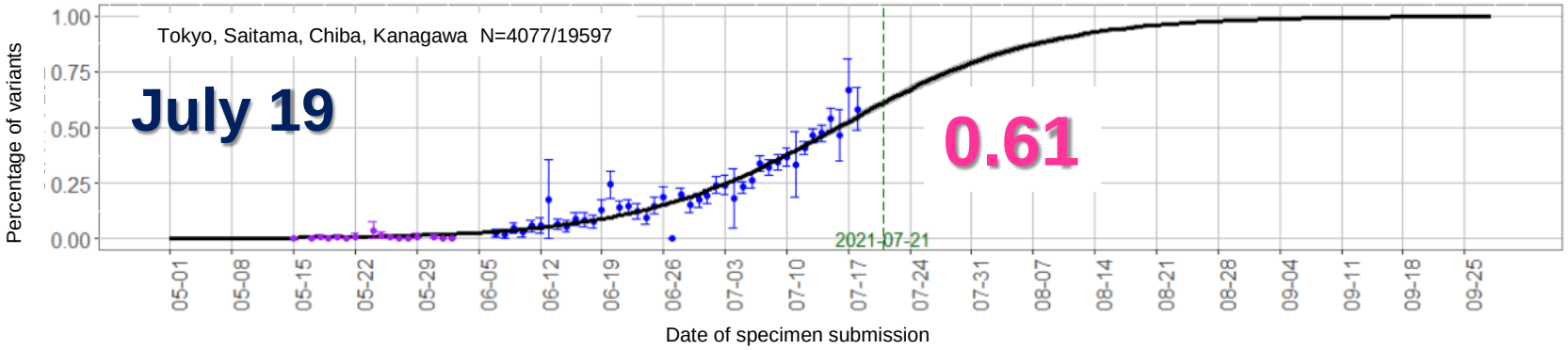
SARS-CoV-2 Variants

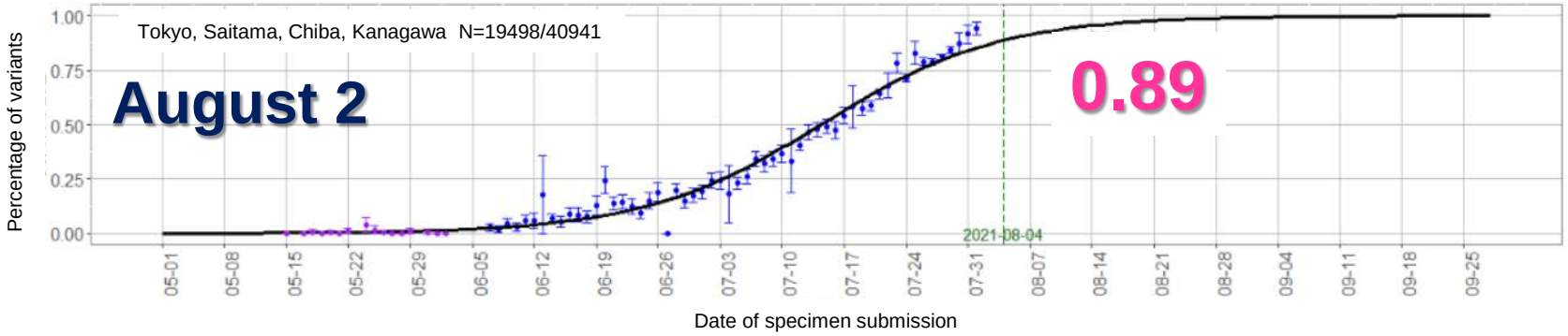
Alpha	**N501Y**, A570D, P681H, T716I, S982A, D118H, Δ69-70, Δ144/145
Beta	**N501Y**, **E484K**, L18F, D215G, R264I, K417V, A701V
Gamma	**N501Y**, **E484K**, etc. (17 mutations)
Delta	**E484Q, L452R mutations**

Weaker vaccine efficacy + greater infectivity

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

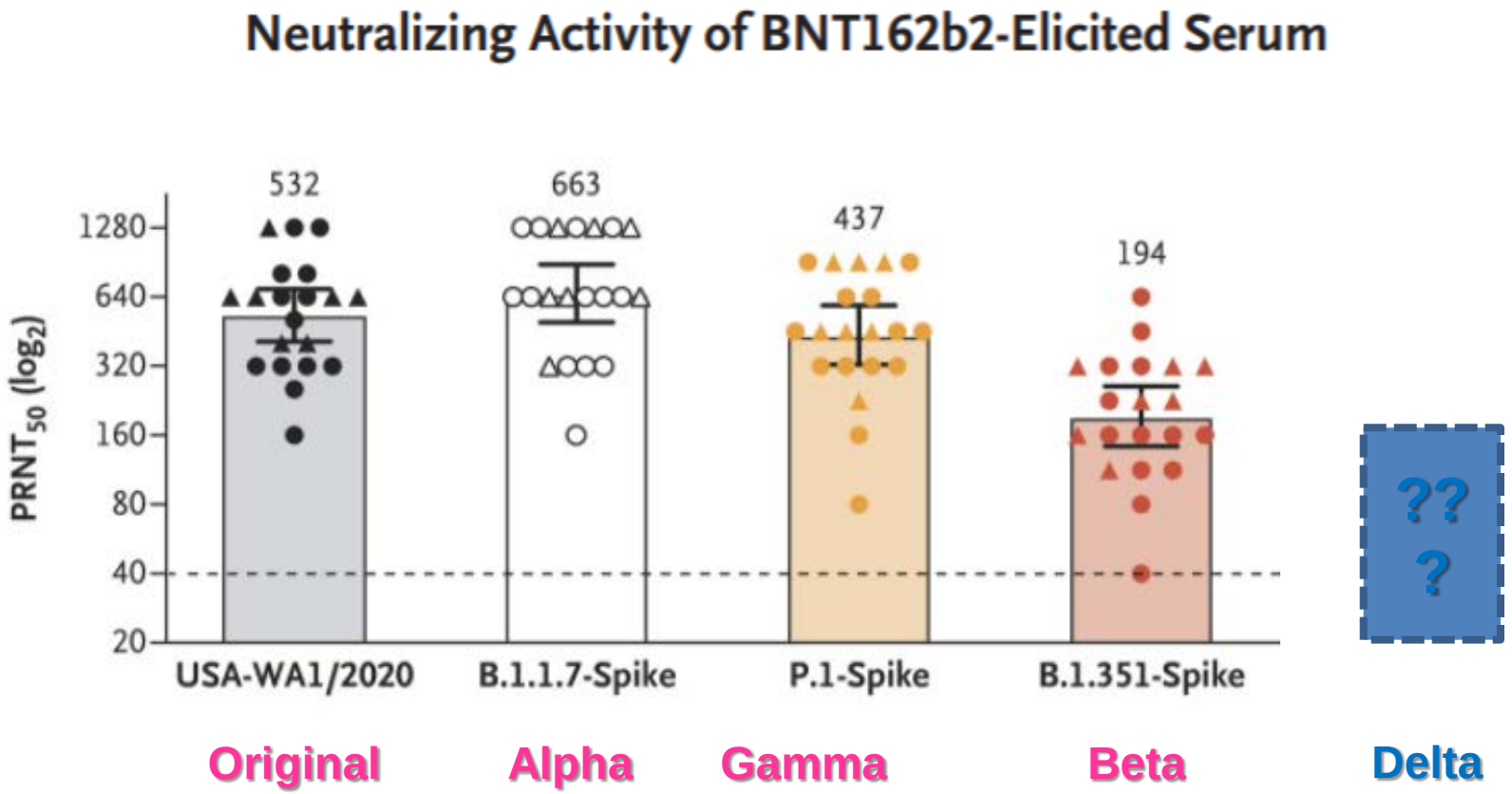






Ministry of Health, Labour and Welfare's COVID-19 Advisory Board materials
(42,44,46th meeting, accessed August 18, 2021)

Neutralizing Activity against Variants
Antibodies Induced by the mRNA Vaccines



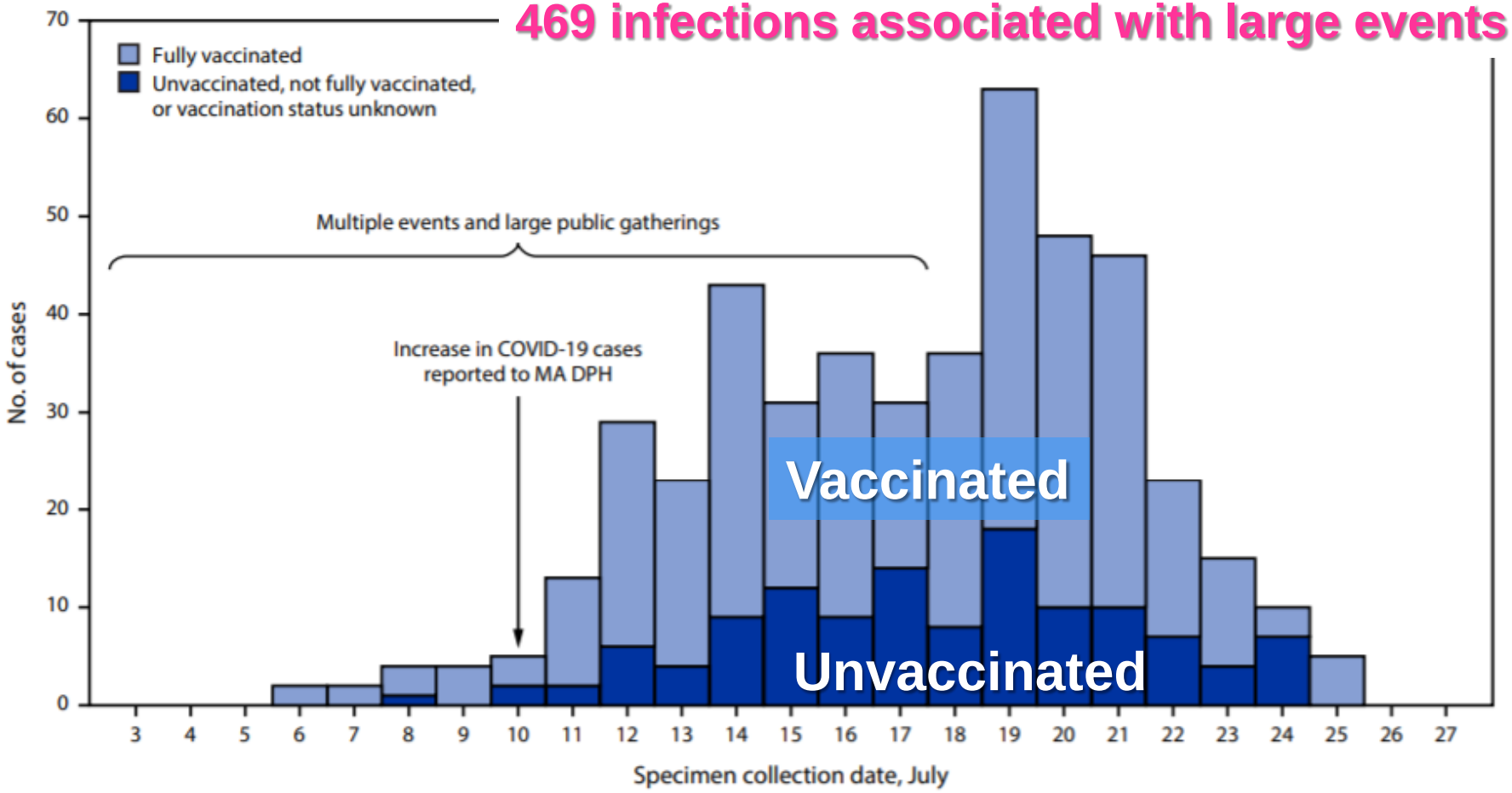
Study summary and methods of assessment: Evaluation of the neutralizing activity of serum antibodies on SARS-CoV-2 variants using 20 samples obtained from 15 participants in the pivotal trial of the Pfizer mRNA vaccine

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

Breakthrough Mass Infection in Massachusetts, USA

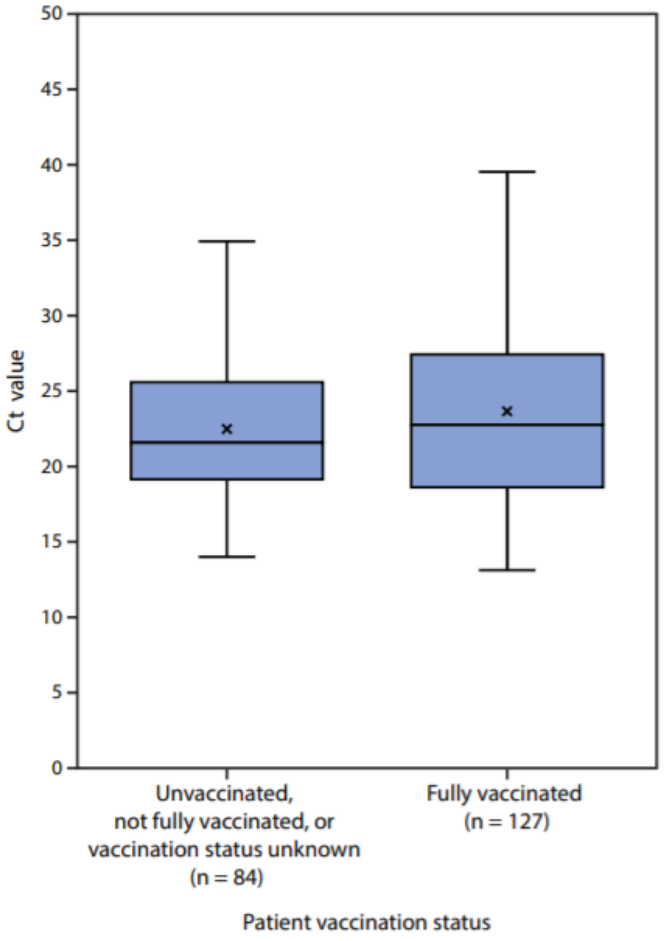
MMWR Vol 70. No 31, August 6, 2021

469 infections associated with large events



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

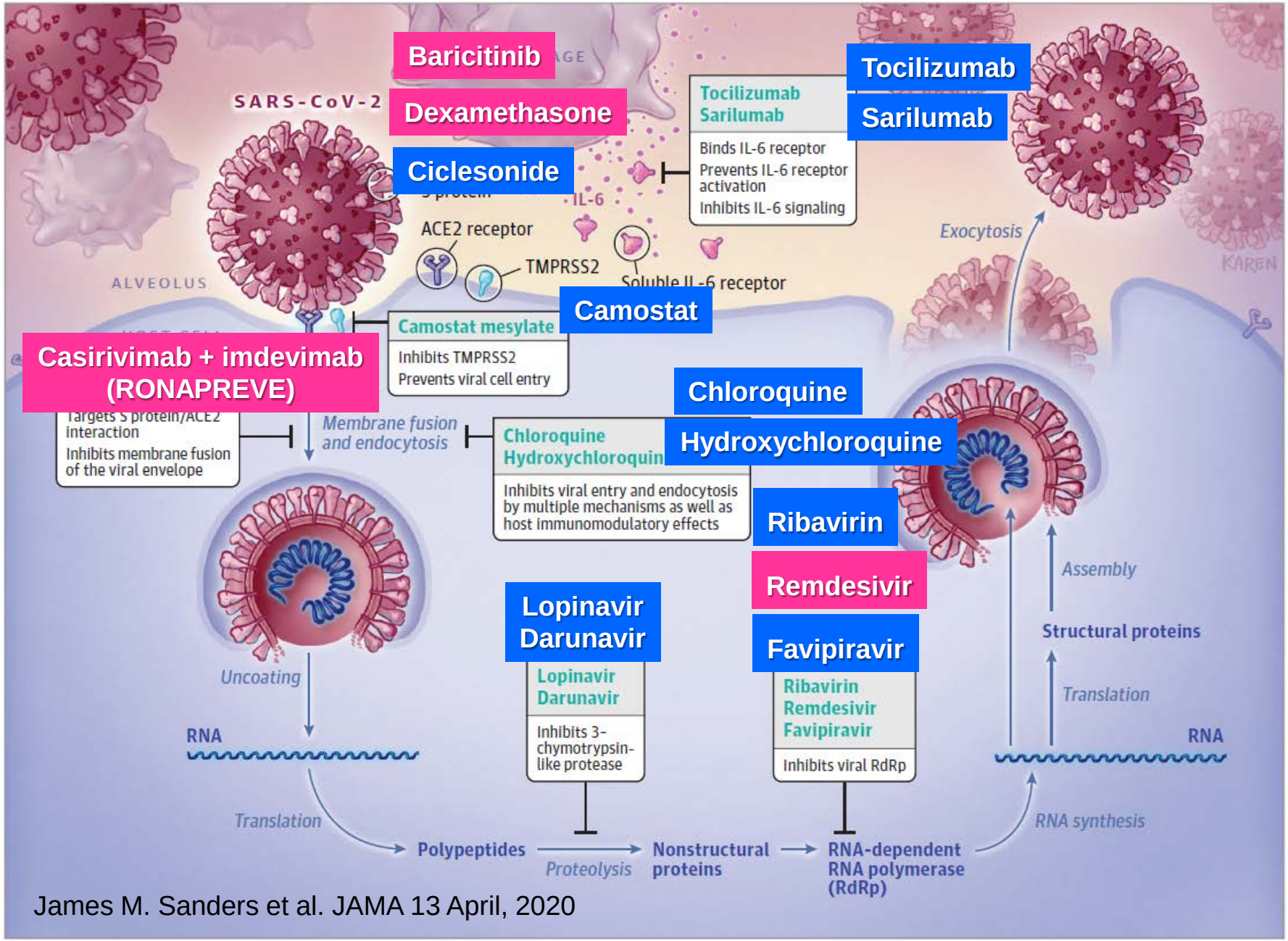
The Delta variant is highly infectious and vaccine resistant

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**

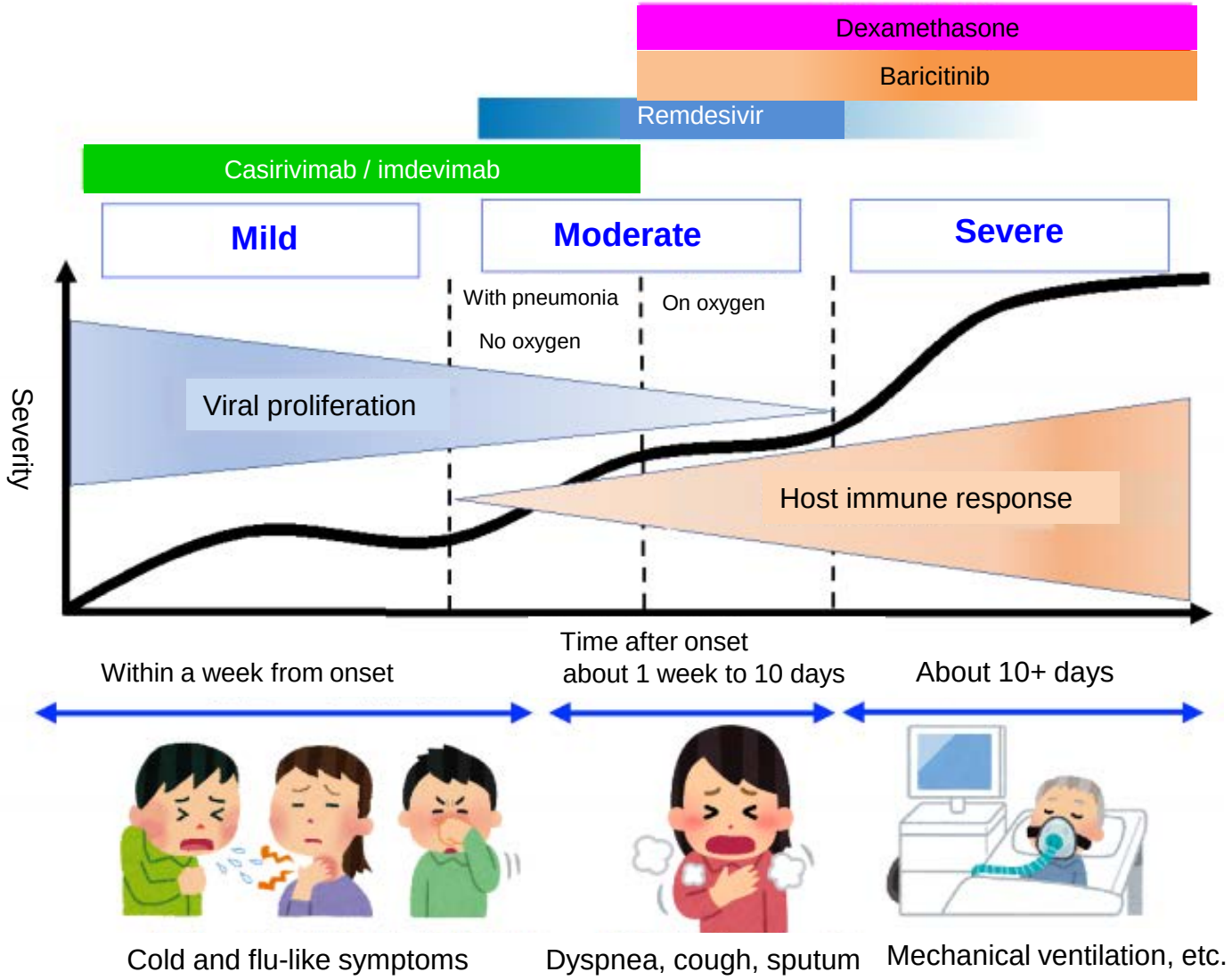
1. National Institute of Infectious Diseases Genomic and epidemiological study of a novel coronavirus, SARS-CoV-2
https://www.niid.go.jp/niid/images/research_info/genome-2020_SARS-CoV-MolecularEpidemiology.pdf（accessed August 16, 2021）
3. Nat Commun. 2021 Feb 8;12(1):848

Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)



James M. Sanders et al. JAMA 13 April, 2020

COVID-19 Severity and Treatment



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

COVID-19 pharmacotherapy

Antivirals — Remdesivir (RNA synthesis inhibitor)

+

Anti-cytokine storm agents — Dexamethasone (immunosuppressant)

+ Baricitinib (JAK inhibitor)

Anticoagulants — Low-molecular-weight heparin, etc.

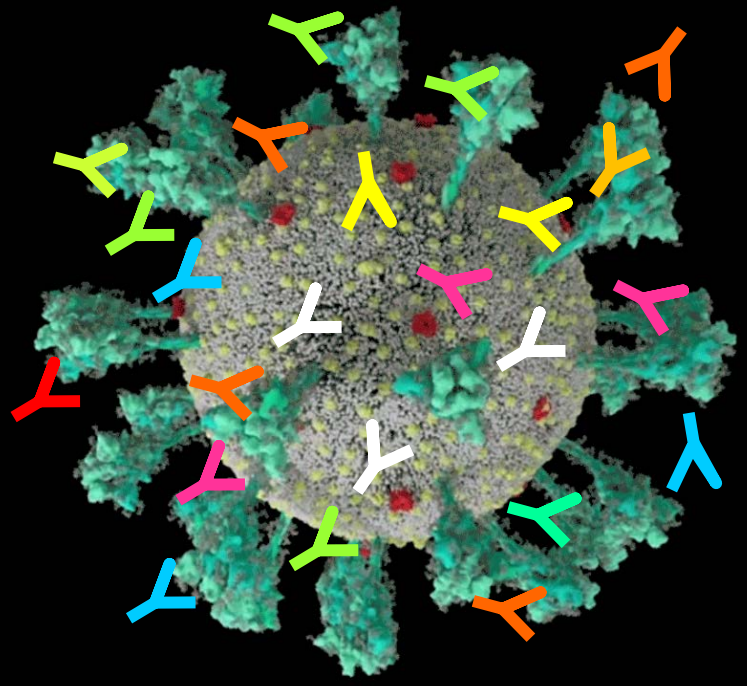
+

Antivirus antibodies — Casirivimab + imdevimab (RONAPREVE)

New Coronavirus Infections: A Guide to the Treatment of COVID-19, Version 5.2 (Revised July 30, 2021)

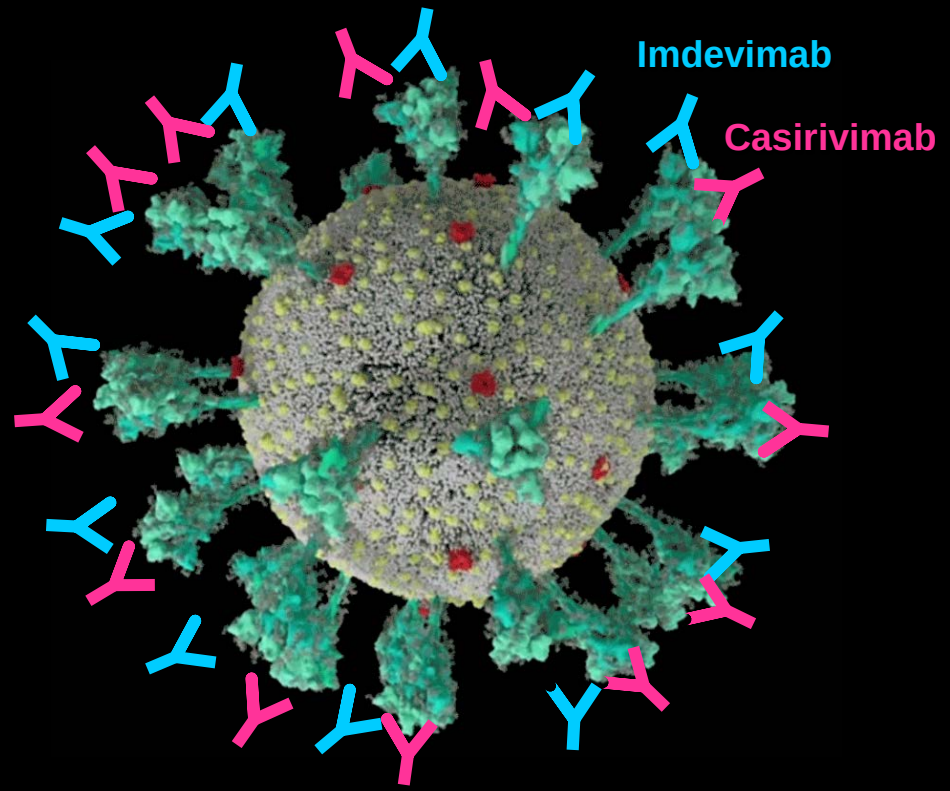
Illustration of Monoclonal Antibodies

Infection-induced antibodies



Large diversity
Immunological memory

Anti-spike protein monoclonal antibodies



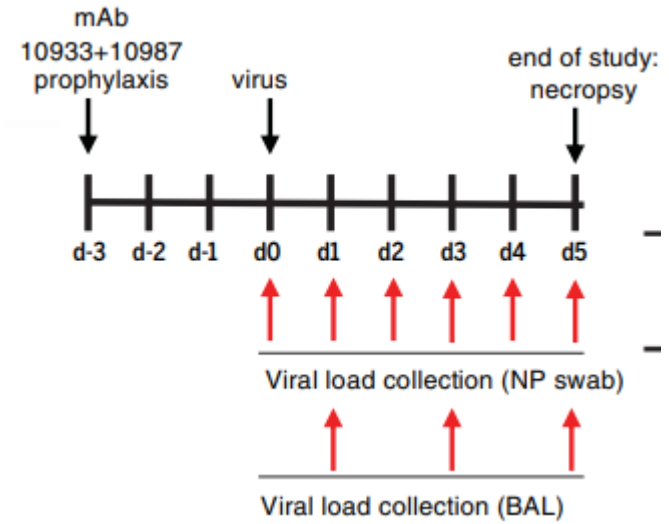
Spike-protein specific
Large dose required, but eliminates

Scudellari et al., Nature 595, 640-4 (2021)

Monoclonal Antibody Cocktail Therapy RONAPREVE

Inhibition of viral replication by antibody cocktail (rhesus macaques)

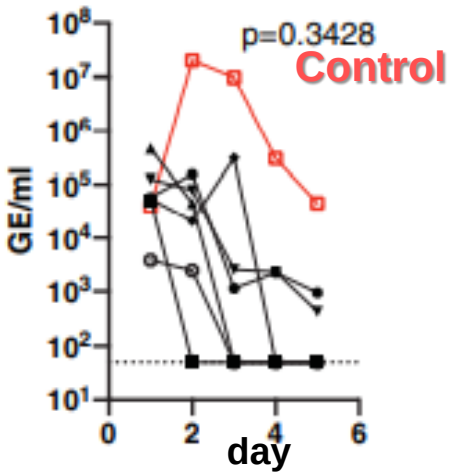
Model of prophylaxis in rhesus macaques



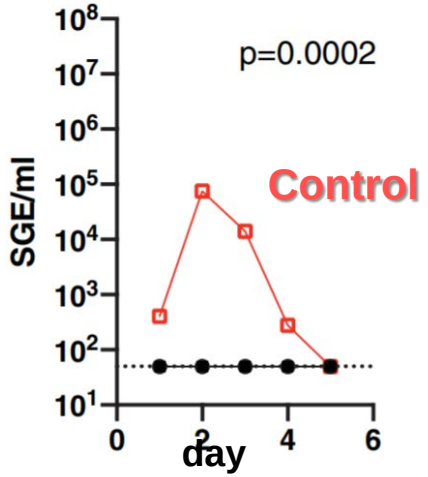
＜Summary of the study and evaluation method>
The amount of virus in bronchoalveolar lavage was evaluated in rhesus macaques (N=6) after prophylactic intravenous administration of the combination of casirivimab and imdevimab. Evaluated by two-tailed t-test (Welch) by alpha level of 10%.

Baum et al., Science 370, 1110–5 (2020)

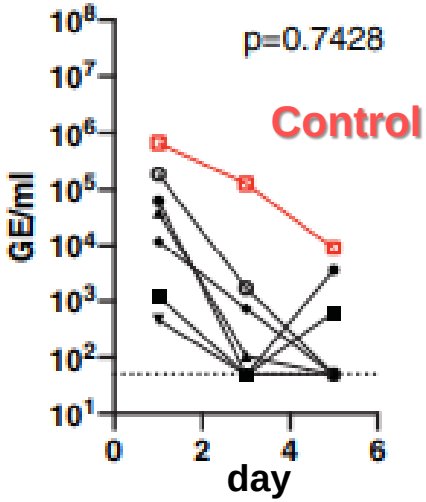
Inoculated virus (NP)



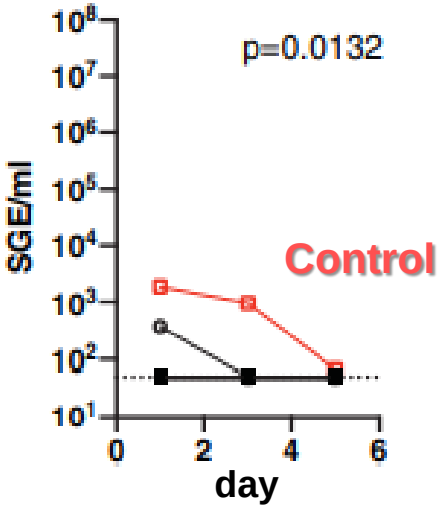
Proliferating virus (NP)



Inoculated virus (BAL)



Proliferating virus (BAL)

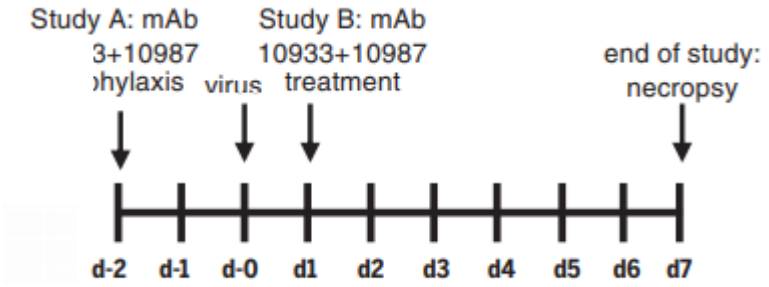


NP: nasopharyngeal
BAL: bronchoalveolar lavage

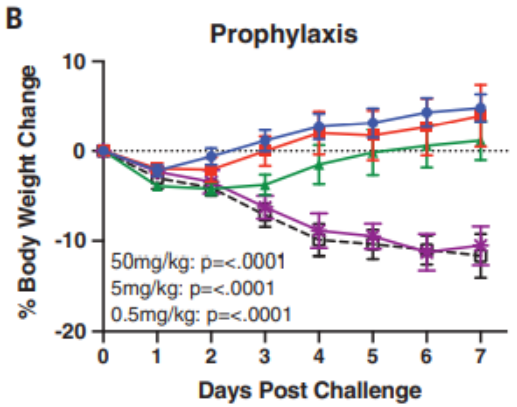
Monoclonal Antibody Cocktail Therapy RONAPREVE

Antibody cocktail suppresses the aggravation of pneumonia (hamster)

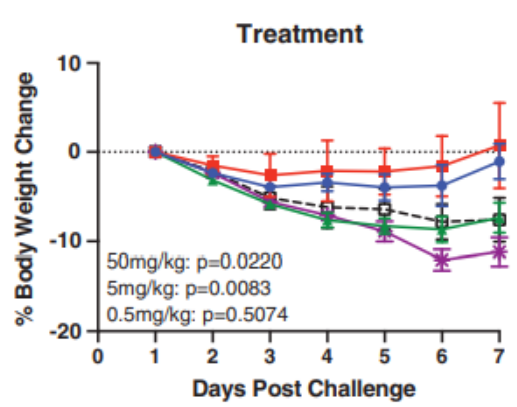
Model of prophylaxis and treatment in hamsters



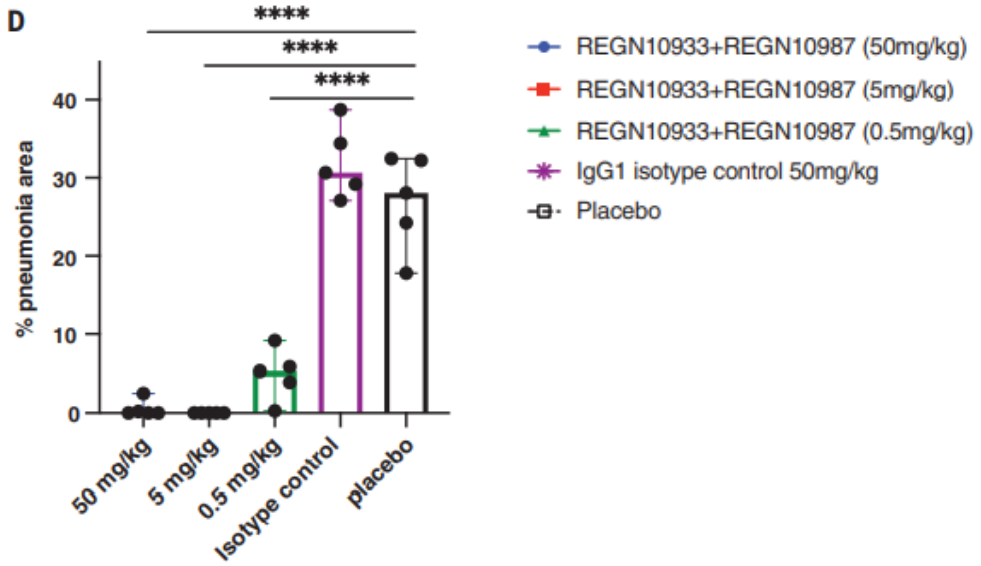
Prophylactic effect (weight loss)



Therapeutic effect (weight loss)



Prophylactic effect (spread of pneumonia)



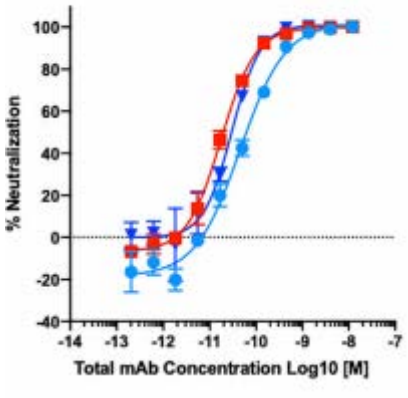
＜Summary of the study and evaluation method＞
Hamsters (N=25) were given placebo or a combination of Casirivimab and Imdevimab intravenously as prophylaxis or treatment, and (B) the effect on weight loss was evaluated, and (D) the percentage of area with pneumonia was evaluated. P value <10% means statistically significant difference.

Baum et al., Science 370, 1110–5 (2020)

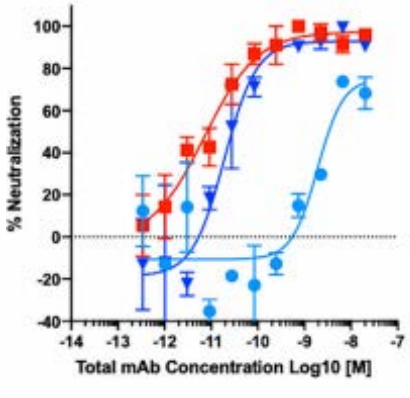
Monoclonal Antibody Cocktail Therapy RONAPREVE

Neutralizing activity of antibody cocktail against variants (*in vitro*)

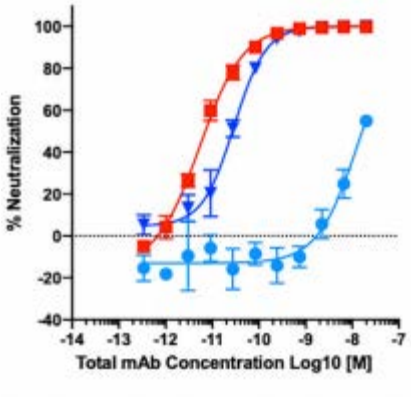
Alpha



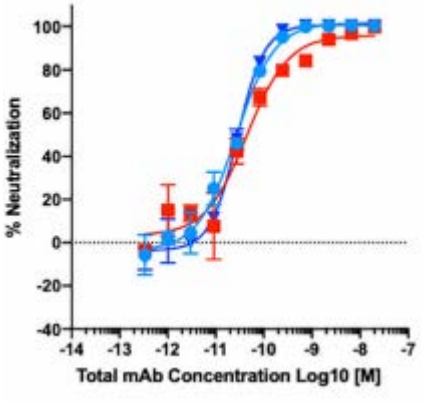
Beta



Gamma



Delta



Neutralizing activity of the cocktail therapy was confirmed against four variants

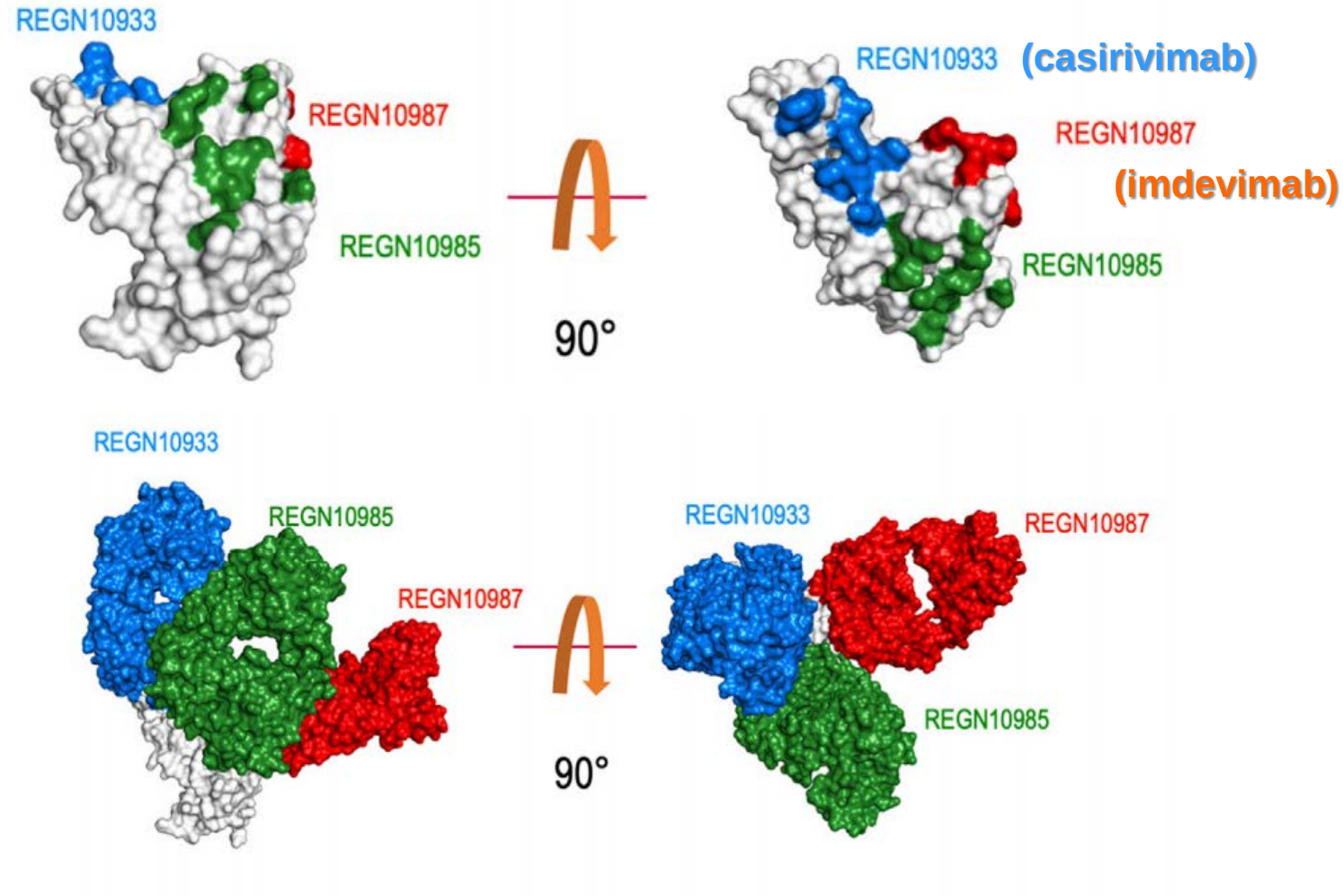
REGN10933 (casirivimab)
REGN10987 (imdevimab)
REGN10933+REGN10987

<Study summary and methods of assessment>
In vitro evaluation of the neutralizing activity of casirivimab and imdevimab, alone and in combination, on SARS-CoV-2 variants

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

Monoclonal Antibody Cocktail Therapy RONAPREVE

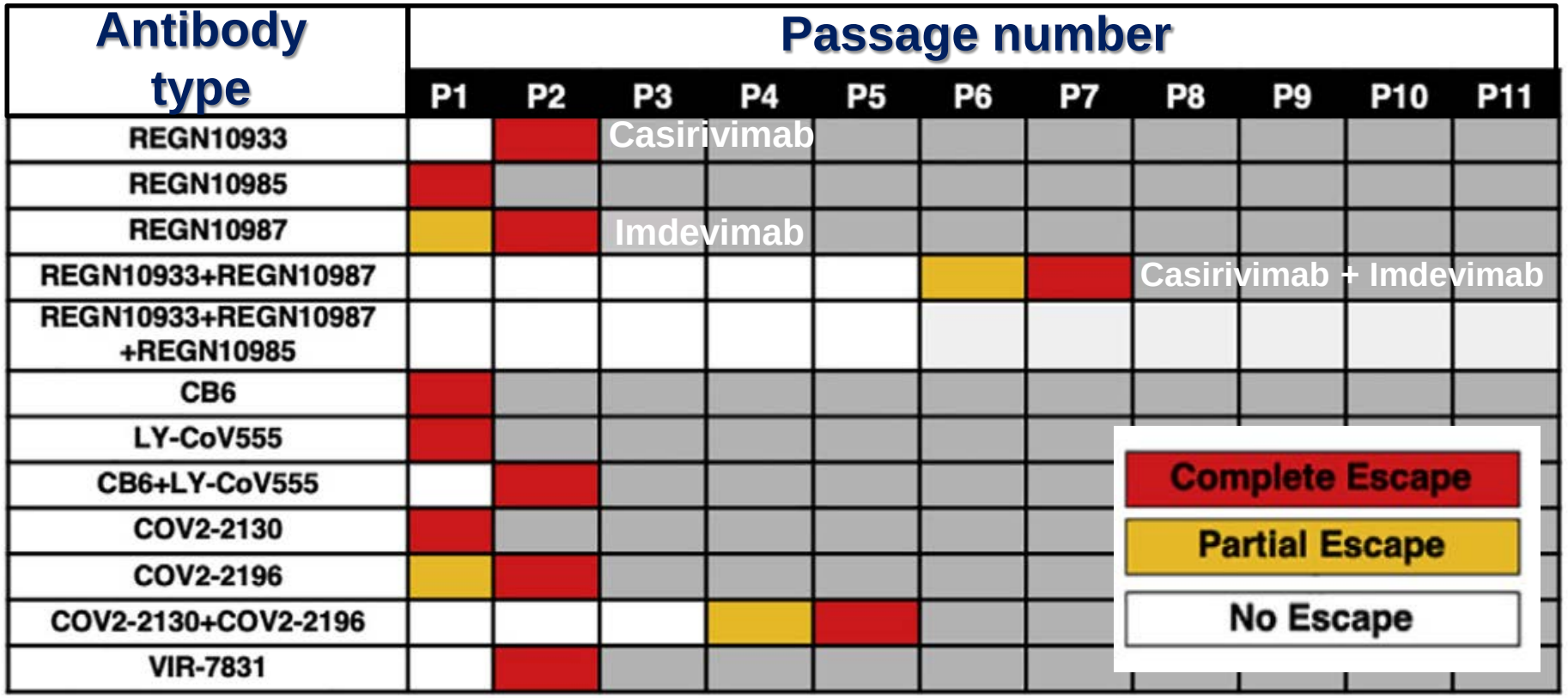
Antibodies binding to viral receptor binding domain



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

Monoclonal Antibody Cocktail Therapy RONAPREVE

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

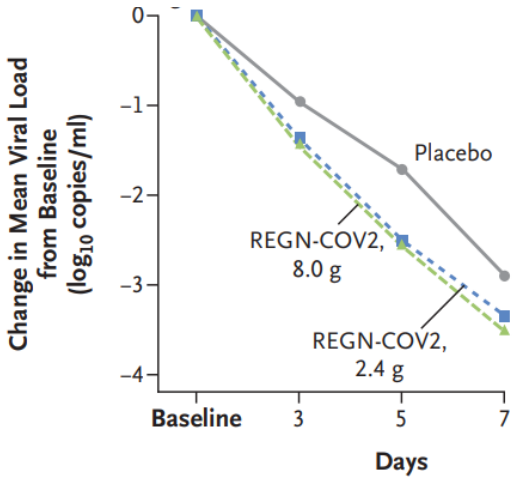


＜Summary of the study and evaluation method>
When a model virus expressing the spike protein of SARS-CoV-2 was infected with a cell line, antibodies were added as a single agent or in combination. It was evaluated whether a resistant virus emerged by subculturing.

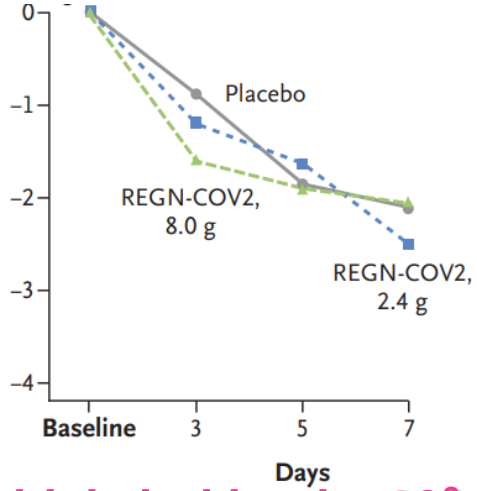
Copin et al., Cell 184, 3949–61 (2021)

Changes in Viral Load Following RONAPREVE Administration (Overseas Data)

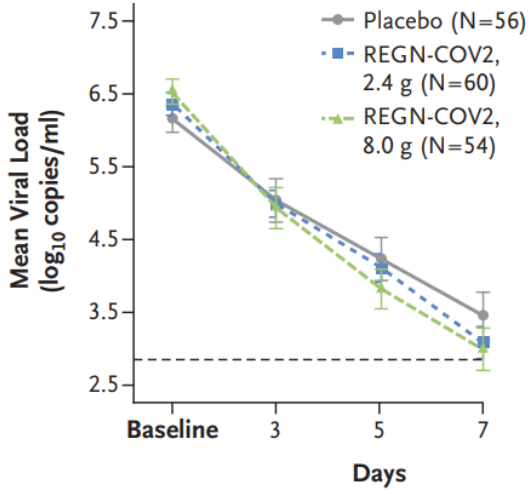
Serum antibody negative group



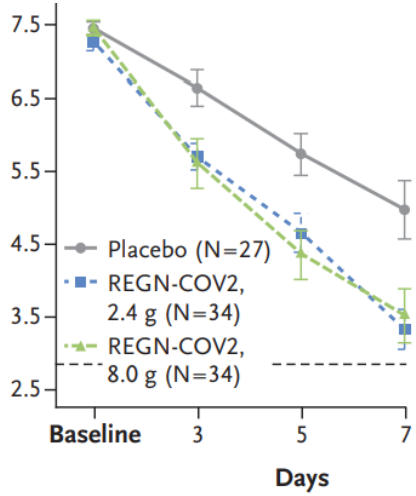
Serum antibody positive group



Initial viral load > 10^4



Initial viral load > 10^6



<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

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.

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)

New COVID-19 Treatments Under Development

A. Plasma therapy/antibody products

1) Bamlanivimab / Etesevimab (**Eli Lilly**)

Monoclonal antibodies developed based on antibodies isolated from the plasma of recovered North American and Chinese COVID-19 patients

2) Sotrovimab (**GlaxoSmithKline**)

Monoclonal antibody developed based on antibodies isolated from recovered SARS patients in 2003

3) AZD7442 (Tixagevimab: AZD8895 / Cilgavimab: AZD1061) (**AstraZeneca**)

Long-acting antibody that combines 2 antibodies derived from recovered COVID-19 patients

B. Small molecule compounds

1) Molnupiravir (MK-4482 / EIDD-2081: **MSD**)

Oral drug that targets RNA polymerase

2) AT-527 (**Chugai Pharmaceutical / Roche / Atea**)

Oral drug that targets RNA polymerase

3) PF-07304814/PF-07321332 (**Pfizer**)

Drug that targets SARS-CoV-2 main protease

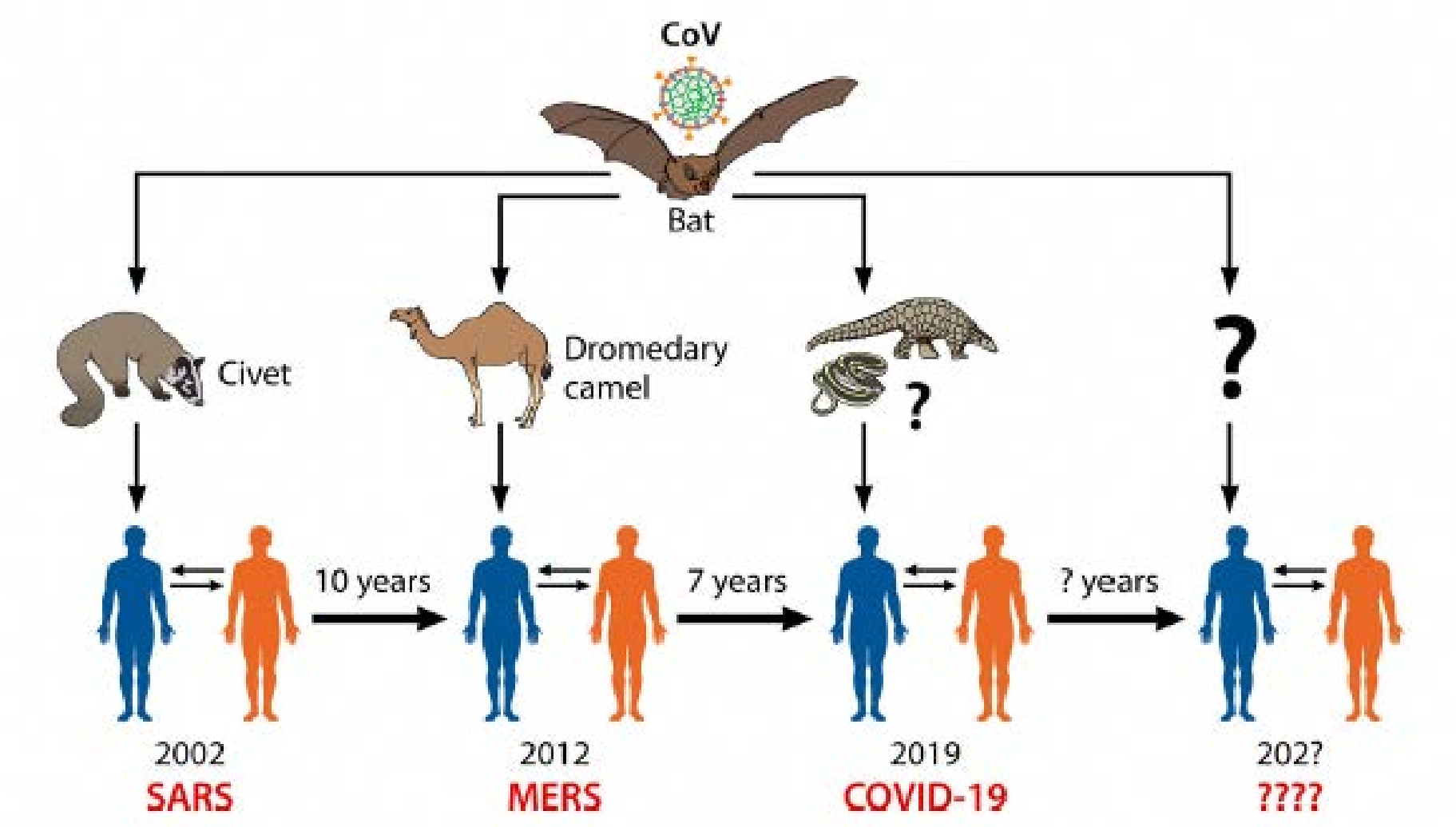
4) S-217622 (**Shionogi**)

Oral drug that targets 3CL main protease

How to Make the Best of the With / Post COVID-19 Age

- How can we control and cope with the fifth wave?
- How can we increase the vaccination rate, 60% to 70%?
- Clusters keep recurring primarily among unvaccinated population.
- The Risk of cluster chains and mega clusters has been declining.
- Revitalizing society and the economy with vaccine passports and negative test certificates.
- The development of specific therapies (oral drugs).
- Making SARS-CoV-2 the “fifth common cold coronavirus.”

Signs of the Emergence of COVID-19



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

“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

Forward-Looking Statements

This presentation may include forward-looking statements pertaining to the business and prospects of Chugai Pharmaceutical Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends.
Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses.

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Notes and Contacts

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INNOVATION BEYOND IMAGINATION