NCGM Fights against COVID-19 – Lessons Learned (3rd Edition) –


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)
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 Reiwa era, and responding accurately to the demands of the times.

February 2023
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.
At NCGM, the first COVID-19 patient was among the patients consulting with the Department of Infectious Disease in late January 2020. Since then, we have treated numerous patients. We had 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, 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 convalescent. 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 ventilation, 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 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 the like this, the nosocomial cluster and absence of the staff greatly affected the hospital operation. (Norio Ohmagari)
Treatment of critically ill COVID-19 patients in the ICU/HCU

Figure 1 shows the changes in the number of intubated patients with COVID-19 up to October 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 whom the 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 70s in the fifth wave of the pandemic. (Tatsuya Okamoto)

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 disease 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 fewer “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 to 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...
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 recommissioned 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, patients 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 lot of PPE for those 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 person; 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 has 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 the 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 determined 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.

Reponses 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, making in a private space such as a single room and inside a unit 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.

For the staff

In the sixth wave 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, this did not solve the problem of the staff shortage because it took several days for the staff to be identified as sick and visited a local doctor for outpatient PCR test and examined course 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 referenced 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). This resulted in smooth testing and shortened the self-quarantine period for the staff.

(Shiho Kubota, Kumi Horii)
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 to the ED increased rapidly, and in the week from April 19 to 25, 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 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, resulting 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.
Health Checkups and Tests Conducted on Returnees on Chartered Flights from Wuhan

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 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.

<table>
<thead>
<tr>
<th>Flight</th>
<th>Date of arrival</th>
<th>Number of returnees</th>
<th>Tested cases at NCGM</th>
<th>PCR testing results (Positive/Negative)</th>
</tr>
</thead>
</table>
| 1      | Thursday, January 29 | 206                 | 199                  | (Positive) 3  
(Positive) 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     |

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

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

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

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

Returnees receiving health checkups.

Returnees undergoing PCR nasopharyngeal swab tests.
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.

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.
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. Currently, hamsters are used worldwide as the most useful animal model to investigate the characteristics of SARS-CoV-2.

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. They 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 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.

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. 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. The Department of Refractory Viral Diseases is advancing clinical application of these compounds.

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 virus. The clone EV533880 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, Mpro), 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, Mpro 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 it 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-24205h, which specifically bind to the active site of Mpro (where proteolysis occurs) and potently inhibit the activity.

Based on the X-ray crystallographic features of an experimental anti-SARS-CoV-2 compound, GRL-24205h, complexed with Mpro, 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 nirapidavir 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. The Department of Refractory Viral Diseases is advancing clinical application of these compounds.

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.
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. 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. 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.

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

3. Adaptive COVID-19 Treatment Trial-1 (ACTT-1) [NCT04207095; Domestic COVRA-1 trial in Japan]
   (Investigator: Norio Ohmagari)
   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)
   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)
   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 β1a by comparing RDV + subcutaneous interferon β1a and RDV + subcutaneous placebo.

6. ACTT-4 [NCT04640168; Domestic COVRA-4 trial in Japan]
   (Investigator: Norio Ohmagari)
   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]
   October 15, 2020 - October 12, 2021
   ITAC trial was a randomized, double-blind, placebo-controlled two-arm trial of hyperimmune intravenous immunoglobulin (IVIG) compared with placebo, led by the NIH and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

Sponsor-initiated clinical trials
NCGM 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®), remdesivir (Vaulogy®), nirmatrelvir/ritonavir (Paxlovid®), and enrolled many subjects. These trials are still ongoing.

(As of September 2022) (Wataru Sugiyama)

References
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, NCJM) 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, clinical therapy for critically ill patients with COVID-19; Principal investigator: Norio Ohmagari, NCJM) and is currently under the operation of the Repository of Data and Biospecimen of Infectious Disease (RIBIND) described later. The case reports 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 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.

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.

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 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 efficacies 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/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/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/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 mumps 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 swabs, and saliva samples 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.

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)
Releasing of Academic Achievements

Peppei Song, Chief, Division of Global Health & Medicine, Center for Clinical Sciences, NCNM
Wataru Sugihara, Director-General, Center for Clinical Sciences, NCNM
Yasuhide Yamada, Director, Medical Research Department, Bureau of Strategic Planning, NCNM

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

The “NCNM Novel Coronavirus Infection Academic Advisory Board” (Current Chair: Wataru Sugihara, 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 NCNM, and exploring possibilities for cross-organizational support. The Advisory Board is comprised of executive members from NCNM, 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 “NCNM COVID-19 Publication Committee” was established in March 2020 to support the publication of papers from NCNM 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 NCNM 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 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 NCNM website for published articles in which NCNM 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 NCNM. 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 countries and areas worldwide. To date, 87 articles including 59 from NCNM have been published, and a dedicated website on COVID-19 has also been created (https://www.globalhealthmedicine.com/site/topics.html).

In addition, the journal is included in PMC (PubMed Central), a 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/PubMed Central, with the goal of creating a global information network for the publication of high-quality original research.

Moreover, NCNM 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. NCNM 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.

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 NCNM staff as authors.

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

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.

(Data as of September 2022)
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 remedy 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 remedy 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 COVREG-IJP, in which 889 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 (REBIND) in April 2021. The REBIND is a repository of patient data and samples that collects the clinical data and clinical samples from patients with emerging/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/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 (NID).

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 Naval 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.

Policy Recommendations

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

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 (ICD) 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 hospital/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.
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, April saw the number of patients visiting the outpatient fever clinic grow 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 Seitchi Hirawasa 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, Yukuo Sekine of JCHO Tokyo Shinjuku Medical Center, Tetsu Yano of JCHO Tokyo Yamate Medical Center, Toshikko Yoji 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 we 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 clinical 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.
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 (MNNA)’ 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)

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 of long-term health system strengthening, especially at subnational level, to prepare for the forthcoming outbreak of infectious diseases.

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)

Strengthening COVID-19 surveillance in Papua New Guinea

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 and strategic supports to strengthen 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;2:152-106) 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)
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, NCNM

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 had 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 medical 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 dailysis 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)
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 swabs 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, 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)
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