

# Feel the NCGM

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National Center for  
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## NCGM Fights against COVID-19 – Lessons Learned (3rd Edition) –



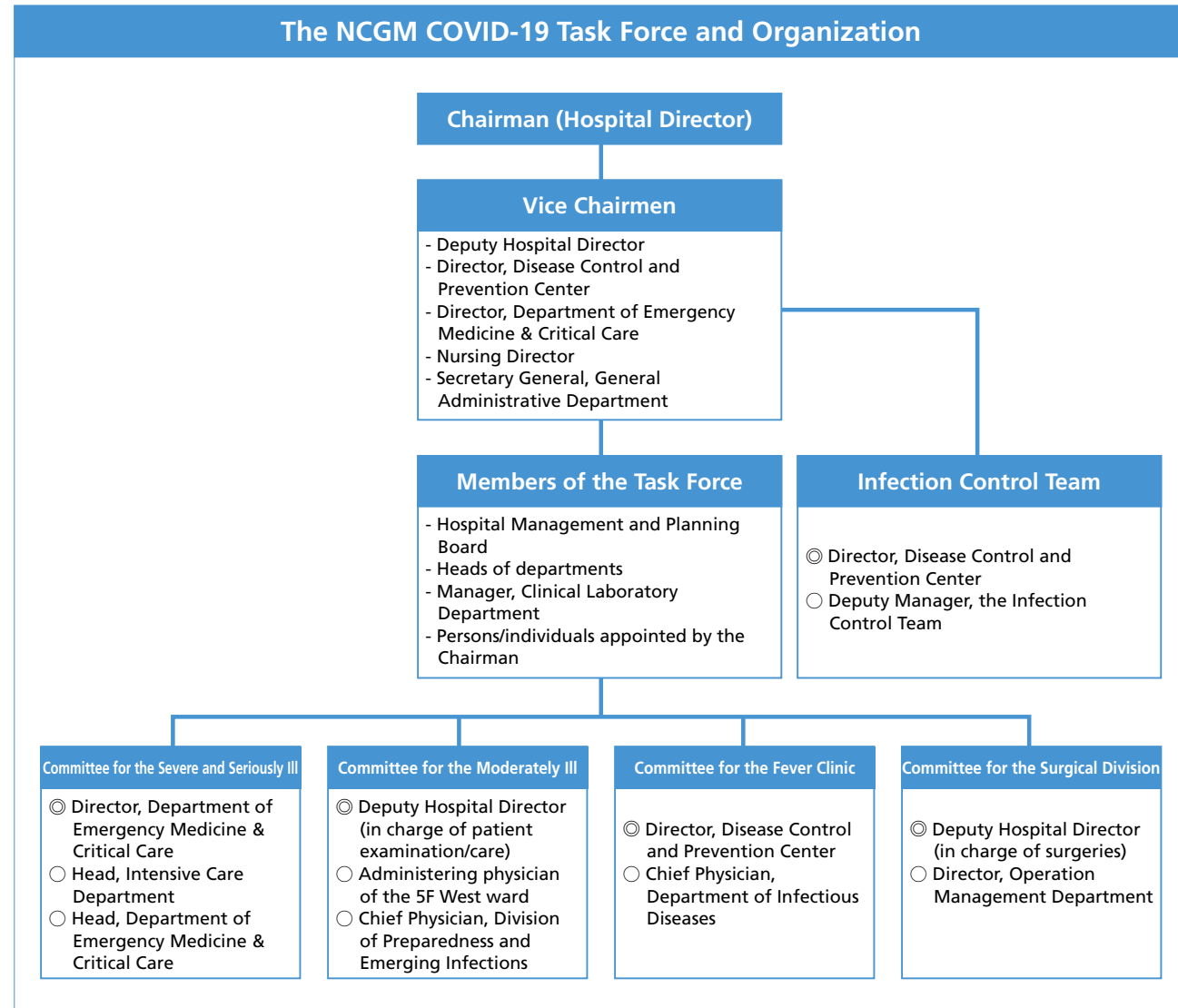
Minister of Health, Labour and Welfare Katsunobu Kato visited the specified infectious disease ward (August 2022).



NCGM staff checking flow lines and infection control measures within the TOKYO2020 PCR test area (August 2021).



In front of the Emergency Department (around 8:30 a.m. in early August 2022)



## Foreword

**Norihiro Kokudo, President**  
National Center for Global Health and Medicine

The National Center for Global Health and Medicine (NCGM) is a national center primarily committed to infection control. Our staff members have strived, as a team, to tackle the novel coronavirus disease 2019 (COVID-19) since the beginning of the pandemic. In late January 2020, we carried out physical examinations and PCR testing of Wuhan returnees. In the succeeding month of February, some staff members boarded the cruise ship anchored in Yokohama to cooperate in addressing the COVID-19 cluster among its passengers. Affected passengers included a few severe cases, and we started providing them intensive care while struggling to find effective ways to control this unknown virus. We also started the compassionate use of an antiviral agent remdesivir, and engaged in joint research with the U.S. National Institutes of Health (NIH) to establish the evidence for the efficacy of remdesivir. Additionally, we promptly published the examination data from 11 initial cases, their treatment methods, and clinical courses on our website and in paper, which were actively utilized by the institutions nationwide that were then treating COVID-19 patients.

Reflecting back on the NCGM's long history of over 150 years, we have responded to numerous pandemics in the past, starting with the Spanish flu in 1919, SARS in 2003, swine flu in 2009, Dengue fever in 2014, and the Ebola hemorrhagic fever outbreaks in 2014, 2018, and 2019. We have always been fully trained and prepared for such crises as one of the four medical institutions in Japan designated for treatment of specific infectious diseases, having a total of four beds available for this treatment (the highest number of beds out of all four institutions). I am really proud of our staff members who have swiftly responded to the current pandemic and have then been battling against COVID-19 with a firm sense of mission.

Subsequently, we have extended our activities in the treatment/research and international medical cooperation in responding to COVID-19 including the development of new therapeutic drugs, convalescent plasma therapy, advanced medical care for critically ill patients, the establishment of COVID-19 Registry Japan (COVIREGI-JP), REpository of Data and Biospecimen of INfectious Disease (RIBIND), fever clinic, and the Shinjuku City COVID-19 Testing Center, support for the mildly ill patients accommodated in hotels, vaccination for government VIPs, operation of the clinic for close contacts at the athlete's village of the Tokyo 2020 Olympic and Paralympic Games, and support for infection control in the Philippines and Papua New Guinea.

Since the beginning of the pandemic, we felt a need for organizational research and development to contain the spread of this unknown disease, and we launched the Novel Coronavirus Infection Academic Advisory Board in early February 2020. This Board covered a wide range of fields related to COVID-19, including its treatment, testing, pathophysiology, and epidemiology, and aided in the development of research protocols, coordinated with the IRB, and managed and advised through the course of trials. More than 135 projects have been undertaken, and 321 papers have already been published in academic journals. This booklet is a record of the NCGM activities mentioned above to address the COVID-19 pandemic. Currently, we are taking a step forward into the post-pandemic world where we balance infection control and social activities. We at NCGM will continue to strive as a team to confront this challenging infectious disease. Through this booklet, I would like to express my respect and gratitude to all of the healthcare providers and the NCGM staff who are fighting against COVID-19.

In the Cabinet meeting of June 2022, the policy decision was made on the integration of NCGM and the National Institute of Infectious Diseases (NIID) after FY2025. While the details of this integration are not yet determined at this moment, NCGM will continue to fulfill our mission as a research and development agency based on national strategies, succeeding our history and tradition of activities from Meiji, Taisho, Showa, Heisei eras to Raiwa era, and responding accurately to the demands of the times.

February 2023

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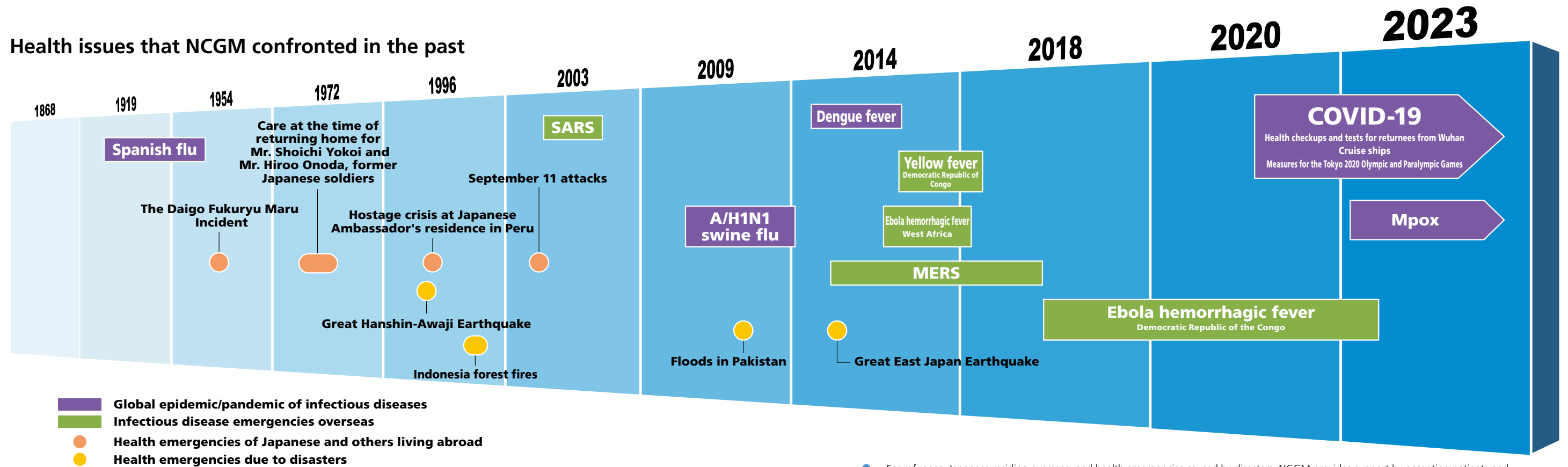
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# 1

## Overview of NCGM History in Response to Various Health Issues and Our Multifaceted Role

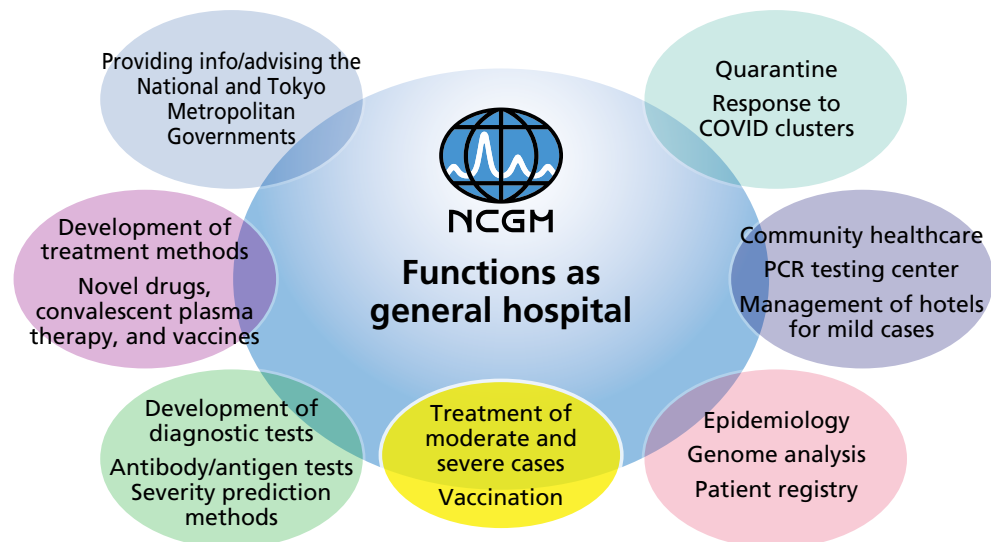
Teiji Takei, Director-General, Bureau of Strategic Planning, NCGM

### Health issues that NCGM confronted in the past



### COVID-19 Responses by NCGM

The one and only medical institution capable of undertaking a multifaceted role in public health and medical treatment



For refugees, Japanese residing overseas, and health emergencies caused by disasters, NCGM provides support by accepting patients and dispatching medical staff. In addition to the illustration above, NCGM has provided assistance to refugees and Japanese residing overseas by dispatching medical staff to a Cambodian refugee camp in 1979, to the International Refugee Assistance Center (Shinagawa) to accept Indochina refugees in 1983, and to a Japanese hostage crisis in Kirghiz in 1999. For health emergencies caused by disasters, NCGM dispatched medical staff in response to the damages caused by the tornado and flood in Bangladesh in 1998, the earthquake in northwestern Turkey in 1999, the great earthquake off the coast of Sumatra and Indian Ocean tsunami in 2005, and the cyclone in Myanmar in 2008.

Ever since the establishment of the Army Temporary Hospital (currently NCGM) in 1868, we have always played a pivotal role in responding to health issues in Japan. We still have the preserved medical records of numerous patients that were treated over 100 years ago at the Tokyo Daiichi Eiju Hospital during the Spanish flu pandemic in 1918-1920.

The accumulation of our experience within this century in confronting emerging/re-emerging infectious diseases such as SARS, A/H1N1 swine flu, MERS, Ebola hemorrhagic fever, and Dengue fever are being put to use in our current COVID-19 response. NCGM will continue to serve as a general hospital

offering advanced medical care to patients with various diseases including infections, and as a medical institution capable of undertaking a multifaceted role in public health and medical treatment by providing advice and information to the government policy-makers, conducting quarantine and responding to COVID-19 clusters. We will be committed to promoting research and development of treatment methods, novel drugs, and vaccines, developing diagnostic tests and severity prediction methods, conducting epidemiological studies, performing genome analysis, creating a patient registry, and taking part in the local healthcare cooperation, international cooperation, research and education.



# 2

## Treatment and Nursing of COVID-19 Patients and Suspected Patients

**Norio Ohmagari**, Director, Disease Control and Prevention Center (DCC), Center Hospital, NCGM  
**Tatsuya Okamoto**, Head, Intensive Care Department, Center Hospital, NCGM  
**Masayuki Hojo**, Head, Department of Respiratory Medicine, Center Hospital, NCGM

**Yuki Hirota**, Manager, 13th Floor Ward, Center Hospital, NCGM  
**Shiho Kubota**, Deputy Manager, Infection Control Team, Center Hospital, NCGM  
**Kumi Horii**, Deputy Manager, Infection Control Team, Center Hospital, NCGM

### From the initial response to the present approach to the “unknown infectious disease”

At NCGM, the first COVID-19 patient was from among the patients consulting with the Department of Infectious Disease in late January 2020. Since then, we have treated numerous patients. We also performed COVID-19 screening tests with PCR and provided medical care to the patients who tested positive and arrived in Japan on the flights from Wuhan, China chartered by the Japanese government on January 29, 2020.

We initially possessed limited knowledge about the clinical features and natural course of this disease, and its treatment. Thus, we treated the patients having respiratory failure with lopinavir/ritonavir, of which *in vitro* activity against SARS-CoV-2 had been confirmed by applying our experience and expertise. In February, many critically ill patients were identified among the patients aboard the cruise ship, Diamond Princess, anchored at Yokohama

Port. In order to treat these patients, we ordered the antiviral drug remdesivir from Gilead Science, Inc. in the U.S.A. and started its compassionate use on the patients. In the same month, we started preparing for global clinical trials of remdesivir in collaboration with the U.S. National Institutes of Health (NIH), and the investigator-initiated clinical trials were launched on March 25, 2020. Meanwhile, we also continued to treat the patients with lopinavir/ritonavir, of which *in vitro* activity against SARS-CoV-2 had been confirmed by previous findings.

Four different clinical trials were conducted over about one year, and the results demonstrated that the efficacy of remdesivir was significantly higher compared to that of placebo, and that the efficacy of remdesivir in combination with baricitinib was significantly higher compared to that of remdesivir alone. Based

mainly on these data, remdesivir and baricitinib were approved in Japan for treating COVID-19 and have become clinically available.

We also participated in a global clinical trial of hyperimmune intravenous immunoglobulin (IVIg), and conducted a multicenter randomized comparative trial to evaluate the efficacy of ciclesonide. While the expected efficacy was not demonstrated in either of the investigated drugs, it is important to conduct clinical trials expeditiously to find effective drugs to cope with emergency situations. In this sense, we think we have played a prominent role in Japan.

Aside from the patients who disembarked from the Diamond Princess, from February to March 2020, many patients having a travel history to Wuhan visited our outpatient department and were diagnosed with COVID-19. We began to observe a pronounced rise in the number of COVID-19 patients who had not apparently traveled to Wuhan in March. Simultaneously, critical cases, mainly involving elderly patients, began to be identified. Correspondingly, the number of COVID-19 inpatients increased. In spite of the nationwide state of emergency declared by the Japanese government on April 7, 2020, as many as 48 patients, including eight patients on ventilators, were admitted to our Hospital at the same time in the following week.

After late April, the number of newly admitted patients gradually decreased, and consequently the total number of inpatients gradually decreased. However, the number of patients began to increase again after ending the state of emergency, leading to the so-called “second wave” of the pandemic. In this outbreak, as opposed to the outbreak from March to May, fewer patients were in critically ill condition - probably because there were fewer elderly patients - and most of the affected people were young adults in their 20s to 30s who acquired the infection mainly in downtown areas. Therefore, the Japanese government did not declare a state of emergency during the second wave.

The Japanese government then strived to enhance the economic activity while trying to prevent COVID-19 transmission. However, this was not an easy task. The number of new COVID-19-positive cases remained high in autumn, and began to increase in Tokyo with the decrease in temperature in December 2020. With rapid increase in the number of new cases, the “third wave” set in at the end of December. Under these circumstances, we also began to accept many moderately to severely affected patients. The Japanese government declared its second state of emergency in January 2021. During the third wave of the pandemic in Tokyo involving more elderly patients and most moderate to severe cases, many medical institutions struggled to accept these patients. Even

after February, clusters of COVID-19 cases were identified one after another in elderly facilities and medical institutions, slowing the decrease in the number of new positive cases and severe cases. The situation finally settled in March, when long-awaited vaccination started for the NCGM staff members. With the cooperation of many staff members from various departments, vaccination was conducted smoothly and swiftly. The former Prime Minister Suga also came to NCGM to be vaccinated.

In the summer of 2021, the fourth wave of the pandemic reached Japan, and the Japanese government declared its third state of emergency. We at the Center Hospital of NCGM renovated the High Care Unit (HCU) to accept COVID-19 patients in severe condition. In this outbreak, the number of critically ill patients reached a record high, many of which were people in their 40s to 60s.

From November to December 2021, the Omicron variant began to be detected in Japan, mainly in people arriving from abroad. NCGM conducted an investigational study in cooperation with the National Institute of Infectious Diseases (NIID) and reported the clinical features of the patients affected by the Omicron variant and the dynamics of the virus. This study helped the Japanese government take measures.

From January to February 2022, the sixth wave of the pandemic reached Japan. This was an even larger wave especially affecting elderly people, who often suffered from debilitating conditions leading to hospitalization. Consequently, many people died throughout Japan. Meanwhile, the number of patients with severe respiratory failure decreased. This was probably owing to the increased vaccination rate.

In July 2022, the seventh wave of the pandemic occurred in Japan. As in the sixth outbreak, this wave also witnessed many elderly people being affected, suffering from debilitating conditions, and hospitalized. Additionally, children and young people with lower risks also suffered from poor eating and laryngeal stenosis due to severe sore throat; and increasing number of patients admitted for other emergency conditions such as trauma and cerebrovascular disease were confirmed as SARS-CoV-2 positive at the admission screening. This changed the composition of inpatients. Furthermore, there was such a situation that as many as 140 staff members in our Hospital took leave from work at the same time. Possibly because the infection with the Omicron variant tended to cause mild symptoms that were often hardly noticeable, the staff and inpatients were affected one after another and thus we had a hard time dealing with them. Like this, the nosocomial cluster and absence of the staff greatly affected the hospital operation.

(Norio Ohmagari)

**症例**  
 当院における新型コロナウイルス(2019-nCoV)感染症患者3例の報告

国立国際医療研究センター

中村 啓二	忽那 賢志	鈴木 哲也	井手 聡	太田 雅之	守山 祐樹
中本 貴人	野本 英俊	秋山裕太郎	宮里 悠佑	藤本 俊司	奥濱 絢子
神田 宏平	氏家 無限	木下 典子	山元 佳	石金 正裕	森岡慎一郎
斎藤 理	早川佳代子	大曲 貴夫			

Key word: 2019-nCoV 感染症

**序 文**

新型コロナウイルス(2019-nCoV)感染症は中国武漢市で2019年12月以降報告されている。2020年2月3日現在、世界では17,267人の患者が報告されている。内訳として武漢市で5,142人(死亡者265人: 致死率5.15%)、武漢市以外の湖北省で6,035人(死亡者85人: 致死率1.4%)、湖北省以外の中国全土で6,090人(12人: 0.19%)、中国以外の国183人(死亡者1人: 致死率0.5%)となっており、中国での症例が大半を占めており、本邦での臨床像の詳細な報告はまだない。臨床像の把握は今後の2019-nCoV感染症の診療および感染防止対策に寄与すると考えられるため当院で経験した3症例をここに報告する。

http://www.kansensho.or.jp/uploads/files/topics/2019ncov/2019ncov\_casereport\_200205.pdf

急性肺炎として加療開始した。その後も38℃台の発熱、咳嗽、喀痰が続き、1月30日に受診。胸部レントゲン検査を施行したところ左下肺野に新たな浸潤影の出現がみられた。胸部単純CTでは両側下葉にスリガラス影と浸潤影の出現があり、2019-nCoV肺炎の可能性が強く疑われ同日入院となった。初診時現症: 意識清明、血圧148/90mmHg、脈106回/分、体温37.8℃、呼吸数16回/分、SpO<sub>2</sub> 97%(室内気)。初診時のReview of systemにて主要な陽性所見(以下ROS(+)): 頭重感・倦怠感・咽頭痛。初診時のReview of systemにて主要な陰性所見(以下ROS(-)): 悪寒・頭痛・咳嗽・喀痰・筋肉痛、咽頭発赤なし、扁桃腫大なし、呼吸音正常で左右差なし、肋骨脊柱角に叩打痛なし。

Clinical cases were quickly reported to provide the information on the “unknown infectious disease” to healthcare providers nationwide



The HCU designated for COVID-19 patients in severe condition, which was operated as the second ICU

## Treatment of critically ill COVID-19 patients in the ICU/HCU

To meet the social demands as a medical institution designated for treatment of specific infectious diseases, the policy to centralize the treatment of critically ill patients at the High Care Unit (HCU) was determined. The HCU was then renovated to depressurize south half of the floor all together, including open beds, to enable the healthcare providers to treat many patients after wearing PPE once. On February 15, 2021 in the late third wave of the pandemic, we opened our HCU with seven beds for patients in severe condition, and treated four intubated patients including long-term ECMO cases until the closure of the unit at the end of March, 2021.

In the fourth wave of the pandemic from April to July 2021, there were no severe cases admitted to the ICU or HCU, whereas in the fifth wave (with the Delta variant) the HCU opened for the second time on August 5, 2021. At that time, the staff of the ICU treated the patients at the HCU in a closed system. With two dedicated ICU specialists, the HCU was operated as the second designated ICU with almost all beds occupied from September, treating 15 intubated patients including two ECMO cases until the closure in October, 2021.

Figure 2 shows the changes in the number of intubated patients by unit from the cruise ship cluster in February 2020 to the fifth

pandemic wave in August 2021. We accepted 57 intubated patients in approximately one and a half year until the end of October 2021, of which the mortality was 39%; ECMO was used for nine patients, of which mortality was 56% (Figure 1). The mortality increased over time, reaching high at 60% in the fifth wave of the pandemic. The proportion of patients with severe obesity also increased, amounting to 73% of the COVID-19 patients in the fifth wave. Looking into the affected people by age, the proportion of elderly people aged 60 and older was higher from the first wave to the third wave of the pandemic, whereas half of the affected people were in their 50s in the fifth wave of the pandemic. (Figure 2)

After the sixth wave of the pandemic (with the Omicron variant) in January 2022, patients with acute respiratory distress syndrome (ARDS) associated with COVID-19 were no longer seen, and post-operative patients tested positive with PCR and patients with medical diseases requiring intensive care are being accepted at the depressurized room of the ICU. As I myself have never experienced a situation where 60% of patients die, I keenly felt the threat of the Delta variant.

(Tatsuya Okamoto)

Figure 1  
Change in the number of intubated patients with COVID-19 (up to Oct. 2021)

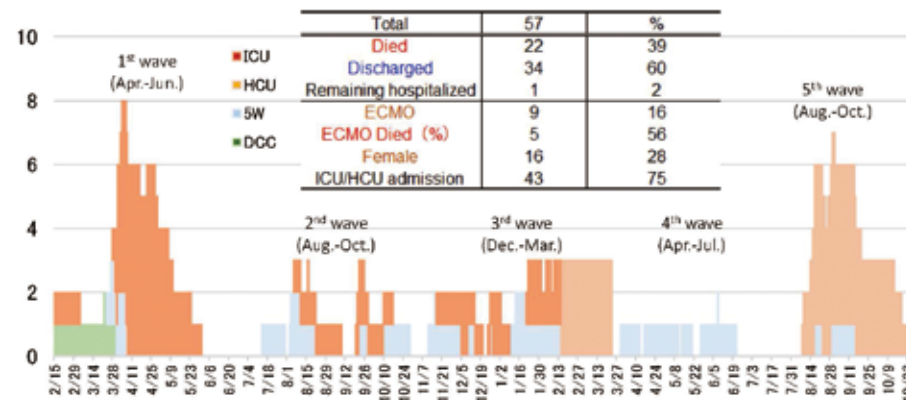
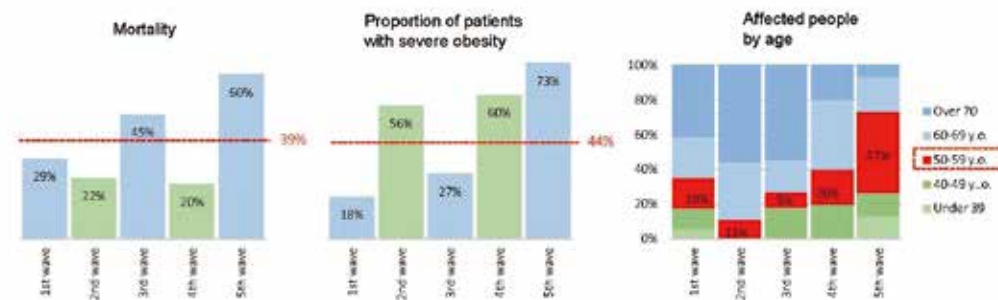


Figure 2  
Clinical features of the intubated patients with COVID-19



## Capacity enhancement for the sixth wave of the pandemic

### Displacement of the Delta variant (fifth wave) by the Omicron variant (sixth wave)

When the Delta variant became dominant and the number of affected patients reached its peak in August 2021, NCGM took the initiative to save lives of people in their prime, who have become critically ill before receiving vaccination, striving to alleviate the stress on the collapsing emergency medical care system. At that time, our Emergency Department (ED) accepted long-waiting ambulance patients exceeding our maximum capacity at night or on holidays, started initial treatment immediately, and transported them to nearby medical institutions accepting COVID-19 patients during the daytime for consecutive days.

In the sixth wave of the pandemic in which the Omicron variant emerged, we also treated many patients in moderate to severe conditions. Their clinical features greatly differed from previous cases; many of those who died were very elderly people hospitalized after developing dehydration due to high fever, disturbance of consciousness, and aspiration pneumonia, and those who survived required long-term rehabilitation for disuse syndrome even after their recovery from the acute phase. As an exit strategy to continuously accept new patients, NCGM strengthened cooperation with nearby hospitals, which actively

accepted the patients surviving the acute phase. Additionally, we continued dispatching our physicians to the municipal hospitals in Tokyo accepting large number of elderly patients with increased risk for severe COVID-19, providing medical cooperation to meet the needs of those hospitals.

### Response to the seventh wave of the pandemic (July to September 2022)

We experienced the seventh wave of the pandemic with the Omicron variant under the government policy of "placing no additional restrictions on socioeconomic activities." As in many other medical institutions, a considerable number of healthcare providers in NCGM were affected during the spread of the infection, and outbreaks occurred in general wards. Like in the sixth wave of the pandemic, there were less people with severe symptoms and few "severe cases" requiring respiratory care with the ventilator or ECMO, while many elderly people intolerant of invasive intensive care died, which was similar to the excess mortality in influenza epidemics. All staff of NCGM have been continuously making efforts to avoid infection, or to not transmit the virus to colleagues and patients even if infected, and are now overcoming several weeks of tense situation.

(Masayuki Hojo)

## Accepting COVID-19 patients in general wards

The sixth wave of the COVID-19 pandemic started from December 17, 2021. The cases surged fiercely and our Hospital had to accept many patients.

About a month later, on January 28, 2022, it became difficult to accept the COVID-19 patients only in the specified ward, and our ward (general single room ward) also started to accept the patients. Of 41 beds in our ward, 21 were reserved for COVID-19 patients and 20 for non-COVID-19 patients; we thus paid the utmost attention to prevent the infection from spreading among the non-COVID-19 patients.

As we have accepted the COVID-19 patients in our ward four times from the second wave to the fifth wave of the pandemic, we could prepare necessary supplies smoothly; however, the staff accepting those patients were not easily prepared. Now the ward staff mutually reconfirm proper PPE donning/doffing each time before accepting the patients. And we perform N95 mask fitting tests to ensure a close facial fit. Furthermore, after accepting the COVID-19 patients, we check ourselves in the mirror placed at the

PPE donning area before entering a patient's room.

There are photos at the doffing area showing how to remove PPE properly. As the steps to remove PPE must be strictly observed, we make sure to reconfirm them every time, not considering them easy because "we have done it several times." Additionally, we perform zoning of contaminated and clean areas, and mutually reconfirm if all the staff understand the zoning properly and can care patients without bringing contaminated items in the clean area. We also train nurses in their first year so that both patients and nurses can stay safe and secure. We separate the rooms for non-COVID-19 and COVID-19 patients



Staff checking proper PPE donning



using partitions placed in the hallway. While the COVID-19 patients are isolated in their rooms, the non-COVID-19 patients may go out of their rooms for examinations and rehabilitations. We therefore provide sufficient explanation and ask for cooperation to the non-COVID-19 patients to not go across the partitions. We also precisely determine the patient transportation path so that infectious and non-infectious patients never come into contact.

So far, no infection clusters have occurred in our ward, and we are confident that we are caring for the COVID-19 patients with a high level of awareness.

In the seventh wave of the pandemic, we have been accepting the COVID-19 patients since July 25, 2022. Even in this highly infectious wave, we are maintaining secure care as before. We will continue to care for infectious patients confidently in cooperation with colleagues.

(Yuki Hirota)

Well equipped with disinfecting wipes and gloves to prevent infection



## To prevent nosocomial infection

### Bed management

Until after the fifth wave of the pandemic, many patients often became severely ill and required treatment with the ventilator or extracorporeal membrane oxygenator (ECMO), and thus we repurposed part of our HCU into a COVID-19 care unit to treat critically ill patients. Before opening the unit, we reconfirmed PPE donning/doffing of the staff and performed zoning in cooperation with the deputy manager nurse of the HCU.

Before the Delta variant surge in the fifth wave, inpatients in general wards have never developed the infection; however, after the appearance of the Omicron variant in the sixth wave, increasing number of inpatients and healthcare providers in the general wards tested COVID-19 positive. After the subvariant BA.5 became dominant, the number of affected people further increased.

When any of the hospital staff or inpatients tested positive, the ward manager prepared a list of people closely contacting the infectious person from two days before onset, based on which the Infection Control Team (ICT) identified those applicable to close contacts and provided instructions for PCR test and follow-up. The close contact person in hospital is defined as a patient staying in the same room with an infected patient; a person who has had conversation with an infected person for more than 15 minutes without both or either one wearing a mask; and a person who have long contacted an infected person for more than 30 minutes even if both wearing a mask.

The nurses providing patient care are frequently in contact with the patients; therefore, if they are infected, they precisely confirm the details and time of care to determine patients closely contacting them very carefully. If the infected nurse has been on night duty during the potentially infectious period, care should

be taken for the nap room used. As the nap room users may stay without wearing a mask and given that it is a completely close room without sufficient ventilation, we check the order of use by the infected person and the time between uses by next users to determine if there are close contacts.

When an inpatient has become a close contact person, we provided care to the patient under single room or cohort isolation, or coordinated bed control with the manager nurse to request the transfer of the patient to a single room of other ward depending on the situation.

As of September 2022, the Japanese government determines the lifting of restrictions on movement for close contacts after the sixth day; however, as we have experienced that many cases tested positive on the sixth day, we maintain the previous definition of 7-day isolation and lift the isolation immediately after confirming a negative PCR result on the seventh day.

### Responses to COVID-19 outbreak

When multiple infection cases were found in the same ward, we checked the status with the ward staff and examined the cause of the spread of infection and the countermeasure. Consequently, it was found as a cause that patients had been watching TV in the ward lobby or taking meals while sitting closely to each other. We then took a countermeasure of placing the chairs and wheelchairs one meter (or two meters if possible) apart in the same direction so that patients keep a distance from others without facing each other while watching TV in the lobby, and made it standardized and known to all staff (Figure 1. Measure to prevent infection when using the lobby).

Until the emergence of the Omicron wave, universal mask wearing has been advocated; however, masking in a private space such as a single room and inside a curtain in a large room has been determined at the discretion of each patient and not strongly requested. However, after the increase in infected healthcare providers with the emergence of the Omicron variant in the sixth wave, we made sure that the patients should wear a mask when healthcare providers enter their room to prevent them from becoming close contacts, and that healthcare providers should put a mask on the patients who cannot it wear by themselves before starting care. Additionally, we made it mandatory for healthcare providers to wear an N95 mask and the face shield during the meal assistance and oral care of the patients removing a mask. These efforts led to the decrease in patients and healthcare providers identified as close contacts.

### Measures for the staff

In the sixth wave of the pandemic with the Omicron variant, the number of infected staff increased, and the staff unable to work also surged because their family member has been infected or has become a close contact, which made it difficult to secure certain number of staff. Similarly in Japan, there was a concern about securing healthcare staff. Then the secretariat of the COVID-19 Measure Promotion Division of the Ministry of Health, Labour and Welfare (MHLW) announced the notification titled "Measures to confirmed rapid spread of COVID-19" (dated January 5, 2022 [partly revised on January 14, 2022]). Given this notification, the self-quarantine period for those who closely contacted the patients infected with the Omicron variant was shortened from 14 days to 10 days, and the period was lifted on the seventh day if tested PCR negative on the sixth day. Along with this change, we provided outpatient PCR tests at the Department of Infectious Diseases if the staff in our Hospital has become sick or close contacts. However,



Figure 1 Measure to prevent infection when using the lobby

- Move couches to secure a large space in the lobby.
- Keep patients apart as much as possible, accommodating at most 6-7 patients.
- Restrict the traffic of people in the area as shown in the photo when there are many patients.

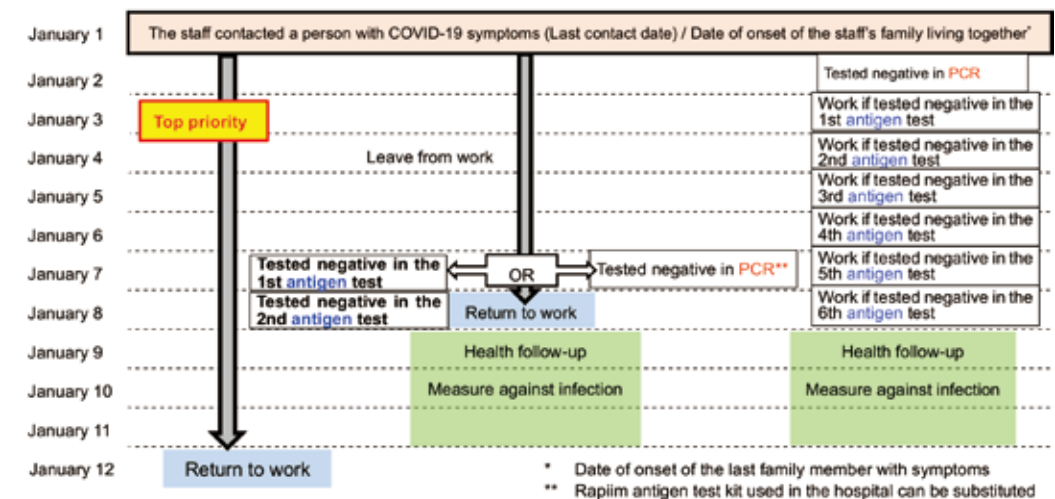
this did not solve the problem of the staff shortage because it took several days for the staff's family members who became sick and visited a local doctor to obtain PCR results and increasing number of the family members could not receive PCR tests immediately after being identified as close contacts due to the lack of symptoms.

Then, in order to secure the staff, we coordinated with the physician of the Department of Infectious Diseases, the manager nurse, and the Pediatric Department to ensure consultation of the sick family members of the staff, and also established a system in cooperation with the executive members and the Administrative Department of the Hospital to provide PCR tests to the family members of the staff identified as close contacts. This resulted in smooth testing and shortened the self-quarantine period for the staff.

After the sixth wave of the pandemic, the self-quarantine period for essential workers identified as close contacts had been shortened or changed several times, and each time the ICT examined how to deal with close contacts in the Hospital based on the infection status within the Hospital and reference publications. We also revised manuals in a timely manner, developing an easy-to-understand flow to deal with the staff who became sick or those identified as close contacts (Figure 2. Flow to deal with the staff identified as close contacts), and made them known to the entire staff.

(Shiho Kubota, Kumi Horii)

Figure 2 Flow to deal with the staff identified as close contacts



# 3

## How We Fought against COVID-19 Pandemic at Our Emergency Department

**Akio Kimura**, Director, Department of Emergency Medicine and Critical Care, Center Hospital, NCGM  
**Ryo Sasaki**, Head, Department of Emergency Medicine and Critical Care, Center Hospital, NCGM  
**Kentaro Kobayashi**, Chief Physician, Department of Emergency Medicine and Critical Care, Center Hospital, NCGM

In the clinical practice for COVID-19 at our Emergency Department (ED), the crucial task was not just to provide initial management for suspected patients but to identify severity (triage) and isolate those patients to prevent them from becoming a source of nosocomial infection in addition to the safety of healthcare providers.

As a measure to prevent infection in the ED, we made it mandatory to wear the mask for all patients against droplet transmission. Healthcare providers must strictly observe standard precautions for droplet and contact transmissions, and wear N95 masks and goggles at all times during the initial management at the ED to prevent aerosol exposure (Photo 2). In crowded ED situations, however, donning and doffing such equipment was time-consuming.

With the spread of community transmission, we had to treat all patients with fever and respiratory symptoms brought by ambulances as suspected patients, and thus had to respond confronting as if we had a considerable number of COVID-19 patients. To select highly suspicious patients, we started screening all patients brought to the ED using a checklist shown in Figure 1, which included questions about the history of overseas travels and close contacts, fever and symptoms of respiratory system, etc.

Figure 1 Check list

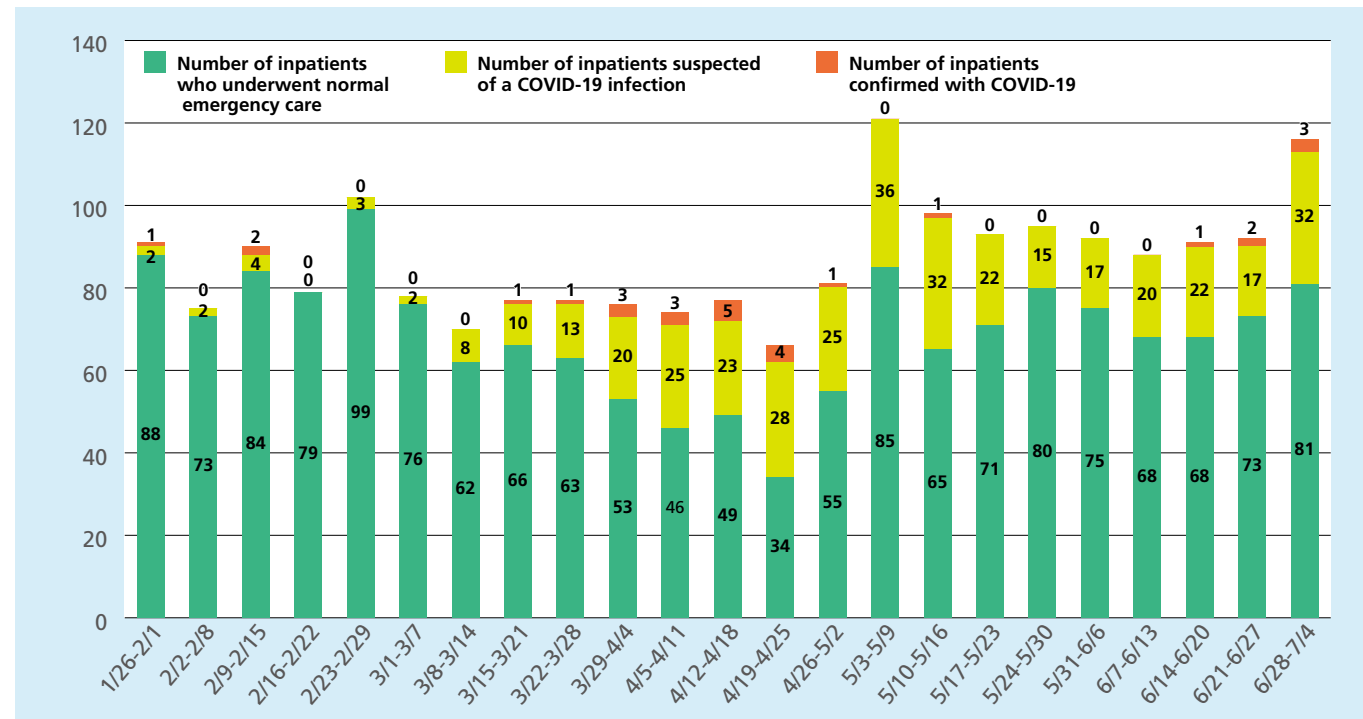
**Checklist for COVID-19**  
**Surgical masks must be provided to all patients!!**

**[Social history in suspected COVID-19 infections]**

- Fever over 37.5°C (99.5°F)
- Respiratory symptoms, cold symptoms
- Loss of sense of taste and/or smell
- Close contact with a COVID-19 patient
- Fever and respiratory symptoms of individuals in the same household
- Overseas travel history in past 2 weeks
- Contact with returnees from overseas countries
- Attendance of mass gathering events in past 2 weeks
- Visit to city center/nightlife district

Figure 2 shows the change in the number of non-COVID-19 patients receiving normal emergency care, suspected COVID-19 patients, and confirmed COVID-19 patients brought by ambulances to our ED per week during the “first wave” of the pandemic. From late March 2020, when community transmission of COVID-19 was prevalent, the number of potentially infectious patients admitted to the ED increased rapidly, and in the week from April 19 to 25,

Figure 2 Change in the number of admitted patients in the first wave of the pandemic in 2020



almost half of patients required emergency hospitalization were suspected or confirmed COVID-19 patients, suggesting that a greater part of the clinical practices at the ED was performed under the alert for COVID-19. Later, it became possible to use rapid PCR results and to stop unnecessary precautions after confirming



Photo 1 Entrance to the ED. The negative pressure room is located to the right of the entrance.

their infection status, which gradually reduced the burdens on the ED staffs against infection. The outbreaks repeatedly surged and subsided subsequently, and every case required different measures at the ED depending on the characteristics of each waves.

In the “second wave” of the pandemic in mid-June 2020, the number of COVID-19 clusters increased among night-time workers in the hot spots such as Kabuki-town, Tokyo, and new questions were added to the above-mentioned screening checklist asking about occasions to visit nightlife districts. In those days, rapid antigen tests became available, which greatly improved the infection screening accuracy. In the “third” and “fourth” waves of the pandemic, there were no significant changes in our practices at the ED; however, in the “fifth wave” with the Delta variant (around August 2021), increasing number of young patients required intensive care and many hospitals were overcrowded in accepting patients in severe condition. Our ED was overwhelmed with critically ill patients waiting for vacant beds, and had to accommodate two patients in a single room (Photo 4).

In the “sixth wave” of the pandemic (around December 2021), the number of severe COVID-19 cases greatly decreased due to the displacement by the Omicron variant. However, number of less severe patients were remarkably increased and considerable number of beds were required for COVID-19 patients at each local area, resultingly beds for non-COVID-19 emergency patients went short, causing nationwide confusion in emergency medical system.

In the “seventh wave” of the pandemic (around August 2022), the number of COVID-19 patients more than doubled due to the strengthening of viral transmission. The suspected COVID-19 patients also rapidly increased and consequently our ED was overcrowded. In spite of such circumstances, we continued to treat as many patients as possible, providing screening including rapid antigen test and estimating urgency of patients after arrival, inside an ambulance, but outside the Hospital.



Photo 2 All healthcare providers at the ED wore N95 masks and goggles at all times.



Photo 3 Negative pressure room. Patients suspected with COVID-19 have been basically treated in the negative pressure room installed in the ED. If the room is occupied, other two rooms are available for isolation purposes.



Photo 4 (Monitor screen of the ED) Single rooms for COVID-19 patients at the ED each accommodating two patients



# 4

## Health Checkups and Tests Conducted on Returnees on Chartered Flights from Wuhan

**Satoshi Kutsuna**, Former Chief Physician, Division of Preparedness and Emerging Infections, Disease Control and Prevention Center (DCC), Center Hospital, NCGM  
**Takeo Kawamata**, Former Special Advisor to the President, NCGM

On January 23, 2020, the Chinese government imposed a lockdown in Wuhan and its nearby cities, trapping many Japanese and their families who were unable to travel back to Japan. The Japanese government evacuated a total of 829 nationals on chartered flights from January 29 (the first flight) to February 17 (the fifth flight).

NCGM responded to the government's urgent request to conduct health checkups and PCR tests on returnees. It was a mission carried out under a critical situation, in which the WHO declared a Public Health Emergency of International Concern (PHEIC) on January 30.

Individuals detected with fever at the Haneda Airport quarantine were directly taken to a hospital, and other returnees were transported to NCGM on five to seven buses. First, temperatures were taken and questionnaires were filled out on the bus. After disembarking, returnees were checked in at the entrance of the conference room (auditorium) and received medical consultation by a physician. Those with symptoms were taken to the Department of Infectious Diseases, and those suspected of infection were hospitalized. Those who were asymptomatic underwent blood tests and PCR nasopharyngeal swab tests. Rice balls, bread, and tea were distributed, and they were taken on the bus to accommodations provided by the government.

Many of the returnees included small children under age six and Chinese speakers, requiring attentive care, such as help from pediatric specialists, provision of nursing rooms and rest areas, and medical interpreters. The number of NCGM staff involved in this



Buses carrying returnees on the first chartered flight from Wuhan arrives at NCGM

mission topped 356 within an approximate span of five days (107 physicians, 115 nurses, 24 clinical technicians, and 110 clerical staff).

Of the 793 returnees who received PCR tests at NCGM, eight tested positive (Refer to the table below). Here, a striking new fact was discovered in our country, that positive cases were seen in asymptomatic individuals. This had a huge impact on the public. It was the beginning of our challenge against the novel COVID-19.



NCGM staff awaiting the arrival of Wuhan returnees at the site of health checkup and PCR testing



NCGM staff in protective clothing, awaiting the arrival of Wuhan returnees



Returnees receiving health checkups



Returnees undergoing PCR nasopharyngeal swab tests

Flight	Date of arrival	Nnumber of returnees	Tested cases at NCGM	PCR testing results (Positive/Negative)
1	Thursday, January 29	206	199	(Positive) 3 (Negative) 196
2	Thursday, January 30	210	197	(Positive) 2 (Negative) 195
3	Friday, January 31	150	140	(Positive) 2 (Negative) 138
4	Friday, February 7	198	194	(Positive) 1 (Negative) 193
5	Monday, February 17	65	63	(Positive) 0 (Negative) 63



A staff meeting held on the initial day after caring for returnees on the first chartered flight from Wuhan



# 5

## Cruise Ships: Diamond Princess and Costa Atlantica

Hajime Inoue, Former Director-General, Bureau of Strategic Planning, NCGM

A major spread of COVID-19 was seen on board the Diamond Princess cruise ship, which docked in Yokohama on February 3, 2020. We were faced with an unprecedented challenge of isolating, quarantining, and providing medical care to approximately 3,700 passengers and crews, with limited clinical knowledge of this disease.

NCGM dispatched a team of medical providers including physicians and nurses to the Diamond Princess, and accepted many severely-ill patients for treatment. This was done in response to a request made by MHLW taking command of the situation. From early March until late April, an on-land quarantine of the captain and crew members totaling near 240 took place at the dormitory of the National Tax College in Wako City, Saitama Prefecture. This mission was commanded by NCGM specialists who supervised a diverse team of professionals gathered from around the world for support.



The Diamond Princess docked in Yokohama Port



Inside the captain's cabin. Meeting held every evening at 9:00 PM with the captain.  
 Captain Gennaro Arma (seated second from the left)  
 Gaku Hashimoto, former State Minister of Health, Labour and Welfare (seated third from the right)  
 Hanako Jimi, former Parliamentary Vice-Minister of Health, Labour and Welfare (seated second from the right)

Furthermore, a crew boarded on the Costa Atlantica cruise ship docked in Nagasaki Port was confirmed with COVID-19 on April 20. Making use of the Diamond Princess experience, NCGM dispatched staff to Nagasaki in an effort to contain the virus.



An NCGM staff boarding the Costa Atlantica docked in Nagasaki Port, in response to a request for quarantine (Hajime Inoue)

### On-Land Quarantine of Diamond Princess Crew Members Conducted by a Multinational Team



On-land quarantine check-in



Taken in front of a message board filled with words of gratitude from the captain and crew members who underwent quarantine



Quarantine team members of the Diamond Princess crew



Meeting held every day by quarantine team members



Commemorative photo taken of multinational team members after completion of quarantine inspection



# Development Research of COVID-19 Therapies Led by NCGM

**Hiroaki Mitsuya**, Director-General, Research Institute, NCGM  
**Yukihito Ishizaka**, Vice Director-General, Research Institute, NCGM  
**Yoshihiro Kawaoka**, Director, Research Center for Global Viral Diseases, NCGM  
**Katsushi Tokunaga**, Director, Genome Medical Science Project-Toyama, Research Institute, NCGM

**Wataru Sugiura**, Director-General, Center for Clinical Sciences, NCGM  
**Daisuke Tokita**, Director, Department of Clinical Research Promotion, Center for Clinical Sciences, NCGM  
**Shinichiro Morioka**, Deputy Chief Medical Director, Disease Control and Prevention Center, Center Hospital, NCGM

## Research of COVID-19 by the NCGM Research Institute (NCGMRI)

To develop therapeutic and prophylactic agents for COVID-19, we need to establish an animal model that has similar symptoms to those seen in humans. The Research Center for Global Viral Diseases of the NCGMRI has shown that a hamster infected with SARS-CoV-2 (Figure 1) exhibits symptoms such as severe pneumonia, which is seen in humans.<sup>1)</sup> Currently, hamsters are used worldwide as the most useful animal model to investigate the characteristics of SARS-CoV-2.

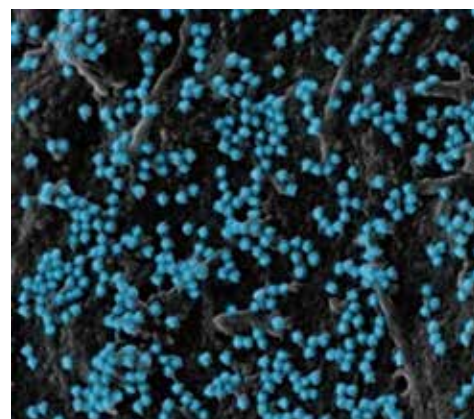


Figure 1  
Scanning electron microscopy image of SARS-CoV-2, the causative virus of COVID-19 (viruses are colored in blue). Diameter: 80–220 nm (1 nm = 10<sup>-9</sup> m)

Since the start of the pandemic caused by SARS-CoV-2, various variant viruses have emerged, for which the Research Center for Global Viral Diseases is leading the world in investigating the characteristics of these variants and the effects of therapeutic agents on them. We demonstrated that the Omicron variant, which emerged at the end of 2021 and is still prevalent, was less lung proliferative and pathogenic than previously prevalent variants.<sup>2,3)</sup> We also investigated therapeutic agents (monoclonal antibodies and antiviral agents) developed to combat SARS-CoV-2 and identified which ones were retained efficacy against Omicron variants.<sup>4,5)</sup>

The world-leading research by the Research Center for Global Viral Diseases does not just help select appropriate therapeutic agents for COVID-19 in medical settings, but also provides essential risk-assessment information about the variants, which administrative agencies can use to develop and implement countermeasures against COVID-19.

As mentioned above, while monoclonal antibodies are currently used as specific drugs for COVID-19, it is crucial to prepare a monoclonal antibody with a wide variety of neutralizing activities against emerging virus variants for antibody therapy to continue to be effective.

By using peripheral blood cells of the COVID-19 patients visiting NCGM, the Department of Intractable Diseases of the NCGMRI succeeded in cloning a number of complete human monoclonal antibodies that bind to the spike proteins on the surface of the viruses.<sup>6)</sup> The clone EV053286 exerts antiviral activity against all virus variants analyzed in a neutralization assay using Vero E6 cells (wild variant, Alpha variant, Delta variant, Beta variant, Gamma variant, Kappa variant, and Omicron subvariants BA.1, BA.2, BA.4, and BA.5). It also neutralized escape variants for which the antibody cocktail developed by Regeneron is ineffective, and suppresses infection in the experiment using a mouse. Currently it is being investigated for clinical use, and this kind of methodology is expected to be effective for potential new variants.

The Department of Refractory Viral Diseases of the NCGMRI is developing therapeutic agents targeting the proteolytic enzyme of SARS-CoV-2 (main protease; M<sup>pro</sup>). M<sup>pro</sup> is an essential enzyme for replication of SARS-CoV-2, and its composition (amino acid sequence) is similar in many coronaviruses at high level. Of note, M<sup>pro</sup> is hardly mutated even if SARS-CoV-2 mutation occurs on the spike protein of the virus and allows it to become an escape variant, and is thus considered a suitable target in the development of a therapeutic agent for COVID-19. The Department of Refractory Viral Diseases identified candidate therapeutic agents such as GRL-2420<sup>5h</sup>, which specifically bind to the active site of M<sup>pro</sup> (where proteolysis occurs) and potently inhibit the activity.<sup>7,8)</sup>

Based on the X-ray crystallographic features of an experimental anti-SARS-CoV-2 compound, GRL-2420<sup>5h</sup>, complexed with M<sup>pro</sup>, the Department also continued redesigning and organic synthesis (optimization) to synthesize an orally available low molecular weight compound TKB-245 (Figure 2), which is about hundreds of times more potent than currently used remdesivir, molnupiravir, or nirmatrelvir that had been developed during the early pandemic. Compounds such as TKB-245 and TKB-248 have been confirmed to inhibit the infectivity/proliferation of all investigated SARS-CoV-2 variants equally and potently *in vitro*, and upon oral administration to a mouse model<sup>9)</sup>. The Department of Refractory Viral Diseases is advancing clinical application of these compounds.

(Hiroaki Mitsuya Yukihito Ishizaka Yoshihiro Kawaoka)

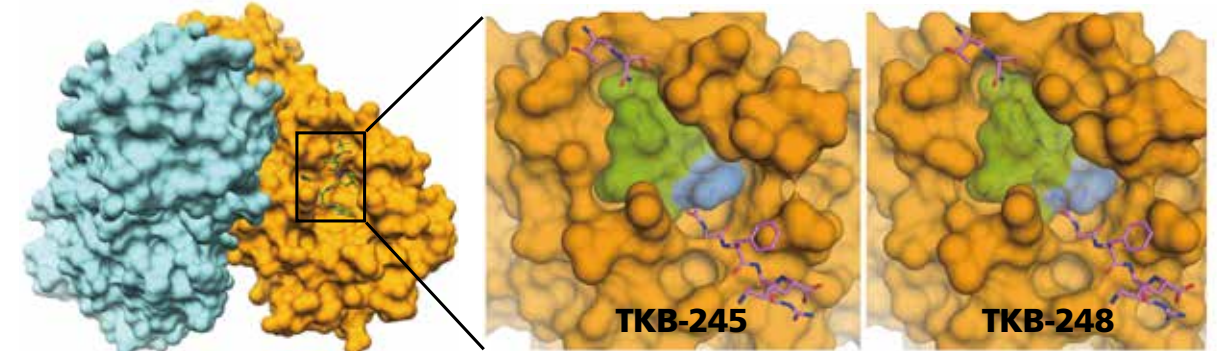


Figure 2  
X-ray crystal structure of the proteolytic enzyme essential for SARS-CoV-2 infection and proliferation (M<sup>pro</sup>). Two M<sup>pro</sup> molecules polymerize (dimerize) to acquire proteolytic function (left). The M<sup>pro</sup> inhibitor specifically binds to the active site of the enzyme that processes immature viral proteins through proteolysis to produce mature viral proteins, and eventually inhibits transmission and proliferation of the virus. The X-ray crystallographic analysis shows the potent M<sup>pro</sup> inhibitors TKB-245 and TKB-248 binding to the “cavity” of the enzyme’s active site.

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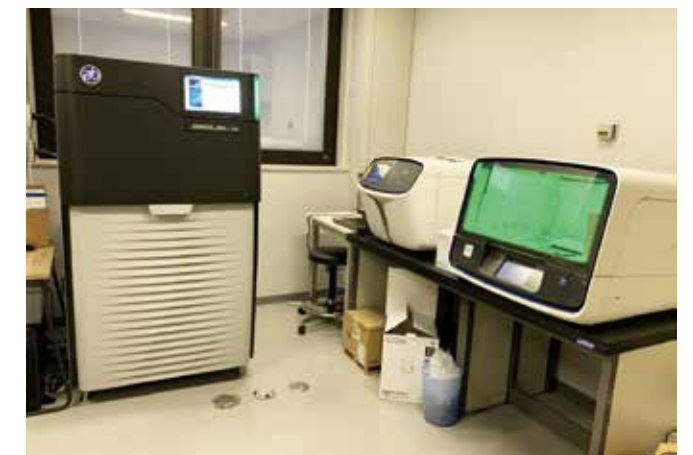
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## COVID-19 human genome research

The Genome Medical Science Project of the NCGMRI is conducting research and analysis on two topics related to host (human) genome. One is the exploration of genetic factors involved in severe cases of COVID-19. We have already published three papers in international journals, including the results of the genome-wide association study using samples obtained from the patients at the NCGM Hospitals, the results from participating in global joint researches, and the results of detailed analysis targeting human leukocyte antigen (HLA) complex especially important for immune system. The other is the exploration of a genetic factor affecting the level of antibodies produced by the COVID-19 vaccine and attenuation of the antibody response. We have published the results of detailed analysis of HLA complex as a promising candidate genetic factor in an international journal.

We believe it will be important to conduct association analyses using data of both mutation of pathogen COVID-19 genome and diversity of host human genome.

(Katsushi Tokunaga)



Short-read and long-read genome sequencers used for genome analyses



## Clinical studies and trials led by or jointly conducted by NCGM

NCGM has so far conducted various development researches of COVID-19 therapies. We initially conducted specified clinical trials and investigator-initiated clinical trials of antiviral agents, and are currently engaged in vaccine development (Figure 1). We are also planning several studies on antibody preparations and vaccines.

### Ongoing specified clinical trials

1. Exploratory single-arm study to evaluate the safety and immunogenicity of KD-414 as a booster vaccine for SARS-CoV-2 in healthy adults [KAPIVARA study] (Investigator:

### Mugen Ujiie)

October 22, 2021 - in follow-up

A single-center specified clinical trial to evaluate the safety and immunogenicity of the inactivated vaccine KD-414 as a booster in healthy adults who received two mRNA vaccinations for

SARS-CoV-2.<sup>1)</sup> The primary endpoint is the immunogenicity after booster vaccination of KD-414 compared with that after vaccination of mRNA vaccine.

2. Randomized controlled trial of convalescent plasma therapy [COVIPLA-RCT] (Investigator: Sho Saito) February 24, 2021 - Completed enrollment in December 2021

A two-arm, randomized, open-label, multicenter specified clinical trial to evaluate the efficacy of convalescent plasma therapy for COVID-19.<sup>2)</sup> Given the approval of the antibody cocktail therapy Ronapreve® (generic name: casirivimab [genetical recombination]/imdevimab [genetical recombination]), the enrollment was completed in December 2021.

3. PMX specified clinical trial [X-code trial] (Investigator: Shinyu Izumi) September 28, 2020 - Completed enrollment in March 2022 (in analysis)

A multicenter specified clinical trial to evaluate the efficacy and safety of a blood purification therapy (PMX therapy) for moderate to severe COVID-19.<sup>3)</sup>

### Ongoing investigator-initiated clinical trials jointly conducted by NCGM

1. Adrenomedullin AMP-2-COVID2 trial (Led by University of Miyazaki; NCGM investigator: Norio Ohmagari) June 24, 2021 - in progress

Adrenomedullin is a circulatory adjusting peptide which exhibits anti-inflammatory effect. It is expected to prevent patients with moderate pneumonia from becoming severe.

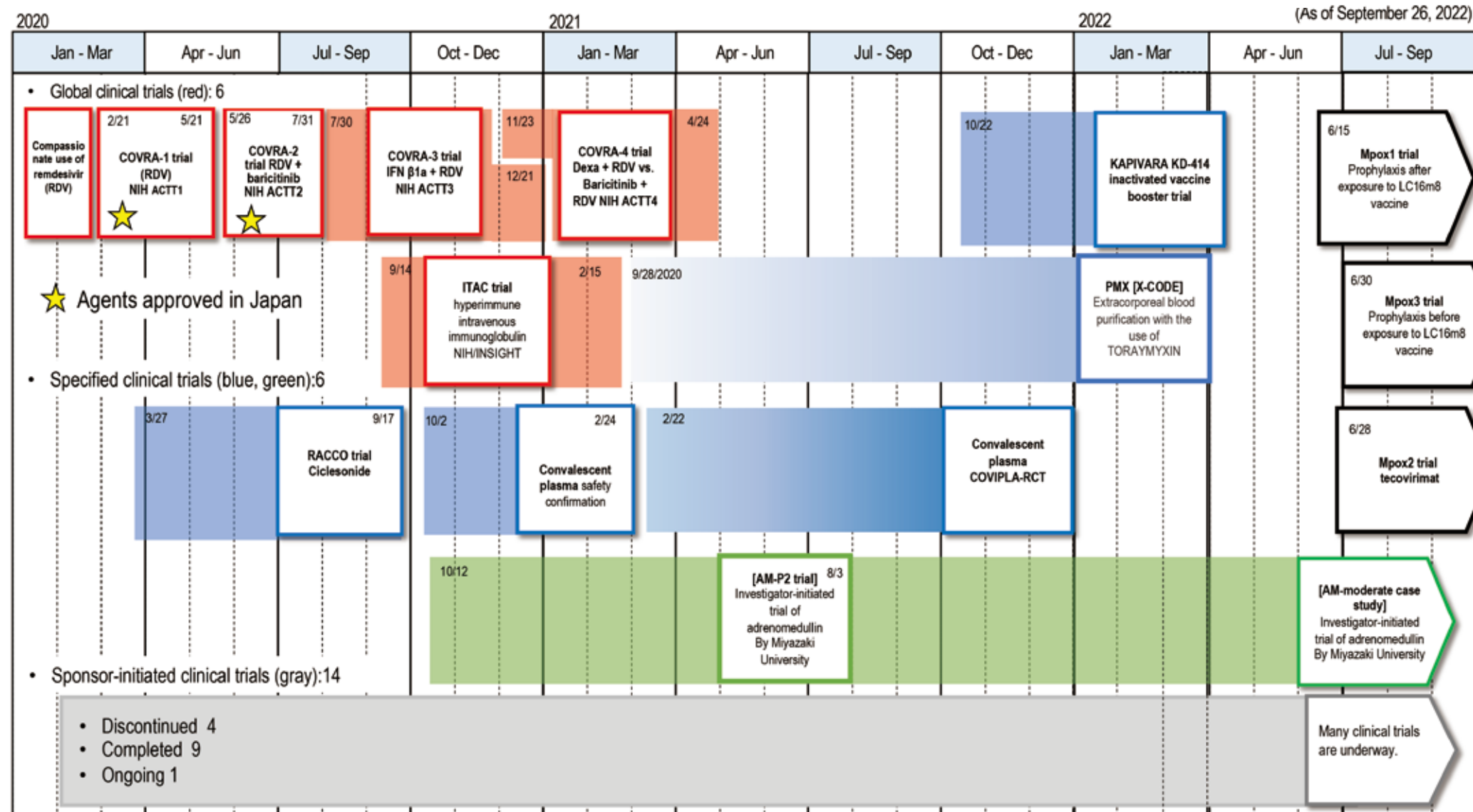
2. Adrenomedullin AMP-2-COVID trial (Led by University of Miyazaki; NCGM investigator: Norio Ohmagari) November 2, 2020 - March 1, 2022

This trial started with the expectation to prevent critically ill patients on a ventilator from aggravation and completed enrollment.

3. Ephedra Herb extract (Led by Kitasato University; NCGM investigator: Norio Ohmagari) March 30, 2021 - January 7, 2022

An exploratory Phase III trial to evaluate the efficacy and safety of Ephedrine alkaloids-free Ephedra Herb extract in patients in the early stage of infection.

Figure1 Study plans to develop drugs and vaccines for emerging/re-emerging infectious diseases in NCGM (January 2020 - August 2022)



Blue indicates clinical trials led by NCGM; green indicates clinical trials led by other institutions

**Specified clinical trials/investigator-initiated clinical trials led by NCGM (completed)**

**1. Specified clinical trial of ciclesonide [RACCO trial]**

**(Investigator: Haruhito Sugiyama)**  
**March 27, 2020 - Completed enrollment on September 17, 2020**

An exploratory Phase II trial was initiated by NCGM in 22 facilities in Japan and 90 subjects were enrolled.<sup>4)</sup> Since significant exacerbation of pneumonia was seen in the ciclesonide inhalation group, NCGM announced not to recommend the use of this agent in the press release on December 23, 2020.

**2. Compassionate use of remdesivir (RDV) (Investigator: Norio Ohmagari)<sup>5)</sup>**

Given the offer of compassionate use of RDV from the Embassy of the United States to the Chief Medical and Global Health Officer of MHLW, three critically ill patients admitted to NCGM received RDV for the first time in Japan.

**3. Adaptive COVID-19 Treatment Trial-1 (ACTT-1) [NCT04280705; Domestic COVRA-1 trial in Japan]**

**(Investigator: Norio Ohmagari)<sup>6)</sup>**  
**February 21, 2020 – May 21, 2020**

ACTT-1 was a placebo-controlled, double-blind, two-arm trial to evaluate the efficacy and safety of RDV in moderate to severe hospitalized adult patients. Given the results of this trial, RDV was approved on May 7.

**4. ACTT-2 [NCT04401579; Domestic COVRA-2 trial in Japan] (Investigator: Norio Ohmagari)<sup>7)</sup>**

**May 26, 2020 - July 31, 2020**  
 ACTT-2 was a double-blind, two-arm trial to evaluate the combination of RDV and baricitinib tablet compared to the combination of RDV and placebo tablet in moderate to severe hospitalized adult patients. Baricitinib was approved as the third therapeutic agent for COVID-19, following remdesivir and dexamethasone.

**5. ACTT-3 [NCT04492475; Domestic COVRA-3 trial in Japan] (Investigator: Norio Ohmagari)<sup>8)</sup>**

**July 30, 2020 - December 21, 2020**  
 ACTT-3 was a double-blind, 2-arm trial to evaluate the efficacy of RDV in combination with interferon  $\beta$  1a by comparing RDV + subcutaneous interferon  $\beta$  1a and RDV + subcutaneous placebo.

**6. ACTT-4 [NCT04640168; Domestic COVRA-4 trial in Japan] (Investigator: Norio Ohmagari)<sup>9)</sup>**

**December 18, 2020 - August 2, 2021**  
 ACTT-4 was a double-blind, two-arm trial to evaluate the efficacy of RDV in combination with dexamethasone compared with RDV in combination with subcutaneous baricitinib.

**7. Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) clinical trial (NCT04546581; Investigator: Norio Ohmagari)<sup>10)</sup>**

**October 15, 2020 - October 12, 2021**  
 ITAC trial was a randomized, double-blind, placebo-controlled two-arm trial of hyperimmune intravenous immunoglobulin (hIVIG) compared with placebo, led by the NIH and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

**Sponsor-initiated clinical trials**

NCGM is proactively involved in sponsor-initiated clinical trials for the development of therapies. So far, NCGM has participated in clinical trials of therapeutic agents, including molnupiravir (Lagevrio<sup>®</sup>), nirmatrelvir/ritonavir (Paxlovid<sup>®</sup>), and enrolled many subjects. These trials are still ongoing.

(As of September 2022) (Wataru Sugiura)

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**Studies on the post-COVID-19 conditions (Post-acute sequelae of COVID-19)**

**Introduction**

It is now known that there are symptoms that are prolonged in patients who contracted COVID-19 (PASC: post-acute sequelae of COVID-19) from around July 2020. In order to provide accurate information on PASC, the Disease Control and Prevention Center (DCC) of NCGM has conducted five surveys since August 2020 with the cooperation of patients affected by COVID-19. This allowed us to determine the epidemiology of PASC, identification of risk factors for symptom appearance and prolongation, impact on quality of life and social productivity, and association with antibody titers, humoral factors, and genome.

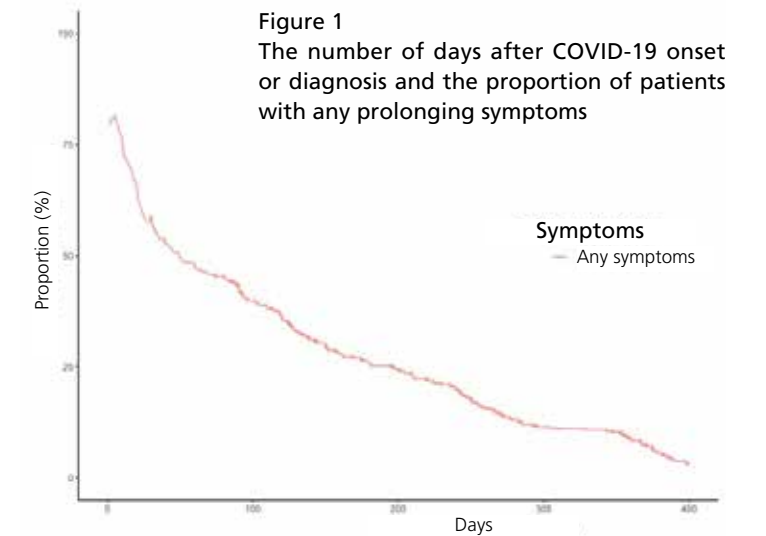
**Epidemiological data reports on the post-acute sequelae of COVID-19**

In April 2021, we conducted a questionnaire survey of patients who participated in the COVID-19 convalescent plasma therapy screening at the Center Hospital of NCGM from February 2020 to March 2021. Of the 526 participants, 457 responded to the questionnaire (response rate 86.9%). The median age of the responders was 47 years; 50.5% were female, and 84.4% were patients with mild disease.<sup>1)</sup>

Symptoms of COVID-19 were classified as follows: (1) Acute symptoms (symptoms that resolve within one month): fever, headache, decreased appetite, arthralgia, sore throat, myalgia, diarrhea, and sputum; (2) Acute to prolonged symptoms (symptoms that prolong beyond one month): fatigue, dysosmia of taste, dysosmia of smell, cough, and dyspnea; and (3) Post-acute symptoms (symptoms that appear after recovery): alopecia, decreased concentration, memory impairment, and depression. Symptoms that appear after recovery: alopecia, poor concentration, memory impairment, and depression.

Figure 1 shows the number of days since onset or diagnosis and the percentage of patients with some residual symptoms. Some symptoms were still present in 120 patients (26.3%) at six months and in 40 patients (8.8%) at 12 months after COVID-19 onset or diagnosis.

Next, we analyzed the risk of occurrence and prolongation of fatigue, taste and smell disorders, and hair loss. Compared to men, women were more likely to experience fatigue, taste and smell disorders, and alopecia, and more likely to have prolonged taste disorders. In addition to being female, younger and thinner individuals were more likely to develop taste and smell disorders. It was also found that patients with some PASC had a lower quality of life compared to those without PASC<sup>2)</sup>, and this could lead to a decrease in productivity in society.



**Figure 1**  
 The number of days after COVID-19 onset or diagnosis and the proportion of patients with any prolonging symptoms

**Post-acute sequelae of the Omicron variant**

Telephone interviews were conducted with 128 patients infected with Omicron strain who were admitted to the Center Hospital of NCGM between December 2021 and February 2022, and 53 patients responded regarding sequelae after recovery. The frequency of post-acute sequelae of Omicron strain was compared among 502 persons diagnosed with COVID-19 before the Omicron strain emerged, after matching age, gender, presence or absence of obesity, and vaccination history. The results showed that 5.6% of the Omicron group had at least one sequelae, compared to 55.6% of the target group (p=0.003)<sup>3)</sup>. This indicates that the Omicron strain tended to have fewer sequelae than the earlier strains.

**Future approach**

As of September 2022, the clinical features, pathology, and therapy of PASC have not been established. The DCC will continue its efforts to provide accurate information to patients suffering from the PASC, and to elucidate the clinical features and discover effective therapeutic agents.

(Shinichiro Morioka)

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# 7

## From COVID-19 Registry JAPAN (COVIREGI-JP) to REBIND

**Nobuaki Matstunaga**, Chief, Division of Clinical Surveillance, AMR Clinical Reference Center, Center Hospital, NCGM  
**Norio Ohmagari**, Director, Disease Control and Prevention Center (DCC), Center Hospital, NCGM  
**Kazuo Izumi**, Director, Department of Research Resource, Center for Clinical Sciences, NCGM  
**Wataru Sugiura**, Director-General, Center for Clinical Sciences, NCGM

### COVID-19 REGISTRY JAPAN (COVIREGI-JP)

#### Introduction

It has been two and a half years since the identification of pneumonia clusters due to novel coronavirus in Wuhan, China in December 2019. COVID-19 keeps changing in clinical manifestations, clinical course, severity, case fatality rate, etc. over time under the influence of the spread of variants. To comprehend this information in real time and directly return the data to public health and clinical settings, we have initiated a registry study of COVID-19 hospitalization cases since March 2020 (COVIREGI-JP) (<https://covid-registry.ncgm.go.jp/>) (Figure 1).

#### Overview of the registry study

This is an observational study that has been initiated with the MHLW Grant-in-Aid for Scientific Research (Title: Development of clinical therapy for critically ill patients with COVID-19; Principal investigator: Norio Ohmagari, NCGM) and is currently under the operation of the REpository of Data and Biospecimen of INFectious Disease (RIBIND) described later. The case reports are developed focusing on the basic information, demographic data, epidemiological data, clinical data regarding hospitalization and treatment, and infectiological data, and are revised according to the changes in the situation. The number of cases registered was 10,000 in October 2020 and 40,000 in May 2021, and data of over 70,000 cases have been accumulated as of September 2022.

#### Achievement of the registry study

Aside from obtaining academic results, we promptly analyze the collected data and provided outcomes to relevant administrations and municipalities. We also returned the outcomes to participating

Figure 1 Website

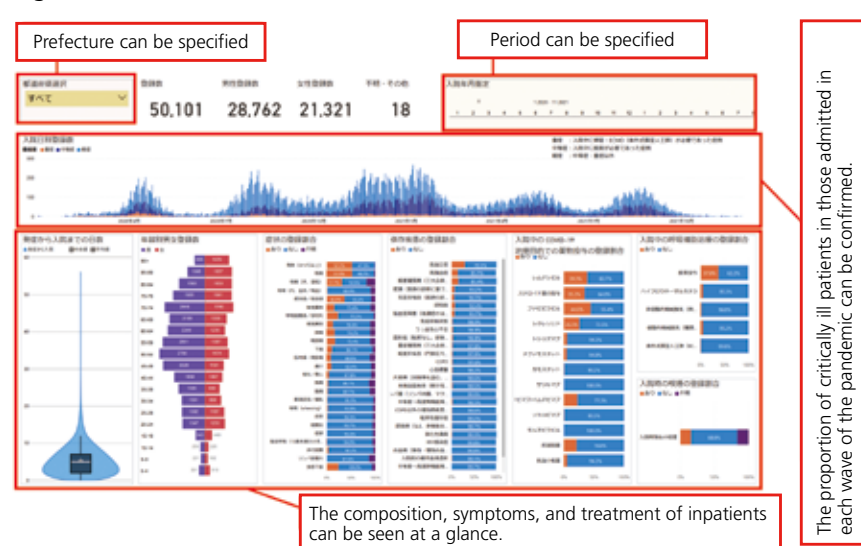


institutions with a view to advance the study in a multi-faceted manner. Our current achievements are shown below.

#### Dashboard

In March 2021, we established the “Dashboard” that facilitated visual browsing of the registered cases. The Dashboard is a tool to show the registered data with easy-to-understand tables and graphs. This allows high level overview of the change in the number of critically ill patients, age and gender composition, symptoms, comorbidities, medication, respiratory support therapy, smoking status, etc. It also enables the users to specify the relevant areas and periods to display the case data within the ranges.

Figure 2



The “visually perceptible” data of the COVID-19 inpatients is available for anyone including the general public and healthcare providers (<https://covid-registry.ncgm.go.jp/dashboard/>) (Figure 2).

#### Academic publications

We share the registered data with the institutions registering information to help them understand their current status and prepare statistical reports. We also provide opportunities for the institutions to research nation-wide data if they submit an application for data use and a study plan, and obtain approval by the peer review committee. As of September 2022, 110 data from single facilities and 50 data from multiple facilities are made available. And we have reported 29 papers.

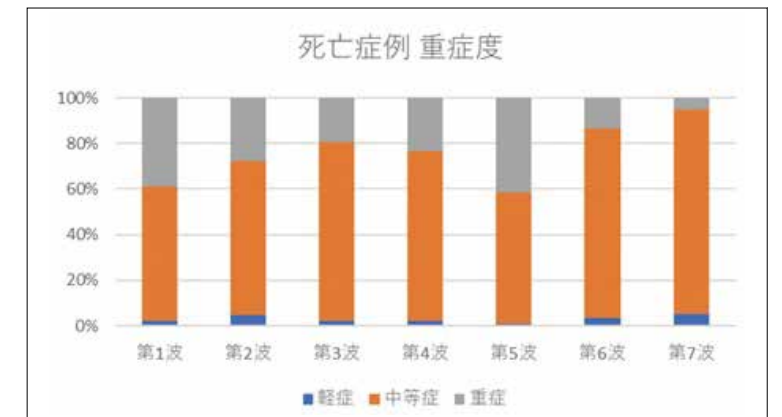


Figure 4 Cases of death from COVID-19 analyzed by the COVID-19 Advisory Board of MHLW

Figure 3 Symposium



To broadly provide findings from the studies utilizing the registry data, the “COVIREGI Study Report Symposium” is held periodically, mainly focusing on the reporting of study outcomes. (Figure 3)

In the third Symposium held on July 26, 2022, the Secretariat presented the comparison of the outbreak with the Delta and Omicron variants using the Dashboard. Despite the fact that the patients admitted during the Delta outbreak were primarily in their 30s to 50s and those during the Omicron outbreak were in their 70s and older, the proportion of patients who eventually used respiratory support therapy with oxygen or steroid therapy decreased in the Omicron outbreak. This suggested the effect of vaccination status. The summary of study outcomes is updated timely on the website to facilitate information disclosure to the general public and healthcare providers.

#### Providing information to administrations and municipalities

Parallel to preparing academic papers, we provide information to administrations and municipalities in a timely manner to reflect our study in the national policy. Here we will introduce a part of our achievements.

In the COVID-19 Advisory Board of MHLW held on September 7, 2022, the cases of death from COVID-19 were analyzed given the increased number of deaths from the disease since July 2022. In the comparison of death cases between the fifth and the sixth to seventh wave of the pandemic, the rates of ventilator/nasal high flow use and steroids prescription were lower in the sixth to seventh wave. Additionally, 90% of the cases required oxygen in both the waves. In comparison to the sixth wave, the rates of ventilator/nasal high flow use and steroids prescription further decreased in the number of deaths in the seventh wave. It was assumed that the proportion of patients with respiratory failure

due to serious COVID-19 pneumonia decreased with the increase in proportion of people receiving third and fourth vaccination. As this report does not include statistical investigation, further study will be necessary. (Figure 4)

We have been providing our study conference materials to the Tokyo Novel Coronavirus Response Headquarters. Our study provided an opportunity to start the study on the epidemiological data of COVID-19 in Tokyo in 2021. We are sharing the data, including epidemiological characteristics, rate of medication use and respiratory support therapy, and severity of COVID-19 patients in Tokyo, with the cohort of the participating institutions in Tokyo.

To obtain further findings from epidemiological studies, we need to share data with participating institutions to analyze the factors associated with exacerbation and death from various aspects, promote cross-sectional and longitudinal studies concerning efficacy of medication and association with lifestyle, and evaluate long-term prognosis, which will contribute to academic and political achievements.

(Nobuaki Matstunaga)

## REpository of Data and Biospecimen of Infectious Disease (REBIND)

### Introduction



The coronavirus disease 2019 (COVID-19) has rapidly spread over the world to become a pandemic, and the pathogen, SARS-CoV-2, is still causing frequent worldwide spread and convergence while mutating repeatedly. To promptly respond to future emerging/re-emerging infectious diseases including COVID-19, it is essential to collect broad range of clinical data quickly like COVIREGI-JP, and to collect biological samples for immediate use by researchers. Therefore, MHLW determined to collect medical information and biological samples of emerging/re-emerging infectious diseases including COVID-19 to establish a public repository that can be used for research and development. The REpository of Data and Biospecimen of Infectious Disease (REBIND) was thus launched in 2021 under the operation of MHLW.

### Purpose and concept

The purpose of the REBIND is to establish a system that enables rapid collection and provision for use of the clinical data and samples of all emerging/re-emerging infectious diseases.

To promote the use in research and development, the REBIND is also available to the third parties in Japan not involved in the collection of clinical data or samples. Therefore, written consents have been obtained from the sources regarding the use in academic researches and product developments of companies, and the use for human and pathogen genome data analyses. Additionally, the terms of use specify that the outcomes of the use of such data/samples belong to the user, securing the rights of the users. Moreover, the REBIND management do not use the data/samples maintained at the REBIND in principle to secure fairness and transparency, except in cases necessary for operation or requested from the government for infection control.

### Operation

Based on the Article 56-39 (3) of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious

Diseases (Act No. 114 of October 2, 1998), NCGM is entrusted by MHLW and operates the REBIND jointly with the National Institute of Infectious Diseases, which is the "facility" of MHLW, under the cooperation of Tohoku University, Tohoku Medical Megabank Organization, the Institute of Medical Science of the University of Tokyo, and the University of Tokyo Hospital (Figure 1). The Steering Committee to discuss the operation policies and the Use Review Committee to accept medical information and samples and review applications for data/sample provision are also established with participation of third parties as members.

In principle, medical institutions involved in the treatment of infectious diseases in Japan are responsible for the collection of data and samples as collaborating research organizations specified in the "Ethical Guidelines for Medical and Biological Research Involving Human Subjects" (those not conducting research based on research plans but only collecting samples and data from the research targets and providing them to research institutions).

The COVIREGI-JP has been operated under administration costs of the REBIND since 2021 when the REBIND was launched. However, as the COVIREGI-JP is an opt-out registry study and the procedure for use is different from that for the REBIND, it is operated in the way before launch of the REBIND.

### Data and samples handled

The REBIND currently includes COVID-19 as a target disease. It plans to add mpox and pediatric hepatitis as target diseases in FY2022.

The medical information on COVID-19 is collected using electronic data capture (EDC) for the same items as those in the COVID-19 registry study COVIREGI-JP. Other data collection methods are also being introduced, such as semiautomatic collection from electronic health records and receipt processing systems, aiming to save labor and improve data accuracy in medical institutions. The samples being collected at this moment are blood, nasopharyngeal swab, and saliva for COVID-19, and the blood samples are used to prepare plasma, DNA, and peripheral blood mononuclear cells (PBMCs), and nasopharyngeal swab and saliva samples to isolate viruses. Other samples such as stools will be added in the future. The data and samples collected for other research will also be accepted after the review by the REBIND Use Review Committee.

For the data and samples maintained at the REBIND, third parties in Japan can apply for the use. The data and samples of REBIND will be available to such parties after the approval of the research plan to use them by the Ethical Review Board and approval of use by the REBIND Use Review Committee. All the collected clinical data

Figure 1 Operation

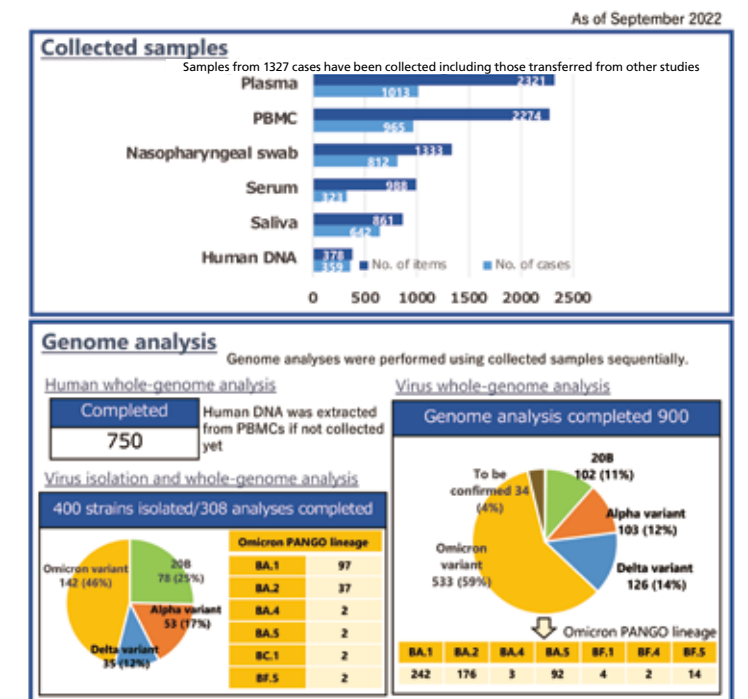
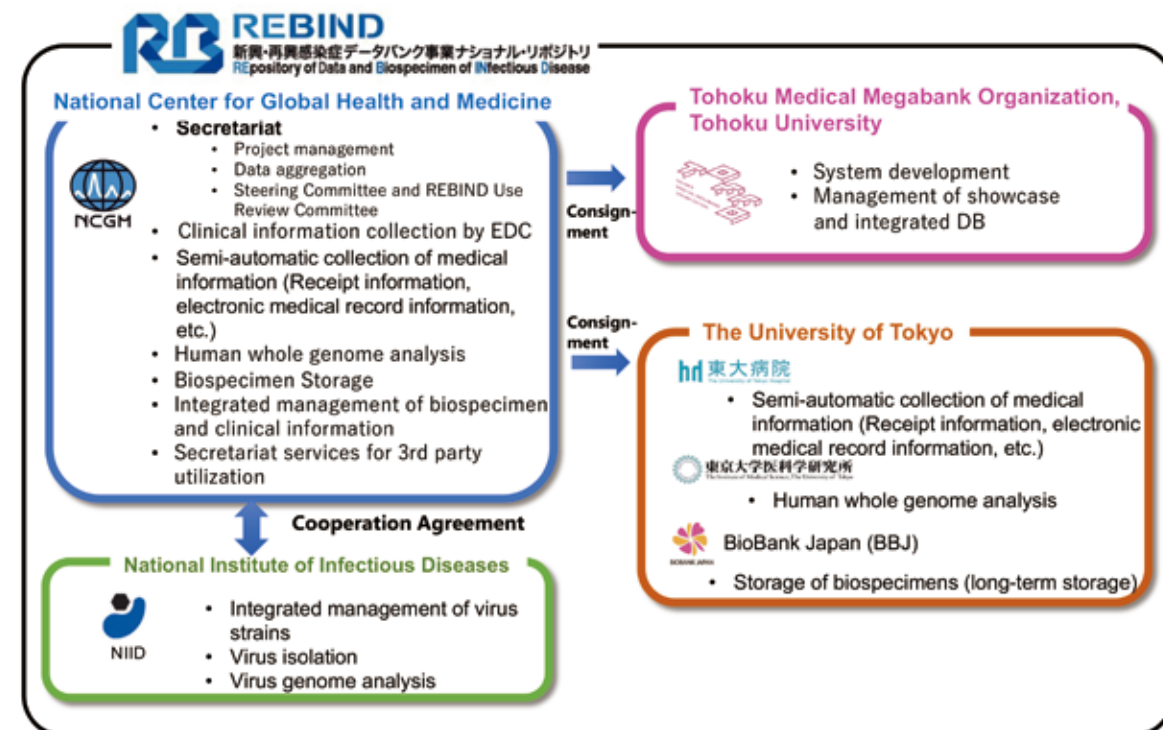


Figure 2 Progress (as of September 2022)

and the data pertaining to the human whole-genome analysis and virus whole-genome analysis obtained from the collected samples are available for use in principle. All samples, except for those for long-term storage, are available for use in principle.

### Progress

The collection of data and samples for the REBIND was started by NCGM in October 2021, and then by 14 medical institutions nationwide in FY2021, including all designated medical institutions for specified infectious diseases. In FY2022, the participation of medical institutions, mainly designated medical institutions for Class I infectious diseases, will be further promoted.

All the data and samples collected for the REBIND so far are from inpatients with COVID-19. As of September 2022, 486 cases have been registered at the medical institutions participating in the REBIND, and samples from 1327 cases have been collected, including those transferred from other studies (Figure 2). As the clinical data is or will be obtained for each sample, all samples will be maintained with relevant data.

For the use of these data and samples, as of September 2022, small number of applications are to be accepted on a trial basis, and the general applications will be accepted after the trial operation.

Lastly, we would like to express our sincere gratitude to the patients, their families, and healthcare providers who have been taking care of COVID-19 patients for their cooperation with the COVIREGI-JP and the REBIND, and appreciate their continued support.

(Kazuo Izumi)



8

# Releasing of Academic Achievements

**Peipei Song**, Chief, Division of Global Health & Medicine, Center for Clinical Sciences, NCGM  
**Wataru Sugiura**, Director-General, Center for Clinical Sciences, NCGM  
**Yasuhide Yamada**, Director, Medical Research Department, Bureau of Strategic Planning, NCGM



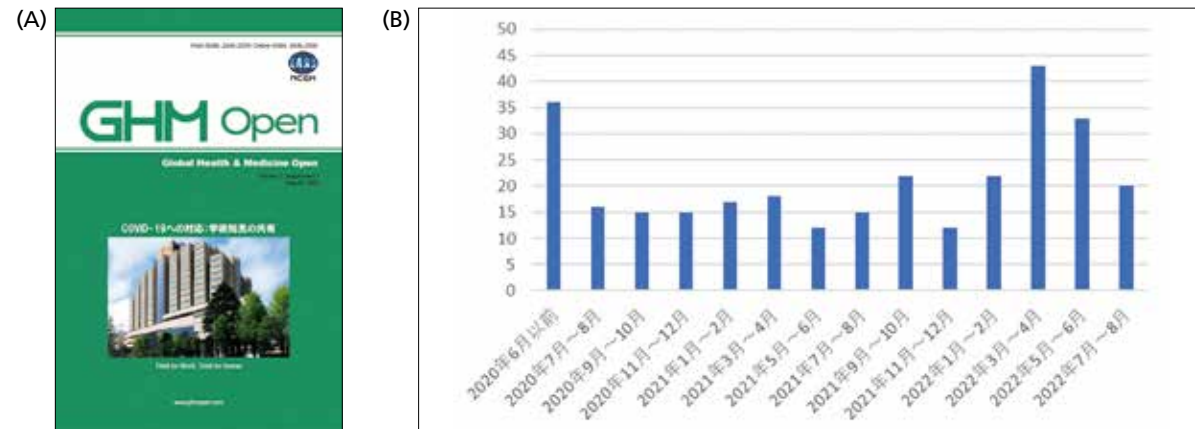
The Meeting of NCGM COVID-19 Academic Advisory Board / Publication Committee held on October 25, 2022.

The "NCGM Novel Coronavirus Infection Academic Advisory Board" (Current Chair: Wataru Sugiura, Director of the Center for Clinical Sciences) was established on February 7, 2020 for the purpose of consolidating research and development information on COVID-19, utilizing limited resources within NCGM, and exploring possibilities for cross-organizational support. The Advisory Board is comprised of executive members from NCGM, including the President, the staff from the Center Hospital, Research Institute, Center for Clinical Sciences, and Bureau of International Health Cooperation, and 64 meetings have been held so far. New research proposals are registered with the Committee at the beginning of the project, and the progress of ongoing research proposals is updated as needed to capture the evolving status of COVID-19 research and development. To date, 136 projects have

been registered.

Apart from the Academic Advisory Board, the "NCGM COVID-19 Publication Committee" was established in March 2020 to support the publication of papers from NCGM in a strategic and timely manner. The committee has met 41 times so far, with the President, center executives and researchers attending to share updates on the COVID-19 papers and discuss ways to advance the timely dissemination of academic information in response to the pandemic. To date, 296 academic papers on COVID-19 with NCGM staff as authors have been published. Of these, 281 papers (116 in clinical research, 29 in basic research, 66 in epidemiological research, and 70 in global health research) published by July 2022 are collected and published as a collection of research

Figure 1 (A) Cover page of the collection of research achievements and (B) changes in the number of publications for papers related to COVID-19 with NCGM staff as authors.



achievements with the topic "Response to COVID-19: Sharing Academic Findings", and Japanese abstracts are summarized by field (Figure 1).

In addition, Japanese abstracts and bibliographic information are also available on the NCGM website for published articles in which NCGM staff are the first or corresponding authors (Figure 2). Many papers on important topics are summarized, including gender differences in risk of severe diseases, antibody titer after vaccination and smoking/drinking habits, predictors of silent hypoxia, prolonged symptoms after COVID-19 illness, characterization of Omicron/BA.2 mutant strains, prediction of severe condition by interferon-lambda 3 (IFN λ3), and effects of vaccination on the elderly.

Since the outbreak of COVID-19, many articles containing the latest research findings have been published on Global Health & Medicine (<https://www.globalhealthmedicine.com>) – an international, open-access, peer-reviewed journal, published by NCGM. In particular, the three issues of "GHM Special Topic: COVID-19" (April 2020, Vol.2, No.2; April 2021, Vol.3, No.2; April 2022, Vol.4, No.2) (Figure 3, A-C) collected a range of articles describing COVID-19 based on frontline data from Japan, China, the United States, Italy, the United Kingdom, and other counties and areas worldwide. To date, 87 articles including 59 from NCGM have been published, and a dedicated website on COVID-19 has also been created (<https://www.globalhealthmedicine.com/site/topics.html>).



Figure 2 COVID-19 related papers are available on the NCGM website. <https://www.ncgm.go.jp/covid19/academicpaper.htm>

In addition, as the journal is included in PMC (PubMed Central, a free full-text archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health's National Library of Medicine), all published article are available on PubMed/PMC, with the goal of creating a global information network for the publication of high-quality original research.

Moreover, NCGM launched the second international academic journal – GHM Open (Print ISSN 2436-293X, Online ISSN 2436-2956; <https://www.ghmopen.com>) – in August 2021, with the goal of creating a network to share global health information and findings from basic science and clinical science for use in practice. To date, 8 papers on COVID-19 have been published in GHM Open. NCGM will continue to communicate its response experience and research findings on COVID-19 through scientific papers, SNS and websites as a shared asset for humanity.

(Data as of September 2022)

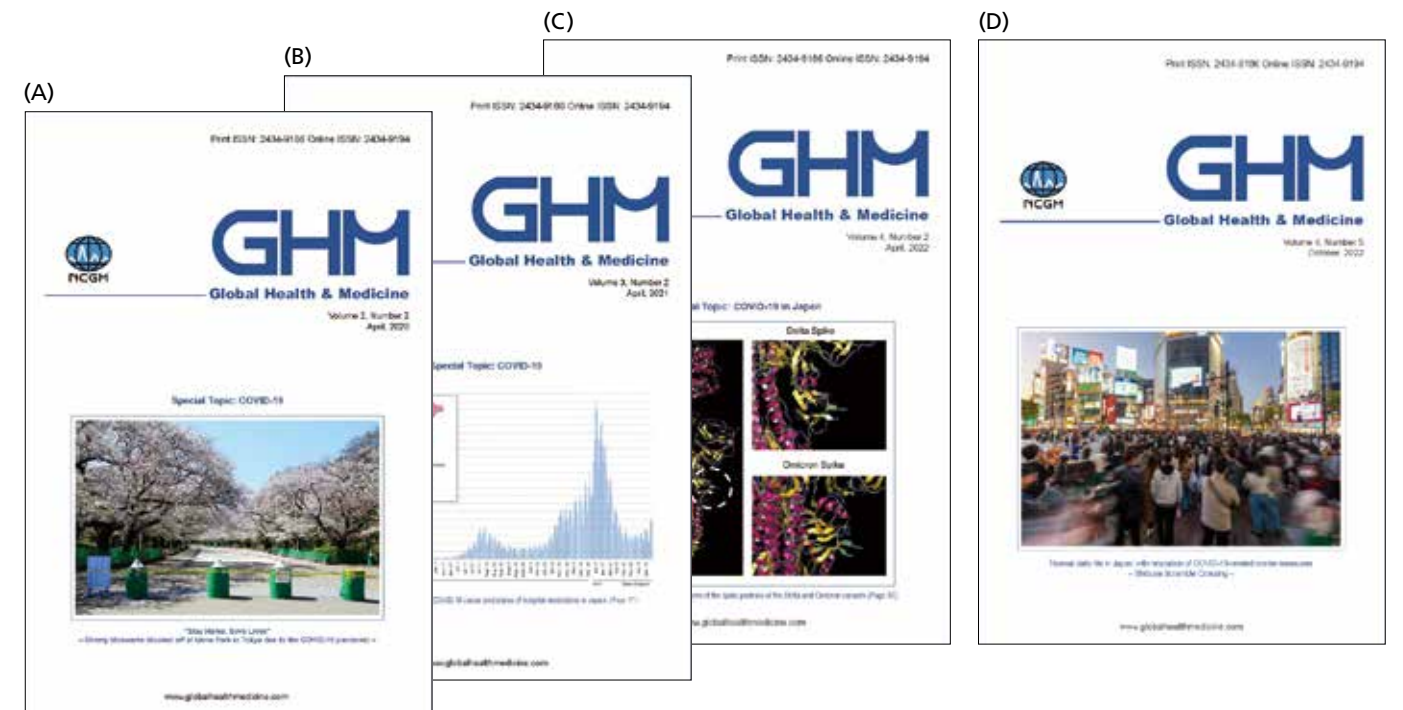


Figure 3 Three issues of "GHM Special Topic: COVID-19" published in (A) April 2020, (B) April 2021, (C) April 2022, and (D) the latest issue published in October 2022.



# 9

## Policy Recommendations

**Norio Ohmagari**, Director, Disease Control and Prevention Center (DCC), Center Hospital, NCGM

Medical institutions and the administration must work in unison to handle the COVID-19 pandemic. We at NCGM have contributed to various cases from administrative issues to policy recommendations. Our staff members were dispatched to support MHLW in their mission to address the issues on the Diamond Princess which had anchored in Yokohama Port in February 2020. Also, we supported the members of the United States Public Health Service Commissioned Corps, a subordinate body of the Department of Health and Human Services (HHS) that visited Japan to help American citizens on the cruise ship return to their home country. Their mission was to assess the situation of American COVID-19 patients who were critically ill and hospitalized in Japan and support them and their family. NCGM helped the team collaborate with Japanese medical institutions in providing care to the patients and their families (Photo 1).

Due to these circumstances, an unapproved drug remdesivir was decided to be subject to compassionate use not only to critically ill American patients but also Japanese and other international COVID-19 patients. It was administered to nine patients in Japan. In order to develop necessary drugs for COVID-19 treatment speedily, we started preparing for global clinical trials of remdesivir in collaboration with the U.S. NIH, which was commissioned by MHLW, and launched the investigator-initiated clinical trials on March 25, 2020 (Photo 2). We also established the COVID-19 registry COVIREGI-JP, in which 689 institutions participated and 72,758 cases were registered as of September 26, 2022. Following that, we established the REpository of Data and Biospecimen of Infectious Disease (RIBIND) in April 2021. The REBIND is a



Photo 1 Commemorative photo taken on the day before departure of the United States Public Health Service Commissioned Corps.

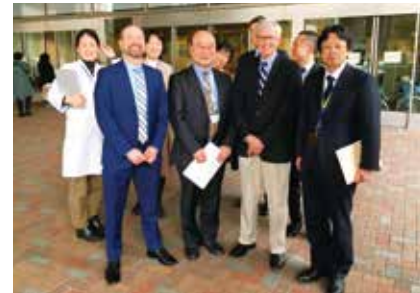


Photo 2 Taken with two doctors who visited us from the U.S. NIH for the meeting of global clinical trials.



Photo 3 Press conference with the Tokyo Governor Yuriko Koike.

repository of patient data and samples that collects the clinical data and clinical samples from patients with emerging/re-emerging infectious diseases for centralized management and for the promotion of development and research inside and outside Japan as a "preparation" to combat COVID-19 and future emerging/re-emerging infectious diseases. The REBIND has been commissioned to NCGM by MHLW as part of the measures against emerging/re-emerging infectious diseases and is operated jointly with the National Institute of Infectious Diseases (NIID).

NCGM has been playing an active part in the treatment of COVID-19 in Tokyo. Especially in the seventh wave of the pandemic in the summer of 2022, we treated many COVID-19 patients at our Hospital. During the COVID-19 outbreaks, the entire emergency care system in Tokyo came under increasing strain, and in many hospitals the malfunction due to nosocomial infection, etc. led to limited capacity to accept ambulances. Under such circumstances, the Emergency Department of NCGM accepted many ambulances. There were many cases where ambulances carrying COVID-19 patients had difficulty in finding an available hospital, and we accepted many of them at the same time and treated the patients in the car.

Since February 2020, we have dispatched our staff members to the Expert Meeting on Novel Coronavirus Disease Control convened by MHLW, where they provide advice and made proposals to the government from the standpoint of medical experts engaged in the treatment of COVID-19. We have also dispatched our staff members to the Novel Coronavirus Infection Monitoring Meeting held by the Tokyo Metropolitan Government to attend as advisers for the Government's measures against COVID-19, assessing the spread of COVID-19 and the status of medical institutions weekly and providing advice on the measures (Photo 3). Additionally, we dispatched our staff as members of the Development Committee for "Coronavirus Disease 2019 (COVID-19) Treatment Guidelines" and "Coronavirus Disease 2019 (COVID-19) Pathogen Testing Guidelines," and contributed to the establishment of national treatment guidelines. Our executive members have frequently communicated with the staff from the Cabinet Secretariat, MHLW and the Tokyo Metropolitan Government and shared the COVID-19 status information, and we have provided frank opinions regarding the medical care system from the viewpoint of staff in the field. On August 23, 2022, the Minister of MHLW, Mr. Kato, visited NCGM and had a meeting, where we reported detailed current status in medical settings and exchanged frank opinions for improvement of the medical care system.

# 10

## Responses to COVID-19 Outbreak in Hospitals/Facilities

**Yumiko Fujitomo**, Chief, Information and Education Division, AMR Clinical Reference Center, Center Hospital, NCGM

The AMR Clinical Reference Center has continued its activities as part of the Infection Control Team of Tokyo Center for Infectious Disease Control and Prevention (iCDC) to help hospitals and elderly facilities in Tokyo deal with the COVID-19 outbreak. We as infection control specialists assist in the specialized tasks involved in epidemiological studies and nosocomial infection control in the respective hospitals/facilities in response to the requests from municipalities, and have provided assistance in 52 outbreak cases (in 47 hospitals and five facilities) from July 2021 to August 2022. We have been acting to aid early termination of the outbreaks, and to help create a foundation for voluntary and continuous updating of

measures in preparation for future COVID-19 outbreaks. Many of the hospitals/facilities have enhanced their ordinary measures against

COVID-19 and have become capable to respond to the patients on their own according to our advice during the assistance period.

In the autumn of 2021, we visited four Tokyo metropolitan schools (special schools, junior high and high schools) to provide infection control education. This has taken place upon request of the Tokyo Metropolitan Board of Education as part of the measures to prevent infection clusters in metropolitan schools. We discussed with the teachers how to prevent infections in various settings at the schools where many students stay.

Insights gained from our mission are utilized for education of the staff in Tokyo metropolitan hospitals and health centers, and are being reflected in the establishment of a new system and preparation for outbreaks expected in healthcare institutions.



Preventive measure with zoning



Infection control education at a Tokyo metropolitan school



Advice on ventilation was also given



Infection control education is vital for healthcare providers to work safely. Implementing basic measures in a constant and continuous manner is the key.



# 11

## The Fever Clinic and the Community-Based "Shinjuku Model" System

**Makoto Tokuhara**, Former Director, Division of Regional Medical Liaison and Public Relations, Center Hospital, NCGM

The spread of COVID-19 infections gave rise to serious problems concerning the need for widespread PCR testing and securing a sufficient number of hospital beds. NCGM started an outpatient fever clinic on March 9, 2020, establishing a system of PCR testing for patients with referrals from other medical institutions or who were residents of Shinjuku City. However, by April the number of patients visiting the outpatient fever clinic grew to more than 100 per day, overwhelming its capacity, since doctors were required to conduct medical consultations, perform various medical tests, and prescribe medications in addition to PCR testing. Furthermore, the increased workload strained the staff of the Hospital's Department of Infectious Diseases which managed the outpatient fever clinic, leading to concerns that the care of severely ill patients would suffer (Graph 1).

During a meeting between the President, the Hospital Director and other top-level NCGM officials, the creation of a COVID-19 response network was proposed, connecting the Shinjuku municipality office, Shinjuku Medical Association, and core hospitals in Shinjuku City. We were able to garner support from the Shinjuku City Medical Association President Seiichi Hirasawa and the directors of seven core hospitals in Shinjuku City (Yuko Kitagawa of Keio University Hospital, Tamotsu Miki of Tokyo Medical University Hospital, Kazunari Tanabe of Tokyo Women's Medical University Hospital, Nobuo Sekine of JCHO Tokyo Shinjuku Medical Center, Tetsu Yano of JCHO Tokyo Yamate Medical Center, Toshihiko Tujii of Ohkubo Hospital, and Tatsu Nakazawa of Seibo Hospital). On April 11, we met with Shinjuku Mayor Kenichi Yoshizumi to present our proposal of the "Shinjuku Model" COVID-19 Medical Care System (Chart 1).

The "Shinjuku Model" is based on two major strategies of setting up a PCR Testing Center and of assisting in the management of hospital beds for COVID-19 patients. The purpose of the system is to enable smooth and efficient PCR testing by establishing a PCR Testing Center to which patients could be referred by local clinics and medical offices if so required. Another function of the system was to assist in securing a sufficient number of hospital beds required by the City's Public Health Office, by coordinating efforts

between the seven core hospitals in the municipality. Mayor Yoshizumi made the bold decision to go forward with our "Shinjuku Model" proposal, and the plan was announced at a press conference on April 15 held by the Shinjuku City Mayor, the President of the Shinjuku City Medical Association, and the President of NCGM.

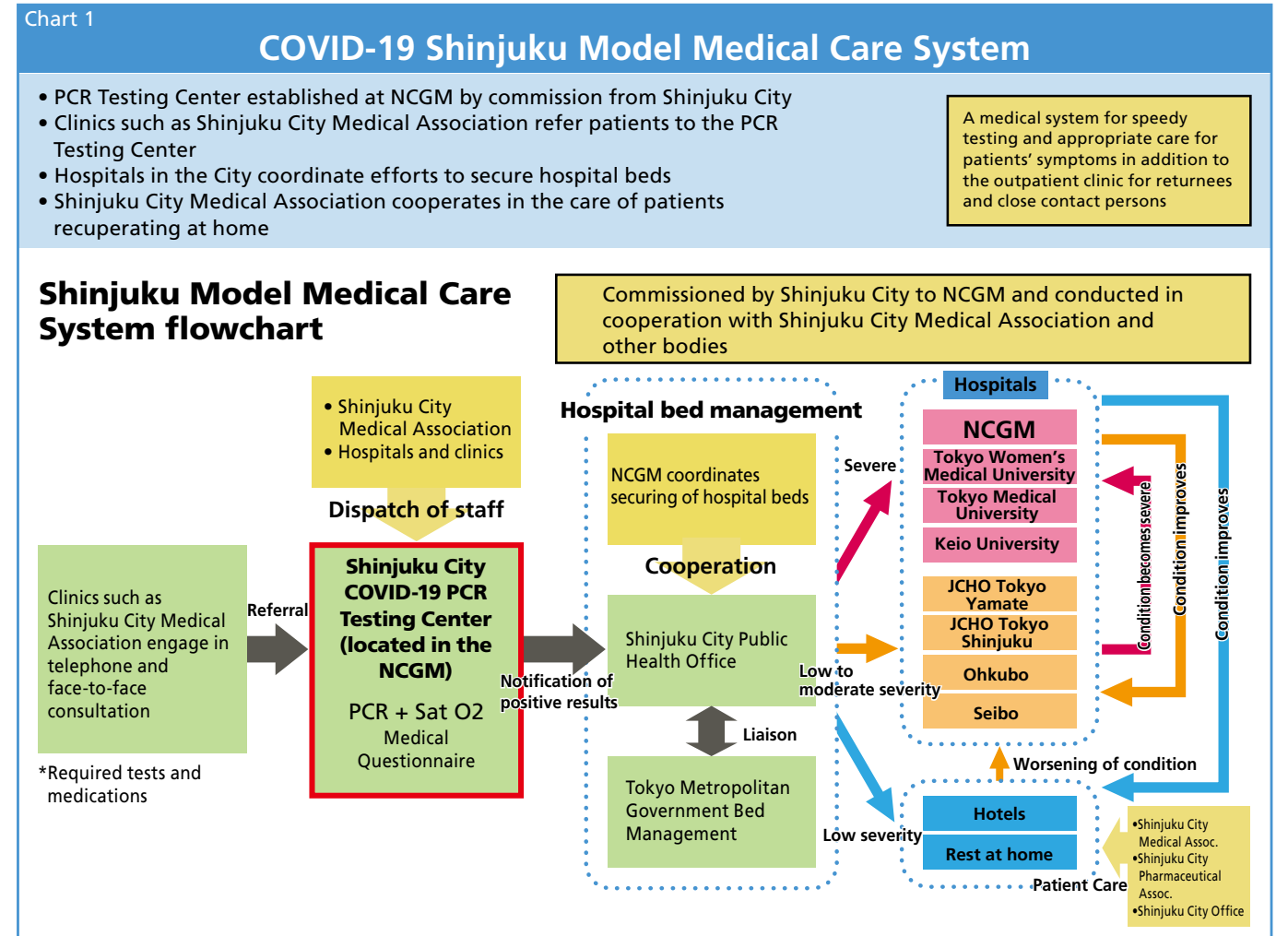
Shinjuku City commissioned NCGM to establish the "Shinjuku City COVID-19 PCR Testing Center" within the Hospital (Photo 1, 2). This was an unprecedented undertaking for NCGM, and were faced with many obstacles, but with the cooperation of the various departments, the Testing Center was able to commence operations on April 27. The launch of the Testing Center was only made possible by the knowledge and experience we gained through our involvement in the medical crises of the charter plane returnees from Wuhan, the passengers of the Diamond Princess cruise ship, and our outpatient fever clinic. The Testing Center is staffed solely by those working within Shinjuku municipality, with doctors, nurses, clinical laboratory technicians, and clerical workers from Shinjuku's seven core hospitals as well as doctors of the Shinjuku City Medical Association. The Testing Center was set up to enable the testing of 200 people on weekdays between 9:00 and 11:00 AM, but in actuality we conducted testing for almost 300 patients on some days (Graph 2). The operation of the "Shinjuku City COVID-19 PCR Testing Center" was started by Shinjuku City in August 2020 and was relocated onto the compound of Shinjuku Public Health Office. Core hospitals are cooperating in its operation, and NCGM is also continuing to perform testing.

It has been about one year since the initiation of the "Shinjuku Model" system. During the third wave of the pandemic, the daily number of COVID-19-positive cases exceeded 2,000 in Tokyo, causing difficulty in the control of hospital beds. Under such circumstances, the "Shinjuku Model" system greatly contributed to the facilitation of functional bed control, enabling hospital admission of new patients soon after the discharge of recovered patients, and admission of patients depending on the severity of their symptoms, through close communication between the personnel in charge in each core hospital and those in the Public Health Office.



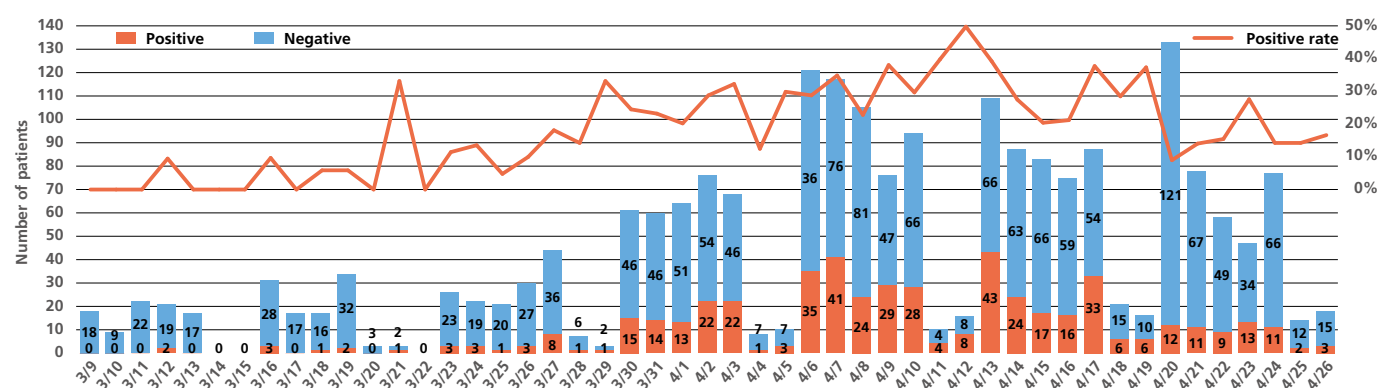
Photo 1 Katsunobu Kato, Minister of Health, Labour and Welfare (front row, 3rd from the right) inspects the "Shinjuku Model" (April 23, 2020)

Photo 2 "Shinjuku City COVID-19 PCR Testing Center" launched in the NCGM Center Hospital grounds by commission from Shinjuku City

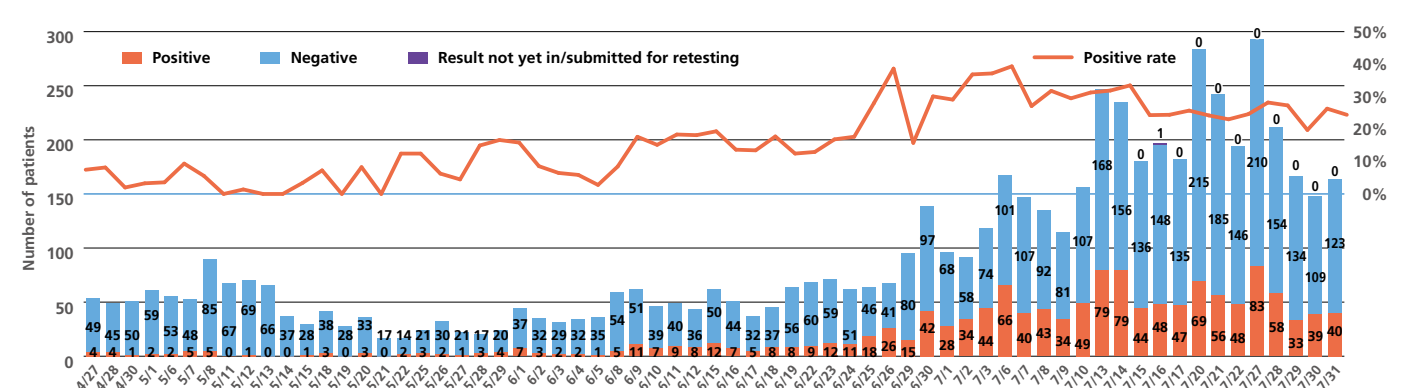


Source: The Shinjuku City press conference on April 15, 2020

Graph 1 : Transition of outpatient fever clinic consultations \*Numbers between March 9 and April 26, 2020 include PCR testing of emergency medical care patients, outpatients and inpatients



Graph 2 : Transition patient numbers at Shinjuku City COVID-19 Testing Center (2020)





# 12

## International Cooperation and Joint International Research

**Azusa Iwamoto**, Director, Division of Global Networking, Department of Global Network and Partnership, Bureau of International Health Cooperation, NCGM  
**Motoyuki Tsuboi**, Division of Global Health Policy and Research, Department of Health Planning and Management, Bureau of International Health Cooperation, NCGM

**Takeshi Nishijima**, Division of Global Health Programs Department of Health Planning and Management, Bureau of International Health Cooperation, NCGM  
**Tatsuo Iiyama**, Director, Department of International Trial (DIT), Center for Clinical Sciences, NCGM  
**Masato Ichikawa**, Manager, Public Relations Section, Department of International Trial (DIT), Center for Clinical Sciences, NCGM

### Support for foreign residents in Japan

The COVID-19 pandemic revealed the difficult situations of foreigners living in Japan, who are likely to be marginalized. The Bureau of International Health Cooperation of NCGM participates in 'Migrants' Neighbor Network & Action (MINNA)' together with 'Our SDGs Task Force for Foreigners', 'Services for Health in Asian African Regions (SHARE)', and The Institute of Developing Economies', to promote improvement of access to health-related information and services for foreign residents in Japan.

We have been engaged in the following activities:

- (1) Dissemination of health information necessary for foreign residents (by posting messages on the huge SNS Facebook page managed by Vietnamese living in Japan [No. of reach: 300,000], and conducting online questionnaire survey on the impact of COVID-19)
- (2) Creation of a pathway for foreign residents in difficult situations to access necessary healthcare services (establishment of 'COVID-19 Vaccination Information Center for International Citizen (COVIC)' to help them obtain vaccination vouchers by telephone consultation [Photo 1])
- (3) Exploration to find ways to solve social, economic, and cultural issues that affect the health of foreign residents (ex: seminar series to promote collaboration among administration,

- consultation services for foreigners, public health centers, occupational health staff, etc.)
- (4) Collaboration with the initiatives inside and outside Japan that support foreigners and other vulnerable populations (e.g: publication of 'Health Handbook for Vietnamese Workers in Japan' in cooperation with International Organization for Migration Vietnam).

Looking ahead to the post-COVID-19 world, we will continue our efforts to further reinforce cooperative relationship with various partners, including foreigner communities, and tackle issues faced by foreigners and other vulnerable populations. (Azusa Iwamoto)



Photo 1 Responding to telephone consultation from foreign residents with the NPO staff at the COVID-19 Vaccination Information Center for International Citizen(COVIC)

### Strengthening COVID-19 surveillance in Papua New Guinea



Photo 2 Dr. Tsuboi discussing strengthening the surveillance system with the local staff.

From December 2021 to March 2022, I was involved in on-site activities in Papua New Guinea as an epidemiology consultant for the World Health Organization (WHO) COVID-19 Incident Management Team through the Global Outbreak Alert and Response Network (GOARN), an international framework established by WHO to promptly dispatch and operate infection control teams in times of global crises due to infectious diseases.

At that time in Papua New Guinea, the third wave of the COVID-19 pandemic with the Delta variant ended and the fourth wave with

the Omicron variant was about to occur. Under such circumstances, I contributed to implementation of surveillance activities for COVID-19 response and provided various technical/strategic supports to strengthening the surveillance system at the COVID-19 control center of the country during the dispatch period, based on the experience of being engaged in multiple control measures against COVID-19 in Japan, including

analyses of epidemiological situation of COVID-19 on the cruise ship (Glob Health Med. 2020;2:102-106) and at airports/ports (Clin Infect Dis. 2022;74:1614-1622), and in collaboration with the National Department of Health while considering sustainability in the resource-limited settings.

(Motoyuki Tsuboi)

### COVID-19 response by WHO Regional Office for the Western Pacific

I have been appointed as a technical officer for antimicrobial resistance at WHO Regional Office for the Western Pacific in Manila, the Philippines, and appointed as a member of the WPRO COVID-19 Incident Management Support Team to be in charge of clinical management, infection prevention and control, and research and science to provide support to WHO country offices and Member States.

We take this pandemic as an opportunity to support development of long-term health system strengthening, especially at subnational level, to prepare for the forthcoming outbreak of infectious diseases.

One of our support is the reinforcement of oxygen supply system in the Member States. Based on the situation and demands of each Member State and from the viewpoint of long-term usefulness,

we support supplying pressure swing adsorption (PSA) oxygen generators to 11 countries to prepare for future outbreaks of COVID-19 and other respiratory diseases.

With support from the Disease Control and Prevention Center (DCC), WHO held meetings with the governments of Mongolia, Laos, and Cambodia with the goal of improving their medical systems to adjust their care pathway to cope with COVID-19 pandemic.

The DCC shared the information on Japan's response to the outbreak with the Omicron variant so that Member States can learn from Japan's experience.

(Takeshi Nishijima)



Photo 3 WHO-organized teleconferences which invited the Disease Control and Prevention Center (DCC) and the governments of Mongolia, Laos, and Cambodia





Photo1 Online international meeting of the WHO R&D Blueprint

## Joint International Research Projects

### Cooperating with other countries in the research and development of medical products to combat COVID-19

Researchers and industrial companies around the world have been committed to develop diagnostic tools, treatments, and vaccines to tackle the COVID-19 pandemic. Humanity has never witnessed such an unprecedented number of research and development projects for a single infectious disease being carried out simultaneously throughout the world. NCGM has been involved in international medical cooperation for 30 years, and is providing global cooperation to the current pandemic by carrying out research and development activities.

In relation to the current pandemic, the Department of International Trials of the NCGM Center for Clinical Sciences, which conducts overseas clinical trials and clinical research, participated in international initiatives such as the WHO R&D Blueprint, the Global Health Security Initiative (GHSI), and the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R). We also provided cooperation and assistance to more than 40 countries/areas in securing evidences and complying with regulations for provision of technical services such as medication and laboratory tests (Photo 1: Online international meeting of the WHO R&D Blueprint). We promote clinical trials of drugs and vaccines, and clinical performance tests of diagnostic equipment while complying with international laws and regulations, and provide academic and technical assistance to establish clinical trial platforms in each country (Photo 2: Clinical trial in Thailand).

Although a number of vaccines and therapies have been developed aiming for the containment of the pandemic by 2022, the development and research is still ongoing to respond to the emergence of variant strains, and repeated increase and decrease of patients requiring treatment across the world. At the end of 2021, the ARO Alliance for ASEAN & East Asia (ARISE), an Asian platform to promote prompt clinical development in global emergency situations including the current pandemic, was established primarily by NCGM (Photo 3: Signing ceremony of ARISE). Promoting international development and research with various Asian institutions participating in the ARISE and cooperating with Western groups as a representative group from Asia, we are advancing our activities to ensure delivery of necessary vaccines and diagnostic treatments to healthcare providers in the field.

As long as globalization and international travel continue to accelerate, there will always be a risk of infection by viruses and other pathogens spreading across the borders. To counter these threats common to all humankind, a global response is required. As a research institution with a mission to promote international medical cooperation, we will continue to work in collaboration with institutions inside and outside Japan to develop diagnostic tools, therapies, and vaccines to overcome the COVID-19 pandemic.

(Tatsuo Iiyama, Masato Ichikawa)



Photo 2 Clinical trial in Thailand

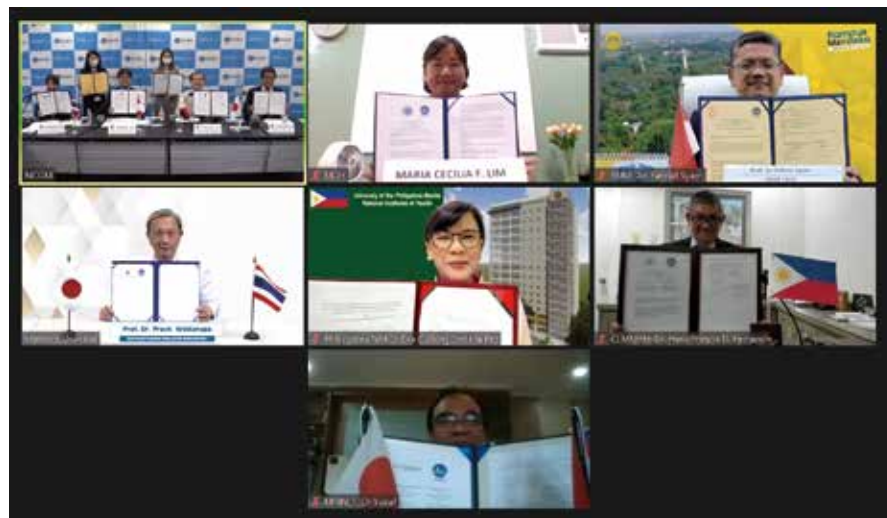


Photo 3 Signing ceremony of ARISE

# 13

## Experience in Providing Medical Support to Temporary Medical Facilities

**Nobuaki Inoue**, Director, Division of Human Capacity Building, Department of Human Resource Development, Bureau of International Health Cooperation, NCGM

### 1. Summary of activities

From February 21 to April 20, 2022, we implemented supportive activities at two temporary medical facilities.

#### Recovery accommodation facility with enhanced medical function (February 21 to February 28, 2022)

We were stationed in a hotel that has been newly designated as a quarantine facility to accept high-risk patients and pregnant patients with COVID-19 in mild condition. A physician was stationed at the facility during daytime to primarily provide care to high-risk patients in mild condition when they needed examination and transportation. Beds equipped with monitors, oxygen concentrators, and ECG monitors were placed in the hotel lobby, and we treated the patients in cooperation with the nurses dispatched from all over Japan and staff from the Tokyo Metropolitan Government.

#### Facility dedicated for the medical care of elderly patients (March 1 to April 20, 2022)

After March 2022, we were dispatched to the facility dedicated for the care of elderly patients. The facility opened at the end of February as a temporary medical facility under the special measures law, and it accepted patients from elderly facilities who tested positive and treated those patients for whom we could deal with supplemental oxygen, infusion, antibiotics, antiviral drugs, etc. We also directly accepted dialysis patients and elderly patients emergently transported to the facility. The facility initially had approximately 50 beds, and then increased its capacity to accommodate approximately 120 beds.

We provided a wide range of medical assistance, including the health check at admission, giving instructions for health management during admission based on the patients' underlying diseases, and response to the newly emergent symptoms, exacerbation, and falls during admission.

### 2. Looking back the activities

We had a chance to work at the medical facilities newly established by the Tokyo Metropolitan Government to respond to the medical demands due to increased number of infected people. While in the surge of people requiring medical care and lack of attending physicians, we believe we have been able to render some help. We especially thought that our activities, which have been promoted in close communication with other staff concerned, to find feasible solution with limited medical resources in the place with insufficient medical supply system were applicable to medical settings in low- and middle-income countries where the Bureau of International Health Cooperation is mainly engaged in their duties.

Meanwhile, we had difficulties while performing our duties in the facility, which was not originally used as a medical institution, at almost the same level as we do in a hospital. We do not know when we will experience similar situations again, but we consider we need to discipline and train ourselves for future emergencies.

(Nobuaki Inoue)



Beds placed in the recovery accommodation facility with enhanced medical function



Entrance of the Yellow zone in the facility dedicated for the medical care of elderly patients. Partitions were placed to prevent people coming and going from contacting.



# 14

## Measures for the Tokyo 2020 Olympic and Paralympic Games

**Yasunori Ichimura**, Division of Global Health Policy and Research, Department of Health Planning and Management, Bureau of International Health Cooperation, NCGM  
**Toyomitsu Tamura**, Director, Division of Public Relations and Communications, Department of Human Resource Development, Bureau of International Health Cooperation, NCGM

### Support to the Tokyo 2020 Infectious Disease Control Centre (IDCC)

Upon request from the Tokyo Organizing Committee of the Olympic and Paralympic Games, the Bureau of International Health Cooperation of NCGM supported the IDCC for public health surveillance. Five physicians experienced in managing surveillance data and working for the government/relevant agencies took responsibility in rotation, contributing to this work of a total of 69 person-days for 65 days from July 6 to September 8, 2021.

Our primary duty was the support for a daily report of public health surveillance including syndromic surveillance and environmental surveillance, and we helped organize and standardize the method to collect the necessary data on the report items, which were shared every day among the relevant organizations before, during, and after the Olympic and Paralympic Games, and also helped prepare the report. Additionally, we gathered data on COVID-19 cases among the authorized persons of the Games, checked the people who reported the symptoms among athletes and listed persons requiring action, and made as required summaries of the results of screening tests, and COVID-19 cases. Moreover, we organized data on relevant tests and surveillance. This information was reported to the supervising team of the IDCC properly to facilitate subsequent responses.

Through the practical experience in information management of diseases in the global event of the Olympic and Paralympic Games in the face of the spread of COVID-19, we had an opportunity to review responses to health emergency management on infectious diseases inside and outside Japan.

(Yasunori Ichimura)



### Contribution to enhance infection control measures at the athlete's village of the Tokyo 2020 Olympic and Paralympic Games

NCGM contributed to the establishment and management of the PCR test area of COVID-19 for the athletes who were identified as close contacts in the athlete's village of the Tokyo 2020 Olympic and Paralympic Games. We provided PCR tests with nasopharyngeal swab to the athletes for 14 consecutive days per person in this area.

NCGM dispatched the staff from the Bureau of International Health Cooperation and the National College of Nursing, Japan to the athlete's village for 53 days. The total number of dispatched staff was 275, including 58 medical doctors, 97 nurses, and 120 administrative staff.

In this test area, the following seven tasks were primarily performed:

- (1) Establishment and operation of the test system (infection control, patient registration, management of test results, preparation of emergency procedures, etc.)
- (2) Test implementation (reception, sample collection, guidance, environmental maintenance, etc.)
- (3) Technical support (training of sample collection, etc.)
- (4) Equipment management (placement and replenishment of equipment and materials, etc.)
- (5) Simple statistical analysis (reporting of results, descriptive statistics, etc.)
- (6) Language support (interpretation in English, French, Spanish, etc.)
- (7) Administrative procedures (arrangement of village entry procedures, etc.)

As a result, we dealt with a large number of samples and contributed to the enhancement of infection control measures with the staff of the Olympic and Paralympic Games. These activities were highly evaluated, for which we received a certificate of appreciation from Seiko Hashimoto, the President of the Tokyo 2020 Organizing Committee.

(Toyomitsu Tamura)



Photo 2 Certificate of appreciation from President Seiko Hashimoto to the NCGM President Norihiro Kokudo.

Photo 1 PPE donning/doffing training in the test area of the athlete's village.

# 15

## In Closing: Preparing for the Post-COVID-19 Era

**Teiji Takei**, Director-General, Bureau of Strategic Planning, NCGM

Despite the fact that all the countries in the world have been making substantive efforts to end the COVID-19 pandemic for more than three years, future prospects still remain uncertain. Even if this pandemic comes to an end, there is no end to the ongoing battle between humans and emerging/re-emerging infectious diseases. Just in the past two decades of this century, we have witnessed numerous emerging/re-emerging diseases around the globe; SARS, H5N1 highly pathogenic avian influenza, the A/H1N1 swine flu, MERS, Ebola hemorrhagic fever, Zika fever, and now COVID-19. These diseases have threatened our lives and caused social and economic turmoil.

In the post-COVID-19 era, we must build back effective healthcare and social systems to fight against the threats of emerging/re-emerging diseases to prepare for next infectious disease crisis. NCGM is committed to playing a pivotal role in continuously protecting human lives and society from emerging/re-emerging infectious diseases, based on an academic foundation in fields broadly ranging from basic medical science to highly advanced medical care and social medicine.



Blue Impulse's flight celebrating the Tokyo 2020 Paralympic Games opening ceremony on August 24, 2021. The photo taken from the 16th floor of the Center Hospital of NCGM looking in the direction of Yoyogi.



## Acknowledgements

We are going into the fourth year since NCGM has started the treatment and research of COVID-19. After July 2021 when we issued the second edition of the Feel the NCGM Special Issue, we repeatedly experienced the big waves of COVID-19 pandemic in Japan, including the fifth, sixth, seventh and eighth outbreaks. In the fifth wave of the pandemic with the Delta variant, many patients became critically ill, whereas the patients were mostly in mild to moderate conditions during the sixth through eighth waves in which the Omicron variant was dominant. Meanwhile, in the seventh and eighth waves, the number of deaths increased due to increased total number of COVID-19 patients, and as of February 1, 2023, the cumulative number of deaths from COVID-19 exceeded 68,000.

In the meantime, NCGM actively promoted activities such as research on "long-COVID" and infection control in the Tokyo 2020 Olympic and Paralympic Games. We would like to express our deepest gratitude to everyone who contributed and continue to support NCGM to date.

Due to the surge in COVID-19 cases, the Center Hospital of NCGM partially limited healthcare services, and either prohibited or restricted visitors. Kohnodai Hospital of NCGM also restricted visitors. We thank all our patients and their families for understanding and cooperating with us.

NCGM will continue to work in unity to confront COVID-19 to save lives of affected patients and help them recover as soon as possible. We greatly appreciate your continued support.

All staff at NCGM



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