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Special Topic: COVID-19

People flock to Tokyo's Ueno Park for cherry blossom parties with the relaxation of COVID-19 restrictions after four years

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COVER PHOTO OF THIS ISSUE

In April 2023, Tokyo's Ueno Park was crowded with people as cherry blossoms were in full bloom there and party restrictions due to the COVID-19 pandemic have been lifted for the first time since spring 2020. COVID-19 has been specified as "the Designated Infectious Disease" in Japan since February 1, 2020, and the government's Novel Coronavirus Response Headquarters decided to reclassify COVID-19 as a Category V infectious disease from May 8, 2023 under the Infectious Diseases Control Law since the disease has become less lethal.

(*Photo by Riri Saito*)

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EDITORIAL

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Impact of COVID-19 pandemic on surgical outcomes after hepatopancreatobiliary (HPB) surgery

Chikara Shirata, Nermin Halkic*

Department of Visceral Surgery, Lausanne University Hospital CHUV, University of Lausanne (UNIL), Lausanne, Switzerland.

Abstract: COVID-19 pandemic has disrupted healthcare systems worldwide, causing the postponement or cancellation of millions of elective surgeries. It is essential for hepatopancreatobiliary (HPB) surgeons to well understand the perioperative risk and management of HPB surgery during the COVID-19 pandemic, including the impact of preoperative COVID-19 infection and timing of surgery, the impact of COVID-19 infection on postoperative mortality, the postoperative pulmonary complications in patients with perioperative COVID-19 infection, and the postoperative complications without pulmonary involvement. Perioperative COVID-19 infection increases the risk of postoperative mortality and pulmonary complications in patients undergoing abdominal surgery. Furthermore, in some regions, the COVID-19 vaccine's availability is still limited, leading to an increase in the number of cases and potential medical collapse, which could hinder the improvement of HPB postoperative mortality rates. The timing of surgery for COVID-19 positive patients should be carefully considered, balancing the potential risks of delay with the risks of surgery during the infection.

***Keywords*:** COVID-19, SARS-COV-2, pandemic, hepatopancreatobiliary surgery, complication

The COVID-19 pandemic, which started in December 2019, has caused significant disruption in healthcare systems worldwide by creating enormous pressure on hospital capacity (*1*). This situation has impacted surgical patients both with and without COVID-19. Research conducted by the COVIDSurg collaborative has revealed that 28.4 million elective surgeries, including 2.3 million cancer surgeries, were cancelled or postponed due to a shortage of intensive care capacity over a 12–week period of peak disruption to hospital services in 2020 (*2-4*). Another issue is that the fear of perioperative mortality in patients undergoing major surgery for hepatopancreatobiliary (HPB) cancer, related to COVID-19, also affected the allocation of surgery. It is therefore essential for HPB surgeons to well understand the perioperative risk and management of HPB surgery during the pandemic.

Impact of preoperative COVID-19 infection and timing of surgery

Patients who preoperatively test positive for COVID-19 should delay their surgery until they have fully recovered from the virus due to its negative impact for patients undergoing surgery. As a result of an international study by COVIDSurg Collaborative and GlobalSurg Collaborative, it was proposed that surgeries should be postponed for patients confirmed positive for COVID-19 preoperatively, for at least 7 weeks after diagnosis and if persistent symptoms of COVID-19 infection have subsided (*5*). However, for some emergency surgeries, such as resection of advanced cancers, delaying surgery has the potential risk of oncology, and timing of surgery should be tailored for each patient (*5*). Advantages of delaying surgery should be balanced against the potential risks of delay for patients with HPB cancer, which can be rapidly progressive.

Impact of COVID-19 infection on postoperative mortality

COVIDSurg Collaborative has reported a mortality of 23.8% for patients with perioperative COVID-19 infection (26.1% preoperative infection and 71.5 % postoperative infection), compared to a 4% mortality for patients without perioperative COVID-19 infection between January and March 2020 (*6*). A meta-analysis of 2,947 patients with perioperative COVID-19 infection has demonstrated a 20% postoperative mortality rate although these were a mixture of different surgical specialties (*7*). For elective liver and pancreas cancer surgery, an international study conducted by McKay SC, *et al*. reported that perioperative COVID-19 infection was associated with significantly higher mortality

(patients with COVID-19; 9.4% *vs*. patients without COVID-19; 2.6%) during the first 3 months of the COVID-19 epidemic (*8*). Martinez-Mier G, *et al*. have performed a comparative analysis of two periods (pre-COVID-19 and COVID-19 period) and demonstrated a negative impact of COVID-19 period (2020–2021) on HPB surgical outcomes with a higher mortality in Mexico (*9,10*). However, in Italy, there was no significant difference in 30–day postoperative mortality after liver and pancreas surgery between the pre-COVID-19 and COVID-19 periods (*11,12*).

Postoperative pulmonary complications in patients with perioperative COVID-19 infection

Patients undergoing abdominal surgery during the pandemic may be at increased risk of postoperative pulmonary complications due to the effects of the virus on the respiratory system. Several studies have investigated this issue, providing valuable insights into the impact of COVID-19 on surgical outcomes. One study by the COVIDSurg Collaborative examined mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection (*6*). The study included over 1,100 patients from 235 hospitals across 24 countries. The results showed that postoperative pulmonary complications occur in 50% of patients with perioperative COVID-19 infection and are associated with high mortality (23.8%) (*6*). Another study by the STARSurg Collaborative and COVIDSurg Collaborative investigated the impact of the pandemic on postoperative pulmonary complications in patients undergoing surgery. The results showed that COVID-19 infection showed a significant association with the development of postoperative pulmonary complications (*13*). A third study by the COVIDSurg Collaborative and GlobalSurg Collaborative examined the effects of preoperative isolation on postoperative pulmonary complications after elective surgery. The study found that preoperative isolation did not reduce the incidence of postoperative pulmonary complications after elective surgery. In fact, the incidence of pulmonary complications was slightly higher in patients who were isolated preoperatively compared to those who were not isolated (*14*). The COVID-19 pandemic has posed significant challenges to the management of patients undergoing abdominal surgery, with an increased risk of postoperative pulmonary complications.

Postoperative complications without pulmonary involvement

An international cohort study has revealed that COVID-19 was associated with late postoperative bleeding, bile leakage, and grade B/C pancreatic fistula (*8*). However, their study lacks data around the time of COVID-19 infection to definitively attribute complications to COVID-19 infection. Therefore, no definitive relationship between factors has been mentioned. They suggested that patients sustaining complications were more likely to require longer hospital stays, increasing the risk of developing nosocomial COVID-19 infection, thus potentially giving the appearance of a higher rate of surgical complications (*8*).

There is limited data available on whether complications without pulmonary involvement have increased after HPB surgery during the COVID-19 pandemic. However, it is important to carefully consider potential impacts of the pandemic on postoperative care and to take appropriate measures to minimize risk of complications and ensure optimal outcomes for patients.

Did COVID-19 vaccinations improve outcomes after HPB surgery?

In 2021 and 2022, the availability of COVID-19 vaccinations has increased (*15,16*), which could be effective to reduce the number of infections and severity of cases (*17*). A retrospective study published in 2023 found that mortality rates among patients undergoing liver transplantation during vaccination period (September 2021 to March 2022) have equalized with pre-COVID-19 (*18*). On the other hand, Fu N, *et al*. suggested that the vaccination itself did not influence survival prognoses in patients undergoing pancreatectomy for pancreatic adenocarcinoma (*19*). Furthermore, in some regions, the COVID-19 vaccine's availability is still limited (*20*), leading to an increase in the number of cases and potential medical collapse, which could hinder improvement of HPB postoperative mortality rates. Additionally, other factors may still impact HPB postoperative mortality rates despite widespread use of COVID-19 vaccines. Therefore, it is not yet entirely clear whether COVID-19 vaccinations directly contribute to improvement of HPB postoperative mortality rates. Nevertheless, widespread use of COVID-19 vaccines is expected to significantly contribute to an improvement of patient health.

In summary, the COVID-19 pandemic has disrupted healthcare systems worldwide, causing postponement or cancellation of millions of elective surgeries. Perioperative COVID-19 infection increases risk of postoperative mortality and pulmonary complications in patients undergoing abdominal surgery. There is limited data on the impact of COVID-19 on postoperative outcomes in HPB surgery. The timing of surgery for COVID-19 positive patients should be carefully considered, balancing the potential risks of delay with risks of surgery during the infection. The impact of COVID-19 vaccination on the outcomes after HPB surgery has not yet been clarified.

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**Address correspondence to*:
Nermin Halkic, Department of Visceral Surgery, Lausanne University Hospital CHUV, Rue du Bugnon 46, 1011 Lausanne, Switzerland.
E-mail: nermin.halkic@chuv.ch

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An overview of the reclassification of COVID-19 of the Infectious Diseases Control Law in Japan

Kanako Kitahara*, Yoshihiro Nishikawa, Hirokazu Yokoyama, Yoshinobu Kikuchi, Masami Sakoi

Office for COVID-19 and Other Emerging Infectious Disease Control, Cabinet Secretariat, Government of Japan.

Abstract: Japan's responses to COVID-19 have been conducted based on the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Infectious Diseases Control Law) and the Act on Special Measures against Novel Influenza, *etc*. (the Act on Special Measures), as COVID-19 is classified as the category of "the Novel Influenza *etc*." under the Infectious Diseases Control Law. The government's Novel Coronavirus Response Headquarters decided to reclassify COVID-19 as a Category V infectious disease under the Infectious Diseases Control Law in May 2023 since the disease has become less lethal. Accordingly, the countermeasures such as surveillance and medical care are going to be reviewed, and COVID-19 prevention actions will depend on personal choices (Prior to the review in May, mask usage will be changed from 13 March). However, this does not mean that infection control measures are no longer necessary; it is recommended that such measures be taken in certain settings in order to prevent the elderly and those who at a high risk of severe illness from being infected, even after the disease is classified as Category V.

***Keywords*:** COVID-19, the Infectious Diseases Control Law, the Act on Special Measures

Introduction

In December 2019, multiple outbreaks of pneumonia of an unknown cause were reported in the City of Wuhan, Hubei Province, People's Republic of China (*1*), and this was later determined to be the novel coronavirus disease 2019 (COVID-19). The first case in Japan was confirmed on January 15, 2020 (*2*). As for the legal position of COVID-19, it had been specified as "the Designated Infectious Disease" since February 1, 2020 based on the enforcement of the Cabinet Order for the determination of Designated Infectious Diseases according to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Act No. 114 of 1998, hereinafter referred to as "the Infectious Diseases Control Law"), and then it has been defined as "the Novel Influenza *etc*." since February 13, 2021 under the same law due to a law amendment. Measures have been implemented based on the Infectious Diseases Control Law and the Act on Special Measures against Novel Influenza, *etc*. (Act No. 31 of 2012, hereinafter referred to as "the Act on Special Measures") (Figure 1) (*3*). On January 27, 2023, approximately three years after the first reported case in Japan, the government's Novel Coronavirus Response Headquarters decided that COVID-19 will be classified as a Category V infectious disease starting on May 8, 2023 under the Infectious Diseases Control Law.

This article describes the legal framework regarding COVID-19 response, namely the Infectious Diseases Control Law and the Act on Special Measures, and outlines the reclassification of the category of the disease under the Infectious Diseases Control Law.

Legal significance of COVID-19 under the Infectious Diseases Control Law and the Act on Special Measures

The Infectious Diseases Control Law is to provide necessary measures concerning the prevention of infectious diseases and medical care for patients with infectious diseases in order to prevent outbreaks and the spread of infectious diseases, to thereby improve and promote public health (*4*). Under the Infectious Diseases Control Law, the term "infectious disease" refers to Category I Infectious Diseases, Category II Infectious Diseases, Category III Infectious Diseases, Category IV Infectious Diseases, Category V Infectious Diseases, Novel Influenza *etc*., Designated Infectious Diseases, or New Infectious Diseases; measures that can be taken for each category are stipulated in advance. As mentioned earlier, COVID-19 has been defined as "the Novel Influenza *etc*." under the Infectious Diseases Control Law.

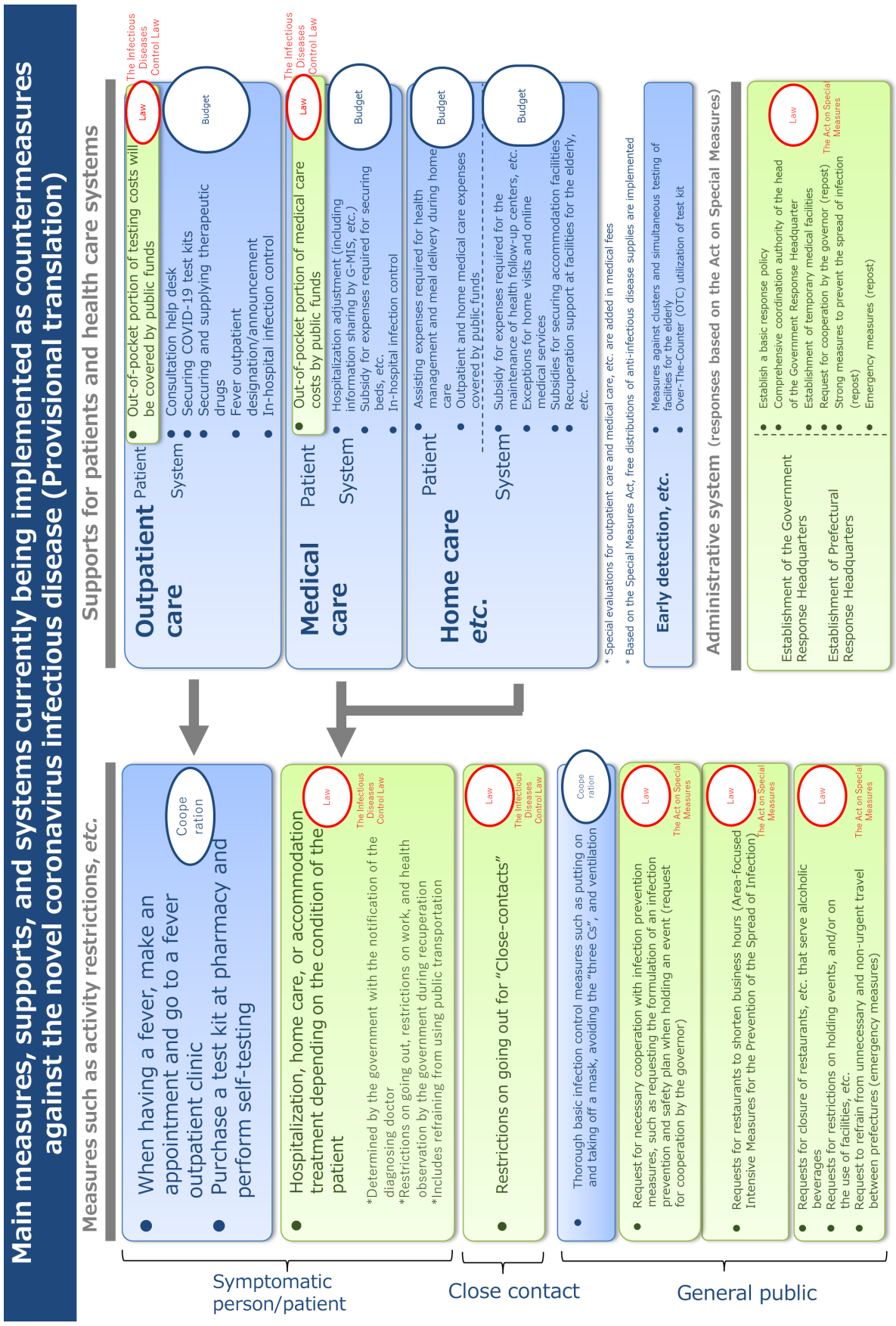

Figure 1. Main measures, supports, and systems currently being implemented as countermeasures against COVID-19 (the 110th Novel Coronavirus Infection Control Advisory Board, Document 4, Ministry of Health, Labour and Welfare).

The Act on Special Measures stipulates a system for a prompt initial response and comprehensive countermeasures to be taken throughout the economy and society in a unified manner, and its aims are to protect the lives and health of people and minimize the impact on the lives of the people and the national economy (*5*). Novel Influenza *etc*., Designated Infectious Diseases, and New Infectious Diseases under the Infectious Diseases Control Law are defined as "Novel Influenza *etc*." in the Act on Special Measures; it stipulates countermeasures such as "Measures under the State of Emergency" and "Area-Focused Intensive Measures for Prevention of the Spread of Infection", as well as requests for cooperation from local residents. In response to COVID-19, requests were made to refrain from leaving home and to restrict the use of facilities including schools as emergency measures were based on the provisions of the Act on Special Measures (Article 45).

Except in cases where Novel Influenza is recognized to be less than or as severe as seasonal influenza, The government's Response Headquarters headed by the Prime Minister will be established based on Article 20 of the Act on Special Measures. The government's Response Headquarters must hear the opinions of "the Council for the Promotion of Countermeasures against Novel Influenza *etc*." and formulates the Basic Policies for the Disease Control. Based on this policy, measures against novel influenza *etc*. will be implemented in prefectures. According to Article 21 of the Act on Special Measures, the government's Response Headquarters will be abolished "when the disease is clearly equal to or less severe than seasonal influenza" or "when it is no longer considered as a Novel Influenza *etc*.". In other words, when COVID-19 is classified as Category V from a "Novel Influenza *etc*." according to classification review under the Infectious Diseases Control Law, responses based on the Act on Special Measures, including The government's Novel Coronavirus Response Headquarters and the Basic Policies for Novel Coronavirus Disease Control, will be abolished.

Previous discussions on reclassification of COVID-19 under the Infectious Diseases Control Law

Since November 2022, the Novel Coronavirus Infection Control Advisory Board (ADB), organized by the Ministry of Health, Labour and Welfare has discussed the reclassification of the disease under the Infectious Diseases Control Law (*6*). On December 1, 2022, based on the response to COVID-19 and preparing for future outbreaks and the spread of infectious diseases that might seriously impact the lives and health of people, the Infectious Diseases Control Law was enacted with amendments to enhance outpatient and inpatient medical care. These changes also seek to allocate medical personnel and infectious disease supplies, to strengthen the system of public health centers and testing, and to improve the information infrastructure. Moreover, an amendment was added in the process of deliberating the law, stating that the "classification of COVID-19 in the Infectious Diseases Control Law will be promptly reviewed". Based on the discussion and this reviewed provisions, the Infectious Disease Subcommittee of the Health and Welfare Science Council also held deliberations, and their opinion was compiled as "the status of COVID-19 in the Infectious Diseases Control Law" on January 27, 2023 (*7*). The conclusions of this report were as follows. Although the severity of COVID-19 has decreased, compared to the early stage of the pandemic, the number of individuals infected with the Omicron strain has increased due to the variant's high transmissibility. Attention needs to be paid to the burden on the medical care system and the increase in the number of deaths, and attention must be paid to the possibility of a new variant emerging in the future. Nevertheless, allowing restrictions on private rights in a uniform manner is not appropriate since these restrictions should be kept to a minimum, and specially for many patients with mild symptoms. COVID-19 is not considered to "have a serious impact on the lives and health of the public", so the current situation is no longer commensurate with the restrictions on private rights under the Infectious Diseases Control Law. Therefore, COVID-19 should now be reclassified as a Category V infectious disease since it does not correspond to a Novel Influenza *etc*. Since the changes in the classification and various measures will have major impacts on people's living, these changes should be implemented after approximately three months of preparation. If the scientific circumstances change in the future, such as the emergence of novel variants with significantly different pathogenicity from Omicron, then this policy would need to be immediately reviewed.

Based on these discussions, The government's Novel Coronavirus Response Headquarters that held on the same day decided on the "Policy for Changing the Status of the Novel Coronavirus Infection under the Infectious Diseases Control Law" (*8*). This policy indicated that, unless there are special circumstances such as the emergence of a variant with significantly different pathogenicity from the Omicron, COVID-19 does not correspond to a Novel Influenza *etc*. under the Infectious Diseases Control Law and thus will be reclassified as a Category V infectious disease starting on May 8, 2023. However, the decision was also made to hear the opinions of the Infectious Diseases Subcommittee of the Health and Welfare Science Council again before the change, and that implementation would take place after final confirmation of changing the classification at the planned time.

Future outlook

Along with the change in the classification of COVID-19

under the Infectious Diseases Control Law, there will be a revision of the policies and measures implemented thus far. The details of the revision were indicated in the aforementioned Decision of The government's Novel Coronavirus Response Headquarters (*8*). Filing of notification of outbreaks of COVID-19 based on the Infectious Diseases Control Law will be discontinued, and there will be a shift from notifiable disease surveillance to the monitoring of infection trends by sentinel surveillance with designated medical facilities, with continued genome surveillance. The decision was also made to announce a specific policy regarding public financial support for medical care of patients and a medical care system for COVID-19 by approximately early March 2023. Vaccination will continue to be implemented under the Immunization Act (Act No. 68 of 1948) regardless of the change in COVID-19's status under the Infectious Diseases Control Law.

The government's Novel Coronavirus Response Headquarters indicated that effective indoor ventilation and hand hygiene will be still recommended, while mask usage will require further deliberation from the perspective of respect of personal choice, certain recommended settings of mask usage that should be publicized by the government, and trends and situation of COVID-19, then the result should be released at an early date with information of the timing of revision of mask policy. At the 115th and 116th ADB, future infection control measures were discussed, and also mask wear was reviewed on February 10, 2023 at the subcommittee on the basic response policy under the Council for the Promotion of Countermeasures against Novel Influenza (32nd meeting) (*9*). Based on this discussion, The government's Novel Response Headquarters made a decision regarding the "Revised view of mask usage" on the same day (*10*). The decision indicated that the current recommendation to wear a mask indoors will be changed, and that personal choices should be respected, leaving the wearing of a mask up to the individual, instead of guided by the Government's decision as a uniform rule. Given a preparatory period, the review is set to take effect starting on March 13, 2023, and from April 1 for schools. For graduation ceremonies in schools to be held before April 1, the suggestion was made that children and students could attend ceremonies without wearing a mask from the perspective of event's educational significance. As for the certain recommended settings of mask usage that should be publicized by the government, following settings were demonstrated: When in medical institutions, when visiting medical institutions and nursing homes where people at high risk of more severe disease lives, crowded settings such as crowded commuter trains and buses (excluding those that permit seating for all passengers, such as Shinkansen, commuter liner, highway bus, charter bus *etc*.), when people at high risk of severe illness during the spread of infection go to crowded places. The "Industry Guidelines", which are compiled by industry groups voluntarily for infection control measures, will be abolished due to the transition to a Category V infectious disease. As individuals and business implement voluntary infection control measures, the Government will continue to support the efforts of individuals and businesses by providing necessary information, even after the change in COVID-19's status under the Infectious Diseases Control Law.

Based on these measures, preparations for the transition will be made at each site until May 8, 2023 when COVID-19 will be reclassified as a Category V infectious disease. (*The revised policy regarding public financial support for medical care of patients and a medical care system for COVID-19 was released on March 10, 2023.)

Conclusion

Due to the change in the classification of COVID-19 under the Infectious Diseases Control Law, infection control measures that have been implemented based on this law and the Act on Special Measures will be reviewed. However, this does not mean that infection control itself will become unnecessary; rather, continuing to ensure the cooperation of the public with infection countermeasures is essential while obtaining their assent. Necessary infection control measures should be implemented in accordance with the characteristics of the disease, including the protection of the elderly and people suffering from underlying diseases who are at high risk of severe illness.

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**Address correspondence to*:
Kanako Kitahara, Office for COVID-19 and Other Emerging Infectious Disease Control, Cabinet Secretariat, Government of Japan, 1-6-1 Nagatacho, Chiyoda-ku, Tokyo 100-8968, Japan.
E-mail: kanako.kitahara.z4t@cas.go.jp

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Social implications of a change in the legal classification of COVID-19: The need for pandemic prevention, preparedness, and healthcare system strengthening

Norio Ohmagari*

National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: In Japan, there has been a discussion of the potential reclassification of the novel coronavirus infectious disease 2019 (COVID-19) as an infectious disease under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Infectious Diseases Control Law), beginning in late 2022. To make an informed decision, the societal impact of COVID-19 needs to be carefully considered to ensure that any reclassification does not negatively impact healthcare or society as a whole. The disease burden of COVID-19 remains considerable and is likely to persist for an extended period of time. Consequently, numerous special measures have been taken in the healthcare system to cope with COVID-19. Several of these measures must be implemented. Thus, the healthcare system needs to be strengthened in the future. This will result in adequate prevention, preparation, and a response to future pandemics.

***Keywords*:** the Infectious Diseases Control Law, transmissibility of infection, public health

Introduction

Three years have passed since the onset of the global novel coronavirus infectious disease 2019 (COVID-19) epidemic. In Japan, discussion of the reclassification of the disease under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Infectious Diseases Control Law) began toward the end of 2022. One of the primary drivers of the discussion is the decreased risk of severe morbidity and mortality associated with the disease. Nevertheless, there are concerns regarding the lingering deleterious ramifications of the disease control measures on society. Consequently, the presumption is that a shift in the disease classification under the Infectious Diseases Control Law could abate the measures' negative societal impact. Nonetheless, any change in the classification of the disease must be grounded in a profound understanding of its current impact on society, and such a change must not adversely affect healthcare and society as a whole.

This study provides an evaluation of the present medical status of COVID-19 and its impact on society. In addition, it discusses pertinent aspects that need to be considered in the development of the healthcare system when contemplating future changes to the classification of COVID-19.

Current medical status of COVID-19 and its impact on society

Severity of COVID-19

Comparing the severity of COVID-19 to that of influenza poses a challenge. However, if people who are tested and test positive are considered to be those seeking medical care, then utilizing the positive cases as the denominator to evaluate the rate of severe cases and deaths may provide useful insights into the level of medical care required. To this end, on December 21, 2022, the Ministry of Health, Labour and Welfare presented data to its Advisory Board on COVID-19, indicating a decrease in severity to similar levels only for people seeking medical care (*1*). A point worth noting is that COVID-19 has been associated with prolonged symptoms and a heightened risk of exacerbating pre-existing comorbidities. The risk of worsening comorbidities triggered by COVID-19 has also been noted. Individuals hospitalized with COVID-19 are reported to be at an increased risk of cardiovascular events (*2*). These facts may represent a significant additional burden of the disease.

Transmissibility of infection

This disease is highly contagious, with the Omicron

variant exhibiting greater transmissibility compared to both the seasonal and 2009 H1N1 influenza strains (*3*). The elevated level of transmissibility serves to account for the considerable number of positive cases, hospitalizations, and fatalities stemming from COVID-19.

Impact on public health

The COVID-19 pandemic has led to a significant number of positive cases, a vast number of hospitalizations, and an elevated death toll, thus imposing a substantial medical burden on healthcare facilities, compounded by pre-existing medical requirements. Moreover, the lingering post-illness symptoms associated with COVID-19 (*4*) and the heightened risk of developing subsequent health complications, such as cardiovascular diseases, have been identified as additional burden on the healthcare system. Hence, the medium- to long-term ramifications of this disease on public health are immense. To address this challenge, various public health and medical interventions currently in place must be sustained. Accordingly, the establishment of a sustainable healthcare system is imperative.

On the one hand, the disease commonly referred to as COVID-19 has been designated as a distinct illness known as "a novel coronavirus infection" under the Infectious Diseases Control Law. Consequently, medical facilities that offer both outpatient and inpatient care are substantially restricted to those officially designated by the government for the purpose of medical treatment and testing. Therefore, healthcare facilities that lack such government recognition are not mandated to accommodate patients diagnosed with COVID-19. Despite the increased medical workload resulting from the aforementioned circumstances, the current healthcare system is no longer equipped to handle the demands posed by this disease. To remedy this situation, the number of medical facilities capable of providing COVID-19 treatment must be increased.

Points to be considered after the change in classification

The emergence of COVID-19 has imposed a considerable supplemental strain on existing medical demands. The majority of the current support mechanisms for patients and the medical system, such as outpatient care, inpatient care, and home care, are vital and must be sustained. Although a considerable number of these measures are not legally mandated, they are implemented through funding by both central and local governments. Naturally, as the healthcare system adapts to cope with the exigencies posed by the pandemic, redundant services that are no longer required will need to be discontinued.

A system to coordinate hospitalization

Coordinating hospitalization for dialysis patients, pregnant women, and children poses a significant challenge. Consequently, local governments need to provide support for coordination of hospitalization at present. In the long run, a collaborative hospitalization system needs to be established among medical facilities and it needs to operate independently of local government support. Although autonomous coordination among medical facilities is underway in some regions, significant regional disparities persist. Despite established methods of preventing severe disease, treatment, and vaccination, many medical facilities refuse to accept COVID-19 cases due to their special classification under the Infectious Diseases Control Law. An important point, however, is that the pathogenesis of COVID-19 is well-understood and that the disease can be treated similar to other illnesses. The current classification under the the Infectious Diseases Control Law impedes the ability of medical facilities to effectively address the disease. Therefore, the classification of COVID-19 under the Infectious Diseases Control Law should be modified accordingly to allow for better management of the disease.

Several medical facilities and facilities lack experience in accommodating COVID-19 patients and thus lack the necessary infrastructure to respond efficiently. Despite the reclassification, continued government and local medical facility support needs to be provided to facilitate the smooth acceptance of COVID-19 patients in medical facilities and facilities for the elderly that have limited experience in handling such cases. Such support would include medical care and infection control. Acute respiratory infections, including COVID-19 and influenza, are anticipated to remain a significant medical and nursing care challenge in Japan's super-annuated population. A robust regional healthcare infrastructure needs to be developed to effectively manage these illnesses, while concurrently preparing for future pandemics. Establishing a robust and resilient healthcare system will help to avoid the confusion experienced during the current pandemic and better navigate future crises.

Outpatient clinics

Moreover, there is a pressing need to increase the number of medical facilities capable of providing outpatient care. The current classification of outpatient care presents a significant obstacle to entry, and hence, its reclassification is imperative. Amidst the ongoing pandemic, Japan has witnessed the commercial availability of COVID-19 and influenza test kits, which can now be directly utilized by consumers. This has facilitated independent testing and significantly curtailed the need for patients to visit medical facilities.

The anticipated surge in medical demand due to COVID-19 is considerable. Furthermore, ailments like the common cold, which do not necessarily require specialized treatment, impose a considerable strain on Japan's healthcare system. To alleviate this burden, patient self-care for acute respiratory infections needs to be promoted, utilizing self-testing kits and other pertinent tools.

Conclusion

Therefore, the disease burden imposed by COVID-19 is substantial, and anticipating its prolonged persistence is imperative. To address COVID-19, government agencies have introduced specialized measures to facilitate both outpatient and inpatient care. Several of these interventions will require sustained implementation. Strengthening healthcare systems is critical to meeting prevailing healthcare needs. Such endeavors will enable adequate prevention, preparation, and a response to future pandemics.

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**Address correspondence to*:
Norio Ohmagari, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku, Tokyo 162-8655, Japan.
E-mail: nohmagari@hosp.ncgm.go.jp

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Tools and factors predictive of the severity of COVID-19

Masaya Sugiyama*

Department of Viral Pathogenesis and Controls, National Center for Global Health and Medicine, Ichikawa, Japan.

Abstract: The outbreak of the novel coronavirus infection caused worldwide confusion. The problem with this infection is that it causes severe illness in some patients, resulting in a high rate of death if appropriate treatment is not given. If patients with severe illness that requires treatment are appropriately identified, treatment can be focused on these patients. However, in the early days of the COVID-19 outbreak, the inability to predict and diagnose the disease led to hospitals being overwhelmed. Therefore, various methods for the diagnosis of severe disease were developed early on, and various methods are still being investigated to predict high-risk patients. The currently available prediction methods are divided into those that predict the onset of severe disease and those used to determine the severity of the disease. Specifically, the main methods include genetic factors, serum humoral factors, laboratory tests, and diagnostic imaging. Since each of these factors has different features, using them in combination is likely to be advantageous.

***Keywords*:** SARS-CoV-2, severe illness, serum marker, genetic variation, artificial intelligence

Introduction

Coronavirus disease 2019 (COVID-19), which is caused by Severe Acute Respiratory Syndrome Coronavirus type 2 (SARS-CoV-2) infection, reached epidemic proportions worldwide. SARS-CoV2 is highly infectious and can rapidly spread if infection control measures are not taken, leading to an exponential increase in the number of COVID-19 cases.

COVID-19 causes mild to moderate symptoms in the early stages of infection, and many COVID-19 patients recover without sequelae. Some patients, however, transition from mild or moderate to severe symptoms (*1*). Although it would be desirable to detect patients with severe disease in the early stages of infection, identification of such patients has been difficult. Additionally, since delayed treatment leads to a lower survival rate for those who become severely ill, it is ideal to intervene early in the treatment of only those patients who are likely to develop severe illness.

At the beginning of the COVID-19 pandemic, hospitals received so many patients that they were quickly overwhelmed, delaying treatment for many and thus causing people to suffer. Therefore, several clinical studies evaluated predictive markers for detecting critically ill patients because of the high demand for such markers. This review summarizes these predictive markers of COVID-19 severity.

Predictive markers using biochemical tests

Laboratory biomarkers are inexpensive, rapid, and readily available. As such, they have become the preferred means of monitoring and predicting disease outcomes and prognosis.

Since laboratory biomarkers have always supported clinical decision-making in various infectious diseases, a better understanding of the profile of specific biomarker changes and differences in COVID-19 prognosis might help in the development of risk stratification methods in the treatment of patients with this disease.

At the beginning of the pandemic, a number of research teams reported markers that are predictive of severe disease, primarily based on laboratory tests. A large number of papers evaluating patients with different characteristics, such as country of residence, race, and testing parameters, were reported. Recently, several meta-analyses have been reported that have analyzed these numerous results and evaluated which factors were truly associated with the development of severe symptoms.

Malik *et al.* conducted a meta-analysis of 32 studies including 10,491 patients with COVID-19, based on laboratory tests reported to be predictive of the development of severe disease (Table 1) (*2*). Their meta-analysis indicated the following factors as being significantly predictive of severe symptoms: lymphopenia, thrombocytopenia, and elevated levels of D-dimer, C-reactive protein (CRP), procalcitonin (PCT), creatine kinase (CK), aspartate transaminase (AST), alanine transaminase (ALT), creatinine, and

lactate dehydrogenase (LDH). Multiple laboratory tests associated with severe illness have been narrowed down to identify the factors that really are important.

Predictive markers related to underlying disease

In addition to laboratory tests, the presence of underlying diseases has been reported to be associated with the onset of severe illness. In a report by Mudatsir *et al.*, it was confirmed that patients with underlying diseases are more likely to develop more severe symptoms (*3*). They included 19 papers documenting 1,934 mild and 1,644 severe COVID-19 cases, and identified the potential risk factors for severe illness. They assessed the influence of underlying diseases in addition to laboratory tests. Regarding laboratory tests, as reported in other meta-analyses, low levels of lymphocytes and hemoglobin, and elevated blood levels of leukocytes, AST, ALT, creatinine, blood urea nitrogen, high-sensitivity troponin, CK, high-sensitivity CRP, interleukin 6, D-dimer, ferritin, LDH, and PCT, as well as a high erythrocyte sedimentation rate (ESR) were all associated with severe COVID-19.

In particular, several comorbidities, including chronic respiratory disease, cardiovascular disease, diabetes mellitus, and hypertension, were more frequently observed in patients with severe COVID-19 (Table 2). A larger number of comorbidities were also observed in patients with severe COVID-19 than in those with mild disease. Further, dyspnea, anorexia, fatigue, increased respiratory rate, and increased systolic blood pressure were observed more often in patients with severe COVID-19 compared to those with mild COVID-19. These symptoms could thus be useful baseline parameters in the development of prognostic tools for COVID-19.

Table 1. Laboratory tests which are independently associated with higher risk of COVID-19 poor outcomes

Features	Pooled-OR (95% CI)	*p* value
Lymphopenia	3.33 (2.51–4.41)	< 0.00001
Thrombocytopenia	2.36 (1.64–3.40)	< 0.00001
Elevated D-dimer	3.39 (2.66–4.33)	< 0.00001
Elevated CRP	4.37 (3.37–5.68)	< 0.00001
Elevated PCT	6.33 (4.24–9.45)	< 0.00001
Elevated CK	2.42 (1.35–4.32)	0.003
Elevated AST	2.75 (2.30–3.29)	< 0.00001
Elevated ALT	1.71 (1.32–2.20)	< 0.00001
Elevated creatinine	2.84 (1.80–4.46)	< 0.00001
LDH	5.48 (3.89–7.71)	< 0.00001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C reactive protein; LDH, lactate dehydrogenase; PCT, procalcitonin. This table was modified from Malik P, *et al.* BMJ 2020.

Table 2. Underlying diseases which are independently associated with higher risk of COVID-19 poor outcomes

Features	Pooled-OR (95% CI)	*p* value
Chronic respiratory disease	2.31 (1.37–3.89)	0.002
Cardiovascular diseases	1.71 (1.05–2.78)	0.03
Diabetes mellitus	2.10 (1.32–3.34)	0.002
Hypertension	2.32 (1.43–3.78)	0.0007
Dyspnea	3.28 (2.09–5.15)	< 0.00001
Anorexia	1.83 (1.00–3.34)	0.05
Fatique	2.00 (1.25–3.21)	0.004
Dizziness	2.24 (1.08–4.65)	0.03
Respiratory rate	0.57 (0.14–1.01)	0.01
Systolic blood pressure	0.33 (0.14–0.52)	0.0005

This table was modified from Mudatsir M, *et al*. F1000Reasearch 2021.

Predictive markers using humoral factors

Interleukin-6 (IL-6)

In previous analyses of humoral factors associated with the severity of illness, IL-6 has often been the focus of attention since the early days of COVID-19 (*4-6*). Indeed, use of inhibitors of the IL-6 pathway have been indicated as a potentially useful treatment strategy (*7*). Data showing that IL-6 is associated with severe disease showed a significant difference in its median value between hospitalized and non-hospitalized groups (*8*). Significant differences were also found between the short and long hospitalization groups. This indicates that IL-6 has utility as a biomarker of the degree of severity of illness. However, since these studies analyzed patients after hospitalization for severe disease, it is not clear whether IL-6 is a useful predictor of the severity of illness. On the other hand, as shown in Figure 1, IL-6 levels in COVID-19 have been reported as being not as high as in previous IL-6-related diseases, indicating data that IL-6 is unlikely to be a main constituent of the

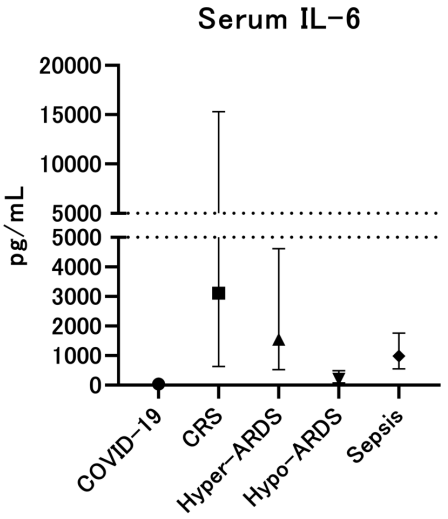

Figure 1. Serum IL-6 levels in cytokine related inflammatory diseases. Serum IL-6 concentrations of COVID-19, CRS, hyper-ARDS, hypo-ARDS, and sepsis are shown in this graph. This data is original and is not published. Hyper-ARDS, hyperinflammatory acute respiratory distress syndrome; Hypo-ARDS, hypoinflammatory acute respiratory distress syndrome; CRS, cytokine release syndrome.

disease (*4*).

In Japan, IL-6 testing is approved by health insurance for the assessment of severe systemic disease. It is regulated for the purpose of diagnosing the severity of severe illness in patients with severe disease, but not for the prediction of the onset of severe illness. By this test, physicians may be able to determine if high IL-6 is the cause of the severe disease.

Interferon-lambda 3 (IFN-λ3)

From the beginning of the COVID-19 outbreak, our research team has been searching for diagnostic markers that can predict which patients will transition to severe or critical illness (*9*). By measuring approximately 70 humoral factors in the blood, our research team was able to identify several factors that are characteristically altered in patients with severe or critical disease before the disease worsened. These factors include IFN-λ3, C-X-C motif chemokine (CXCL) 9, CXCL10, IL-6, and C-C motif ligand (CCL) 17 (*10*). At the time of that study, results regarding CXCL9, CXCL10, and IL-6 had also been previously reported from overseas, and our results corroborated those, while IFN-λ3 and CCL17 were newly reported biomarkers of disease severity. These markers were found to be more accurate as predictive markers than previous laboratory tests and humoral factors (*10*). In fact, these two biomarkers are now included in the Japanese insurance system as tests that can be used to predict severe or critical COVID-19. Use of the IFN-λ test in real-world clinical practice reproduced the IFN-λ kinetics shown in our first paper (*11*).

IFN-λ3 is a member of the gene family called type III interferons, and is one of the most widely conserved genes in living organisms (*12,13*). In humans, the presence of IFN-λ1 to 4 has been shown, with their number varying among organisms. In viral and other infectious diseases, IFN-λs are involved in the initial response to infection and are characterized by the expression of a large number of receptors for IFN-λs, especially in epithelial tissues. This suggests that IFN-λs play a different role than IFN-α/β, which are known to act in the whole body.

Although a relationship between COVID-19 and the IFN-λ family has been suggested, details of this relationship are not yet clear. The extremely high sequence homology of the human IFN-λ family makes it difficult to quantify them separately, and it is common practice to analyze the IFN-λ family together (*12,13*). By quantifying the IFN-λ family members separately, our research team showed for the first time in humans that IFN-λ3 is important in COVID-19 (*10*).

Analysis of changes in IFN-λ3 during the course of COVID-19 revealed that patients transitioning from mild to severe disease show a characteristic peak value a few days before the transition (*9*). The change is characterized by a transient high value followed by a rapid decrease, with no cases being observed in which the value remained persistently high (Figure 2, A-C). Furthermore, in the course of the decrease in IFN-λ3 values, the patients' condition became severe, requiring oxygen and ventilators. With regard to the peak value, the higher this value, the more severe the symptoms tended to be, although we are currently in the process of accumulating more data on this point.

CCL17

CCL17 (also known as Thymus and activation-regulated chemokine, TARC) is a chemokine known to be associated with the activation of antibody-producing cells (*14*). The blood level of CCL17 in healthy humans is about 1,000 pg/mL at birth, decreasing to about 400 pg/mL during subsequent growth. CCL17 is particularly associated with allergies, and high levels of CCL17 in atopic dermatitis and asthma are associated with severe symptoms. In atopic dermatitis, in which the testing for CCL17 is covered by insurance, the higher the serum CCL17 level, the more severe the condition (*14*).

On the other hand, low levels of CCL17 are found to be associated with severe symptoms in COVID-19 (*9*); humans who recovered from mild disease with COVID-19 had levels similar to those in healthy individuals, while those who went on to develop severe disease already had levels below 87.5 pg/mL in the early, mild stage of infection (Figure 2, D and E). This suggests that CCL17 might be a predictive marker of severe disease that can be used in the early stages of COVID-19 infection.

At the time of the report, this result was a new phenomenon, as there were few reports showing an association between low CCL17 levels and disease. Thus, at this point, our research team believes that this phenomenon is specific to COVID-19 severity, although the detailed mechanism is not clear.

Based on previous reports and our review, it has not been reported that CCL17 values tend to decrease with increasing age. While it is clear that elderly people are more susceptible to severe disease, it is also clear that this is limited to a subset of the elderly. Based on these facts, our research team speculates that this phenomenon of CCL17 decline is due to SARS-CoV-2 infection. Basic analysis is currently underway to elucidate the mechanism of this phenomenon.

Predictive markers using genetic factors

The viral life cycle requires human host genes. Polymorphisms in human genes involved in viral entry and replication might contribute to disease prognosis and outcome. In other words, human genetic polymorphisms might affect the course of COVID-19. The most studied genes are those that interact directly with spike proteins

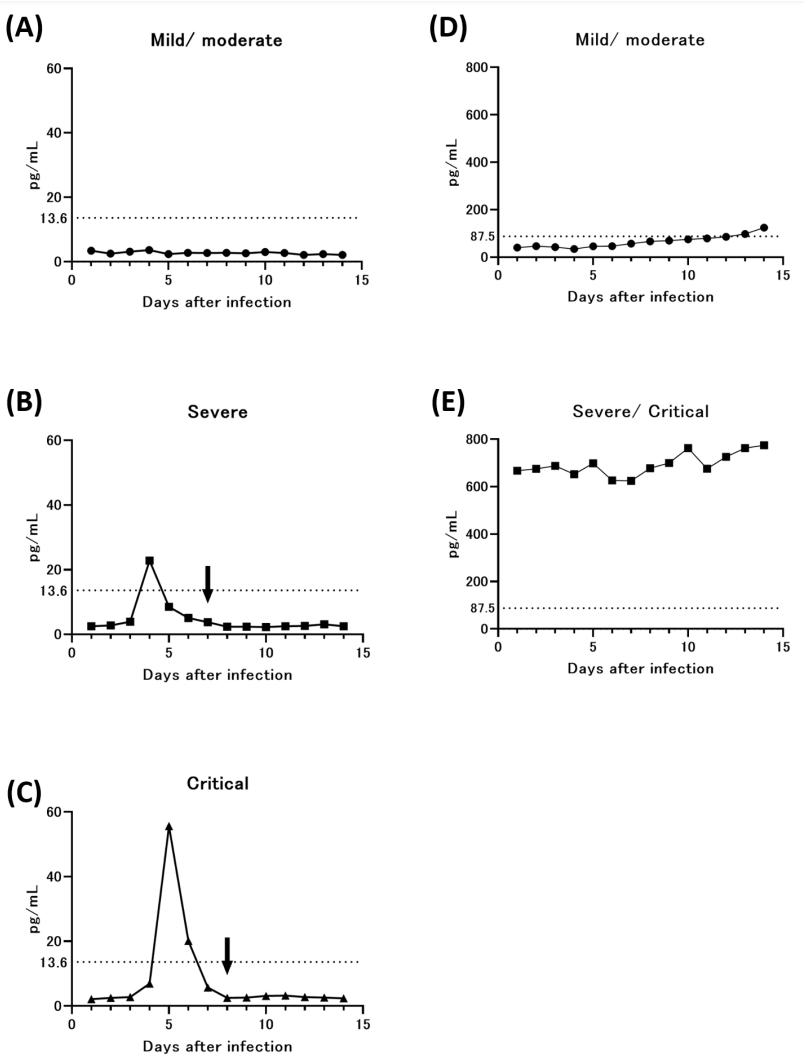

Figure 2. Dynamics of serum IFN-l3 and CCL17 levels in COVID-19. Representative profiles of serum IFN-λ3 and CCL17 are shown in COVID-19 patients. The dynamics of serum IFN-λ3 are in **(A)** mild/ moderate, **(B)** severe, and **(C)** critical patients. The dynamics of serum CCL17 are in **(D)** mild/ moderate, **(E)** severe/ critical patients. The threshold line for predicting severe and critical illness was set at more than 13.6 pg/mL for IFN-λ3 and less than 87.5 pg/mL for CCL17. Arrow shows the point of the onset of severe or critical symptoms. This data is original and is not published.

(*15*). Single nucleotide polymorphisms (SNPs) in ACE2 and TMPRSS2 might contribute to selective binding of SARS-CoV-2. Since there are many published reports on the involvement of these genes in viral entry (*16*), a meta-analysis has been conducted on this, although its data is still awaited (*17*).

ACE1 rs4646994 is an insertion or deletion polymorphism. Meta-analysis showed that this genetic polymorphism is significantly associated with an increased risk of developing severe COVID-19 (*17*), as observed in the allelic model (D *vs*. I, $p < 0.0001$), dominant model (DD *vs.* II + ID, $p < 0.0001$), homozygous model (DD vs. II, p = 0.0004), and additive model (DD *vs*. ID, $p = 0.0006$), while there was no association in the recessive model (DD + ID *vs.* II, $p = 0.55$) (Table 3). These results suggested that the deletion mutation was associated with severe disease.

A meta-analysis evaluating ACE2 rs2285666 polymorphism and the risk of severe disease showed a significant association between them. A significant association between ACE2 rs2285666 polymorphism and an increased risk of developing severe COVID-19 was found in two genetic models (recessive GG *vs.* GA + AA, $p = 0.005$; additive GG *vs.* GA, $p = 0.02$), indicating an increased risk of developing COVID-19 with an extremely significant difference between those with and without these polymorphisms. In contrast to the above findings, the remaining three genetic models showed no statistically significant differences in the onset of severe illness (allele G *vs*. A, $p = 0.15$; dominant GG + GA *vs.* AA, $p = 0.64$; homozygous GG *vs*. AA, $p = 0.11$) (Table 3) (*17*).

The meta-analysis also established a significant relationship between TMPRSS2 rs12329760 polymorphism and the high risk of developing severe COVID-19 only in the allelic model (C *vs.* T, $p = 0.04$), although no association was found in the remaining models (Table 3). However, since fewer than 10 studies

Table 3. Genetic factors which are independently associated with higher risk of COVID-19 poor outcomes

Features	Pooled-OR (95% CI)	*p* value
ACE1 rs4646994		
D allele *vs*. I allele	1.62 (1.28–2.05)	0.0001
DD *vs*. DI+II	2.06 (1.45–2.93)	0.0001
DD+DI *vs*. II	1.20 (0.66–2.20)	0.55
DD *vs*. II	2.29 (1.44–3.62)	0.0004
DD *vs*. DI	1.99 (1.35–2.95)	0.0006
ACE2 rs2285666		
G allele *vs*. A allele	1.64 (0.83–3.25)	0.15
GG+GA *vs*. AA	1.33 (0.40–4.39)	0.64
GG *vs*. GA+AA	2.14 (1.26–3.66)	0.005
GG *vs*. GA	2.14 (1.14–4.01)	0.02
GG *vs*. AA	1.98 (0.85–4.61)	0.11
TMPRSS2 rs12329760		
C allele *vs*. T allele	1.32 (1.01–1.73)	0.04
CC+CT *vs*. TT	1.56 (0.45–5.37)	0.48
CC *vs*. CT+TT	1.38 (0.99–1.92)	0.05
CC *vs*. CT	1.29 (0.91–1.81)	0.15
CC *vs*. TT	1.74 (0.47–6.44)	0.41

D allele, deletion allele; I allele, insertion allele; DD, DD genotype; II, II genotype. This table was modified from Saengsiwaritt W, *et al*. Rev Med Virol. 2020.

were included in the meta-analysis of this genetic polymorphism, tests of funnel plot asymmetry, meta-regression analysis, and sensitivity analysis were not performed.

In addition, a large number of other genetic polymorphisms have been reported to be associated with the severity of COVID-19 (*16,18-20*). However, no genetic polymorphisms strongly associated with severe disease that could be used for diagnosis have been reported, suggesting that genetic factors have a limited impact on the severity of the disease.

Predictive AI model using biochemical and humoral factors

When the COVID-19 pandemic initially began, there were no effective drugs or treatments available because there was not enough information on or experience with this disease. Therefore, there was an urgent and important need to find new technologies for its early diagnosis, detection, and treatment. Artificial intelligence (AI) driven by multi-model data was used as a solution in this situation. During the COVID-19 pandemic, AI provided cutting-edge applications in terms of determining its pathogenesis, best practices, and treatment. The application of AI to diagnosis also helped predict disease progression, enabling the early detection and treatment of high-risk patients.

Li *et al.* investigated AI quantification of initial chest CT in COVID-19 patients for predicting disease progression and clinical outcomes (*21*). In their study, the CT severity score (CT-SS) was calculated according to the extent of lesions, and ground-glass opacity and consolidation volume were quantified by AI. In terms of imaging parameters, consolidation volume was the most effective in discriminating non-severe from severe patients (AUC = 0.796, $p < 0.001$), as well as identifying the presence of critical events (AUC = 0.754, $p < 0.001$). The results showed that consolidation volume and age were the two major predictors of disease progression.

Similarly, Yang *et al.* applied chest CT-SS as an imaging tool for evaluating the progression of COVID-19 (*22*). In their model, the optimal CT-SS threshold for identifying severe COVID-19 was 19.5, with a sensitivity of 83.3% and specificity of 94%. This suggests that CT-SS can rapidly and objectively assess the severity of pulmonary lesions in patients with COVID-19.

Yan *et al.* developed a predictive model based on the XGBoost model (*23*). They identified three important clinical characteristics from more than 300 factors as being useful for predicting COVID-19 outcomes: LDH, lymphocyte count, and high-sensitivity CRP. The model was able to predict survival of COVID-19 patients with greater than 90% accuracy.

Description of predictive markers of severe symptoms in representative guidelines

Blood tests are helpful in understanding the condition of patients, and should be performed in patients with risk factors for severe disease or those with moderate or severe disease. Many studies have been conducted in many countries, especially on biomarkers (markers of severity of illness) that contribute to the determination of severity of illness and patient prognosis. The use of these biomarkers is expected to improve the quality of medical care and the effective use of medical resources.

Guidelines provided by the Japanese Ministry of Health, Labour and Welfare (MHLW) provide an introduction to predictive markers for severe disease. This guideline presents a recent meta-analysis, which describes the following markers as being associated with severe or critical symptoms: lymphocytopenia, thrombocytopenia, and elevated levels of D-dimer, CRP, PCT, CK, AST, ALT, creatinine, and LDH.

In addition, a report was introduced that showed a higher percentage of genetic mutations associated with decreased interferon alpha production in severe cases. Furthermore, IFN- λ3 is known to be elevated in the blood of patients infected with SARS-CoV-2 from about 1 to 3 days before symptoms indicating the need for oxygen administration. This measurement in patients hospitalized due to SARS-CoV-2 positivity could predict the severity of the disease.

TARC (CCL17) levels are also known to be low in the blood of patients infected with SARS-CoV-2 from the early onset of COVID-19 until the onset of severe disease in patients who develop severe disease that requires oxygen administration.

On the other hand, although there is no explicit mention of predictive markers of severe disease in

the NIH guidelines, some markers were introduced as described below. Patients with certain underlying comorbidities are at an increased risk of developing severe COVID-19 progression. These comorbidities include being over 65 years of age, having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, chronic kidney disease, pregnancy, being a smoker, being a transplant patient, and receiving immunosuppressive therapy. Hence, medical professionals should closely monitor these patients until they have clinically recovered. Laboratory tests include complete blood counts (fractions) and metabolic profiles (*e.g.*, liver and renal function tests) are available, although inflammatory markers such as CRP, D-dimer, and ferritin are not regularly measured as a part of standard care, their results might be prognostically useful (*24-26*).

It is essential to note that our research team could not find adequate information for predictive markers of severe symptoms in the UK or WHO guidelines(*27*). As many papers have been reported on predictive markers of severe symptoms, adequate evidence needs to be accumulated to prepare for the next pandemic.

Conclusion

This unprecedented infectious disease that struck humanity has led to numerous studies worldwide. For new infectious diseases, in order to control them at as early a stage as possible, diagnostic and therapeutic methods should be developed as early as possible. Numerous studies have been conducted since the beginning of the COVID-19 outbreak to predict the severity of COVID-19. A number of tools for predicting severe illness have been reported, including genetic factors, humoral factors, and diagnostic imaging techniques.

Historically, respiratory infections have recurred many times, and there is no doubt that another outbreak will occur in the near future. It is hoped that these biomarkers and diagnostic techniques developed all over the world for the COVID-19 pandemic will be useful in the future as well.

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**Address correspondence to*:
Masaya Sugiyama, Department of Viral Pathogenesis and Controls, National Center for Global Health and Medicine, 1-7-1 Kohnodai, Ichikawa 272-0817, Japan.
E-mail: msugiyama@hosp.ncgm.go.jp

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Clinical trial experience in Japan and future issues in developing drugs to treat COVID-19

Ayako Mikami[1,2,*], Junko Terada-Hirashima[1], Daisuke Tokita[1], Wataru Sugiura[1]

[1] Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Center for Clinical Research, National Center for Child Health and Development, Tokyo, Japan.

Abstract: The National Center for Global Health and Medicine plays a central role in the treatment and research of infectious diseases in Japan. It has conducted various research and development activities on drugs to treat coronavirus disease 2019 (COVID-19) with clinical questions as starting points. Clinical trials are essential in developing new treatment modalities, but we have noticed some characteristic difficulties in clinical trials on emerging and re-emerging infectious diseases. For example, since there is no standard of care when an emerging infectious disease starts to spread, establishing an appropriate control group is complicated, and many things are hurried at the start of trials. This means there is little time to arrange a placebo, and conducting blinded, randomized, controlled trials has been difficult. Another issue characteristic of infectious disease has been that progress in enrolling subjects is affected by the spread of the disease. It was also a struggle to select institutions that provide medical care on the front lines of infectious disease and conduct clinical trials regularly. To start multicenter clinical trials expeditiously, a regulated and structured network is thus considered necessary. From the perspective of implementation, it is preferable to conduct decentralized clinical trials (DCTs) that do not depend on people coming to the medical institution, while from the perspective of preventing infections during the spread of COVID-19, wide adoption of eConsent is desirable. Based on the experience of COVID-19, new measures must be taken to prepare for emerging and re-emerging infectious diseases in the future.

***Keywords*:** COVID-19, clinical trial, specified clinical trial, investigator-initiated clinical trial

Introduction

The National Center for Global Health and Medicine (NCGM) is one of Japan's national centers for advanced and specialized medicine, and it plays a central role in treating and researching infectious diseases. In 2009, when novel influenza A (H1N1) was spreading globally, NCGM worked with the Ministry of Health, Labour and Welfare and the National Institute of Infectious Diseases to gather information and provide measures to counter it and inform the general public (*1,2*). During the recent coronavirus disease 2019 (COVID-19) pandemic, three patients with severe disease hospitalized in the NCGM in the early stage were administered remdesivir (RDV) for the first time in Japan through compassionate use. All three patients who received it recovered and were discharged from the hospital. At the same time, various research and development activities on therapeutic drugs started from early in the pandemic. In the early stages, specified clinical trials and investigator-initiated trials on antiviral agents and medical devices were carried out, and efforts were also made to develop antibody preparations and vaccines.

For research and development to progress, a detailed pathological understanding is essential. Therefore, from the early stages of COVID-19, the NCGM collected specimens that would be the foundation for various studies and conducted observational studies (registries) of patients hospitalized for COVID-19 in Japan (*3*) to elucidate the details of the condition.

Clinical trials based on pathological conditions are essential in bringing novel treatment modalities to clinical settings. When possible, double-blinded, randomized, controlled trials are preferable for evaluating treatment modalities. However, while planning and leading clinical trials on COVID-19, we noticed some difficulties peculiar to clinical trials on emerging and re-emerging infectious diseases. The studies that have been performed at our hospital are described, and relevant issues are summarized (Figure 1).

The main clinical trials conducted thus far at the NCGM are outlined below.

Specified clinical trials under the Clinical Trial Act

A multicenter, open-label, randomized, controlled, phase II study to evaluate the efficacy and safety of inhaled ciclesonide for asymptomatic and mild patients with

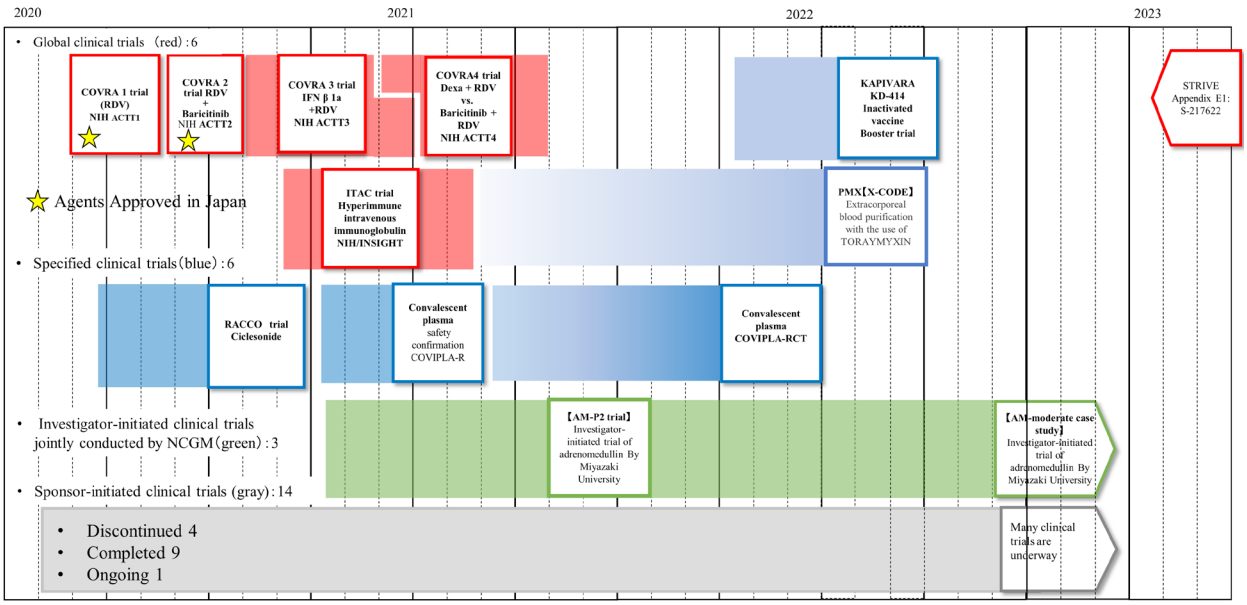

Figure 1. COVID-19-related clinical trials conducted at the National Center for Global Health and Medicine (NCGM) since 2020. Red indicates a global collaborative investigator-initiated clinical trial led by NCGM. Green indicates an investigator-initiated clinical trial in which NCGM participated as a sub-institution, blue indicates a specific clinical study led by NCGM, gray indicates an Industry-sponsored clinical trial.

COVID-19 (RACCO trial)

Enrollment started on March 27, 2020, and was completed on September 17, 2020.

This was the first specified clinical trial planned for COVID-19 at our hospital (*4*). An exploratory phase II trial was started at 22 institutions in Japan led by the NCGM, and 90 people were enrolled. They were randomized into a ciclesonide group and a symptomatic treatment group, and were observed for exacerbation of pneumonia until the eighth day after administration. Exacerbation was seen in 39% (16/41) of the ciclesonide group and 18% (9/48) of the control group. Since significant exacerbation was seen in the ciclesonide group (*5*), it was announced in a press release dated December 23, 2020, that the use of this drug is not recommended for asymptomatic to mild COVID-19 patients.

Exploratory study of the efficacy and safety of direct hemoperfusion using a polymyxin B-immobilized polystyrene column (PMX-DHP) for COVID-19 patients (X-CODE)

Enrollment started on September 28, 2020, and was completed in March 2022 (analysis underway).

This was a multicenter, joint, specified clinical trial to evaluate the efficacy and safety of polymyxin b hemoperfusion (PMX-DHP) blood purification therapy using Toraymyxin® (Toray Medical Co., Ltd, Tokyo, Japan) for moderate to severe COVID-19 (*6*). The control group was a historical control from a COVID-19 registry (COVIREGI) (*3*). The mechanism seems to inhibit the characteristic rapid decrease in lymphocytes in COVID-19, as well as to improve the abnormalities in the coagulation-fibrinolysis system and increase oxygenation by removing activated leukocytes and cytokines, which are risk factors for the aggravation of COVID-19–related pneumonia, with the use of Toraymyxin.

An open-label, randomized, controlled trial to evaluate the efficacy of convalescent plasma therapy for COVID-19 (COVIPLA-RCT)

Enrollment started on February 24, 2021, and was completed in December 2021.

Ahead of this study, a specified clinical trial was conducted to confirm safety. Plasma was collected from people who had contracted COVID-19 and recovered (convalescent plasma) (*7*), and this plasma was administered to mild COVID-19 patients at risk of severe disease in a multicenter, joint, specified clinical trial that investigated the effect in preventing severe disease (*8*). Patients were randomized into a convalescent plasma group and a standard of care group, and the severity of disease was evaluated in an unblinded manner. A point in this study that differs from other antibody studies is that the neutralizing activity of convalescent plasma was measured before administration to subjects. Given that the antibody cocktail therapy Ronapreve® (generic name: casirivimab [genetic recombination]/imdevimab [genetic recombination] [Chugai Pharmaceutical Co., Ltd., Tokyo Japan]) was approved, and enrollment was ended in December 2021.

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)

This was started on October 22, 2021, with follow-up ongoing.

Healthy adults vaccinated twice with a SARS-CoV-2 mRNA vaccine were given a booster with inactivated vaccine KD-414 (*9*). This is a single-center, specified clinical trial to evaluate safety and immunogenicity (*10*). The primary endpoint is immunogenicity after booster vaccination with KD-414 compared with that after primary immunization with an mRNA vaccine.

Investigator-initiated clinical trials led by NCGM

A multicenter, adaptive, randomized blinded controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults (Adaptive COVID-19 Treatment Trial (ACTT)) (COVRA-1 trial)

Enrollment started on February 21, 2020, and was completed on May 21, 2020.

ACCT-1 was a placebo-controlled, double-blind, comparative trial to evaluate the efficacy and safety of RDV in adult COVID-19 patients hospitalized with moderate to severe disease. A total of 1,063 patients were entered in the trial overall, of whom 15 were entered from the NCGM. An interim report showing the efficacy of RDV was published, and based on those results, RDV was approved in Japan on May 7. In the final analysis, patients who were administered RDV had a median recovery time of 10 days (95% confidence interval [CI]: 9–11), whereas in the patients who received the placebo, it was 15 days (95% CI: 13–18) (rate ratio for recovery 1.29; 95% CI: 1.12–1.49; $p < 0.001$, by the log-rank test) (*11*).

A multicenter, adaptive, randomized, blinded, controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in Hospitalized Adults (Adaptive COVID-19 Treatment Trial (ACTT-2)) (COVRA-2)

Enrollment started on May 26, 2020, and was completed on July 31, 2020.

ACTT-2 was a double-blind, placebo-controlled trial comparing the combined use of RDV and baricitinib (JAK inhibitor) and the combined use of RDV and a placebo in patients hospitalized with moderate to severe COVID-19. One patient was entered from NCGM. The results of the analysis of the 1,034 patients entered in the trial showed that the recovery time was significantly shorter in the combined RDV and baricitinib group than in the RDV plus placebo group, by about 1 day ($p = 0.03$), confirming the effectiveness of the combination (*12*). Baricitinib was the third drug to receive regulatory approval as a treatment for COVID-19 in Japan, following RDV and dexamethasone.

A multicenter, adaptive, randomized, blinded, controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults (Adaptive COVID-19 Treatment Trial (ACTT-3)) (COVRA-3)

Enrollment started on July 30, 2020, and was completed on December 21, 2020.

ACTT-3 was a double-blind, comparative trial led by a team at the United States National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) to verify the efficacy of RDV in combination with interferon β-1a. The trial compared subcutaneously administered RDV plus interferon β-1a with subcutaneously administered RDV plus placebo. Worldwide, 969 patients were enrolled, of whom 19 were enrolled at NCGM. In patients hospitalized with COVID-19 pneumonia, combination therapy with interferon β-1a plus RDV was not superior to RDV alone. Patients who required high-flow oxygen at baseline had worse outcomes after interferon β-1a administration than the group that received the placebo (*13*).

An international, multicenter, adaptive, randomized, double-blind, placebo-controlled trial of the safety, tolerability, and efficacy of anti-coronavirus hyperimmune intravenous immunoglobulin for the treatment of adult hospitalized patients at onset of clinical progression of COVID-19 (Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC))

Enrollment started on October 15, 2020, and was completed on October 12, 2021.

The ITAC trial was a randomized, double-blind, placebo-controlled trial led by the NIH and Network for Strategic Initiatives in Global HIV Trials (INSIGHT) that compared hyperimmune intravenous immunoglobulin (hIVIG) and a placebo. Worldwide, 593 patients were enrolled; from Japan, Fujita Health University and NCGM participated and enrolled eight patients and six patients, respectively. The results of this trial demonstrated that hIVIG did not show efficacy against COVID-19 (*14*).

A multicenter, adaptive, randomized, blinded, controlled trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized adults (Adaptive COVID-19 Treatment Trial (ACTT-4)) (COVRA-4)

Enrollment started on December 18, 2020, and was completed on August 2, 2021.

ACTT-4 was a double-blind, comparative trial that compared the combination of RDV and dexamethasone

and the combination of RDV and subcutaneously administered baricitinib. Worldwide, 1,010 patients were enrolled, of whom four were enrolled from NCGM. In hospitalized COVID-19 patients who required supplemental oxygen administered by low-flow, high-flow, or non-invasive mechanical ventilation, the mechanical ventilation-free survival by day 29 was the same with baricitinib plus RDV and dexamethasone plus RDV. However, with dexamethasone, there were many more adverse events, treatment-related adverse events, and severe or life-threatening adverse events (*15*).

A multicenter, adaptive, randomized, controlled trial platform to evaluate safety and efficacy of strategies and treatments for hospitalized patients with respiratory infections (Strategies and Treatments for Respiratory Infections & Viral Emergencies (STRIVE))

Enrollment started on February 16, 2023, and is in progress.

STRIVE is a master protocol designed to evaluate the safety and efficacy of unapproved treatments, approved treatments, and their sequential and combined use for the purpose of optimizing the health status of hospitalized patients receiving acute treatment for respiratory infections. Appendix E1 shows a randomized, placebo-controlled, multicenter, joint international clinical trial that evaluates the clinical efficacy when ensitrelvir therapy is added to the standard of care (SOC) in patients hospitalized with COVID-19.

Investigator-initiated clinical trials jointly conducted by NCGM

Prevention of aggravation of mechanical ventilation-required pneumonia caused by COVID-19 using adrenomedullin - Investigator initiated phase IIa trial (AM-P2-COVID)

Enrollment started on November 2, 2020, and was completed on March 1, 2022.

This was a phase II trial led by the University of Miyazaki to examine whether adrenomedullin, a circulation-regulating peptide that shows an anti-inflammatory action, can prevent aggravation in severe COVID-19 patients on mechanical ventilation. Enrollment has ended.

Prevention of aggravation of moderate pneumonia caused by COVID-19 using adrenomedullin - Investigator initiated phase IIa trial (AM-P2-COVID2)

Enrollment started on June 24, 2021, and is in progress.

This is a phase II trial led by the University of Miyazaki to examine whether adrenomedullin administration could inhibit the progression of lung injury and injury of other organs in COVID-19 patients with moderate pneumonia, and whether patients could recover earlier (*16*).

The exploratory study investigating the efficacy and safety of Ephedrine alkaloids-free Ephedra Herb extract (EFE) in patients with COVID-19 in the early stages of infection– Double-blind, randomized, multicenter phase I / II controlled trial–

Enrollment started on March 30, 2021, and was completed on January 7, 2022.

This was an exploratory phase I/II trial led by Kitasato University that examined the efficacy and safety of EFE (*17*) for COVID-19 patients with early infection.

In addition, NCGM is actively working in corporate trials for drug development. To date, it has participated in many sponsor-initiated trials, including for molnupiravir (Lagevrio®, MSD Co.,Ltd., Tokyo, Japan), nirmatrelvir/ritonavir (Paxlovid®, Pfizer Inc., New York, US), tixagevimab/cilgavimab (Evusheld®, AstraZeneca K.K., *Tokyo, Japan*), and tocilizumab (Actemra®, Chugai Pharmaceutical Co., Ltd.).

Future issues

We have planned much studies based on scientific evidence with clinical questions as a starting point. Let us now consider several issues for the future that have become clear from our experience in investigator-initiated clinical trials for emerging infectious diseases.

The RACCO trial is a specified clinical trial targeting COVID-19, and the first in which the NCGM led the planning. Randomization was done, but because of the difficulty of preparing a placebo for inhaled ciclesonide by the start of the trial, it ended up being an open-label comparison with the symptomatic treatment group (*4*). When the study was planned in March 2020, there were still few trials related to COVID-19, and so we felt our way in the planning without establishing endpoints. Since it was an open-label trial with the concept of evaluating the antiviral effect, we decided to make computed tomography images for which the evaluators could be blinded to the primary endpoint (*4*). However, looking back now, that may not have been appropriate. Deciding in the early stage what to make the primary endpoint for a new infectious disease was difficult. In addition, we had no clinical trial network in the field of infectious disease, and so finding institutions with which to conduct a clinical trial was a struggle. Hospitals treating COVID-19 patients had performed few clinical trials up to that time and were unfamiliar with them in some cases, and time was also needed for ethical procedures. Moreover, COVID-19 spread in waves; when it was not prevalent, subjects could not be enrolled, and when cases were abundant, the great burden in care settings meant little progress was made in enrollment (*18*). From our experience in

planning this multicenter clinical study in the early stage of the COVID-19 pandemic, we keenly felt the importance of creating a network during regular times. During that same period, an observational study on the administration of ciclesonide was started in Japan, but since some physicians preferred observational studies in which ciclesonide could be administered with certainty, enrollment was challenging. Starting observational studies without thorough consideration in situations when it is not known whether there will be a treatment effect is in some cases a hindrance to implementing the randomized, comparative trials that are essential for evaluating efficacy and safety. Therefore, an implementation should be carefully considered.

The KAPIVARA trial conducted with healthy adults is a phase II trial assessing safety and efficacy of the inactivated vaccine KD-414 as a booster dose (*7*). It was predicted that inactivated vaccines may produce fewer antibodies than mRNA vaccines; however, from the results of a company phase I/II trial, there were expected to be fewer adverse effects than with mRNA vaccines (*19*). Considering the strong and frequent adverse events seen with mRNA vaccines, there was also predicted to be a certain level of need for inactivated vaccines. This study was planned in the summer of 2021, when the primary immunization of many people in Japan with an mRNA vaccine had been completed, and so it was predicted that if KD-414 were available on the market, it would be used in many situations as a booster dose for people whose primary immunization with an mRNA vaccine had ended. Therefore, KD-414 was given as a booster dose to people whose primary immunization with mRNA was over, and, with reference to guidelines on evaluating vaccines (*20*), information was collected on SARS-CoV-2 antigen-specific antibody titers, neutralizing antibody titers, cell-mediated immunity, cytokine production, and other factors as endpoints of immunogenicity (*10*). However, no method has been established for evaluations when the type of vaccine for primary immunization and booster immunization differ. It was unclear whether antibody titers need to be elevated as much as with mRNA vaccines to prevent COVID-19 infection and an outbreak, and we struggled to set an endpoint.

When obtaining consent for research or treatment, paper consent forms are assumed in Japanese regulations, and it was thus necessary for healthcare workers to meet directly with patients for informed consent. There was also a possibility of infection from paper consent forms, and so caution was required in the handling of consent documents. Our hospital rules specified the use of pens in the patient room when obtaining consent, and that consent forms and papers brought into the patient room should not be taken immediately into clean areas, but first be stored for a fixed time in an intermediate area and then brought into the clean area. In the future, from the perspective of conducting decentralized clinical trials (DCTs) that do not depend on people visiting the medical institution and, from the perspective of preventing infection when COVID-19 is spreading, the wider use of eConsent will be preferred (*21*).

Participation in the series of ACTT trials on RDV was a valuable experience of direct participation from Japan in international clinical trials led by the NIH/NIAID. The NIAID has programs for times of infectious disease outbreaks, including the implementation of clinical trials for Ebola hemorrhagic fever and providing support in other countries before the COVID-19 pandemic. Within several days of the NCGM announcing participation in the ACTT trials, a team consisting of an NIAID research nurse, pharmacist, clinical laboratory technician, and clinical trial office worker came to Japan. We were surprised and deeply grateful for the strong support provided up to the start of the clinical trial. At the same time, the ACTT trial was started at a stage when the COVID-19 situation was unclear, thus, it was a clinical trial with an adaptive design in which revisions were made, such as the criteria for patient enrollment and the validity of endpoints, while the study design itself was being implemented. For that purpose, online conferences were held every week and as needed with the participation of all institutions involved in the clinical trial. These meetings were a place where all stakeholders, including research investigators, pharmaceutical company representatives, government representatives, and biostatisticians, could meet and discuss the content and progress of the trial. We were overwhelmed at how the trial protocol was flexibly adapted to the constantly changing situation of the infectious disease and carried out. All these results were built on the full consideration and preparations from regular times with regard to emerging and re-emerging infectious diseases. The lack of preparation in Japan for COVID-19 is undeniable, and we need to examine these valuable experiences one by one and develop measures for the onset of the next infectious disease.

For our participation in the ACTT trials and their implementation as trials in Japan, the Japanese Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency provided the most rapid and flexible responses allowable within the current pharmaceutical regulations. This was done with total understanding of the significance for the country of participation from Japan in the ACTT trials. However, questions remain on the point of whether the results of these trials conducted in Japan were used to full advantage at the time of actual pharmaceutical approval of RDV and other drugs. Clinical trials conducted in Japan with Japanese subjects have absolute value in evaluating the effectiveness of a drug, but when both time and resources are limited, as in the COVID-19 pandemic, verifying all treatments within Japan can be

difficult. Therefore, ways that will allow the Japanese people to quickly and safely use effective drugs need to be debated and decided from regular times, while maintaining the motivation to conduct clinical trials in Japan. This will involve questions such as how to use the results of clinical trials conducted only in other countries for pharmaceutical approval during future epidemics of new infectious diseases, and how to differentiate them from results of trials in which Japan participated.

Conclusion

There are hindrances in conducting disease-specific clinical trials, such as cases when the time from the outbreak of an infectious disease until the start of treatment is limited, the possibility of infecting healthcare workers exists, or the epidemic spreads in waves. Because of this, our experience with COVID-19 needs to be marshaled, and we need to start preparations, so that we are ready for an outbreak of the next emerging or re-emerging infectious disease. Clinical trials are essential for the development of drugs and treatment methods with evidence, and studies need to be planned with designs matched to the phase of development.

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**Address correspondence to*:
Ayako Mikami, Center for Clinical Sciences, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: mikami-ay@ncchd.go.jp

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COVID-19 vaccination program in Cambodia: Achievements and remaining challenges

Ikuma Nozaki[1,2,*], Masahiko Hachiya[1], Chieko Ikeda[1]

[1] Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Policy Adviser to the Ministry of Health, JICA, Cambodia.

Abstract: Since Cambodia has been recognized as one of the low- and middle-income countries with a successful COVID-19 vaccine program, its program approaches were reviewed based mainly on press articles and announcements from the Ministry of Health. From the beginning, the government's proactive approach to securing vaccines and its flexibility prior to WHO Emergency Use Listing (EUL) contributed greatly to the success of the program. Vaccines were provided by COVAX and other countries, but more than half of the vaccines secured were Chinese vaccines purchased with government funds. The rollout of the vaccine has also been flexible, moving from a strategy of prioritizing risk groups and essential workers to one of expanding the campaign from population centers to rural areas, as well as gradually expanding the target age group, eventually targeting the population age 3 and older. As a result of this high level of commitment by the government and its flexible response, Cambodia has achieved 95% primary series coverage of the entire population, including those not eligible for vaccination. Although the sixth booster is now being administered in Cambodia and vaccination every six months was recommended, several challenges might be anticipated in continuing this program, including the lack of clear global guidance on how to sustain and modify the COVID-19 immunization program and vaccine fatigue after COVID-19 outbreaks have been controlled. How these challenges are overcome and how the COVID-19 vaccine program remains need to be carefully observed into the future.

***Keywords*:** Cambodia, COVID-19, vaccination, policy

Introduction

Cambodia is considered one of the countries with successful COVID-19 vaccination, having achieved the vaccination targets of the World Health Organization (WHO) Global COVID-19 Vaccination Strategy in a Changing World (*1*): 100% of health care workers, 100% of the high-risk population, and 70% of the general population (*2*).

Reviewed here are the progress of and changes in the program, with a focus on information released by the Ministry of Health and reported in the press, and the factors that contributed to its success and the remaining challenges are also discussed.

Selection and securing of vaccines

The Cambodian Government has consistently been proactive in securing vaccines and announced its budgetary commitment to purchase them early on (*3,4*). At the beginning of December 2020, the government had publicly announced its policy of using only vaccines approved by the WHO (*5,6*), but by mid-January 2021 the policy had changed (*7*). Since there were no WHO-approved vaccines at the time, some countries had begun to use vaccines produced in China, and infections were increasing among migrant workers and others returning from Thailand. The government decided to introduce Chinese-made vaccines (*8,9*), an idea that had been proposed (*10*), and began vaccinations in February 2021 (*11-13*). Afterwards, according to information shared at the March 2022 Health Partners Group meeting, government purchases, donations from other countries, and procurement through the COVAX Facility (*14*) have been actively pursued, and 44,454,860 doses had been successfully procured as of the end of March 2022 (Table 1). Of these, 64.1% were government purchases, all of which were from China. In addition, the initial policy was to introduce vaccines that could be stored at refrigerated temperatures, since maintaining an ultra-cold chain would be difficult in Cambodia, but equipment has been upgraded and vaccines that require an ultra-cold chain, such as Pfizer and Moderna, have also been introduced (*15*). Most of the vaccines were two primary series, but some J&J vaccines with a single primary series were procured (*16*), and they were used primarily

Table 1. Vaccine availability in Cambodia as of March 25, 2022

Source of vaccine	Name of vaccine	Doses received
(A) Procurement by RGC		
China	Sinovac (CoronaVac)	24,500,000
China	Sinopharm (BBIBP-CorV)	4,000,000
Total (A)		28,500,000
(B) Donation		
China	Sinopharm (BBIBP-CorV)	3,800,000
China	Sinovac (Coronavac)	4,500,000
UK	AZ(Vaxzevria)	415,040
Australia	Pfizer-BioNTech (Comirnaty)	2,350,530
Poland	AZ(Vaxzevria)	300,000
Hungary	AZ(Vaxzevria)	523,100
Total (B)		11,888,670
(C) COVAX Facility and dose sharing		
COVAX Facility	SII (COVISHIELD)	324,000
	AZ (Vaxzevria)	324,000
	Sinovac (Coronavac)	424,800
	Moderna (Spikevax)	188,160
Dose sharing	AZ (Vaxzevria) -Japan	1,315,500
	AZ (Vaxzevria) -Netherlands	290,400
	J&J (Ad26.COV-S) - US	1,060,100
Total (C)		3,926,960
(D) ASEAN allocation		
ASEAN allocation	Pfizer-BioNTech (Comirnaty)	139,230
Total (D)		139,230
Grand total (A+B+C+D)		44,454,860

Data source: WHO Cambodia, UNICEF Cambodia, (Mar 31, 2022) Update on COVID-19 vaccination roll-out in Cambodia [Meeting Presentation] Health Partner Group Meeting, Phnom Penh, Cambodia.

for vaccination in rural areas where access was difficult.

As the above process shows, the Chinese vaccines, as the first to be introduced in Cambodia and the pillar of the vaccination program since then, were introduced prior to the WHO Emergency Use Listing (EUL) recommendation. The Date of EUL Recommendation for Sinopharm was May 7, 2021 and that for Sinovac was June 1, 2021 (*17*). In addition, the Cambodian Government has expanded the target age group to include children, as described below, even though the WHO did not recommend the use of the vaccine for children in order to prioritize the elderly due to an insufficient vaccine supply (*18*). At the time, the only vaccine that had a WHO EUL recommendation for children age 12 and older was Pfizer, and even that was limited to use in children with comorbidities that put them at significantly higher risk of serious COVID-19 (*19*). The target age was subsequently expanded to include children age 3 and older in Cambodia (*20*). The Sinopharm vaccine, which had received regulatory approval for children age 3 and older in China, the country of production (*21*), was also not recommended under the EUL for use in children under the age of 18 (*22*). However, the Cambodian Government seems to have decided to adopt the Sinopharm vaccine, which had received regulatory approval in China for use in children over the age of 3 and which had relatively few reports of adverse reactions, for the vaccination of children; this was eventually expanded to children over the age of 3 partly because of the difficulty in obtaining a sufficient quantity of Pfizer's vaccine to cover about 5 million children ages 3–17, which account for 30% of the national population (*23*).

These proactive approaches by the government are considered to have played a significant role in the success of the COVID-19 vaccination program in Cambodia. In addition, the government plans to establish a domestic production capacity in cooperation with the Chinese company Sinovac as part of its long-term strategy to secure vaccines (*24*).

Changes in the strategic plan for vaccination, including target populations

The Cambodian Government initially developed a "National Deployment and Vaccination Plan for COVID-19 Vaccines" under the auspices of the National Immunization Program of the Ministry of Health, with support from the WHO (*25*). The formulation of a Deployment Plan is also a condition for application to the COVAX Facility and is based on the premise of how to effectively use vaccines in insufficient quantities. The strategy was to prioritize health care workers, essential service providers such as the military and police, and the elderly (Table 2). When the first batch of the vaccine arrived in the country in February 2021, vaccination of priority populations was initiated according to this plan. The consistent policy since the program's beginning has been that vaccination is voluntary and free of charge (*26*). However, during serious outbreaks measures were taken to require the presentation of a vaccination card in order to enter public spaces (*27*).

In March 2021, the "Master plan for COVID-19 vaccine deployment throughout the Country" was issued at the initiative of the Ministry of Health's National Committee for COVID-19 Vaccination, which expanded the vaccination coverage to 10 million people age 18 and older, perhaps because of the prospect of procuring sufficient quantities of the vaccine (*28*).

Around that time, Cambodia also experienced serious community outbreaks of COVID-19, forcing many cities to lock down in May 2021. In response, the Cambodian Government, led by the Supreme National Economic Council, launched the "Strategic Plan for the COVID-19 Vaccination Campaign to Build Socio-economic Immunity in Cambodia by 2021" (*29*), also known as the "Blossom Plan." This introduced a new geographical prioritization system that promotes mass vaccination campaigns in metropolitan areas starting with Phnom Penh and other major cities (*30*). This campaign was expanded to cover more areas, eventually covering the entire country.

As a result of these successful efforts, the nationwide expansion of the vaccination program progressed faster

Table 2. Priority groups and target populations in the National Deployment and Vaccination Plan for COVID-19 Vaccines

No.	Priority groups	Total target population	Vaccination strategies
1	Health care workers including auxiliary workers	36,894	At fixed sites (health care facilities)
2	Essential government staff including the army and police to maintain law and government services	289,721	At fixed sites (health care facilities) and army barracks and police stations
3	Village Health Support Group (Volunteers) and those involved in the immunization and health program	50,074	At fixed sites (health care facilities)
4	Elderly population (over the age of 65)	944,932	At fixed sites (health care facilities) and in villages
5	High-risk adults from 18-64 years of age (with diabetes, hypertension, etc.)	1,521,426	At fixed sites (health care facilities) and in villages
6	Garment factory workers	621,275	Vaccination at factories

Data source: Cambodian Ministry of Health. National Deployment and Vaccination Plan for COVID-19 Vaccines. Jan 29, 2021. Phnom Penh, Cambodia.

than expected and was likely to reach the originally planned population of 10 million over the age of 18 by November 2021 (*31*). Therefore, in July 2021, the Cambodian Government, led by the Commission for COVID-19 Vaccination Nationwide, launched the "Action plan on COVID-19 vaccination for children and teens ages 12 to 18" to expand the target age group from age 12 and older (*32,33*). Since the government set the vaccination coverage target at more than 90% of the total population including children (*32*) and vaccination was included as a condition for reopening schools (*34,35*), the target age group for vaccination was subsequently expanded, ultimately encompassing individuals 3 years and older (*36*).

In addition, reports of infections among vaccinated people in neighboring countries have led to discussions of the need for additional vaccinations (*37*). In Cambodia, an "Action Plan for the COVID-19 Booster to Increase Immunity against COVID-19" was formulated in September 2021 (*38*), and boosters were initiated. In the earlier cases in neighboring countries such as Thailand and Indonesia, AstraZeneca and other Western-made vaccines were used for additional vaccinations because infection continued among health care workers and others who had completed the primary series with the vaccines produced in China. In Cambodia, where Chinese vaccines were also mainly used, a "mixed and harmonized vaccination regime" or a "same type of vaccine regime" was instituted, and vaccination with available vaccines was recommended 4–6 months after the completion of primary series vaccination. As of December 2022, the 6th booster of the COVID-19 vaccine had just started (*39*).

Monitoring progress

To monitor the progress of this vaccine program, the Cambodian Government introduced a new online data system at the beginning of the program (*40*). There were apparently some glitches in the beginning, but after fixes the system is still able to report progress daily, broken down by target age, gender, type of vaccine received, and how many booster shots (Table 3). This progress has been reported daily on the Ministry of Health's social media account, together with epidemiological information such as the number of COVID-19 cases and deaths (*41*). Information about adverse reactions to the vaccine was also collected, but there seemed to be a bias since few people had bothered to report reactions after they returned home. Despite some challenges, such as an immunization coverage rate exceeding 100% for some groups due to an inaccurate denominator for the target group caused by an incomplete national registration system and a migrant population, this system has been recognized as a successful national example in digital health care. The potential for further development, including expansion to routine immunization and linkage with other health care-related data systems, is being discussed.

Achievements and remaining challenges

As described above, the high level of commitment by the Cambodian Government and its flexible response have been successful. As a result, Cambodia has achieved 95% primary series coverage of the entire population, including those not eligible for vaccination (under the age of 3), in combination with the effects of public health and social measures such as mask wearing, physical distancing, and hand hygiene, which have so far been successful in preventing serious outbreaks of COVID-19 in the country (*2*). This has also contributed to the recovery of socioeconomic activity, with the country ranking 4th in the Nikkei COVID-19 Recovery Index, which evaluates more than 120 countries and regions in terms of infection management, vaccine rollouts, and social mobility (*42*).

One of the challenges for the future is how to continue the COVID-19 vaccination program. The US, as a new step in the country's recovery, has issued a recommendation to incorporate the COVID-19 vaccine into the routine immunization schedule (*43*). This is to streamline clinical guidance for health care providers by including all currently licensed, approved, and routinely recommended vaccines in one document. However, despite the clear statement that inclusion of the

Table 3. COVID-19 Vaccination Program Report posted on the Ministry of Health's Facebook account on December 31, 2022

Items	1st dose		2nd dose		3rd dose		4th dose		5th dose	
	Total	Female	Total	Female	Total	Female	Total	Female	Total	Female
1.Sinopharm	3,748,614	1,838,225	3,596,389	1,770,169	178,926	99,125	22,232	11,608	8,536	4,977
2.AstraZeneca (Covishield)	165,656	79,867	157,736	77,392	57,354	30,063	124,064	66,366	82,500	38,963
3.AstraZeneca (Japan)	184 061	89,710	176.786	82,904	965,356	434,510	6,881	2,389	0	0
4.AstraZeneca (UK)	452	133	81	36	414,507	136,526	0	0	0	0
5.Sinovac (≥18)	5,229,149	2,724,659	5,059,944	2,609,828	3.329,573	1,822,178	153,169	84,597	92,449	48,978
6.Janssen (Johnson & Johnson)	1,053,151	549,307	0	0	0	0	0	0	0	0
7.AstraZeneca (KR)	0	0	0	0	320,639	177,068	116	46	0	0
8.Moderna	0	0	2	1	217,119	113,874	135,517	57,263	0	0
9.AstraZeneca (Netherlands)	0	0	2	1	268,295	139 097	16,119	6,515	0	0
10.Pfizer	252	29	410	30	433,770	230,018	1,801,009	909,530	712,931	359,815
11.AstraZeneca (Poland)	0	0	0	0	240,045	126,849	53,233	23,585	0	0
12.AstraZeneca (Hungary)	0	0	0	0	237,674	125,575	231,202	150,626	0	0
13.AstraZeneca (Italy)	0	0	0	0	270,409	146,531	650,903	388,852	122,115	33,564
Age ≥ 18	10,381,335	5,281,930	10,044,501	5,089,668	6,930,667	3,581,414	3,194,445	1,701,377	1,018,531	486,297
Sinovac (12-18)	1.849,480	914,787	1,795,280	891,880	1,218,791	649,599	57,694	31,794	32,939	18,305
Pfizer (12-18)	0	0	1	0	424,984	214,788	765,087	425,134	177,274	98,676
Sinovac (6-12)	2,095,130	1,031,452	2,067,637	1,022,907	1,440,609	735,211	227,765	119,633	0	0
Sinovac (5)	428,662	216,578	377,640	192,068	88,313	45,942	14,594	7,429	0	0
Sinovac (3-5)	487,362	248,394	322,021	164,635	68,859	35,289	4	3	0	0
Pfizer Pediatric (6-12)	0	0	1	0	195,729	100,604	473,117	248,858	3	0
Pfizer Pediatric (5)	1	1	0	0	57,000	29,570	34,825	17,886	0	0
Grand total	15,241,970	7,693,142	14,607,081	7,361,158	10,424,952	5,392,417	4,767,531	2,552,114	1,228,747	603,278

Vaccination progress compared to the population of 16 million (grand total): **95.26%**

Vaccination progress compared to the target population of 10 million (age ≥18): **103.81%**	Vaccination progress compared to the target population of 1,827,347 (ages 12-18): **101.21%**	Vaccination progress compared to the target population of 1,897,382 (ages 6-12): **110.42%**	Vaccination progress compared to the target population of 303,317 (age 5): **140.86%**	Vaccination progress compared to the target population of 610,730 (ages 3-5): **79.80%**

Data source: Ministry of Health Cambodia, Facebook account at *https://web.facebook.com/MinistryofHealthofCambodia*

COVID-19 vaccine would not supersede state regulations on immunization requirements for school children, there has been much discussion, including opposition from the Republican Party (*44*). In Cambodia, administration of the sixth booster has begun and vaccination every 6 months will be recommended, but several challenges might be anticipated in continuing the program.

First, there is still no clear global guidance on how to sustain and modify the COVID-19 immunization program. In Cambodia, the tentative plan seems to be to continue with the currently available vaccine every 6 months. However, there is insufficient evidence on the frequency, timing, target age groups, and types and combinations of vaccines for additional vaccinations, while there are recommendations such as including the COVID-19 vaccine in routine immunization (*45*), and COVID-19 boosters will likely be recommended periodically for high-risk groups (*46*). The hope is that evidence will be assembled and global guidance such as WHO position papers on COVID-19 vaccines will be issued.

Second, there is the need to secure vaccines. Cambodia has partnered with Sinovac to produce vaccines domestically, but some reports indicate that Chinese-made vaccines such as those from Sinopharm and Sinovac are less effective against the omicron variant than mRNA vaccines and other vaccines (*47,48*). Although the WHO EUL recommendation for bivalent vaccines against the omicron variant has been issued and some countries are beginning to introduce them (*17*), they are not yet available in Cambodia. Difficult decisions will presumably be required regarding which vaccines are most effective and how to use them to combat a virus that continues to mutate.

Third, immunization coverage targets need to be determined and maintained. Cambodia has not seen the vaccine hesitancy that has often been observed in other countries, the COVID-19 epidemic has begun to subside in Cambodia, and people's sense of urgency and concern about the disease has begun to decline, hampering the expansion of vaccination with booster doses (*49*).

In conclusion, Cambodia has so far successfully implemented a COVID-19 vaccination program with a high level of government commitment and flexibility in

securing vaccines, determination of target populations according to susceptibility and vaccine availability, and implementing an online data system. How the Cambodian Government overcomes the aforementioned challenges to continuing and maintaining its COVID-19 vaccine program will need to be observed.

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**Address correspondence to*:
Ikuma Nozaki, Bureau of International Health Cooperation, The National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: i-nozaki@it.ncgm.go.jp

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Treatment options for patients with severe COVID-19

Momoko Morishita, Masayuki Hojo*

Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: The coronavirus disease 2019 (COVID-19) pandemic has affected the world for over 3 years. Treatment options have improved substantially during this period, including antiviral drugs, antibody drugs, immune-based agents, and vaccination. While these improvements have reduced mortality rates in patients with COVID-19, some patients still develop severe illness. In this review, we aimed to provide an overview of treatments for patients with severe COVID-19 from study reports and clinical experience. We discussed the treatments from two perspectives: respiratory care and drug treatments. In the respiratory care section, we discussed the usefulness of high-flow nasal cannula therapy and non-invasive ventilation as an alternative to invasive ventilation. In the drug treatments section, we focused on three classes for severe COVID-19 treatment: antiviral drugs, immune-based agents, and anticoagulation therapy. We did not discuss antibody drugs and vaccination, as they are not used for severe COVID-19 treatment.

***Keywords*:** high-flow nasal cannula therapy, remdesivir, immune-based agents, anticoagulation therapy

Introduction

Since the first case of coronavirus disease 2019 (COVID-19) was reported in the city of Wuhan, China, at the end of 2019, the COVID-19 outbreak has continued for over 3 years. During this pandemic, there have been more than 700 million confirmed cases and six million deaths globally (*1*). Despite the challenges posed by this pandemic, the development of effective vaccines has reduced the incidence of severe COVID-19, hospitalizations, and mortality rates (*2*). Nevertheless, older patients or patients with underlying medical conditions remain vulnerable to severe or critical illness and death.

In this review, we summarized the treatment options for patients with severe COVID-19. Severe illness is defined by the International Diseases Society of America (IDSA) as patients with $SpO_2 \leq 94\%$ on room air, including patients on supplemental oxygen (*3*). In Japan, COVID-19 severity is classified into four categories; mild, moderate I, moderate II, and severe by the Ministry of Health and Welfare. The IDSA's definition of severe illness is equivalent to the moderate II and severe categories in Japan, and patients with moderate illness can easily progress to severe illness. Thus, we focused on treatments for patients receiving supplemental oxygen, which is a similar condition to patients with severe illness according to IDSA's definition.

Respiratory care

High-flow nasal cannula therapy (HFNC)

In acute respiratory failure, HFNC reportedly reduces intubation by 15% compared to conventional oxygen therapy (*4,5*). The usefulness of HFNC in patients with COVID-19 is discussed in several case series (*6-9*). Demoule *et al*. reported that HFNC reduced the intubation rate at day 28 compared to conventional oxygen therapy (55% *vs*. 72%; $p < 0.0001$) (*6*). Other studies have also suggested that with close monitoring, HFNC can be an effective tool (*7*). Another advantage of HFNC is that patients on HFNC can easily adapt a prone position. In patients with COVID-19, a prone position has been suggested to reduce intubation risk (*10*), which is consistent with non-COVID-19 acute respiratory distress syndrome (ARDS) (*11,12*). However, a concern is that HFNC may delay intubation resulting in poor prognosis. Kang *et al*. demonstrated that early intubation (within 48 h HFNC initiation) was associated with lower overall intensive care unit (ICU) mortality than late intubation (*13*). Therefore, Roca *et al*. suggested the ROX index as a tool to predict HFNC failure (*14*). Although it might be difficult to implement this index in all hospitals, close monitoring is necessary after HFNC initiation.

Nosocomial infections are another concern when using HFNC. The risk of droplet dispersion, aerosol generation, or infection transmission reportedly depends on the conditions of HFNC use (*5*). Properly fitted HFNC masks and the wearing of surgical masks by patients can

improve the situation (*15-17*). In our hospital, Katsuno *et al*. reported that half of the patients on HFNC (8/15 cases) were treated successfully, and no nosocomial infections occurred (*18*).

In conclusion, with adequate use and close monitoring, HFNC may play an important role in reducing the number of patients with COVID-19 who require invasive mechanical ventilation.

Non-invasive ventilation (NIV)

NIV is another alternative to intubation in hypoxic conditions (*19,20*). However, NIV effectiveness in ARDS is controversial due to high mortality and intubation rates (*21*). The guidelines do not recommend NIV use in ARDS (*22*). In COVID-19 cases, results vary depending on the study (*23-26*), and nosocomial infections also play a role in avoiding COVID-19 treatment with NIV. Moreover, Frat *et al*. reported that in immunocompromised patients, NIV had a higher risk of mortality and intubation than HFNC (*27*). There is no solid evidence to support or reject the use of NIV in COVID-19 treatment. More rigorous studies are needed to determine its efficacy; however, NIV may be considered an alternative to intubation in COVID-19 treatment.

Invasive mechanical ventilation

For patients with poor oxygen status, invasive mechanical ventilation is unavoidable. The COVID-19 mortality in patients on invasive mechanical ventilation was initially reported to be 88% (*28*). However, this figure excluded the patients who continued the treatment in the ICU. With advances in treatments, the mortality rates range from 26–39% (*29-33*). This data is consistent with ARDS without COVID-19 (*21*) and is not much worse than previous respiratory pandemics (*34*).

Intubation timing is controversial. Some studies support early intubation (*35,36*), whereas others have revealed no relationship between intubation timing and mortality (*37,38*). However, Riera *et al*. revealed that in later periods of the pandemic, the rate of early intubation diminished (*35*), indicating that clinicians increasingly chose to treat patients non-invasively. Therefore, while this issue remains controversial, we can conclude that with close monitoring, HFNC and NIV treatment could play an important role in avoiding intubation.

Drug treatments

There are three major options for treating patients with severe COVID-19: antiviral drugs, immune-based agents, and anticoagulation therapy.

Antiviral drugs

Remdesivir

Remdesivir is an antiviral drug that inhibits the RNA-dependent SARS-CoV-2 RNA polymerase and perturbs viral replication (*39,40*). Four randomized cotrolled trials (RCTs) have discussed the effectiveness of remdesivir in patients with severe COVID-19 (*41-44*), with varying results. Wang *et al*. reported a trial on remdesivir in 237 patients; however, it was underpowered based on the stringent public health measures in China (*41*). However, in a subgroup of patients observed within 10 days from symptom onset, patients on remdesivir demonstrated faster clinical improvement. The DisCoVeRy trial (*42*) and SOLIDARITY trial (*43*) also revealed negative results for remdesivir in severe cases.

In contrast, the ACTT-1 trial (*44*), which included 85% of patients with severe illness, reported positive results. The primary outcome was the time to recovery, and patients on remdesivir had a median recovery time of 10 days, compared to 15 days in the placebo group (rate ratio for recovery, 1.29; 95% confidence interval (CI,) 1.12–1.49; $p < 0.001$, based on a log-rank test). The difference in results could be due to the difference in patients' condition, oxygen demand, and outcome assessment methods. However, several studies have demonstrated a consistent trend toward the prevention of severe disease. In the ACTT-1 trial, among the 573 patients without NIV, high-flow oxygen, invasive ventilation, or extracorporeal membrane oxygenation (ECMO) at baseline, the incidence of new NIV or high-flow oxygen use was lower in the remdesivir group than in the placebo group (17% [95% CI, 13–22] *vs*. 24% [95% CI, 19–30]) (*44*). In the DisCoVeRy trial, among patients without mechanical ventilation or ECMO at randomization, remdesivir significantly delayed the need for new mechanical ventilation or ECMO or death (HR 0.66 (95% CI, 0.47–0.91), $p = 0.01$). Moreover, in the SIMPLE-2 study, patients with moderate COVID-19 treated with remdesivir revealed a better clinical status on day 11 compared to the placebo group (*45*).

These findings suggest that remdesivir may improve clinical outcomes for moderate disease or patients with early-stage COVID-19. In summary, remdesivir may prevent severe illness in patients with COVID-19 requiring oxygen. It is key to initiate remdesivir in the early stage. Moreover, the National Institute of Health recommends the treatment of hospitalized patients requiring oxygen with remdesivir but does not recommend remdesivir for patients requiring mechanical ventilation (*46*).

Immune-based agents

Corticosteroids

Corticosteroids are believed to modulate the excessive immune response to COVID-19 (*47*). They have been widely used for COVID-19 treatment; however, their use remains controversial (*48,49*). The RECOVERY trial (*50*) revealed the effect of dexamethasone in

addition to standard care. The primary outcome was 28-day mortality; 22.9% in the dexamethasone group and 25.7% in the control group died within 28 days (age-adjusted rate ratio, 0.83; 95% CI, 0.75–0.93; $p < 0.001$). In the subgroup of patients on invasive mechanical ventilation and patients on oxygen, the mortality incidence was lower in the dexamethasone group than in the usual care group. However, there was no significant difference in the subgroup without oxygen treatment. Moreover, seven RCTs revealed the effectiveness of corticosteroids in severely/critically ill patients (*51*), and IDSA recommends corticosteroids only for patients who require oxygen (*3*).

However, the duration and dosage of corticosteroids are controversial. Regarding the duration, long-term corticosteroid use may be a risk factor for prolonged COVID-19 infection (*52*). We reported a case of prolonged COVID-19 infection with non-Hodgkin lymphoma treated with rituximab. In our case, corticosteroids were administered for more than 100 days, and after the reduction of corticosteroids, the PCR test became negative, which indicates the possibility that corticosteroids prolonged the COVID-19 infection.

Regarding corticosteroid dosage, some studies discussed prednisolone pulse therapy for patients with COVID-19. The effect of prednisolone pulse therapy is controversial, and the results depend on the studies. Salvarani *et al*. reported no significant difference was observed in time to discharge between the prednisolone pulse group and the standard care group (*53*). However, no side effects were increased in the pulse group; thus, Salvarani *et al*. concluded that prednisolone pulse may be beneficial in some severe cases.

In summary, corticosteroids moderate the immune response to COVID-19 and improve mortality in severe cases. However, the appropriate dose and duration of corticosteroids should be elucidated in future studies.

IL-6 inhibitors (tocilizumab)

IL-6 is one of the cytokines that cause acute inflammation and cytokines storm in patients with COVID-19 (*54*). Tocilizumab is a monoclonal antibody that binds to IL-6 receptors and inhibits IL-6-mediated signaling (*55*). Many case series and observational studies have revealed the effectiveness of tocilizumab in patients with COVID-19 (*56-58*). Ten RCTs (*59-68*) have been conducted, and three of them (EMPACTA, REMAP-CAP, and RECOVERY) met the primary endpoints. However, varying results have been reported; there are two reasons for this. First, most of the enrolled patients were severely ill; however, the mortality in control groups ranged from 5–30%, and each study included patients from various backgrounds (*69*). The REMAP-CAP and RECOVERY trials included mostly severely ill patients and demonstrated the effectiveness of tocilizumab. They concluded that in severely ill patients, tocilizumab had a higher tendency to be effective than in moderately ill patients. Second, corticosteroids were used simultaneously. The percentage of patients treated with corticosteroids differed among the trials, ranging from 4% to 88% (*70*). In the RECOVERY trial (*66*), the effect on 28-day mortality was reported only in the subgroup with corticosteroids.

In the subgroup without corticosteroids, no significant difference was observed in 28-day mortality (rate ratio, 1.16; 95% CI, 0.91–1.48), hospital discharge (rate ratio, 0.98; 95% CI, 0.79–1.22), and invasive mechanical ventilation or death (rate ratio, 0.99; 95% CI, 0.82–1.18). The World Health Organization (WHO) REACT working group also reported in a meta-analysis that the odds ratio for the association of IL-6 antagonist treatment with 28-day mortality was 0.77 (95% CI, 0.68–0.87) and 1.06 (95% CI, 0.85–1.33) in the subgroup on corticosteroids and without corticosteroids, respectively (*71*). This result suggests that the effect of tocilizumab is apparent only with corticosteroids and is consistent with the RECOVERY trial. Based on these studies, WHO recommends combined treatment with corticosteroids and IL-6 receptor blockers for patients with severe COVID-19 (*72*). Tocilizumab is an effective treatment in combination with corticosteroids.

Janus kinase (JAK) inhibitors (baricitinib)

Baricitinib is a JAK inhibitor that targets JAK1 and JAK2 (*73*). COVID-19 induces cytokine release syndrome, and many cytokines employ intracellular signaling pathways mediated by JAKs; therefore, JAK inhibitors moderate immune response to COVID-19 (*74*). In addition, baricitinib might interrupt virus entry into cells (*75,76*).

Three RCTs discussed the effect of baricitinib (*77*). The ACTT-2 trial analyzed the effect of baricitinib and remdesivir in 1,033 patients (*77*). The primary outcome was the time to recovery. Patients receiving baricitinib and remdesivir had a median time to recovery of 7 days, compared to 8 days for the patients on placebo and remdesivir (rate ratio for recovery, 1.16; 95% CI, 1.01–1.32; $p = 0.03$). In the subgroup analysis, patients on NIV or high-flow oxygen had the largest benefits. Other subgroups did not reveal statistical benefits. The COV-BARRIER trial evaluated the effect of baricitinib in combination with standard care (*78*). The study excluded patients on invasive mechanical ventilation or patients without oxygen therapy and enrolled 1,525 patients. The primary outcome was the percentage of patients with disease progression, defined as increased oxygen demand. No significant difference was observed in disease progression by day 28. However, in the baricitinib group, 28-day all-cause mortality was significantly lower than in the standard care group. The largest benefit was observed in patients with NIV or high-flow oxygen.

The RECOVERY trial was the third and largest trial and included 8,156 patients (*79*). By day 28, 514 of 4,148

patients (12%) in the baricitinib group and 546 of 4,008 patients (14%) in the usual care group had died (age-adjusted rate ratio, 0.87; 95% CI, 0.77–0.99; $p = 0.028$). This study also revealed that patients on NIV had the largest benefit. A meta-analysis (*79*) also revealed a 43% reduction in mortality with JAK inhibitors.

In conclusion, baricitinib may be recommended for use in severe to critically ill patients, especially with NIV or HFNC. WHO suggests the use of baricitinib, in combination with corticosteroids and IL-6 receptor inhibitors (*72*).

Anticoagulation therapy

A relationship between COVID-19 infection and thromboembolic diseases has been reported (*80-85*). Elevated D-dimer has been associated with lower mortality rates (*86*), and observational studies revealed that anticoagulation therapy improves survival rates in hospitalized patients (*87,88*). The choice of and dosage of anticoagulant is controversial (*89*). The INSPIRATION trial used enoxaparin (*90*), and the RAPID trial used heparin (*91*). In the INSPIRATION trial, an intermediate dose of enoxaparin (1 mg/kg) revealed no significant difference in mortality and bleeding events compared to the normal dose (40 mg daily) (*90*). The RAPID trial compared therapeutic and prophylactic doses of heparin; the therapeutic dose of heparin reduced all-cause mortality (*91*), although a larger study revealed contrary results in critically ill patients (*92*). The HEP-COVID trial compared the therapeutic dose of enoxaparin to that of heparin and revealed that enoxaparin significantly reduced all-cause mortality (*93*). It was concluded from the ACTION trial that there was insufficient evidence to support the use of oral anticoagulants in hospitalized patients (*94*).

In conclusion, it is difficult to determine which dosage and treatment should be used in patients with severe COVID-19; however, heparin or enoxaparin is recommended for hospitalized patients.

Conclusion

We reviewed the treatment options for patients with severe COVID-19. Regarding respiratory treatments, HFNC may be an effective alternative to intubation, under close monitoring and appropriate for preventing nosocomial infections. Regarding drug treatments, we recommended three treatments: antiviral drugs, immune-based agents, and anticoagulation therapy. Immune-based agents should be selected based on the illness severity and may be used as a single agent or in combination. We have reviewed several reports on different treatment options for severe COVID-19; however, there are insufficient studies on the choice, timing, and duration of treatments. Further confirmatory evidence is warranted.

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**Address correspondence to*:
Masayuki Hojo, Department of Respiratory Medicine, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
Email: mhojo@hosp.ncgm.go.jp

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Association between SARS-CoV-2 anti-spike antibody titers and the development of post-COVID conditions: A retrospective observational study

Yusuke Miyazato[1], Shinya Tsuzuki[1,2,3], Akihiro Matsunaga[4], Shinichiro Morioka[1,2,5,*], Mari Terada[1,6], Sho Saito[1], Noriko Iwamoto[1], Satoshi Kutsuna[7], Yukihito Ishizaka[4], Norio Ohmagari[1,2]

[1] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan;
[2] AMR Clinical Reference Center, National Center for Global Health and Medicine Hospital, Tokyo, Japan;
[3] Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium;
[4] Department of Intractable Diseases, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan;
[5] Emerging and Reemerging Infectious Diseases, Graduate School of Medicine, Tohoku University, Miyagi, Japan;
[6] Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan;
[7] Department of Infection Control, Graduate School of Medicine, Osaka University, Osaka, Japan.

Abstract: The symptoms that persist after an acute coronavirus disease 2019 (COVID-19) are referred to as post-COVID conditions. Although the cause of post-COVID conditions remains unclear, the host immune response to SARS-CoV-2 may be involved. Hence, we aimed to investigate the effect of serum antibody titers against SARS-CoV-2 on the development of post-COVID conditions. We conducted a retrospective observational study of COVID-19-recovered individuals who attended the clinic at the National Center for Global Health and Medicine between January 2020 and April 2021. Serum SARS-CoV-2 anti-spike antibody titers were measured and a questionnaire survey was used to collect information on the presence of post-COVID conditions and demographic characteristics of the participants. Participants were then divided into two groups: high peak antibody titer group [≥ 0.759 OD450 value], and low peak antibody titer group [< 0.759 OD450 value] and compared their frequency of post-COVID conditions. Of 526 individuals attending the clinic, 457 (86.9%) responded to the questionnaire. We analyzed the data of 227 (49.7%) participants with measurements of serum antibody titers during the peak period. The incidence of depressed mood was significantly higher in the group with higher antibody titers (odds ratio: 2.34, 95% CI: 1.17–4.67, $p = 0.016$). There was no significant difference in the frequency of the remaining symptoms between the two groups. Among post-COVID conditions, the depressed mood was more frequent in the group with high serum antibody titers which suggests a difference in pathogenesis between depressive mood and other post-COVID conditions that requires further investigation.

***Keywords*:** antibody titer, COVID-19, post-COVID condition, questionnaire survey, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) is a global threat and has caused many deaths; furthermore, the sequelae of COVID-19, known as post-COVID conditions, also have a considerable social impact.

Several studies have identified risk factors for the development and progression of post-COVID conditions (*1-4*). However, the pathophysiology of these conditions remains unclear. The possible pathogenesis of post-COVID conditions has been classified by the National Institute for Health Research according to at least four categories (*5-6*), and inadequate antibody response is one of the potential underlying mechanisms that has been identified.

It has been reported that vaccination is effective in the prevention and treatment of post-COVID conditions and multisystem inflammatory syndrome in children (*7-9*), suggesting that the host antibody response may be involved in the development of these conditions. This study investigated the relationship between the development of post-COVID conditions and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anti-spike serum antibody titers.

Materials and Methods

Questionnaire

We conducted a retrospective observational study at an outpatient clinic of the Disease Control and Prevention Center in the National Center for Global Health and

Medicine (NCGM), Tokyo, Japan. In February 2022, we mailed a self-report paper-based questionnaire on post-COVID conditions to individuals aged 20 years or over who had recovered from acute COVID-19 and attended the outpatient clinic in NCGM for a pre-donation screening test for COVID-19 convalescent plasmapheresis (*10*) between January 2020 and April 2021. Patients underwent testing for SARS-CoV-2 anti-spike serum antibody titers at the visit. The questionnaire also included the demographic characteristics of the participants.

Participants were asked to complete and return the questionnaire. Participation was voluntary and confidential and reminders were sent to patients at 2 weeks and 1 month after mailing the questionnaire. The questionnaire was based on questionnaires from previous studies and discussions among the authors (*1,2,11-14*). The questionnaire content is described in our previous study (*4*). The following post-COVID conditions were assessed in the questionnaire: fatigue, cough, dysosmia, dysgeusia, shortness of breath, hair loss, depressed mood, loss of concentration, and memory disturbance. These were classified as ongoing or late-onset symptoms, as described in our previous study (*4*). Furthermore, the severity of COVID-19 was categorized according to previously published reports (*1,2*): *i*) mild, no oxygen therapy; *ii*) moderate, oxygen therapy without mechanical ventilation; *iii*) severe, mechanical ventilation with or without extracorporeal membrane oxygenation. Since the most of participants were treated at other medical facilities, we were unable to verify the severity of illness in their medical records and collected information only from the results of the questionnaire.

Measurement of SARS-CoV-2 anti-spike antibody titers

Recombinant SARS-CoV-2 spike protein (full-length) was purified using Expi293 expression system and coated on the MaxiSoap 96 well enzyme-linked immune-sorbent assay plate (ThermoFisher Scientific, Waltham, MA) overnight at 4ºC. After blocking with 1% BlockAce (KAC, Kyoto, Japan), the 1/100 diluted patient serum samples were applied, and then incubated with anti-human IgG conjugated with horseradish peroxidase (GeneTex, Irvine, CA). The captured anti-spike antibody titers were detected with 3,3',5,5'-tetramethylbenzidine substrate solution (Nacalai Tesque, Kyoto, Japan) and their absorbance (OD450) was measured at 450 nm wave-length using a microplate reader (Bio-Rad, Irvine, CA). The healthy volunteer serums without SARS-CoV-2 infection were used as negative control, whereas the infected patients' serums with high amount of anti-spike antibodies were used as positive control. Each sample was assayed in triplicates.

SARS-CoV-2 anti-spike antibody titers

SARS-CoV-2 anti-spike antibody titers vary according to the time between the onset of acute COVID-19 and testing. Sera were collected between 21 and 60 days after COVID-19 onset, based on previous literature (*15-18*). COVID-19 onset was defined as the date of first appearance of any symptoms associated with acute COVID-19 or the date of diagnosis of COVID-19 in asymptomatic patients. Patients were divided into two groups according to the levels of serum antibody titers, as follows: [≥ 0.759 OD450 value] (high peak antibody titer group) and [< 0.759 OD450 value] (low peak antibody titer group). This is because the cut-off value of antibody titers was not defined and the median antibody titer for this study participants was 0.759 OD450 value.

Statistical analysis

We compared the frequency of each post-COVID condition collected by the questionnaire between two groups, classified according to the SARS-CoV-2 anti-spike antibody titers, using Chi-square tests (or Fisher's exact test if the expected frequency was < 5). To adjust for potential confounders, observed differences in baseline characteristics (sex, age, obesity [body mass index > 25 kg/m^2], smoking, hypertension, diabetes, dyslipidemia, bronchial asthma, severity of acute COVID-19, and administration of antiviral medications and steroids) between the two groups were controlled for by using an inverse probability weighting (IPW)-adjusted analysis (*3,4*). The stabilized weight of each case was based on the propensity score which was calculated by a multivariate logistic regression model predicting the likelihood of having higher/lower SARS-CoV-2 anti-spike antibody titer. Hypertension, dyslipidemia, diabetes, and bronchial asthma were chosen as the confounding variables because of their high prevalence among the participants. Whereas, malignancy and chronic obstructive pulmonary disease, which are also risk factors for severe COVID-19, were not included as variables for adjustment because of their relatively low prevalence. The balance in covariates between the two groups before and after IPW adjustment was assessed using the standardized mean difference (SMD) and a difference in SMD above 20% was interpreted as a meaningful imbalance (*19*). After the IPW adjustment, we performed a generalized linear model analysis to estimate the average treatment effects of higher SARS-CoV-2 anti-spike antibody titers on the development of post-COVID conditions.

P values < 0.05 were considered statistically significant. Sensitivity analyses were performed using two other cut-off values of COVID-19 antibody titers (0.6 and 0.9 OD450 value). Stata 17.0 (StataCorp, College Station, TX, USA) was used to perform all analyses.

Sensitivity analyses

We performed sensitivity analyses with different cut-off values of SARS-CoV-2 anti-spike antibody titers (0.6 and 0.9 OD450 value) because the cut-off value of antibody titers was not defined.

Ethics approval and informed consent

The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013) and the study protocol was approved by the Ethics Committee of the Center Hospital of the NCGM (NCGM-G-004121-00). All study participants provided written informed consent before answering the questionnaire.

Results

Participant characteristics

Of the 526 potentially eligible participants, 457 (86.9%) answered the questionnaire. Of these, 227 (49.7%) had antibodies measured 21–60 days after the onset of COVID-19 and were eligible for inclusion in the analysis. We excluded 230 patients because their serum antibody titers were not measured during the peak period. The characteristics of the participants analyzed are shown in Table 1. The median age was 47 years, 101 participants (44.5%) were male, and 117 (51.5%) had no underlying disease. All of the participants were Japanese. Seventy-one participants (31.3%) had experienced COVID-19 pneumonia. The severity of COVID-19 was mild in 193 (85.0%), moderate in 27 (11.9%), and unknown in the remaining 7 participants. No participants had experienced severe disease.

SARS-CoV-2 anti-spike antibody titers

SARS-CoV-2 anti-spike antibody titers among the study participants did not follow a normal distribution (Figure 1). The median antibody titer was 0.759 [IQR: 0.311–1.348] OD450 value; therefore, analysis was performed between two groups: those with antibodies < 0.759 (*n* =

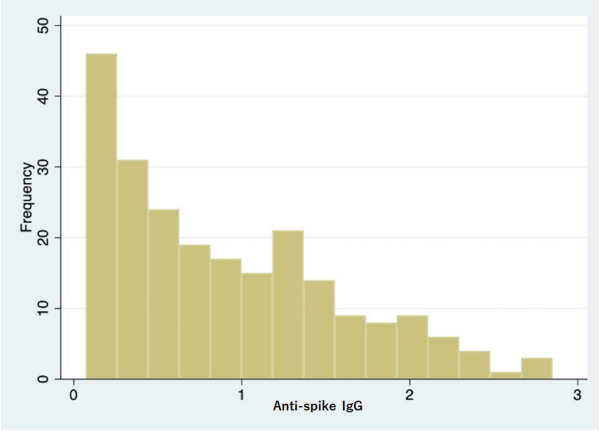

Figure 1. Distribution of SARS-CoV-2 anti-spike antibody titers among the study participants.

Table 1. Characteristics of the study participants

Characteristic	Overall (*n* = 227)	Low antibody titer (*n* = 114)	High antibody titer (*n* = 113)	SMD (before IPW)	SMD (after IPW)	Missing
Age (years), median [IQR]	47 [40–54]	43 [37–51]	51 [45–57]	0.731		0.070
Male sex	101	40	61	0.395	0.126	
Obesity (BMI > 25 kg/m^2)	80	34	46	0.181	0.112	
Smoking	73	38	35	0.024	0.014	
No underlying disease	117	60	57			
Hypertension	35	7	28	0.596	0.020	
Diabetes	17	6	11	0.160	0.057	
Dyslipidemia	30	11	19	0.198	0.006	
Asthma	33	15	18	0.061	0.041	
COPD	1	1	0			
Malignancy	4	1	3			
Use of antivirals	40	6	34	0.382	0.098	13
Use of steroids	26	6	20	0.135	0.164	23
Mild severity	193	90	103			
Moderate severity	27	4	23	0.531	0.098	7
Fatigue	150	73	77			1
SoB	81	37	44			1
Cough	110	50	60			
Dysosmia	118	74	44			
Dysgeusia	97	55	42			
Hair loss	50	21	29			2
Depressed mood	66	28	38			1
LoC	70	30	40			
MD	46	19	27			3

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; IPW, inverse probability weighting; IQR, interquartile range; LoC, loss of concentration; MD, memory disturbance; SMD, standardized mean difference; SoB, shortness of breath.

Table 2. Association between SARS-CoV-2 anti-spike antibody titers and development of post-COVID conditions

Characteristic	Odds Ratio	95% Confidence Interval	*p* value
Fatigue	1.55	0.72–3.31	0.261
Cough	1.88	0.97–3.66	0.061
Dysosmia	0.61	0.30–1.23	0.167
Dysgeusia	1	0.51–1.94	> 0.99
SoB	1.34	0.65–2.77	0.419
Hair loss	1.92	0.91–4.09	0.089
Depressed mood	2.34	1.17–4.67	0.016
LoC	1.85	0.93–3.67	0.079
MD	2.11	0.98–4.52	0.056

Abbreviations: LoC, loss of concentration; MD, memory disturbance; SoB, shortness of breath. Odds ratio indicates the incidence rate ratio of each symptom in the group with higher SARS-CoV-2 anti-spike antibody titers compared to the group with lower antibody titers.

114) and those with antibodies ≥ 0.759 (n = 113).

Correlation between SARS-CoV-2 anti-spike antibody titers and development of post-COVID conditions

The frequencies of each post-COVID condition between the two groups with the high and low antibody titers were analyzed after adjusting for potential confounding factors. There was no significant difference between the two groups in the incidence of fatigue, cough, dysosmia, dysgeusia, shortness of breath, hair loss, loss of concentration, and memory disturbance (Table 2). In contrast, the incidence of depressed mood was significantly higher in the group with a higher antibody titer (OR: 2.34, 95% CI: 1.17–4.67, p = 0.016).

Sensitivity analyses

The same analyses were performed using the antibody titer cut-off values of 0.6 and 0.9 as sensitivity analyses. The antibody titer cut-off value was set at 0.6 and the frequencies of post-COVID conditions were analyzed in the two groups: patients with antibodies < 0.6 (n = 99) and patients with antibodies ≥ 0.6 (n = 128). No significant difference was observed between the two groups in the incidence of fatigue, cough, dysosmia, dysgeusia, shortness of breath, hair loss, and loss of concentration. The incidence of depressed mood (OR: 2.70, 95% CI: 1.35–5.38, p = 0.005,) and memory disturbance (OR: 2.42, 95% CI: 1.14–5.16, p = 0.021) was significantly higher in the group with higher antibody titer (Online Data Tables S1 and S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=65*).

The antibody titer cut-off value was set at 0.9 and the frequencies of post-COVID conditions were analyzed in the two groups: patients with antibodies < 0.9 (n = 127) and patients with antibodies ≥ 0.9 (n = 100). No significant difference was observed between the two groups in the incidence of all the symptoms, but the incidence of depressed mood tended to be higher in the group with a higher antibody titer (OR: 1.85, 95% CI: 0.93–3.68, p = 0.081) (Online Data Tables S3 and S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=65*). The results of the sensitivity analyses showed that changing the cut-off value of the antibody titer did not substantially affect the difference in frequencies of post-COVID conditions between the two groups.

Discussion

In this study, we investigated the effect of antibody titers on the development of post-COVID conditions. We analyzed only participants whose antibodies were tested at a time when antibody titers were likely to be elevated. There was no significant difference in the frequency of ongoing and late-onset symptoms other than depressed mood according to the SARS-CoV-2 anti-spike antibody titers.

A literature search did not reveal any studies showing an association between the SARS-CoV-2 anti-spike antibody titers and the development of post-COVID conditions. A study comparing recovering COVID-19 patients who developed post-COVID conditions with those who did not, found no significant difference between the groups in the magnitude of the antibody titers (*20*), which is consistent with the results of the present study. A previous study suggested that post-COVID-19 conditions are caused by a combination of four conditions: persistent viral infection, reinfection, inadequate immune response, and myalgic encephalomyelitis/chronic fatigue syndrome (*5*). The lack of association between the development of post-COVID conditions and antibody titers can be partly attributed to the combination of multiple mechanisms (*21*).

Depressed mood was the only symptom that was associated with elevated SARS-CoV-2 anti-spike antibody titers in this study. The mechanism by which depressed mood occurs after COVID-19 recovery is not clearly understood, although it has been reported that longer periods of isolation due to COVID-19 might be associated with an increased risk of having depression and anxiety (*22*). Antibody titers are considered to reflect the level of the immune response to COVID-19, and higher levels are more likely to be found in patients with a strong immune response and prolonged period of isolation in the hospital, which may explain the increased risk of developing a depressed mood. In addition, Song *et al.* reported that intrathecal SARS-CoV-2 antibody was associated with neurological symptoms caused by COVID-19 (*23*). Further investigation of the association between the SARS-CoV-2 antibody titers in both cerebrospinal fluid and blood, and neurological post-COVID conditions, including depressed mood, will lead to a more detailed understanding of the pathogenesis of

the diseases.

This study has several limitations. First, the SARS-CoV-2 anti-spike antibody titers were measured only at a time when they were likely to be elevated, so it is unclear whether persistence of high antibody titers is associated with the development or persistence of post-COVID conditions. Moreover, it is possible that participants with low antibody titers at the time of measurement yet with elevated antibody titers at other times were included in the study. Second, only the symptoms extracted from the questionnaire were analyzed in this study; hence, not all post-COVID conditions were investigated. Third, this study was based on a self-reported questionnaire-based survey, which was subject to various biases, such as selection, volunteer, and recall biases. Fourth, the frequency of post-COVID conditions and their association with antibody titers may be altered in epidemic strains that differ from those at the time of the study. Finally, the association between vaccination and the development of post-COVID conditions is unclear because the vaccination history of participants was not obtained in this study. However, considering the timing of the antibody titer measurements, it is likely that few vaccinated participants were included and we reasonably consider that this study evaluated the SARS-CoV-2 anti-spike antibody titers in unvaccinated persons.

In conclusion, the association between the development of specific post-COVID conditions symptoms and antibody titers was investigated, and no association was found except for that between high antibody titers and depressed mood. We postulate that the difficulty in detecting an association between the development of post-COVID conditions and antibody titers is because these conditions are likely to develop through multiple mechanisms. This study suggests that there is a difference in the underlying pathogenic mechanisms between depressive mood and other post-COVID conditions, and further research is needed to investigate this.

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Address correspondence to:
Shinichiro Morioka, Disease Control and Prevention Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: shmorioka@hosp.ncgm.go.jp

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Status of and perspectives on COVID-19 vaccination after lifting of the dynamic zero-COVID policy in China

Mo Zhang[1,§], Yan Wang[2,3,§], Tao Zhang[4], Jing Zhou[2,3,5], Yang Deng[6], Ling Wang[2,3,5,*], Yan Du[1,*]

[1] Clinical Research Unit, Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China;
[2] Laboratory for Reproductive Immunology, Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China;
[3] Shanghai Key Laboratory of Female Reproductive Endocrine-related Diseases, Shanghai, China;
[4] Department of Obstetrics and Gynecology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China;
[5] The Academy of Integrative Medicine of Fudan University, Shanghai, China;
[6] School of Public Health, Shandong First Medical University & Shandong Academy of Medical Sciences, Tai'an, Shandong, China.

Abstract: On December 7, 2022, China's National Health Commission issued the Ten New Covid Rules lifting the dynamic zero-COVID policy. In the interim, vaccination campaigns continue to be promoted. We assessed the potential impacts on the status, perceptions, and attitudes toward COVID-19 vaccines *via* an online self-administered questionnaire. Among 1,170 participants, 1,142 (97.6%) participants were vaccinated against COVID-19, and 51.8% (591/1,142) have already received the booster. More than half of the participants who were vaccinated were ages 31 to 50 (51.8%). Participants believed the following strategies could improve the vaccination rate: timely feedback of the vaccination data (such as safety, efficacy, and other issues of public concern) from authoritative media (95.6%), increasing the number of vaccination sites and availability of vaccines and using more convenient methods of making appointment (95.2%), recommendations from friends and relatives (94.8%), and presenting the qualifications of the staff performing vaccination (89.1%). More measures, including targeted measures for different age groups and timely feedback on the vaccination data including safety and efficacy from authoritative media, are likely to help improve vaccination rates.

***Keywords*:** COVID-19, vaccination, dynamic zero-COVID policy, China

Introduction

Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an outbreak of COVID-19 in Wuhan in late 2019, this highly transmissible infection causing pneumonia has not only posed serious threats to human health and public safety but also resulted in a profound decline in social-economic development in China (*1,2*). Over the past three years, China had been implementing a dynamic zero-COVID policy to block national outbreaks and to keep the mortality rate low (*3*). Currently, the Omicron variant has reignited the pandemic in different countries and regions with enhanced transmissibility but relatively low pathogenicity (*4*). To better balance COVID-19 control and socioeconomic issues, more countries have gradually relaxed their policies (*5,6*).

On December 7, 2022, China lifted its prior severe control policy (*7*). Regular testing requirements and travel restrictions were suspended and people infected with COVID-19 are allowed to self-quarantine at home instead of management in centralized isolation (*7*). According to the National Health Commission, from December 8, 2022 to January 12, 2023, a total of 59,938 deaths related to COVID-19 occurred in hospitals, including 5,503 deaths from COVID-19-related respiratory failure and 54,435 from underlying diseases combined with COVID-19 infection (*8*). The average age of those who died was 80.3; 90.1% were age 65 or older, and 56.5% were age 80 or older (*8*).

The importance of vaccination acceptance

After lifting the zero-COVID policy, some measures such as wearing masks, washing hands, and being vaccinated have been still implemented to reduce transmission to the lowest levels (*7*). Although protection against the omicron variant has waned over time, current studies substantiate the effectiveness and efficacy of a booster against different COVID-19 variants of concern (*9-12*). Studies have also provided evidence that the COVID-19 vaccine has effective protection against SARS-CoV-2-related diseases and is also effective in preventing severe cases and death (*12-14*). According to the US Centers for Disease Control and Prevention (CDC), vaccination is one of the most cost-effective strategies

to effectively control COVID-19 and stop repeated outbreaks through mass immunization (*15*). As for the established herd/population immunity theory, vaccination of the population up to the herd immunity threshold (HIT) may help control the spread of SARS-Cov-2 and provide indirect protection to those who are susceptible and immunocompromised (*16-18*). Vaccine coverage of about 90% is needed to achieve herd immunity, and vaccine coverage may need to be higher for the omicron variant (*19*).

The success of population-level vaccination programs to obtain herd immunity to return to normal life depends mainly on vaccination acceptance. As of January 12, 2023, 1.31 billion people in China had received at least one dose of a COVID-19 vaccine, while the current vaccination rate (the proportion of those receiving a booster) in the country is only 57.92% (*20*).

The current study evaluated the potential impacts of the status, perceptions, and attitudes toward COVID-19 vaccines *via* an online self-administered questionnaire conducted from February to March 2022. The aim of this study was to provide useful information for more aggressive and targeted measures to improve vaccination rates. This study evaluated the vaccination acceptance of the participants and also collected information on opinions and suggestions for designing possible vaccination strategies to improve the vaccine coverage rate, and especially that for vulnerable populations.

Factors associated with COVID-19 vaccination status

The concern about vaccine efficacy has had the largest impact on vaccine hesitancy, followed by adverse reactions (*21*). Several clinical trials on vaccines have reported efficacy and continuous protective effects for the majority of the participants (*9,22,23*). A total of 1,170 participants were included in the final analysis of the current study. As shown here, almost all of the participants were vaccinated against COVID-19 (1,142, 97.6%) (Table 1), which can be attributed to their belief in vaccination efficacy (1,005, 88.0%) (Figure 1A). More than half have already received the booster (591/1,142, 51.8%), which is similar to the national level (57.92%) (*20*). Perceptions and intentions have been identified as important factors influencing vaccination acceptance during the previous 2009 H1N1 pandemic (*24*). Most of the participants thought people engaged in high-risk occupations (1,083, 92.6%) should receive prioritized vaccination, followed by medical workers (913, 78%), people who travel frequently (887, 75.8%), and students or teachers (739, 63.2%) (Figure 1B). In terms of the manufacturer of the vaccine, about three-quarters (845, 74.0%) of the participants have received the Sinovac COVID-19 vaccine (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=64*).

In addition, social and demographic factors may also influence vaccination acceptance (*25*). More than half of the participants who were vaccinated were ages 31 to 50 (591, 51.8%) (Table 1). Compared to the unvaccinated, younger participants (ages 31-50), males (739, 64.7%), participants living in an urban area (925, 81.0%), and participants with a higher level of education were more likely to be vaccinated. Occupation and income were associated with vaccination status as well. Nearly half of the participants (520, 45.5%) who were vaccinated had an annual household income between 30,000–80,000 RMB. In addition, participants who self-rated their health as very healthy (784, 68.7%) or relatively healthy (349, 30.6%) were more likely to be vaccinated.

Studies have suggested that other vaccine-related profiles can also influence people's behavior, such as convenience, price, and recommendations from doctors (*21*). China is a developing country with unequal economic development among regions, so the free vaccination policy has dispelled the price worries of some people and markedly increased the vaccine acceptance and vaccination rate (*26*). Convenient models for making appointments and ubiquitous vaccination sites have greatly increased vaccination rates. Figure 1C shows the vaccination sites. Most participants were vaccinated in hospitals with routine immunization clinics or health centers at different levels (714, 62.5%); some other participants were vaccinated at mobile vaccination units in parks, shopping malls, or sports centers (364, 31.9%).

The current study also obtained opinions and suggestions from the participants to improve the vaccination rate. Participants believed the following strategies could improve the vaccination rate: timely feedback of the vaccination data (such as safety, efficacy, and other issues of public concern) from authoritative media (1119, 95.6%), increasing the number of vaccination sites and availability of vaccines and using more convenient methods of making appointment (1,114, 95.2%), recommendations from friends and relatives (1,109, 94.8%), and presenting the qualifications of the staff performing vaccination (1,043, 89.1%).

Influence of population heterogeneity on vaccination acceptance

Despite the generally positive findings, there were still 28 participants (2.4%) who had yet not been vaccinated, their detailed characteristics are also shown in Table 1. Both adults ages 31 to 50 and older people over the age of 65 accounted for 30% of the unvaccinated. A major factor that influenced general vaccine acceptance was fear and anxiety, and especially fear of adverse reactions (*27*). Recent studies have noted an increased risk of myocarditis in adults younger than 40 particularly associated with the two-dose mRNA vaccine (*28,29*). Some regions adopted vaccination incentives to encourage the unvaccinated and these measures led

Table 1. Characteristics of study participants (*n* = 1,170)

Variables	Total (*n* = 1,170)	Vaccine (*n* = 1,142)	No vaccine (*n* = 28)	*p*
Age (years)				< 0.001
18–30	405 (34.6)	401 (35.1)	4 (14.3)	
31–50	600 (51.3)	591 (51.8)	9 (32.1)	
51–65	136 (11.6)	130 (11.4)	6 (21.4)	
> 65	29 (2.5)	20 (1.8)	9 (32.1)	
Sex				0.008
Males	750 (64.1)	739 (64.7)	11 (39.3)	
Females	420 (35.9)	403 (35.3)	17 (60.7)	
Ethnicity				0.757
Han	1,113 (95.1)	1,086 (95.1)	27 (96.4)	
Man	34 (2.9)	33 (2.9)	1 (3.6)	
Mongolian	6 (0.5)	6 (0.5)	0 (0)	
Zhuang	3 (0.26)	3 (0.26)	0 (0)	
Chinese Korean	3 (0.26)	3 (0.26)	0 (0)	
Bai	2 (0.17)	2 (0.18)	0 (0)	
Yi	2 (0.17)	2 (0.18)	0 (0)	
Tujia	2 (0.17)	2 (0.18)	0 (0)	
Miao	1 (0.09)	1 (0.09)	0 (0)	
Kazakh	1 (0.09)	1 (0.09)	0 (0)	
Other	3 (0.26)	3 (0.26)	0 (0)	
Level of education				0.071
Middle school or lower	180 (15.4)	172 (15.1)	8 (28.6)	
High school, vocational school, junior college	506 (43.2)	498 (43.6)	8 (28.6)	
University, college	348 (29.7)	337 (29.5)	11 (39.3)	
Graduate school	136 (11.6)	135 (11.8)	1 (3.6)	
Marital status				0.068
Married	754 (64.4)	732 (64.1)	22 (78.6)	
Single	369 (31.5)	365 (32.0)	4 (14.3)	
Divorced	37 (3.2)	36 (3.2)	1 (3.6)	
Widowed	10 (0.9)	9 (0.8)	1 (3.6)	
Residence				0.005
Urban	953 (81.5)	925 (81.0)	28 (100)	
Rural	217 (18.5)	217 (19.0)	0 (0)	
Living alone				0.829
Yes	311 (26.6)	303 (26.5)	8 (28.6)	
No	859 (73.4)	839 (73.5)	20 (71.4)	
Annual household income [RMB]				0.039
< 30,000	178 (15.2)	171 (15.0)	7 (25.0)	
30,000–80,000	527 (45.0)	520 (45.5)	7 (25.0)	
80,000–150,000	233 (19.9)	229 (20.1)	4 (14,3)	
150,000–300,000	139 (11.9)	134 (11.7)	5 (17.9)	
> 300,000	93 (7.9)	88 (7.7)	5 (17.9)	
Occupation				< 0.001
Company employee	510 (43.6)	505 (44.2)	5 (17.9)	
Medical worker	118 (10.1)	116 (10.2)	2 (7.1)	
Student, teacher	114 (9.7)	114 (10.0)	0 (0)	
Civil servant, government employee	53 (4.5)	51 (4.5)	2 (7.1)	
Freelancer	29 (2.5)	25 (2.2)	4 (14.3)	
Driver	23 (2.0)	22 (2.0)	1 (3.6)	
Service worker (catering, express delivery, sales clerk, barber, security guard, *etc.*)	15 (1.3)	14 (1.2)	1 (3.6)	
Self-employed	12 (1.0)	10 (0.9)	2 (7.1)	
Logistics, cold chain staff	5 (0.4)	5 (0.4)	0 (0)	
Flight attendant, airport staff	1 (0.09)	1 (0.09)	0 (0)	
Customs personnel	1 (0.09)	1 (0.09)	0 (0)	
Seafood market staff	1 (0.09)	1 (0.09)	0 (0)	
Other	288 (24.6)	277 (24.3)	11 (39.3)	
Self-rated health status				< 0.001
Very healthy	797 (68.1)	784 (68.7)	13 (46.4)	
Relatively healthy	360 (30.8)	349 (30.6)	11 (39.3)	
In poor health	13 (1.1)	9 (0.8)	4 (14.3)	

to young adults' decreased confidence in and distrust of the vaccine (*30*). Older adults who were unsure of being vaccinated against COVID-19 or who refused vaccination would rather take nonpharmaceutical measures like wearing a mask and washing their hands frequently (*31*). They were concerned about the safety

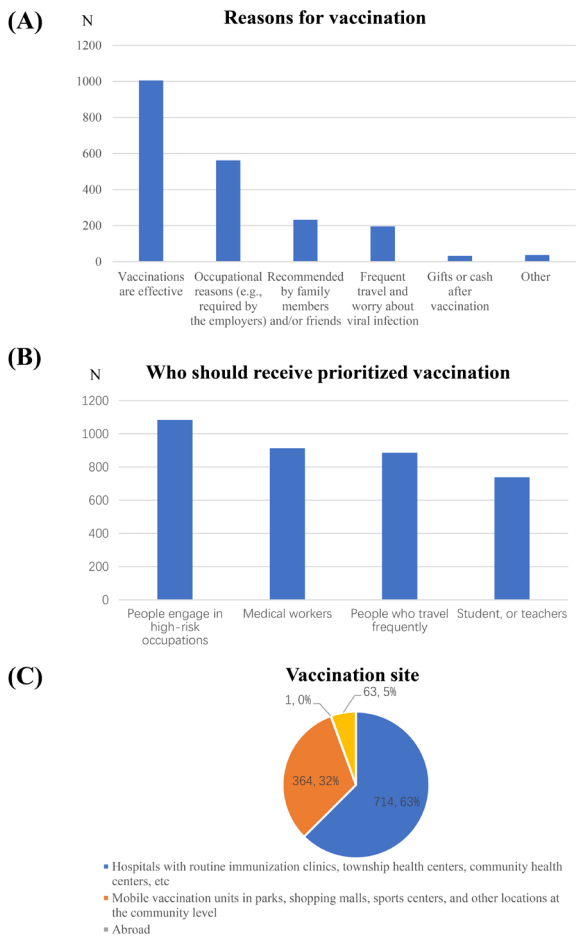

Figure 1. Actions and factors associated with COVID-19 vaccination. (A) Reasons for vaccination; **(B)** Who should receive prioritized vaccination; **(C)** Vaccination site.

and efficacy of the vaccine. Rare but severe events involving thrombosis and the potential increased risk of blood clots may have had a profound effect on their vaccination acceptance (*32*). Individuals with cancer or other severe comorbidities were unsure about the personal benefits of vaccination and eventually refused (*33*). In addition, older adults with family members younger than 18 years of age refused to be vaccinated for fear of affecting younger family members (*34*).

Despite the low reported risk of COVID-19 vaccination affecting fertility, a small proportion of the female population, and especially pregnant women, still have doubts about infertility and concerns about exposing their babies to potential harm (*35,36*). Another reason may be the fear of menstrual disruption (*37-39*). About half of the participants (548, 46.8%) had children (under 18 years of age) in their families, and more than half (326, 59.5%) were unwilling to let their children be vaccinated. Concern about vaccine efficacy has the greatest impact on vaccine hesitancy, followed by adverse reactions (*36*). Incidents such as the Changchun Changsheng vaccine incident have severely undermined public trust (*40*). At the same time, negative reports on adverse events without valid evidence continuously alter and distort the public perceptions of vaccine safety and efficacy and eventually lead to vaccine hesitancy or even vaccine refusal (*41*). Parents are skeptical of the vaccine development process and also afraid of adverse reactions, which may be overlooked in the rush to develop vaccines (*42*). Moreover, the fact that immunosuppressants may affect the immunogenicity of the vaccine played a role in whether parents allowed their children to be vaccinated (*43*). The adolescents themselves believed that they had no risk of infection and that their symptoms would not be severe if they were infected (*44*). Adolescents with a history of immune-related diseases or other primary diseases in particular refused vaccination unless convincing evidence indicated clear benefits to them (*42,44*). Moreover, clinical trials on the COVID-19 vaccine for adolescents (younger than 18) are still lacking and real-time dissemination of information on vaccine efficacy among adolescents is still limited.

Conclusions and Suggestions

The current results indicated a high level of COVID-19 vaccine acceptance among the adult population in China during the pandemic. With accurate perceptions and proper understanding of the purpose of COVID-19 vaccines, coverage at the population level has improved. However, challenges still remain as a small fraction of eligible people is still not vaccinated. Moreover, there is reluctance to vaccinate children.

To achieve and maintain herd immunity, we recommend the following multifaceted efforts. First, developing more safe and effective vaccines is crucial in the face of a drastic change in policy and the uncertainty of viral mutation. Second, age group heterogeneity affects vaccination and therefore targeted measures need to be taken for different age groups. Third, timely feedback on vaccination data, including safety and efficacy, from authoritative media can dispel skepticism regarding the necessity and efficacy of vaccines and effectively improve the acceptance rate.

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[§]*These authors contributed equally to this work.*
**Address correspondence to*:
Yan Du, Clinical Research Unit, Obstetrics and Gynecology Hospital of Fudan University, No. 128 Shenyang Road, Shanghai 200090, China.
E-mail: sophiedu_61@163.com

Ling Wang, Laboratory for Reproductive Immunology, Obstetrics and Gynecology Hospital of Fudan University, 419 Fangxie Road, Shanghai 200011, China.
E-mail: Dr.wangling@fudan.edu.cn

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Evolving partnership: A National Center for Global Health and Medicine Resilient Training Model for clinical research professionals during the COVID-19 pandemic

Sifa Marie Joelle Muchanga*, Mieko Hamana, Marlinang Diarta Siburian, Maria Ruriko Umano, Nattha Kerdsakundee, Maria Rejane Umano, Masato Ichikawa, Tatsuo Iiyama

Department of International Trials, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: The clinical trial industry has encountered challenging circumstances in which the increasing number of trials outpaces the number of trial specialists. For instance, there has been an unprecedented demand for clinical trials following the Covid-19 pandemic, which has worsened the global shortage of qualified personnel. It is therefore imperative to produce more qualified clinical trial professionals. An adaptive and collaborative training model was implemented by the National Center for Global Health and Medicine through the Department of International Trials. This aimed at building capacity among health workers in developing countries and providing them with the skills to be able to conduct all phases of the clinical trial from protocol design to publication of results. It also seeks to foster collaboration and partnership between local health workers and international experts. Since 2016, we have implemented a Japan-led training program, and since 2020, the COVID-19 pandemic has ushered in a shift from a single Train-the-trainer model (ToT) to a mixed model, the Evolving Partnership Training (ePT). In this model, we applied four different methods: train-the-trainer, needs-oriented training, open symposiums, and advanced learning. The total number of training participants increased exponentially from a total of 41 between 2016–2020 to 2,810 in 2021. Our experience has proven that despite the constraint of the pandemic, the ePT is a viable approach compared to a single method for providing quality training and increasing the number of participants.

Keywords: clinical trial professionals, evolving partnership training, National Center for Global Health and Medicine, training, train-the-trainer

The number and complexity of clinical trials has been increasing while the number of clinical trials professionals has not evolved in an equivalent way (*1*). Records from the WHO International Clinical Trials Registry Platform (ICTRP) that include observational and interventional studies compiled from different registries, had shown a continuous increase in number of registered studies all over the WHO regions since 1999 (*2*).

For example, on December19th, 2022 a total of 436,709 studies have been registered on *ClinicalTrials.gov* reporting a very steady increase with the advent of COVID-19 that accounts for 8,522 studies (*3*). In parallel, a global concern is raising the problem of shortage of clinical research professionals in all categories combined (*4,5*). This shortage was reported at 15% before the COVID-19 pandemic but has almost doubled to 29% during the post-pandemic period. Such a shortage may alter the proper functioning of clinical research operations (*6*).

According to the United States Food and Drug Administration (USFDA), only 3% of physicians and patients took part in a clinical trial that leads to new therapies and the majority were conducted at top academic institutions limiting the coverage of large proportion of the population (*7*). Only few professionals enter the clinical research industry with qualifications directly from the university (*1*). Medical school curricula allocate less time to educate students about the significance of biomedical research for better health care or to attract students to participate in biomedical research (8). In addition, the majority of clinicians do not receive enough exposure to research methods as part of their clinical development. Even fewer clinicians receive exposure to regulatory processes training, which is part of the core competency for clinicians who are involved in trials heading for regulatory approval (*1*).

Furthermore, the onset of the COVID-19 pandemic revealed to the world how weak health systems were and how little prepared both research communities and governments were for a possible health disaster. Moreover, we are not spared by the occurrence of a

pandemic X in the future (*9*).

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6-R2 (Good Clinical Practice) repeatedly mentions that each trial personnel "should be qualified by education, training and experience to perform tasks" (*10*). It is thus, of high interest to participate in the global efforts of filling the gap that is faced by the clinical research professional community.

Through the Department of International Trials, the National Center for Global Health and Medicine (NCGM), has been committed to improve access to healthcare by promoting international clinical research/ trials between Japan and partners in Asian and African countries.

From 2016 to 2020, we funded and implemented an annual training program using the training of trainers (ToT) model, during which topics related to clinical trials design and operations were discussed. Delegates from Democratic Republic of the Congo, Indonesia, Philippines, Thailand, Vietnam, and Japan joined a 2-week intensive short training program and participated as observer at the multiregional clinical trials seminar organized annually by the Japan Pharmaceutical and Medical Device Agency (PMDA). In order to evaluate the learning comprehension of the participants, pre-tests and post-tests were administered. In addition, all training materials were distributed to them, for their reference. Trainees were required to obtain a minimum of 80 % on the final evaluation test.

With the advent of the COVID-19 pandemic, global movements were restricted and face to face meetings of participants from different countries had become nearly impossible. In collaboration with past trainees, we then developed a new capacity building model which consisted of three pillars in addition to the ToT; first a needs-customized local training, second an advanced e-learning and third an international online symposium. We named the model as the evolving partnership training (ePT) model.

Regarding the needs-customized local training, contents were developed after consultation with past trainees and their supervisors to pin out training needs in their working environment. Each collaborating institution implemented trainings in their setting with a focus on particular topics related to their self-assessed local needs. Theses local trainings were conducted either by face to face, online or hybrid.

From the locally trained participants, 30 were selected to participate in the advanced e-learning program for principal investigators that included six main topics, pre-clinical studies, regulation for clinical trials, epidemiology, biostatistics for clinical research, data management and translational medicine. For the current training, we developed the content in collaboration with Chiba University and St Luke's University; Japanese experts were invited to provide the lectures.

As for the symposium, it is being carried out annually and involves key opinion leaders from various developed and developing countries who share their expertise on selected aspects of clinical trials. Figure 1 illustrates the mathematical model and components of the program.

In total, there were 41 trainees composed of physicians and statisticians who joined the ToT program in Tokyo from 2016 to 2020 – 6 in 2016, 8 in 2018, 14 in 2019, and 13 in 2020. In 2021, when the ePT was introduced, 2,810 professionals were trained locally in their respective countries by joining the local training, the e-learning and the online symposium as shown in the Figure 2.

The present training model, was a concept developed from the concept starting by a one-way ToT to a participative multilateral collaboration that could improve both the quality and the number of trained professionals. This illustrates that not only the funder gives his own orientation but also the learners by defining their needs, have active involvement in the implementation of the program. Participative collaboration in the program design is of great value because the training meets the learners self-assessed needs. We could observe an exponential increase in the number and quality of participants in the training program.

The ePT model is partially closer to the Analyze, Design, Develop, Implementation and Evaluate (ADDIE) (*11*) and to the ToT models (*12*). In fact, the first pillar of the ePT that consisted of the one-way training resulted in training of professionals able to train others in their individual settings. The second pillar that consisted of the local needs-customized training

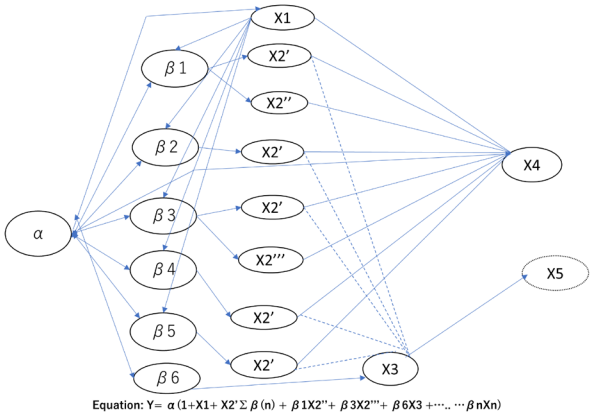

Figure 1. The evolving partnership training model (ePT). The ePT model includes the training of trainers, the need-customized, the advanced e-learning course and the open symposium. The needs-customized trainings were conducted either as: lecture type X2', webinar and conference X2'', or Discussion forum X2'''). α: Initiating Institution; β : Collaborative institution; X: Learning types; X1: training the trainers (ToT) course; X2: Needs – customized course (X2': lecture type; X2'': webinar, conference; X2''': Discussion forum); X3: Advanced e-learning course; X4: Open symposium; Y: number of trainees.

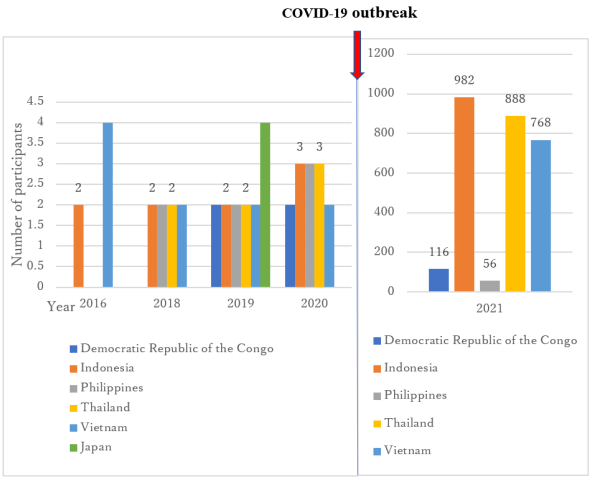

Figure 2. Distribution of training participants per country and per fiscal year. Participants from six countries joined the annual training program lead by the National Center for Global Health and Medicine. The number of participants has gradually increased over time with a remarkable increase in 2021 during the COVID-19 pandemic. *Note*: the scale is different in 2021.

program is similar to the ADDIE model in terms of analyzing the learner's needs and knowledge before designing and producing the content of the training.

For the ADDIE model, before starting to develop a course, you need to do the training needs assessment that would be the basis for the other steps of the implementation of the training and evaluation of the outcome. The difference is that in the ADDIE model the analyses are one-way from the trainers while in the ePT model, there are 2 layers of trainers that collegially develop the content of the training. However, the ePT model does not evaluate the outcome of the training as a whole but each of the ePT components were evaluated separately.

The ePT model is considered to be a mixed model that includes part of ADDIE and ToT, in addition to the multilateral involvement in the design of the content. The added value of the current training model is that the program is needs-oriented, cost-effective and involves partnership in design.

The limitation of the current model, is that we did not evaluate the outcome of the training as a whole in terms of the quality of trained professionals but one should assume that based on the content of the program and the motivation of learners, the program is worthwhile to have been implemented. Another limitation is that the content was not uniform for all the participants involved in the program, however, a needs-customized content is more valuable to solve real time issues faced by the learners to bring the solution to the locals by the locals. We assume that this component of the ePT motivates the participants to take ownership in finding solutions to their perceived problems in their research environment.

In conclusion, the current study has evidenced that despite the constraint of the COVID-19 pandemic, the ePT is a viable approach other than a single method for providing quality training and increasing the number of participants. This model should be one of the solutions, to participate in the global effort for capacity building of clinical trial professionals.

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**Address correspondence to*:
Sifa Marie Joelle Muchanga, Department of International Trials, National center for Global Health and Medicine, 1-21-1, Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: msifa@hosp.ncgm.go.jp

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Current situation and clinical burden of pediatricians for children with eating disorders during the COVID-19 pandemic

Yuki Mizumoto[1,2], Yoshinori Sasaki[1,3], Hikaru Sunakawa[1], Shuichi Tanese[1], Rena Shinohara[1], Toshinari Kurokouchi[1], Kaori Sugimoto[1], Manao Seto[1], Masahiro Ishida[1,4], Kotoe Itagaki[5], Yukino Yoshida[5], Saori Namekata[5], Momoka Takahashi[2], Ikuhiro Harada[6], Shoko Sasaki[7], Kiyoshi Saito[8], Yusuke Toguchi[9], Yuki Hakosima[1], Kumi Inazaki[1], Yuta Yoshimura[1,5], Masahide Usami[1,2,4,*]

[1] Department of Child and Adolescent Psychiatry, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan;
[2] Clinical Center of Children's Mental Health, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan;
[3] Department of Psychiatry and Behavioral Science, Tokyo Medical and Dental University Graduate School, Tokyo, Japan;
[4] Department of Psychiatry, Faculty of Medicine, Fukuoka University, Fukuoka, Japan;
[5] Department of Clinical psychology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan;
[6] Department of Social worker, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan;
[7] Department of Psychiatry, Kansai Rosai Hospital, hyogo, Japan;
[8] Department of Psychiatry, Narimasu Kosei Hospital, Tokyo, Japan;
[9] Department of Psychiatry, Komagino Hospital, Tokyo, Japan.

Abstract: During the COVID-19 pandemic, the incidence of eating disorders (ED) has increased not only in Japan but also worldwide. This online survey for pediatricians showed that caregivers tend to visit specific pediatric institutions or child psychiatry departments when children under junior high school age develop eating disorders. There are few pediatric institutions regarding treatment acceptance for children with ED. Of the 34 respondents, 16 (47.1%) answered that the number of visits for children with eating disorders had "stayed the same", one answered it had "decreased" and 17 (50.0%) answered it had "increased" or "increased very much". In addition, 28 of the 34 respondents (82.3%) experienced difficulties with psychotherapy for children with ED. For treating children with ED, pediatricians usually conducted physical examination and have some clinical burden. ED are increasing in the COVID-19 pandemic. Because children with severe ED need to be hospitalized, child and adolescent psychiatric wards are overcrowded and some children with other mental disorders can't be admitted.

***Keywords*:** eating disorder, Child, COVID-19

During the COVID-19 pandemic, the number of children with eating disorder (ED) who visited the Department of Child Psychiatry at Kohnodai Hospital, National Center for Global Health and Medicine (NCGM), has increased by 2.3 times from 1.3 to 3.1 patients/month from March 2020 to May 2021 (Table 1) (*1-7*).

We conducted a questionnaire survey of pediatricians in Chiba Prefecture to report on the current pediatric setting for children with ED under junior high school age during the COVID-19 pandemic. This online survey was conducted from the end of October to the end of December 2021, targeting approximately 200 pediatricians who belong to the Chiba Association of Pediatricians. This study was conducted with the approval of the Ethics Committee of NCGM (NCGM-S-4398).

The survey response rate was 34 of 200 (17%), of which 32 respondents (94.1%) were working in pediatrics and the remaining two respondents (5.9%) were working in internal medicine. Eighteen respondents (52.9%) worked in general hospitals and 14 (41.2%) in clinics. Regarding the respondent's qualifications, 30 respondents (88.2%) were pediatric specialists, and two respondents (5.9%) were children's mental health specialists.

Regarding the inpatients and outpatients with ED, about 85% of the respondents had experienced treating children with ED: 16 (47.1%) reported that they "currently treat", 13 (38.2%) reported that they "treated in the past but not now", and 5 (14.7%) reported that they "have never treated". When the 16 respondents with current patients with ED were asked about the number of patients under junior high school, 15 of the 16 respondents answered "1–5 children", which accounted for most of the patients, and one respondent answered "21–30 children". Of the 16 respondents, 4 respondents

answered "one child", and one respondent answered "5 or more children".

When the children with ED under junior high school age visited the clinic, height and weight measurements were conducted, followed by blood tests in 34 of the 36 respondents (94.4%). Additionally, "conduct an electrocardiogram" and "clearly inform the patient that specialized treatment is not available" were followed, and "refer the patient because there are no inpatient facilities" was the least common response (Table 2). Of the children with ED who had been hospitalized, 14 respondents (41.2%) reported that "they had been hospitalized in the past but not now", 13 respondents (38.2%) reported that "they had never been hospitalized" and 7 respondents (20.6%) reported that "they were currently hospitalized'. Regarding the age and sex of current hospitalized patients with ED below junior high school age, there were no boys in either primary or junior high school, with primary school girls being the most common (all responses) and junior high school girls (3 out of 7 responses).

In terms of the number of visits for children with eating disorders, of the 34 respondents, 16 responders (47.1 %) indicated "unchanged", 1 respondent indicated "decreased", and 17 respondents (50.0%) indicated "increased" or "very much increased". Furthermore, 28 out of 34 (82.3%) had difficulties with psychological treatment of children with ED.

In terms of problems in treating ED in secondary school students, "lack of referral sources/specialist facilities" was the most common problem encountered by all respondents. This was followed by "dealing with overeating, anorexia and hyperactivity", "diagnosis of depression, anxiety, *etc.*", "psychological treatment" and "parental support". Respondents struggled with managing their symptoms, diagnoses and responses to psychological symptoms, and parental support. In terms of treatment, 6 respondents reported "difficulty in finding a specialist facility to refer to (or be accepted by)", while another 6 respondents reported "lack of a collaborative system", followed by "not knowing the goal of treatment" and "not knowing medications for comorbid

Table 1. ED in the pre- and post-pandemic period

Characteristics	Pre-Pandemic Jan. 2016–Feb. 2020	Pandemic Mar. 2020–May. 2021
Number of children with eating disorders	66	54
Average outpatient/month	1.3	3.1
Boys/Girls	8/58	0/54
Average age	12.3 (8–15)	13.0 (9–15)
Elementary/Junior high school students (rate of elementary school students)	23/43 (34.8%)	11/43 (20.3%)
Rate of inpatients	30.3%	25.9%
Elementary school students	39.1%	63.6%
Junior high school students	25.6%	16.3%
Referral rate from other hospitals	80.3%	80.8%

ED, eating disorders.

Table 2. Problems in the pediatric clinical field

Problems	Not troubling	Not much	Neither	Sometimes	Severe trouble
Diagnosis					
Diagnosis of ED	2 (5.9%)	9 (26.5%)	2 (5.9%)	12 (35.3%)	9 (26.5%)
Diagnosis of developmental disorders	0 (0.0%)	8 (23.5%)	4 (11.8%)	14 (41.2%)	8 (23.5%)
Diagnosis of depression and anxiety disorders	0 (0.0%)	3 (8.8%)	3 (8.8%)	8 (23.5%)	20 (58.9%)
Treatment					
Physical treatment	1 (2.9%)	11 (32.3%)	5 (14.7%)	7 (20.6%)	10 (29.4%)
Psychological treatment	1 (2.9%)	3 (8.8%)	2 (5.9%)	9 (26.5%)	19 (55.9%)
Parental support	0 (0.0%)	3 (8.8%)	1 (2.9%)	14 (41.2%)	16 (47.1%)
Prolonged hospitalization	0 (0.0%)	2 (5.9%)	9 (26.5%)	11 (32.3%)	12 (35.3%)
Behavioralization (*e.g.*, overactivity/overeating)	0 (0.0%)	2 (5.9%)	9 (26.5%)	9 (26.5%)	14 (41.2%)
Few experience					
Treating elementary school children with ED	0 (0.0%)	4 (11.8%)	6 (17.6%)	8 (23.5%)	16 (47.1%)
Treating junior high school children with ED	0 (0.0%)	3 (8.8%)	6 (17.6%)	9 (26.5%)	16 (47.1%)
Dealing with AN	0 (0.0%)	3 (8.8%)	0 (0.0%)	15 (44.1%)	16 (47.1%)
Dealing with overeating	2 (5.9%)	0 (0.0%)	2 (5.9%)	12 (35.3%)	18 (52.9%)
Dealing with overactivity	0 (0.0%)	2 (5.9%)	1 (2.9%)	12 (35.3%)	19 (55.9%)
Collaborate in local area					
Lack of referral specialists	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (23.5%)	26 (76.5%)
Cooperation with schools	0 (0.0%)	5 (14.7%)	3 (8.8%)	14 (41.2%)	12 (35.3%)

ED, eating disorders.

anxiety, depression and other psychiatric symptoms".

The data from this survey were underpowered due to the low response rate. Almost all respondents were pediatricians working in general hospitals or clinics, and almost 90% of them were consultant pediatricians.

Approximately 60% of the pediatricians had experience with inpatient treatment, and currently "elementary school girls" were the most frequently hospitalized, as in previous reports in Japan (1).

This survey showed that the children with ED in pediatric unit during the COVID-19 pandemic was increased compared with the situation before the pandemic as same as the psychiatric department (8). This suggests that when children under junior high school age with ED, they may be more likely to choose a specific pediatric institution and child and adolescent psychiatric institution. However, "lack of referral sources/specialized institutions", "dealing with actual symptoms", "diagnosis and response to psychiatric symptoms" and "parental support" were very serious problems in the Japanese pediatric field. It was found that pediatricians in both general hospitals and clinics carefully follow up patients on an outpatient basis, taking height and weight measurements and performing blood tests, but they observed lack of a specialized hospital to which they could refer patients in an emergency and a lack of coordination between them.

Several reasons for this increase in children with ED visits have been explored, but the evidence is clear. In the clinical setting, regardless of the COVID-19 pandemic, some children with ED need to be hospitalized for treatment, as their excessive eating problems, low body weight and poor nutritional status make it an extremely life-threatening condition.

Several social problems have been observed. Only a limited number of hospitals have wards specializing in child and adolescent psychiatry, and even fewer general hospitals in Japan can provide physical treatment for severely underweight children (1). In addition, the rate of admission to child and adolescent psychiatric wards has increased rapidly due to the rapidly increasing incidence of children with ED. This makes it difficult to treat cases with problems such as severe self-harm, suicide attempts, obsessive-compulsive symptoms, and domestic violence, for which inpatient treatment would be preferable. The clinical implications are that pediatrics and child psychiatry need to work together to manage children with eating disorders in the community.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Address correspondence to:
Masahide Usami, Department of Child and Adolescent Psychiatry, Kohnodai Hospital, National Center for Global Health and Medicine, 1-7-1 Kohnodai, Ichikawa, Chiba 272-8516, Japan.
E-mail: usami.masahide@hospk.ncgm.go.jp

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