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Special Topic: COVID-19

"Stay Home, Save Lives"
– Cherry blossoms blocked off at Ueno Park in Tokyo due to the COVID-19 pandemic –

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Global Health & Medicine

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COVER FIGURE OF THIS ISSUE

"Stay Home, Save Lives" – Cherry blossoms blocked off at Ueno Park in Tokyo due to the COVID-19 pandemic.

Ueno Park is one of the most crowded and vibrant spots for viewing cherry blossoms (Hanami) in Japan. As the cherry blossoms come in season, more than 4 million people visit Ueno Park to view 800 cherry trees in full bloom every year. In a scene completely unlike prior cherry blossom seasons, barricades currently block the entrance to the park due to the COVID-19 pandemic.

(Photo by *Riri Saito*)

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Sustaining containment of COVID-19: global sharing for pandemic response

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Abstract: The coronavirus disease 2019 (COVID-19) outbreak, caused by SARS-CoV-2, has rapidly escalated into a global pandemic. One of our significant concerns is that we have no data as to whether people, who acquired immunity against this deadly virus and recovered from COVID-19, are protected from further infections with the same virus. Moreover, we have no data as to whether this pandemic will persist in our societies and continue vexing us for long periods of time. Implementing science-based response strategy is essential to sustain containment of COVID-19 globally. Rapidly sharing scientific information means providing real-time research data and relevant findings. As an international academic journal, *Global Health & Medicine* publishes this special issue entitled "*GHM Special Topic: COVID-19*". It includes a range of articles describing COVID-19 based on frontline data from Japan, China, the United States, Italy, the United Kingdom, and other countries and areas worldwide. Our hope is that the rapid publication and sharing of information contribute, in whichever possible way, to this global fight against COVID-19.

***Keywords*:** SARS-CoV-2, COVID-19, global health

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly emerging pathogen, and it highly contagious and propagates quickly. The coronavirus disease 2019 (COVID-19) outbreak, caused by SARS-CoV-2, has rapidly escalated into a global pandemic. Globally, as of 26 April 2020, there have been 2,804,796 confirmed cases of COVID-19, including 193,710 deaths, reported to the World Health Organization (WHO) (*1*), and these figures are still rapidly increasing (Figure 1). Even more concerning is that there is currently no evidence that people who have recovered from COVID-19 and who have antibodies are protected from second infection (*2*). "We have a long way to go. This virus will be with us for a long time'' (*3*), as indicated by Dr. Tedros Adhanom Ghebreyesus, WHO Director-General, at a media briefing on COVID-19 held on 22 April 2020.

Among the countries that have reported data to WHO, 78% have a preparedness and response plan in place; 76% have surveillance systems in place to detect cases; and 91% have the capacity to laboratory test for COVID-19. However, only 66% of the countries have clinical referral system in place to care for patients with COVID-19; only 48% have community engagement plan; and only 48% have infection prevention and control programs and standards for water, sanitation, and hygiene in healthcare facilities (*3*).

Implementing the science-based response strategy is essential to achieve and sustain global containment of COVID-19. Rapid share of scientific information means the provision of real-time guidance to epidemiologists working to contain the outbreak, clinicians managing patients, and modelers helping to understand future developments and the possible effectiveness of various interventions. Facing the unprecedented threat by COVID-19, the scientific community has rapidly come together to address this outbreak in an open and collaborative manner to support the global response to this outbreak by rapidly sharing and highlighting research data and relevant findings (*4*).

Since its inception in October 2019, our journal – *Global Health & Medicine* – has been dedicated to publishing high-quality original research that contributes to the advancement of global health and medicine, with the goal of creating a global information network for global health, basic sciences as well as clinical sciences, hoping that they lead to novel clinical applications (*5*). At the Journal, we have worked with authors to publish this special issue on the topic of COVID-19 in a determined effort to rapidly disseminate reliable information to promote science-based response strategy to combat this global pandemic.

This issue of "*GHM Special Topic: COVID-19*" includes a range of articles describing COVID-19. This issue has three features. First, it has collected frontline data on the COVID-19 fight in Japan, including the triple challenges of (*i*) a cruise ship docked at Yokohama, (*ii*) evacuation of Japanese nationals from Wuhan,

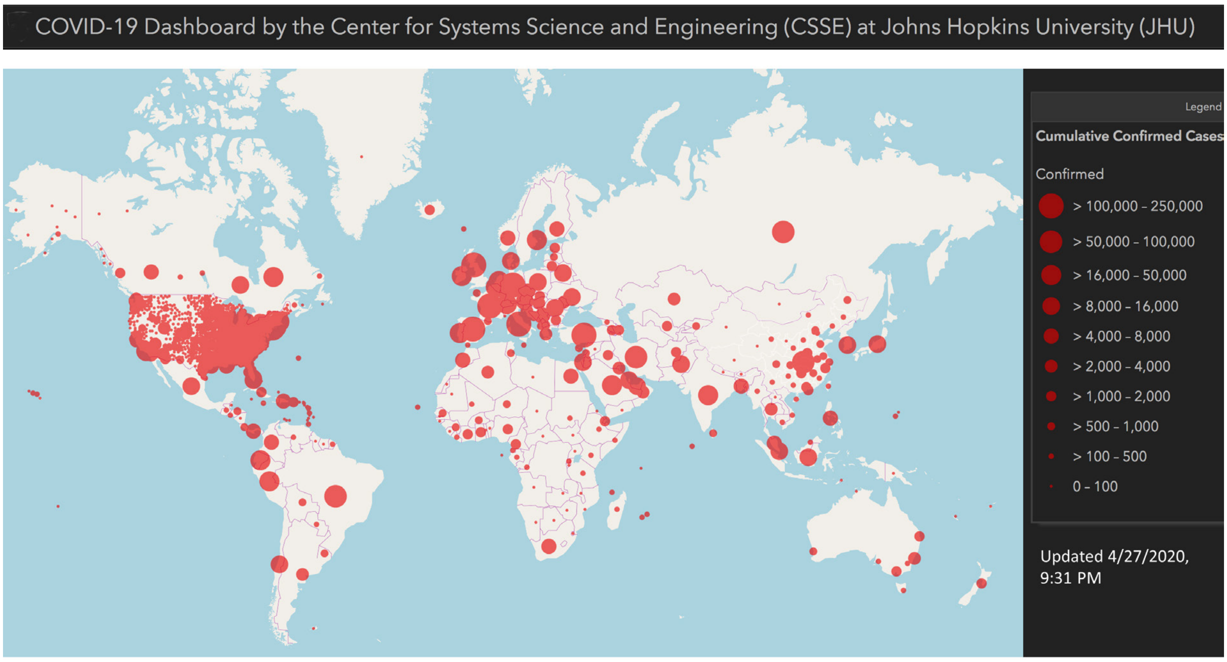

Figure 1. Globally reported confirmed cases of COVID-19 as of April 27, 2020. (Data source: *https://coronavirus.jhu.edu/map.html*).

China, and (*iii*) an increasing number of domestic cases. Jimi (Parliamentary Vice-Minister of Health, Labour and Welfare) and Hashimoto (State Minister of Health, Labour and Welfare) describe the anchorage quarantine approach and the principles of quarantine measures implemented on the cruise ship Diamond Princess. Tsuboi *et al*. report the epidemiology and quarantine measures implemented during the outbreak of COVID-19 on the cruise ship. Hayakawa *et al*. report the quarantine process and results of SARS-CoV-2 infection among returnees to Japan on five charter flights from Wuhan, China. Inoue described the health policy factors relatively unique to Japan in combating COVID-19. Kuwahara *et al*. analyzed the publicly available data on patient characteristics of COVID-19 in Tokyo. Edagawa *et al*. describe the epidemiological features of COVID-19 after declaration of an emergency in Hokkaido and they report 15 cases, including 3 cases requiring mechanical ventilation. Umeda *et al*. describe the nursing care for patients with severe COVID-19 on extracorporeal membrane oxygenation (ECMO) support. Ito *et al*. summarize the major clinical trials of COVID-19 treatments underway and studies currently being conducted or scheduled in Japan.

Second, this issue presents the valuable experiences and lessons learned during the early phases of the fight against the COVID-19 outbreak worldwide. Xu *et al*. describe the main contents of the 3rd to 7th versions of guidelines for the diagnosis and treatment of COVID-19 in China. He *et al*. describe the role and activities of Internet-based healthcare platforms designed for COVID-19 in China. Villa *et al*. describe the response to pandemic in Italy and emphasize that action against this threat must be taken quickly, firmly, and at highest trans-national levels. Kariya reports the rapid spread of COVID-19 in New York and the response of the community. Kutsuna summarizes advances in research and clinical practice regarding COVID-19 based on reported studies worldwide.

Third, a "World Report Series" is featured in this issue to share the actual experiences of frontline clinicians and other healthcare professionals around the world fighting the pandemic. The current status of COVID-19 in places like the United States, the United Kingdom, China, West Africa, Cambodia, and Myanmar is reported in order to be a useful reference for the next phases of the COVID-19 response.

As the COVID-19 pandemic progresses, rapidly sharing scientific information will be crucial to determining science-based response strategy to mitigate and suppress, and thus to better prepare for the probable continuation of the epidemic over the next few years or longer. As an international academic journal, *Global Health & Medicine* will continue to rapidly review and publish COVID-19-related articles to facilitate the real-time sharing of scientific information. It is our hope that this form of sharing contributes, in whichever possible way, to this global fight against COVID-19.

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EDITORIAL

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Scientific solidarity in the face of the COVID-19 pandemic: researchers, publishers, and medical associations

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Abstract: In the face of COVID-19, the scientific community has rapidly come together to address this outbreak in an open and collaborative manner to support the global response to this outbreak by rapidly sharing and highlighting research data and relevant findings. COVID-19 research is being published at a furious pace. Over 6,000 articles have been published as of 20 April 2020, and at least 15 online resource centers/websites for COVID-19 have been created by publishers to enable fast and free access to the latest research, evidence, and data available. Moreover, many evidence-based guidelines for COVID-19 have been issued based on academic articles and summaries of the experiences of frontline medical personnel. Various academic medical associations are also actively sharing information and providing technical support. As an example, 93 guides/proposals/responses to COVID-19 have been issued so far by 50 medical associations in Japan. However, few publications and national situation reports have provided information on the number of infected healthcare workers (HCWs). More publications and national situation reports are urgently needed to provide scientific information to devise specific infection prevention and control measures in order to protect HCWs from infection.

***Keywords*:** COVID-19, publication, sharing data, guideline, healthcare worker

The COVID-19 pandemic is rapidly evolving, and over 150,000 people have unfortunately lost their lives to COVID-19 so far. There are 2,314,621 confirmed cases globally as of April 20, 2020; there are more than 100,000 confirmed cases in the United States (723,605), Spain (195,944), Italy (178,972), Germany (141,672), the United Kingdom (120,071), and France (111,463), and case numbers are increasing rapidly (*1*).

Rapidly evolving healthcare emergencies necessitate the quick dissemination of research. In the face of a common enemy - COVID-19 - the scientific community has rapidly come together to address this outbreak in an open and collaborative manner to support the global response to this outbreak by rapidly sharing and highlighting research data and relevant findings.

Along with medical personnel, researchers are playing a vital part. Since the early stages of the COVID-19 outbreak in China in early 2020, researchers have been working to share timely and transparent epidemiological and clinical data (*2-4*); the pathogen's genome has been sequenced, and those findings have been shared worldwide (*5,6*). Such cooperation is crucial to guiding clinical practice and public health policy. As the epidemic has spread, researchers worldwide have made progress in detecting the virus and analyzing its genetics, routes of transmission, the natural history of infection in humans, rapid detection and diagnosis, clinical treatment, drug screening, and vaccine development (*7-13*).

COVID-19 research is being published at a furious pace. The WHO COVID-19 Database is gathering the latest scientific findings and knowledge (primarily journal articles) on COVID-19; according to the Database, over 6,000 articles have been published as of 20 April 2020 (*14*). The following journals have separately published at least 50 articles - BMJ, Nature, The Lancet, Science, Journal of Infection, The Lancet Infectious Diseases, Journal of Medical Virology, JAMA, *etc*. Many international academic journals such as the New England Journal of Medicine have initiated rapid review and publication procedures for COVID-19 articles to facilitate the real-time sharing of scientific information (*15*).

Moreover, as part of the response to the ongoing COVID-19 pandemic across the world, many publishers- such as Elsevier, Springer, and Wiley - have created a COVID-19 online resource center or website (Table 1) in order to enable fast and free access to the latest research, evidence, and data available to assist researchers, medical personnel, policy makers, and

Table 1. COVID-19 online resource centers/websites allowing free access to the latest research available

Created by	Online resource centers/websites	URL
BMJ	Coronavirus (covid-19) Hub	*www.bmj.com/coronavirus*
Cambridge University Press	Coronavirus Free Access Collection	*www.cambridge.org/core/browse-subjects/medicine/coronavirus-free-access-collection*
Cell Press	Coronavirus Resource Hub	*www.cell.com/2019-nCOV*
Chinese Medical Association Publishing House	COVID-19 Academic Research Communication Platform	*www.medjournals.cn/COVID-19/index.do;jsessionid=14D55661F9CF0965F473D0B5F4EB8974*
Elsevier	Novel Coronavirus Information Center	*www.elsevier.com/connect/coronavirus-information-center*
JAMA Network	Coronavirus Disease 2019 (COVID-19)	*www.jamanetwork.com/journals/jama/pages/coronavirus-alert*
The Lancet	COVID-19 Resource Centre	*www.thelancet.com/coronavirus*
U.S. National Library of Medicine	LitCovid	*www.ncbi.nlm.nih.gov/research/coronavirus*
New England Journal of Medicine	Coronavirus (Covid-19)	*www.nejm.org/coronavirus*
Oxford University Press	Resources on COVID-19	*www.academic.oup.com/journals/pages/coronavirus?cc=us&lang=en&*
PLOS	COVID-19 Updates	*www.plos.org/covid-19*
Science	Coronavirus: Research, Commentary, and News	*www.sciencemag.org/collections/coronavirus*
Springer Nature	SARS-CoV-2 and COVID-19	*www.springernature.com/gp/researchers/campaigns/coronavirus*
SSRN	Coronavirus and Infectious Disease Research page	*www.ssrn.com/index.cfm/en/coronavirus*
Wiley Online Library	COVID-19: Novel Coronavirus Outbreak	*https://novel-coronavirus.onlinelibrary.wiley.com*

Table 2. Some of the guides/proposals/responses to COVID-19 issued by medical associations in Japan

Issued by	Date	Guides/proposals/responses to COVID-19	URL
Japanese Association for Infectious Diseases	Jan. 28, 2020	Responses to the Novel Coronavirus Disease (2019-nCoV)	*www.kansensho.or.jp/uploads/files/topics/2019ncov/2019ncov_taiou_200128.pdf*
	Feb. 3, 2020	Measures to Deal with the Novel Coronavirus Disease (2019-nCoV) – Seeing Patients in General Practice	*www.kansensho.or.jp/uploads/files/topics/2019ncov/2019ncov_sinryo_200203.pdf*
	Feb. 26, 2020	Guidance on Treating COVID-19 with Antivirals (1st Edition)	*www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_antiviral_drug_200227.pdf*
	Feb. 21, 2020	Novel Coronavirus Disease (COVID-19)-From Protective Measures at Ports and Airports to the Stage of Transmission	*www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_mizugiwa_200221.pdf*
	Apr. 2, 2020	Guidance on Clinical Responses to COVID- To Avoid Confusion in Medical Settings and Save the Lives of Patients with Severe Symptoms	*www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_rinsho_200402.pdf*
Japanese Society for Virology	Feb. 10, 2020	Novel Coronavirus Disease	*http://jsv.umin.jp/news/news200210.html*
Japanese Society of Intensive Care Medicine	Feb. 10, 2020	ICU Responses to the Novel Coronavirus Disease (2019-nCoV)	*www.jsicm.org/news/news200210.html*
Japanese Association for Acute Medicine	Mar. 9, 2020	Responses to the Novel Coronavirus Disease (COVID-19)	*www.jaam.jp/info/2020/info-20200309.html*
	Mar. 23, 2020	Basic Notes on Artificial Respiration and ECMO for Patients with COVID-19 in Acute Respiratory Failure (2nd Edition)	*www.jaam.jp/info/2020/files/info-20200323.pdf*
Japanese Society for Infection Prevention and Control	Mar. 10, 2020	Guidelines for Responses to COVID at Medical Facilities	*www.kankyokansen.org/uploads/uploads/files/jsipc/COVID-19_taioguide2.1.pdf*
Japanese Society of Public Health	Mar. 11, 2020	Overview of a Strategy to Respond to COVID Clusters	*www.jsph.jp/covid/files/COVID-19_031102.pdf*
Japan Epidemiological Association	Mar. 12, 2020	Proposal of an Active Epidemiological Survey on COVID	*https://jeaweb.jp/covid/pronouncement/teian20200312.pdf*
Japan Medical Association	Apr. 13, 2020	Novel coronavirus disease- Notification of Prefectural Medical Associations	*www.med.or.jp/doctor/kansen/novel_corona/009135.html*
Japanese Medical Science Federation	Apr. 10, 2020	Recommendations when regarding Surgery on Patients testing positive for or suspected of having the Novel Coronavirus Disease (Revised Version)	*www.jssoc.or.jp/aboutus/coronavirus/info20200402.pdf*

others who are working to address this pandemic.

Based on academic articles providing scientific knowledge and the experiences of frontline medical personnel, many evidence-based guidelines for COVID-19 have been issued to better guide clinical practice and develop standard preventive measures. WHO has issued a series of documents providing technical guidance on COVID-19 (*16*). Thus far, China has issued seven editions of "Clinical Protocols for the Diagnosis and Treatment of COVID-19" and six versions of "COVID-19 Prevention and Control Protocol" (*17*). The latest versions are provided in Chinese and English. In addition, the "Handbook of COVID-19 Prevention and Treatment" can be freely accessed and downloaded from Alibaba Cloud (*18*) and is currently available in Chinese, English, Italian, French, Spanish, Japanese, German, Persian, Indonesian, and Arabic; other language versions contributed by volunteers will also be shared as available to provide practical suggestions and references for medical personnel worldwide.

Various medical associations are also actively sharing information and providing technical support to fight this novel virus. Due to the epidemic, many academic conferences, and especially international conferences, were cancelled, postponed, or convened as virtual events *via* telecoms and web to reduce the concentration and flow of personnel. Despite that setback, academic societies promptly organized experts to conduct relevant research and they issued guidelines in their respective fields.

Taking Japan as an example, we did an online survey and the results showed that 93 guides/proposals/responses to COVID-19 have been issued so far by 50 medical associations in Japan, such as the guides issued by the Japanese Association for Infectious Disease, Japanese Association for Acute Medicine, and Japanese Society for Infection Prevention and Control (Table 2).

The COVID-19 pandemic is a common challenge faced by mankind in an age of globalization. Ensuring broad access to information based on scientific knowledge is a key element. The scientific community is coming together to lead the way in developing a measured and science-based response to the COVID-19 pandemic, and especially in terms of prevention, diagnosis, and treatment, while also accelerating research and development of vaccines and therapeutics in this crucial stage in support of the global efforts to fight this crisis.

Meanwhile, in this crucial stage, a key piece of information that needs to be ascertained is infection of healthcare workers (HCWs). As of 8 April 2020, 22,073 cases of COVID-19 among HCWs from 52 countries have been reported to the WHO. At the present time, however, there is no systematic reporting of COVID-19 infections among HCWs to the WHO, so this number probably under-represents the true number of HCWs infected with COVID-19 globally (*19*). Understanding infection in HCWs is critical to devising specific infection prevention and control measures to protect HCWs from infection; more publications and national situation reports are urgently needed to provide scientific information on COVID-19.

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EDITORIAL

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Call for international cooperation and collaboration to effectively tackle the COVID-19 pandemic

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Abstract: The world is facing an unprecedented challenge in every place that is affected by the spreading COVID-19 pandemic. With China recording fewer and fewer cases, Europe and the Americas have become the epicenter of the pandemic since mid-March 2020, respectively accounting for 54.8% (621,407) and 27.8% (315,714) of 1,133,758 confirmed cases globally as of April 5. Moreover, the number of confirmed cases in the US (273,808), Spain (124,736), Italy (124,632), and Germany (91,714) has exceeded the number in China (82,930) so far. International cooperation and coordination are essential to tackling this pandemic in terms of both assistance with emergency medical supplies and medical technical assistance. Coordinated global action has been called for by the World Health Organization (WHO), G7, G20, the World Trade Organization (WTO), and other bodies. More effective actions are urgently needed to protect the most vulnerable, including older people and people with an underlying medical condition, as well as healthcare workers, who are most frequently exposed and who are vital to the response.

***Keywords*:** COVID-19, public health emergency, international cooperation, international collaboration

The world is facing an unprecedented challenge in every place that has been affected by the spreading COVID-19 pandemic. Since 28 February 2020, the global risk of the COVID-19 outbreak has been upgraded to "very high" by the World Health Organization (WHO) (*1*). On March 11, the WHO Director General announced that COVID-19 can be characterized as a pandemic; this is the first pandemic caused by a coronavirus in history (*2*). This determination was based on a 13-fold increase in cases in the previous two weeks and the number of affected countries across the globe.

As of April 5, there were 1,133,758 cases reported globally, and 62,784 people have unfortunately lost their lives to COVID-19 (*3*). With China recording fewer and fewer cases, Europe and the Americas have become the epicenter of the pandemic since mid-March 2020, respectively accounting for 54.8% (621,407) and 27.8% (315,714) of 1,133,758 confirmed cases globally. Moreover, the number of confirmed cases in the US (273,808), Spain (124,736), Italy (124,632), and Germany (91,714) has exceeded the number in China (82,930) so far.

The COVID-19 pandemic calls for an "unprecedented level" of international cooperation and collaboration to tackle the crisis. A temporary shortage of protective gear was an urgent threat in the early days of the outbreak that exposed medical workers and the public to a greater risk of infection. In China, demands for emergency medical supplies, and especially personal protective equipment such as masks and medical protective clothing, increased at an exponential rate in January and February after the initial outbreak. Given this urgent situation, the international community helped to alleviate shortages of emergency medical supplies. As of March 2, a total of 62 countries and 7 international organizations have donated masks, protective clothing, and other urgently needed emergency medical supplies to China (*4*). For example, on January 28, the Government of Japan decided to provide emergency relief goods through the Japan International Cooperation Agency (JICA) to China. From January 27 to February 27, more than 4.8 million masks, more than 229,000 pieces of protective clothing, and more than 419,000 gloves as well as other emergency medical supplies were donated to China by governments, universities, hospitals, and civil society organizations across Japan (Figure 1). After the capacity to produce emergency medical supplies was restored in China, the Chinese Government provided assistance in the form of medical supplies to at least 89 countries and 4 international organizations (*5*) since the end of February. For example, more than 4.6 million masks, more than 65,000 pieces of protective clothing, more than 155,000 gloves as well as other emergency medical supplies were donated to Japan by China from February

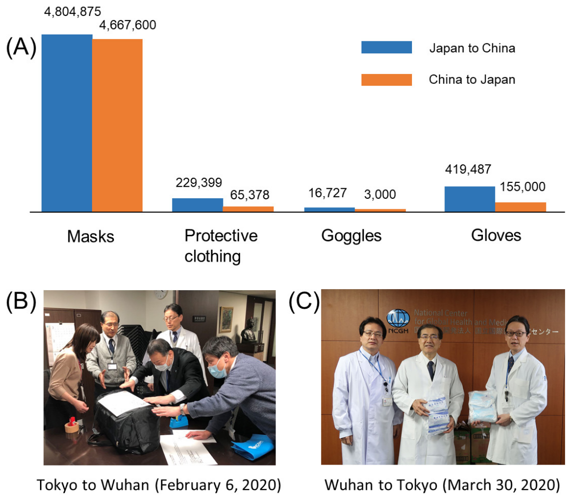

Figure 1. Japan-China mutual support related to emergency medical supplies in tackling COVID-19 pandemic. (A) Emergency medical supplies donated to China by Japan from January 27- February 27 and donated to Japan by China from February 29-March 26, 2020 (data were summarized based on reports from multiple media); **(B)** Masks donated to Wuhan, China by the National Center for Global health and Medicine on February 6, 2020; **(C)** Masks donated to the National Center for Global health and Medicine by Wuhan, China on March 30, 2020.

29 to March 26 (Figure 1).

International cooperation and collaboration are evident not only in assistance in the form of emergency medical supplies assistance but also in medical technical assistance (*6-8*). Upon learning about the coronavirus outbreak, the WHO gathered more than 400 world-class virologists and disease control experts via real and virtual platforms to examine the possible origins of the virus, to devise containment plans, and to identify research priorities. To date, more than 40 guidance documents has been published on the WHO's website (*9*), providing detailed, evidence-based recommendations for governments, hospitals, health workers, members of the public, and others. More than 1 million health workers have been trained through courses on OpenWHO.org. To help countries listen to and understand their communities and ensure that their COVID-19-related responses are relevant and actionable, WHO/Europe launched a behavioral insights tool for rapid, flexible and cost-effective monitoring of public knowledge, risk perceptions, behaviors, and trust (*10*).

Moreover, on March 13, the WHO, the UN Foundation, and partners launched a first-of-its-kind COVID-19 Solidarity Response Fund, which will go towards actions outlined in the COVID-19 Strategic Preparedness and Response Plan to enable all countries – and particularly those most vulnerable and at-risk, and with the weakest health systems – to prepare for and respond to the COVID-19 crisis including rapidly detecting cases, stopping transmission of the virus, and caring for those affected. Donations amounting to more than US$ 108 million have been received from 203,000 individuals and organizations in just two weeks (*11*).

Only coordinated global action will be effective in tackling a threat that, by its very nature, knows no borders. On March 19, the WHO regional directors of Europe, the Western Pacific, and Africa were united in their calls for solidarity to effectively tackle the COVID-19 pandemic (*12*). The following actions were called for: *i*) connecting with each other and coordinating responses to ensure that measures introduced by one nation do not hamper the response in other nations; *ii*) continuing to facilitate the response with resources, acting in solidarity, include everyone, and ensuring that the most vulnerable are supported; and *iii*) encouraging communities and sectors of society to be engaged and to promote an all-of-government response.

The G7 Foreign Ministers' Meeting held via video conference on March 25 emphasized the need to enhance international cooperation to combat COVID-19 and vital support for the WHO in particular, both in terms of the direct response to the crisis as well as the enhancing of health and research systems (*13*). A statement on COVID-19 was released at the G20 Leaders' Summit held on March 26 that called for a transparent, robust, coordinated, large-scale, and science-based global response in the spirit of solidarity to combat this pandemic. A broad convergence of views was evident, including taking all necessary health measures and seeking to ensure adequate financing to contain the pandemic and protect people, and especially the most vulnerable (*14*). In a virtual meeting of the Washington International Trade Association on March 26, six priorities of the World Trade Organization (WTO) were outlined to meet the challenge of COVID-19, including providing a cooperative framework for members to consider their responses, clearly indicating that members have wide latitude to take necessary positive actions to address the crisis, and helping craft coordinated responses to keep trade flows open (*15*).

Viruses know no borders, races, or ideologies. International cooperation and coordination are essential to tackling this pandemic, especially in effective actions to protect the most vulnerable, including older people and people with an underlying medical condition, as well as healthcare workers, who are the most frequently exposed and who are vital to the response.

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Challenges of COVID-19 outbreak on the cruise ship Diamond Princess docked at Yokohama, Japan: a real-world story

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Abstract: The event of the Diamond Princess, with a total of 712 (as of 17 March 2020) persons infected on the cruise ship, attracted global attention as the largest disease cluster outside China for the period 7 to 24 February 2020. Representing the Ministry of Health, Labour and Welfare, the authors were heavily engaged in the quarantine operation on the cruise ship ourselves. During the quarantine period from 5 to 23 February 2020, when the last group of the quarantined passengers left the ship, a series of measures have been conducted under the principles of *i*) zero deaths among all on board, *ii*) rapid establishment and thorough implementation of an infection control system, and *iii*) maintenance of health conditions and relief of anxieties among passengers and crew members. The case of Diamond Princess has implications of more than a cruise ship but deserves full scientific analysis to learn lessons from this operation as well as to study the characteristics, particularly the transmission of COVID-19.

***Keywords*:** COVID-19, cruise ship, Diamond Princess, quarantine

Introduction

The coronavirus disease (COVID-19) outbreak has developed to a global pandemic as declared by the World Health Organisation on 12 March 2020. At the early stage of COVID-19 outbreak, Japan faced triple challenges: domestic cases apparently infected through overseas travels or contact with incoming travellers; evacuation of Japanese nationals from Wuhan, China; and an outbreak on a cruise ship, Diamond Princess, docked at Yokohama with 3,711 persons, consisting of 2,666 passengers (average age 66.0 years) and 1,045 crew members (average age 36.6 years) on board.

The event of the Diamond Princess, with a total of 712 (as of 17 March) persons infected on the cruise ship, attracted global attention as the largest disease cluster outside China for the period 7 to 24 February 2020 (*1*). Naturally, such attention invited both encouragement and criticism. Representing the Ministry of Health, Labour and Welfare, the authors were heavily engaged in the quarantine operation on the cruise ship ourselves. This article mainly describes the events during the quarantine period from 5 to 23 February 2020, when the last group of the quarantined passengers left the ship, with aims to clarify some points to avoid misunderstanding and unfounded criticism.

Anchorage quarantine approach

The Diamond Princess is a British-registered cruise ship (P&O Steam Navigation Co.) operated by an American company (Princess Cruise Lines, Ltd.). The ship left Yokohama, Japan on 20 January 2020, and was scheduled to return to Yokohama after calling at Kagoshima (Japan), Hong Kong, Chan May (Vietnam), Cai Lan (Vietnam), Keelung (Taiwan), and Okinawa (Japan).

A passenger who had been coughing during this voyage disembarked at Hong Kong on 25 January and was confirmed positive for COVID-19 on 1 February. This information was notified *via* International Health Regulation channel to Japanese Government on 2 February, after the ship left the last call port, Okinawa, on 1 February. When the vessel reached Yokohama in the evening of 3 February, the Japanese government declined immediate disembarkation of passengers and adopted the anchorage quarantine approach by sending quarantine officers to the ship.

The quarantine team (Figure 1) surveyed the health condition of all passengers and crew members over the night and identified 273 individuals (264 passengers, 9 crew members) who complained of symptoms or had close contact with the index case. Throat swabs of these persons were tested by reverse transcriptase polymerase

(A) (B)

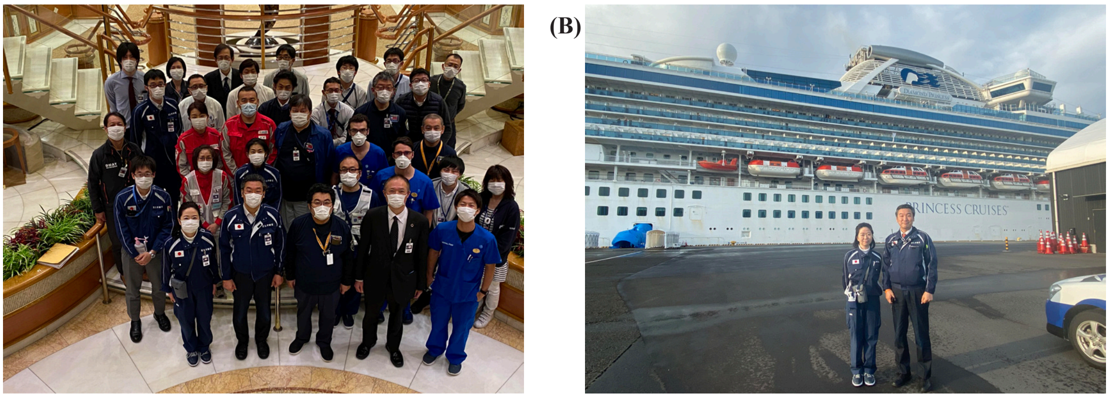

Figure 1. (A), Authors with members from the Ministry of Health, Labour and Welfare and medical team after the disembarkment of all passengers and crew members; (B), Authors after the completion of mission (left: Jimi, right: Hashimoto).

chain reaction (RT-PCR) test, but due to the limited laboratory capacity, test results were reported in several stages. The first report on 5 February revealed positive testing in 10 of 31 samples (32%), signalling a very challenging task ahead. A set of quarantine measures were introduced on 5 February. Full test results were released on 7 February, with 61 persons (60 passengers and 1 crew member) tested positive out of 273 persons, or a positive rate of 22%.

Principle approaches and measures

The enormous challenges to control this outbreak were unprecedented. They included an emerging infection with a novel pathogen with largely unknown characteristics, the unique confined environment of a cruise ship, predominantly senior passengers often with multiple comorbidities, language and culture diversity of passengers and crew members from 57 countries and regions, and complicated command lines among many parties (registered country of the ship, operation company, captain, ministries of Japanese government, local governments and others). Because the PCR tests revealed an apparent and serious outbreak on the ship, immediate disembarkation and onshore quarantine was first considered. However, because of logistic difficulties of transportation and onshore quarantine facility for a large number of possibly infected people, the decision was made to control the outbreak on the ship. At the same time, this decision implied tremendous operations to maintain daily services for more than 3,700 residents in terms of health, food and sanitation including waste disposal, which required massive mobilization of relevant personnel and internal coordination.

While the quarantine aimed to prevent the importation of COVID-19 into Japanese society, the Japanese government took several measures under the principles of *i*) zero deaths among all on board, *ii*) rapid establishment and thorough implementation of an infection control system, and *iii*) maintenance of health conditions and relief of anxieties among passengers and crew members. Some illustrations of what had been done are as follows.

With regard to the measures for "zero deaths", all 712 persons (PCR positive cases) were sent to designated hospitals. In addition, regardless of PCR results, approximate 200 individuals were transported to hospitals or onshore facilities, including those with serious underlying health conditions and/or senior passengers. Physical and mental health consultations were made available on the ship.

Regarding the infection control measures, from 5 February, all passengers were requested to stay in their own cabins until completion of *i*) 14-day observation, *ii*) confirmation by a negative PCR test, and *iii*) health check-up by physicians at disembarkation. Crew members needed to support the daily life of passengers, but those with symptoms waiting for PCR result and close contacts were requested to stop working and self-isolate in the cabins. From 7 February, thermometers were distributed, and daily body temperature was monitored, and PCR tests were performed as needed. Infection control guidance was provided repeatedly to both passengers and crew members. All were strongly urged to wear masks and exercise regular hand sanitation. For crews, observing the rules of infection prevention and control while serving passengers was enforced. Repeated strict instructions were given to observe the practice of zoning on board. Such infection control measures were also applied to support staff coming from outside the ship.

Finally, for maintenance of physical and mental health for passengers and crew, general medical care for health maintenance was secured, including the supply of regular medicines for comorbidities for those who had chronic conditions. Additionally, mental health support was provided for psychological problems such as insomnia and anxiety. To facilitate communication, 2,000 iPhones were distributed, and mobile base stations and Wi-Fi routers were enhanced.

Reflections

The preliminary analysis is available on the website of the National Institute of Infectious Diseases (NIID) (*2*), which carries a crucial graph showing the number of confirmed COVID-19 cases with reported onset dates, from 6 to 17 February 2020. Further updated data until 21 February, when all quarantined passengers were disembarked, appear in the background document (*3*) for the expert taskforce meeting on the new coronavirus infection convened by the Cabinet Secretariat. Note that in these graphs, robust data were missing on 5 and 6 February before body temperature monitoring was started, and PCR testing was not systemically done. Nevertheless, a consistent decline in new PCR-positive cases is observed among passengers after 7 February, two days after quarantine started, although new cases among crew members peaked only on 13 February.

These findings led the NIID to express their preliminary view (*4*) as follows – "Based on the number of confirmed cases by onset date, there is clear evidence that substantial transmission of COVID-19 had been occurring before the implementation of quarantine on the Diamond Princess on 5 February. The decline in the number of confirmed cases, based on reported onset dates, implies that the quarantine intervention was effective in reducing transmission among passengers. Transmission toward the end of the quarantine period, which is scheduled to end for most passengers on 19 February, appears to have occurred mostly among crew or within each passenger cabins". With regards to the 712 hospitalized persons, there were 7 deaths while 527 have been discharged from hospitals (at the time of 18 March 2020). Japanese passengers who returned to their homes were recommended to monitor their health condition and avoid unnecessary outings for additional 14 days. Among those who returned home, 9 (at the time of 18 March 2020) became PCR-positive, but there is no evidence to suggest that they generated a new infection in Japan.

This quarantine exercise required tremendous efforts and faced many challenges that the world had never experienced. Unfortunately, present epidemics in many parts of the world urged countries to adopt drastic restriction of move of people which are presenting similar challenges we had, in even larger scale. Therefore, the case of Diamond Princess has implications of more than a cruise ship but deserves full scientific analysis to learn lessons from this operation as well as to study the characteristics, particularly the transmission of COVID-19.

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Guidelines for the diagnosis and treatment of coronavirus disease 2019 (COVID-19) in China

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Abstract: With the deepening of the understanding and research in coronavirus disease 2019 (COVID-19), the diagnosis and treatment of COVID-19 have been constantly updated and improved. In China, since the implementation of "Guidelines for the Diagnosis and Treatment of COVID-19 (1st Trial Version)" on Jan. 15, 2020, 2nd to 7th versions (including revision of 5th version) was updated from Jan. 18, Jan. 22, Jan. 27, Feb. 4, Feb. 8, Feb. 18 and Mar. 3, respectively. Versions updated subsequently provide more detailed information in many ways than the 1st and 2nd versions, so this paper will introduce the development of the main contents of the 3rd to 7th versions of COVID-19 guidelines in China, which hopes to provide help for clinical medical staff in other countries fighting with this disease.

***Keywords*:** COVID-19, diagnosis and treatment, guideline

Introduction

Since Dec. 8, 2019, some patients presented with pneumonia of unknown origin in Wuhan, Hubei, China. The disease is confirmed as a novel coronavirus infection (*1*) according to the sequencing results and named COVID-19 (*2*). The epidemic has been under control in China recently because of active prevention and control of various forces across the country (*3*). Little is known about COVID-19 because it is a totally new virus (*4*). With the deepening of understanding and research in COVID-19, diagnosis and treatment of COVID-19 have been constantly updated and improved in China. Since the implementation of "Guidelines for the Diagnosis and Treatment of COVID-19 (1st Trial Version)" on Jan. 15, 2020, 2nd to 7th versions (including revision of 5th version) was updated on Jan. 18, Jan. 22 (*5*), Jan. 27 (*6*), Feb. 4 (*7*), Feb. 8 (*8*), Feb. 18 (*9*) and Mar. 3 (*10*), respectively. Versions updated subsequently provide more detailed information in many ways than the 1st and 2nd versions, so this paper will introduce the development of the main contents of the 3rd to 7th versions, which hopes to provide help for clinical medical workers.

Main frame, etiology, epidemiology, and pathology

The comparison of main frame in the 3rd to 7th versions are listed in Table 1. Compared with the 3rd version, the 4th version clarified the epidemiological characteristics and the timeliness of case detection and reporting, added clinical typing, improved the efficiency of diagnosis and treatment. The 5th and 6th versions updated the epidemiological characteristics, classification, and diagnosis and treatment methods again. 7th version added pathology and clinical warning indications of severe and critical cases.

The content of the 3rd version on etiological characteristics is mainly based on study of coronaviruses that have been found previously, its common characteristics are proposed, and it is pointed out that the coronaviruses of unexplained pneumonia in Wuhan belongs to β-corona virus. The 4th version began to list the virology characteristics of COVID-19 separately, with a little bit of difference comparing SARS-CoV and MERS-CoV in genetic traits. At the same time, the homology of this virus and the bat-SL-CoVZC45 was more than 85%. COVID-19 can be found in human respiratory epithelial cells in about 96 hours, while it takes about 6 days to isolate and culture in Vero E6 and Huh-7 cell lines. COVID-19 is sensitive to ultraviolet light and heat. Most disinfectants can inactivate the virus effectively except for chlorhexidine. So hand disinfectants containing chlorhexidine should be avoided.

Epidemiology includes infectious agent, transmission and susceptible population. With the advance of epidemiological investigation, the epidemiological characteristics have been constantly updated (Table 1). The 7th version indicates that the main infectious agent is patient infected with COVID-19, asymptomatic infections can also be infectious agents. Respiratory droplets and contact transmission accounts for most of the transmission, the environment polluted by feces

Table 1. Comparison of main frame, epidemiological characteristics in the 3rd to 7th versions of Guidelines for the Diagnosis and Treatment of COVID-19 in China

Version	Main frame	Infectious agent	Transmission	Susceptible population
3rd	etiology, clinical characteristics, case definition, differential diagnosis, case finding and reporting, treatment, criteria for discontinuation and discharge, transfer principles, nosocomial infection control	N/A	N/A	N/A
4th	etiology, epidemiology, clinical characteristics, diagnostic criteria, classification, differential diagnosis, case finding and reporting, treatment, criteria for discontinuation and discharge, transfer principles, nosocomial infection control	patient infected with COVID-19	respiratory droplet and contact transmission	the crowd is generally susceptible
5th	same as above	addition: asymptomatic infections can also be infectious agent	same as above	same as above
6th	same as above	same as above	addition: aerosols transmission	same as above
7th	etiology, epidemiology, pathology, clinical characteristics, diagnostic criteria, classification, clinical warning indicates severe and critical cases, differential diagnosis, case finding and reporting, treatment, criteria for discontinuation and discharge, transfer principles, nosocomial infection control	same as above	addition: transmission by contact with feces and urine	same as above

and urine might cause aerosols or contact transmission. It is also possible to transmit by aerosol when exposed to high concentrations of aerosols for a long time in a relatively closed environment. At last, the crowd is generally susceptible for this virus.

Based on the currently limited results of autopsy and histopathological specimens, the 7th version adds to the pathologic presentation of the disease. The lung, spleen, hilar lymph nodes and bone marrow, heart and blood vessels, liver and gallbladder, kidney and other organs were described in detail from macroscopic and microscopic perspectives. It is emphasized that this disease mainly causes lung and immune system damage, and most of the other organs have secondary damage. It is worth noting that microthrombus can be seen in most organs. Combined with clinical manifestations and lab results, which suggests the possibility of vascular endothelial damage. More attention should be paid in clinical management for medical staff.

Clinical characteristics

For clinical manifestations, the 3rd version pointed out that "fever, fatigue, dry cough as the main manifestations", while the rare symptoms, serious complications and special manifestations of patients were described. The 4th version added "The incubation period is generally 3-7 days, up to 14 days", clinical symptoms increased "diarrhea". It also pointed out that some patients "no pneumonia performance", "children with relatively mild symptoms", "deaths are more common in the elderly and those with chronic underlying diseases". The 5th version further clarified that the incubation period range is "1-14 days", added "sore throat" performance. The 6th version added "myalgia" performance, and severe cases may appear "multiple organ failure".

For lab results, the 3rd version mainly described the changes in peripheral blood, biochemical and inflammatory indicators. The 4th version proposed the etiological examination method for the first time, "the nucleic acid can be detected in throat wipes, sputum, lower respiratory tract secretions, blood and other samples". The 5th version added "feces" to the pathogen detection samples. The 6th version indicated that "severe and critical patients often have elevated inflammatory factors", and "it is recommended to retain sputum as much as possible and implement lower respiratory tract secretions from patients with endotracheal intubation". The 7th version further increased the content of pathogen examination, added "NGS method" used for nucleic acid detection of samples, and introduced serological (IgM, IgG) examination of pathogens for the first time.

For chest CT scan, there was no change in this area. Update of Clinical characteristics in the 3rd to 7th version is shown in Table 2. The clinical features of the 7th version are described below.

Clinical manifestations

The incubation period is 1-14 days, most of which is 3-7 days. These patients' clinical manifestations were mainly fever, fatigue and dry cough. At the same time, rare symptoms, severe complications and special manifestations were described, such as stuffy nose,

Table 2. Comparison of clinical characteristics, diagnosis criteria in the 3rd to 7th versions of Guidelines for the Diagnosis and Treatment of COVID-19 in China

Version	Clinical manifestations	Lab results	Chest CT scan	Suspected cases	Confirmed cases
3rd	the main clinical manifestations include fever, fatigue and dry cough	peripheral blood: leukocyte counts decreased or normal, lymphopenia. biochemical test: peptase, creatase and myoglobin increased. inflammatory marker: C-reactive protein and blood sedimentation increased, procalcitonin common	multifocal patchy shadows or ground glass opacities	N/A*	N/A*
4th	same as above	addition: the virus nucleic acid could be detected in samples of throat swab, sputum, lower respiratory tract secretion, blood	same as above	Any one in epidemiological history+ any two in clinical manifestations	Suspected cases+ one of the etiological evidence
5th	same as above	addition: feces can detect the virus nucleic acid	same as above	Any one in epidemiological history+ any two in clinical manifestations OR all entries in clinical manifestations	same as above
6th	same as above	same as above	same as above	same as above	same as above
7th	same as above	addition: NGS and serological examination of pathogens (IgM, IgG) can detect the virus nucleic acid.	same as above	same as above	Suspected cases+ one of the etiological** or serology evidence***

*In the 3rd version, patients were divided into suspected cases, confirmed cases, severe cases and critical cases, and the subsequent versions were only divided into suspected cases and confirmed cases. **RT-PCR or Next Generation Sequencing technology (NGS). ***Pathogens (IgM, IgG)

nasal discharge, pharyngalgia, myalgia, diarrhea, *etc.* However, symptoms in children and neonates can be uncharacteristic. Notably particularly, symptoms are relatively mild in children's case, and the elderly and those with chronic underlying diseases have poor prognosis.

Lab results

The lab results were divided into two categories: general examination, pathogenic and serological examination. The former includes peripheral blood, biochemical tests and inflammatory markers. In the early stage of the disease, leukocyte counts decreased or normal and lymphopenia in peripheral blood. Part of patients were increased in peptase, lactate dehydrogenase (LDH), creatase and myoglobin. Most patients have a normal level of procalcitonin with significantly increased levels of C-reactive protein. D-dimer levels are significantly elevated in severe cases, which is a potential risk factor for poor prognosis. Peripheral blood lymphocytes were progressively decreased. Severe and critical cases often have elevated inflammatory factors. The latter includes etiological and serological examination. For etiological examination, COVID-19 nucleic acids can be detected in specimens such as nasopharyngeal swabs, sputum and other lower respiratory secretions, blood, and feces using RT-PCR or/and next generation sequencing technology (NGS). It is more accurate to test lower respiratory tract specimens (sputum or airway aspirates). Submit samples as soon as possible after collection. For serological examination, IgM antibody is detectable 3 to 5 days after symptom onset and specific IgG antibody titer in the recovery phase 4 times higher than that in the acute phase.

Chest CT scan

Chest CT scan indicates multifocal patchy shadows or ground glass opacities. An experienced radiologist or clinician can make a diagnosis of a suspected case based on the imaging features of the lung, but attention should be paid to other viral pneumonia.

Diagnostic criteria

In the 3rd version, patients were divided into suspected cases, confirmed cases, severe cases and critical cases, and the subsequent versions were only divided into suspected cases and confirmed cases. A total of four versions were included in this study (Table 2). The 4th version adjusted to "Wuhan or other areas with continuous transmission of local cases". The 5th version to 7th versions were changed to "Wuhan and surrounding areas, or other communities with case reports". From 4th to 7th edition, the diagnostic criteria was essentially unchanged. It's not hard to find that the nucleic acid of SARS-CoV-2 is the gold standard for the diagnosis of COVID-19. However, considering the possibility of false negatives in nucleic acid detection, suspected cases characteristic manifestations in CT scans can be treated as confirmed cases even if the nucleic acid test is negative. The diagnostic criteria of the 7^{th} version are described below.

Suspected cases

Any one in epidemiological history+ any two in clinical manifestations or all entries in clinical manifestations:

Epidemiological history: *i*) The history of travelling or residence in Hubei province, including areas around Hubei, or other communities where cases have been reported occurred within the previous 14 days; *ii*) Contact with patients with fever or respiratory symptoms who come from Hubei province, including areas around Hubei, or other communities where cases have been reported that occurred within the previous 14 days; *iii*) History of contact with patients who have been infected with COVID-19; *iv*) Clustering onset.

Clinical manifestations: *i*) Respiratory tract symptoms and/or fever; *ii*) Consistent with the pulmonary imaging characteristics of this disease; *iii*) Leukocyte counts decreased or normal and lymphopenia in peripheral blood.

Confirmed cases

Suspected cases + one of the etiological evidence or serology evidence: *i*) COVID-19 nucleic acid positive with real-time fluorescence RT-PCR; *ii*) Results of viral gene sequencing are highly homologous with COVID-19; *iii*) Both COVID-19 specific IgM and IgG antibody were positive; Specific IgG antibody titer in the recovery phase 4 times higher than that in the acute phase.

Clinical classification

The 3^{rd} version did not specifically propose the concept of clinical classification, and the diagnostic criteria for severe type and critical type were proposed in the disease diagnostic criteria. The 4^{th} version was divided into moderate, severe, and critical type. The 5^{th} began to add the clinical classification of "mild type". The 7^{th} version was divided into mild, moderate, severe, and critical type in clinical classification and adds diagnostic criteria for severe type in children because the classification of disease types is conducive to the development of case management and treatment (Table 3), the details are as follows.

Mild type: The clinical symptoms are mild and no pneumonia manifestations can be found in imaging.

Moderate type: Patients have symptoms such as fever and respiratory tract symptoms, *etc.* At the same time, pneumonia manifestations can be seen in imaging.

Severe type: Adults who meet any of the following criteria: respiratory rate (RR) 30 breaths/min; oxygen saturation ≤ 93% in a resting state; arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) ≤ 300 mmHg. Patients with > 50% lesions progression

Table 3. Comparison of clinical classification in the 3^{rd} to 7^{th} versions of Guidelines for the Diagnosis and Treatment of COVID-19 in China

Version	Mild type	Moderate type	Severe type	Critical type
3^{rd}	N/A	N/A	Adults who meet any of the following criteria: respiratory rate 30 breaths/min; oxygen saturation ≤ 93% at a rest state; arterial partial pressure of oxygen (PaO_2)/ oxygen concentration (FiO_2) ≤ 300 mmHg. patients with > 50% lesions progression within 48 hours in lung imaging	Meeting any of the following criteria: occurrence of respiratory failure requiring mechanical ventilation; presence of shock; other organ failure that requires monitoring and treatment in the ICU
4^{th}	N/A	patients have symptoms such as fever and respiratory tract symptoms, pneumonia manifestations can be seen in imaging	deletion: patients with > 50% lesions progression within 48 hours in lung imaging	same as above
5^{th}	the clinical symptoms are mild and no pneumonia manifestations can be found in imaging	same as above	same as above	same as above
6^{th}	same as above	same as above	addition: Patients with > 50% lesions progression within 24 to 48 hours in lung imaging should be treated as severe cases	same as above
7^{th}	same as above	same as above	addition: diagnostic criteria for severe type in children	same as above

within 24 to 48 hours in lung imaging should be treated as severe cases.

Children who meet any of the following criteria: dyspnea except for crying (< 2 months , RR 60 breaths/min; 2-12 months, RR 50 breaths/min; 1-5 years, RR 40 breaths/min; > 5 years, RR 30 breaths/min); oxygen saturation ≤ 92% in a resting state; ventilator support (grunting, movement of alae nasi, three concave sign), cyanosis, intermittent dyspnea; lethargy or fainting; refusal to eat or poor feeding, dehydration.

Critical type: Meeting any of the following criteria: occurrence of respiratory failure requiring mechanical ventilation; presence of shock; other organ failure that requires monitoring and treatment in the ICU.

Clinical warning indication of severe and critical cases

The 7th version added clinical warning indicators. Through the monitoring of these clinical warning indicators, the treatment of intervention can be carried out early. So as to greatly reduce the transformation of mild type to severe type and severe type to critical type, and greatly improve the cure rate. This indication serves as a red flag that the disease may worsen, which helps medical staff make accurate judgments.

Adult: *i*) Peripheral blood lymphocytes progressively decreased; *ii*) Peripheral inflammatory factors such as IL-6 and CRP progressively increased; *iii*) Lactic acid is progressively increased; *iv*) Intrapulmonary lesions progress rapidly in a short period of time.

Children: *i*) RR increased; *ii*) Poor mental response, lethargy; *iii*) Lactic acid is progressively increased; *iv*) Imaging findings show bilateral or multilobular infiltration, pleural effusion, or rapid progression of short-term lesions; *v*) Infants under 3 months of age or underlying diseases, immune deficiency or hypoxia.

Treatment

The contents of treatment in the 3rd to 7th versions are divided into four parts, including: *i*) determine the treatment site according to the severity of the disease; *ii*) general treatment (including general supportive treatment, monitoring related indicators, antiviral treatment, *etc.*); *iii*) treatment of severe and critical cases (including respiratory support, circulatory support, *etc.*); *iv*) traditional Chinese medicine treatment. The treatment regimen needs to be constantly updated (Table 4), the treatment of the 7th version are described below. What's more, the drugs recommended in the 7th version have some theoretical basis in treatment. However, the above drugs still lack the exact clinical data in COVID-19 patients, and the specific efficacy needs to be confirmed by clinical studies. At the same time, medical staff should pay attention to the safety of drugs.

Treatment sites

Suspected cases should be in single room, confirmed cases can be placed in multiple room. Critical type should be admitted to ICU as soon as possible.

General treatment

i), General support for treatment. *ii*), Monitoring related indicators. *iii*), Oxygen therapy in time and Hydrogen-

Table 4. Comparison of treatment in the 3rd to 7th versions of Guidelines for the Diagnosis and Treatment of COVID-19 in China

Version	Treatment sites	Antiviral treatment	Treatment of severe and critical cases	Traditional Chinese medicine treatment
3rd	suspected cases in single room, confirmed cases in multiple room. critical type should be admitted to ICU as soon as possible	α-interferon and lopinavir/ritonavir	therapeutic principles, respiratory support and support of the circulation addition: glucocorticoids and plasma transfusion; strengthen psychological counseling	Different prescriptions are recommended according to the medical observation stage, clinical treatment stage (initial stage, middle stage, severe stage, recovery stage)
4th	same as above	same as above	addition: respiratory support were divided into four parts: oxygen therapy, noninvasive respiratory support, endotracheal intubation respiratory support and ECMO; plasma purification therapy	same as above
5th	same as above	same as above	same as above	same as above
6th	same as above	addition: ribavirin, chloroquine phosphate and arbidol	addition: CRRT, immunoglobulin	clinical treatment period is reclassified as light, ordinary, severe, critical and recovery period
7th	same as above	same as above		same as above

oxygen mixed inhalation gas (H_2/O_2: 66.6% / 33.3%) can be used if conditions permit. *iv*), Antiviral treatment: Alternative antiviral drugs: α-interferon, lopinavir/ritonavir, ribavirin, chloroquine phosphate, arbidol. Medical staff should pay attention to adverse reactions, contraindications and interactions with other drugs. At the same time, simultaneous use of three or more antiviral drugs is not recommended, discontinuation of the use of drugs in the presence of intolerable toxic and side effects. Antiviral treatment of maternal patients should consider the number of weeks of gestation and whether to terminate pregnancy before treatment, and informed. *v*), Antimicrobial therapy: Medical staff should avoid the blind or inappropriate use of antibiotics in the diagnosis and treatment process.

Treatment of severe and critical cases

i), Therapeutic principles: The treatment of primary diseases should also take the basic diseases into account. *ii*) Respiratory support: Oxygen therapy, high-flow nasal cannula oxygen therapy (HFNC) and noninvasive positive pressure ventilation (NIPPV), invasive positive pressure ventilation (IPPV) and rescue therapy are selected according to patient's pulmonary function. *iii*) Support of the circulation. *iv*) Continuous renal replacement therapy (CRRT). *v*) Plasma transfusion: Plasma from recovered persons is used to treat patients with rapid progression, severe or critical cases are suggested. *vi*) Plasma purification therapy: This method can remove inflammatory factors and reduce loss of inflammatory response of the body. *vii*) Immunoglobulin: Tocilizumab can be used in patients with extensive bilateral lung lesions and severe cases, and the laboratory detects elevated IL-6 levels. *viii*) Other treatment: For patients with rapid disease progression, glucocorticoids can be used for a short period of time. Gamma globulin may be considered in children with severe and critical cases. In addition, pregnant women with severe or critical cases should terminate their pregnancy actively, emphasizing caesarian as the first choice. At last, medical staff should strengthen psychological counseling because patients often have anxiety and fear.

Traditional Chinese medicine treatment

Traditional Chinese medicine treatment should be based on different conditions, local climate characteristics, and different physical conditions, and referred to the guidelines for dialectical treatment.

Discharge standards and follow-up plan

From 3rd to 7th edition, the discharge standards are essentially unchanged. For follow-up plan, it was added in the last two editions, the details are as follows. After the patient is discharged from the hospital, there is a risk of infection with other pathogens and COVID-19 due to the immunocompromised body during the recovery period. Follow-up plan has a good promoting effect on the health of discharged patients.

Discharge standards: *i*) Body temperature remains normal for at least 3 days; *ii*) Respiratory symptoms are significantly improved; *iii*) Nucleic acid is tested negative for respiratory tract pathogen twice consecutively; *iv*) Lung imaging shows obvious improvement in lesions.

Follow-up plan: *i*) Designated hospitals should make good contact with the primary medical institutions where patients live and share medical records; *ii*) Patients must continue two weeks of isolation after discharge. Patients and their family members must wear masks and wash hands frequently. Patients should live in an area with frequent ventilation and is disinfection independent; *iii*) The outpatient follow-up will be carried out 2 weeks and 1 month after discharge.

Conclusion

Guided by the research of etiology, diagnostic classification criteria and treatment specifications, each version updates the diagnosis and treatment plan, especially the 7th version. It provided more comprehensive, reasonable, clearer and efficient diagnosis and treatment guidance for clinical medical staff. COVID-19 has a very high ability to infect, however, the mortality of patients infected with COVID-19 is not as high as those infected with MERS or SARS. COVID-19 is a totally new virus without specific antibody or anti-COVID-19 drug, so cut off of transmission routes and isolation of sources of infection are the most effective methods to stop the spread. For patients with severe or fatal organ dysfunction, effective organ support and immune-enhancement methods are crucial for treatment.

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The COVID-19 pandemic preparedness ... or lack thereof: from China to Italy

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Abstract: COVID-19, that emerged in December 2019 in the city of Wuhan, China and is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly evolved into a pandemic. Italy has become one of the largest epicentres outside Asia, accounting now for at least 80,539 infections (cumulative incidence of 95.9/100,000) and 8,165 deaths (case fatality rate 10.1%). It has seriously affected people above the age of 60 years. The International Health Regulations (IHR) revised in 2005 bind governments to disclose vital information regarding the identification and detection of new disease outbreaks regardless of its causative agent. In contrast to the previous SARS epidemic, China timely informed the world about the onset of a new outbreak. It also soon disclosed the clinical characteristics of patients with COVID-19. Unfortunately, despite the fast recognition of the Chinese epidemic, the application of the 2005 IHR was not followed by an effective response in every country and most health authorities failed to rapidly perceive the threat posed by COVID-19. To further complicate matters, IHR implementation, which relies primarily on self-reporting data rather than on an external review mechanism, was limited in speed and further hindered by high costs. The response in Italy suffered from several limitations within the health system and services. The action against this threat must instead be quick, firm and at the highest trans-national level. The solution lies in further strengthening countries' preparedness through a clear political commitment, mobilization of proper resources and implementation of a strict surveillance and monitoring process.

Keywords**:** COVID-19, SARS-CoV-2, global health, pandemic

COVID-19 pandemic: how it began

Future generations will probably remember 2020 as the year when countries' strategies for epidemic preparedness and response were tested and failed in containing the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 probably spilled over to humans from bats in November 2019 (*1,2*) and caused a pneumonia outbreak in the Chinese town of Wuhan (Hubei, China) starting in December 2019 (*3*). Only a few days later, on 10 January 2020, the causative agent was identified and is now known as SARS-CoV-2. Its genome was rapidly sequenced and shared with the global community.

The Chinese government implemented draconian measures to contain the spread of the virus by declaring the lockdown of sixteen towns in the Hubei province (~60 million people) starting from Wuhan on 23 January (*4*).

Meanwhile, Chinese researchers started to disclose data on clinical characteristics of COVID-19 patients. Age and sex disaggregated crude fatality rates (CFRs), and treatments used were reported. The period of incubation was estimated in the range of 2-14 days (median 4-5 days after exposure) (*5*). Clinical evidence showed that 80% of those infected develop a flu-like syndrome, or a pauci-symptomatic or even asymptomatic disease; 15% have severe pneumonia; and 5% need support in an intensive care unit (ICU). Overall, the CFR for COVID-19 was described as ranging from 3.0 to 4.0% increasing proportionally with age, pre-existing comorbidities and disease severity. It reached 14.8% in patients aged ≥ 80 years and almost 50% in critical cases admitted to ICU (*6*).

The transmissibility of this virus, expressed as a basic reproduction number (R0) varying between 2.0 and 3.6 (*7-9*), was considered similar to that of other respiratory pathogens with spreading possibly favored by the presence of asymptomatic carriers (*10,11*). Evidence suggests that the virus is transmitted by droplets and can persist for a few hours in the environment on surfaces (*11*). Unfortunately, in the absence of a vaccine, the current treatment is based on drugs (*e.g.* lopinavir/ritonavir, remdesivir, beta-interferon, and chloroquine) developed for different pathogens that still have to prove their efficacy against COVID-19. The mainstay of COVID-19 control is therefore based on the prevention of its spreading through classic public health measures: hand and respiratory hygiene, quarantine of those infected and of contacts of infectious cases and use of personal protective equipment (*12*).

The role of globalization

The theory of the evolution of virulence in emerging infectious diseases predicts that selection for pathogen virulence and horizontal transmission is higher at the onset of an epidemic but decreases thereafter, as the epidemic depletes the pool of susceptible hosts (*13*). The 1918 influenza pandemic followed this pattern as it was characterized by three different waves (spring of 1918, fall of 1918, and winter 1918-19), of which the second one was the most virulent. It seemed to have partially protected the previously affected populations and regions from the third wave, which was less severe (*14*).

However, the *Spanish flu* pandemic occurred in an era when the world was much less inter-connected with travel that was difficult and expensive. Besides its challenges, globalization brought prosperity as well as the opportunity for people to benefit from the progressive erosion of boundaries and easier transport and communication. Globalization, however, also has a profound impact on the epidemiology of infectious diseases. The traditional patterns of disease spread, and the evolution and conventional responses of health systems was deeply shaped by the dawning of globalization. The continuous increase of the human population and the economic development ongoing in low- and middle-income countries may further exacerbate these dynamics. The phenomena resulting from globalization and unregulated urbanization were already influential in the emergence and spread of some of the most relevant pathogens of the 20^{th} century, such as the agents of SARS, swine flu and Ebola (*15*), not underestimating how the human immunodeficiency virus itself was favored in its global spread (*16*).

Globalization of transport and human movement are likely the main reason underpinning the spread of COVID-19 which has infected, to date, at least 413,467 people in more than 150 countries in all continents except Antarctica and has been responsible for 18,433 deaths (CFR of 4.5%) (*17*).

Increasing the political commitment

Hard lessons were learned following the SARS epidemic in 2003, when the Chinese government delayed key information regarding a novel infectious outbreak in the province of Guangdong (China). After that epidemic, the Member States of the World Health Organization (WHO) revisited the International Health Regulations (IHR) (*18*) which were eventually adopted by the World Health Assembly in 2005 to be implemented in all countries by mid-2007. The new IHR bind governments to disclose vital information regarding the identification and detection of new disease outbreaks regardless of its causative agent. In this occasion, such mechanism resulted in China publicly and rapidly sharing the information and viral genome of SARS-CoV-2.

Unfortunately, in the case of the COVID-19 pandemic, the application of the 2005 IHR that allowed rapid reporting by China was not followed by an immediate response in every country. Governments failed to rapidly perceive the threat posed by COVID-19. In addition, health systems in some countries were ill-prepared to face an emergency such as COVID-19 despite the commitment made by delegates of all countries in 2005, when approving the revised IHR, and their renewed promise in 2015 at the signing off at the highest political level of the United Nations (UN) Sustainable Development Goals (SDG) (*19*). SDG 3 (devoted to health), target 3.D specifies that all countries must strengthen their capacity for 'early warning, risk reduction and management of national and global health risks'. Without strong commitment that translates international resolutions into a well-financed plan on health emergencies, countries remain heavily exposed to the risk of pandemics. To oversee countries' strategic preparedness against emergencies two instruments have been developed: the WHO's IHR Core Capacity Monitoring Framework and the Joint External Evaluation process. However, both tools assess the level of coordination between Public Health and Security authorities, but do not measure how interventions are conducted and their effectiveness. To further complicate matters, IHR rely primarily on self-reporting data rather than on an external review mechanism which would be hindered by higher costs and subsequently limited in speed and frequency.

In any case, governments that have not properly prepared are currently struggling in an attempt to build last-minute epidemic responses addressing the COVID-19 pandemic (*20,21*). They essentially miss a strategic plan for epidemic response ready to be adapted and implemented against the current threat. There is therefore the need to establish proper national preparedness plans and to finance them adequately even if the next epidemic may not appear for some years. Given the easiness with which any epidemic may spread across borders today and the inter-connections existing among countries worldwide, there is an even more urgent need to build an international accountability system that monitors progress by governments in building and financing those plans. This would require regular reporting to the highest possible political level: the UN General Assembly (UNGA).

Lack in epidemic preparedness and delayed response: the case of Italy

Data from the Chinese COVID-19 outbreak, together with the declaration of a Public Health Emergency of International Concern from the WHO's Director-General on 30 January 2020, should have warned governments early on the need to take serious measures to prevent secondary transmission of SARS-CoV-2. However, things happened differently as a second large outbreak of COVID-19 emerged rapidly in Italy on 21 February 2020 (*22*).

At the beginning, the Italian COVID-19 cases were attributed to a single cluster of transmission occurring mainly in the little town of Codogno (Lodi province, Region Lombardy). The city was rapidly locked down together with another ten neighboring villages. Regrettably, the identification of the very first Italian case of COVID-19 failed as, based on some preliminary evidence, the virus appeared to have been circulating unnoticed in Lombardy since mid-January 2020 (*23*). If this were indeed the case, it would suggest that the original guidance provided by the health authorities (*24*) and focused on the recognition of the respiratory syndrome mainly on the basis of recent travels to, or business with, China, or known contact with a case, or the work in a health facility could have misled practitioners preventing them from suspecting COVID-19 in the absence of those conditions. This may have delayed the identification of the epidemic while it was already spreading in the community. Subsequently, efforts to precisely describe the origin of the cluster have been unsuccessful. Meanwhile, the health system and the public services in Lombardy were rapidly placed under serious stress (*25*) and local and national public health authorities were eventually obliged to make unprecedented decisions to pursue reduction of the R0 of SARS-CoV-2 through progressive restriction of citizens' movements up to a total lockdown of the country regardless of the epidemiology of the disease in different parts of Italy.

At the same time, while the Italian public health authorities at regional and national level tried to cope with the growing epidemic, the highly fragmented health systems resulted in a complex situation that became difficult to manage in the absence of a coherent strategy. For instance, some hospitals, especially those in Lombardy, applied the existing plans for responding to maxi-emergencies. These plans unfortunately are meant mainly for short-term natural disasters rather than for infectious epidemics of the COVID-19 type requiring intensive respiratory support. As a result, the effectiveness of response was compromised and as of now in Italy at least 80,539 have been infected with SARS-CoV-2 (cumulative incidence of 95.9/100,000 population) and 8,165 have died (CFR of 10.1%) (*26*). Notably, the cumulative incidence of COVID-19 cases increases with age (Figure 1), and mortality starts to rise from those aged 40-49 years old (Figure 2) (*27*).

The Italian epicentre is located in Lombardy (where the CFR overall is 14.9%), and especially in two provinces: Bergamo (7,458 cases) and Brescia (6,931 cases) (Figure 3). In those cities, like in the capital city of Milan, hospitals are gasping due to the sudden waves of hospitalizations and many patients, not solely among the elderly, requiring admission to ICU and mechanical ventilation. Hospital administrations are now struggling to reform their assets by designating facilities dedicated

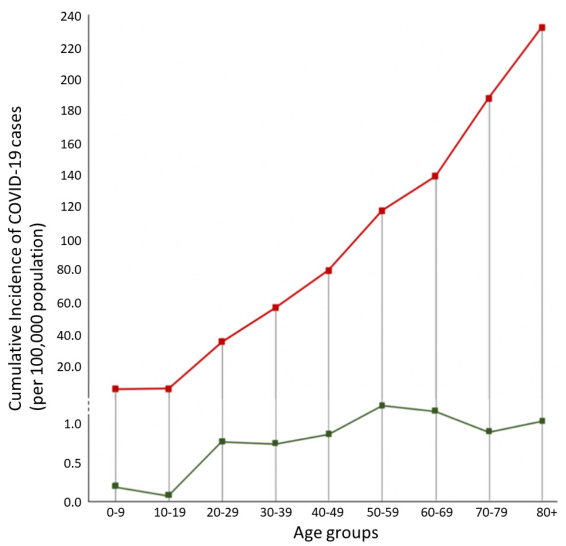

Figure 1. COVID-19 cumulative incidence rates (per 100,000 population) for Italy (red) (*27*) and Japan (green) (*28*) per each age group.

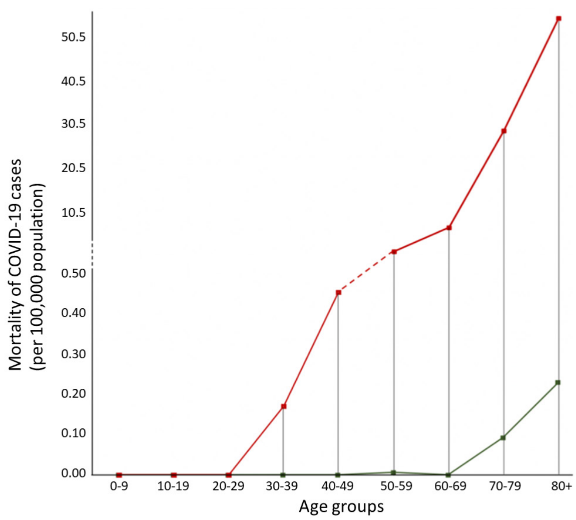

Figure 2. COVID-19 mortality rates (per 100,000 population) for Italy (red) (*27*) and Japan (green) (*28*) per each age group.

only to COVID-19 patients while maintaining other wards fully COVID-19-free in order to limit nosocomial transmission. In addition, due to exhaustion of critical tools for a respiratory outbreak, such as facemasks and respirators, the government is now trying to urgently import them from other countries, including China.

The omen of a large scale COVID-19 epidemic, from its epicentre in China, was almost immediately high due to the presence of an international airport nearby. The first imported cases of COVID-19 were soon documented in Japan (CFR, cumulative incidence, and mortality are reported in Table 1, Figures 1 and 2, respectively) (*28*), Republic of Korea, and Thailand. Nevertheless, political inaction together with the high transmissibility of SARS-CoV-2 have resulted in emergence of multiple clusters of local transmission worldwide. Hence, the WHO definition of COVID-19 as a pandemic on 11th of March 2020 also in the hope to shake the mind of political authorities and motivate governments to ensure people adhere to the international and national policies in all affected countries (*29*).

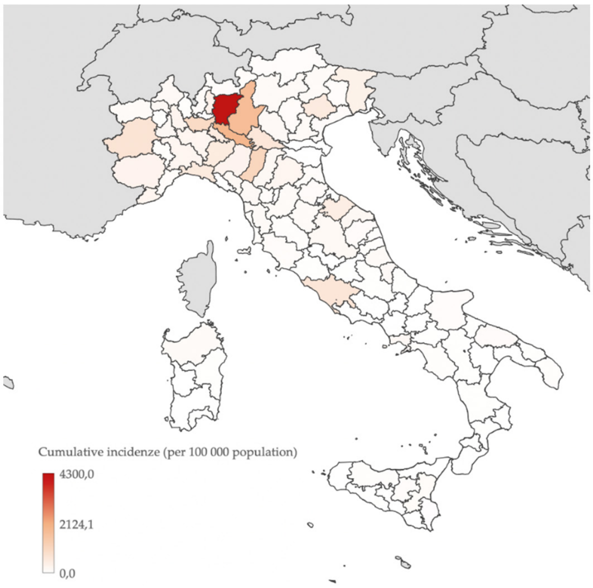

Figure 3. COVID-19 cumulative incidence (per 100,000 population) in Italy by province (*n* = 67,044), 26 March 2020 (*26*).

Conclusions

The COVID-19 pandemic will have epochal economic, social and cultural consequences and a dramatic toll of human lives, but lessons can already be learned. Events like the current one will occur again in the future, will have unpredictable characteristics, and will represent a major threat for all countries from a health, an economic, and a social perspective. The response against this threat must be quick, firm and at the highest trans-national level. A possible solution lies in further strengthening countries' preparedness by obtaining the political commitment required and implementing a strict monitoring process. This, for example, could imply the establishment of a mechanism that ensures reporting of progress at the level of the UNGA where heads of States make decisions, rather than limiting accountability to often powerless and ill-financed health ministries. Whatever the mechanism, innovative thinking is necessary to face health emergencies effectively. SARS-CoV-2 is a pandemic teaching us once more that microorganisms do not respect borders and spread quickly thus having the potential to disrupt economies and societies as a whole.

Acknowledgements

This paper is dedicated to all those people who are bravely fighting the SARS-CoV-2.

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Table 1. COVID-19 reported deaths and case-fatality rates (CFRs) in Italy and Japan

Items	Italy (*27*)		Japan (*28*)	
	Reported deaths, *n* (%)	CFR, %	Reported deaths, *n* (%)	CFR, %
Age				
0-9	0 (0.0)	0.0	0 (0.0)	0.0
10-19	0 (0.0)	0.0	0 (0.0)	0.0
20-29	0 (0.0)	0.0	0 (0.0)	0.0
30-39	12 (0.2)	0.3	0 (0.0)	0.0
40-49	41 (0.8)	0.6	0 (0.0)	0.0
50-59	168 (3.3)	1.5	1 (2.3)	0.5
60-69	541 (10.8)	5.2	0 (0.0)	0.0
70-79	1,768 (35.2)	15.6	15 (34.9)	9.2
80+	2,488 (49.6)	23.7	26 (60.5)	21.0
ND	1 (0.0)	-	1 (2.3)	-
Total	5,019 (100.0)	8.7	43 (100.0)	4.0

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REVIEW

Coronavirus disease 2019 (COVID-19): research progress and clinical practice

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Abstract: Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by SARS-CoV-2. As of March 30, 2020, there have been 693,224 reported patients with COVID-19 worldwide, with 1,446 in Japan. Currently, although aspects of the route of transmission are unclear, infection by contact and by inhaling droplets is considered to be the dominant transmission route. Inflammatory symptoms in the upper respiratory tract persist for several days to 1 week after onset, and in some patients symptoms of pneumonia worsen and become severe. The presence of underlying diseases and advanced age are risk factors for increased severity. Diagnosis is based on detection of SARS-CoV-2 by polymerase chain reaction (PCR) testing of nasopharyngeal swabs or sputum. Symptomatic management is the main treatment for this disease. Although the efficacy of several agents is currently being tested, at present there is no effective therapeutic agent. To prevent infection, in addition to standard preventive measures, measures that counteract infection by contact and droplet inhalation are important. In addition, if procedures that cause aerosolization of virus are used, then measures that prevent airborne infection should be implemented.

Keywords**:** SARS-CoV-2, Japan, COVID-19

Introduction

To date, we know of four types of coronavirus that can infect humans, including those that account for 10% to 15% of the causes of common cold (Table 1). Acute upper respiratory inflammation caused by human coronavirus is less frequent in summer and fall and increases in winter and spring (*1,2*). Large outbreaks are believed to occur in a cycle of 2 to 3 years (*3*). Re-infection with human coronavirus may occur, a finding considered to be due to a relatively rapid reduction in antibody titres (*4*). The proportion of asymptomatic infected patients varies depending on age and is considered to be about 30% in adults (*5,6*).

Species-specific coronaviruses have also been identified (*7*), for example, in dogs, cats, pigs, camels, bats, and sparrows. However, since each of these animal-specific coronaviruses exhibits a high species-specificity, it has been thought that they would not infect other animals across the species barrier.

Severe acute respiratory syndrome (SARS), which first occurred in Guangdong Province, China in 2002, was considered to be caused by transmission of a coronavirus to humans from bats (or the palm civet cat, *Paguma larvata*). Here, human-to-human infection occurred, resulting in 8,098 infected patients and 774 deaths (a mortality rate of 9.6%) (*8*). In 2012, an outbreak of Middle East respiratory syndrome (MERS) was reported in the Middle East (*9*). The reservoirs of coronavirus that led to this disease were bats and dromedary camels, and infection was found to occur mainly by transmission of coronavirus from camels to humans (*10*). As of March 2020, 2,494 infected patients and 858 deaths have been reported (a mortality rate of 34.4%). We therefore knew of two pathogens that caused epidemic coronavirus infection diseases in humans: a coronavirus harbored in animals, especially bats, infected humans with subsequent human-to-human infection.

In December 2019, an outbreak of unidentified pneumonia then occurred in Wuhan City, Hubei Province, China and was found to be caused by a novel coronavirus (SARS-CoV-2) (*11*). Like SARS-CoV, SARS-CoV-2 is classified as a β-coronavirus – a subgenus of coronaviruses (Figure 1). The structure of the gene that encodes the receptor region required for binding is very similar to that of SARS-CoV, suggesting that SARS-CoV-2 enters cells by binding to the ACE-2 receptor, as does SARS-CoV.

The host animal for this SARS-CoV-2 is unknown as of March 2020. However, in China it is evident that many patients were associated with the seafood market in Wuhan City, in the early part of the epidemic period (*12*). Based on this information, speculation suggests that

Table 1. Types of coronavirus and their characteristics

Coronavirus infection	Common cold	SARS	MERS	COVID-19
Causative virus	Human coronavirus (four types)	SARS coronavirus	MERS coronavirus	SARS-CoV-2
Year of outbreak	Every year	2002 to 2003	From 2012	From December 2019
Epidemic region	Worldwide	Guangdong Province, China	Arabian Peninsula including Saudi Arabia	First reported in Wuhan, China, currently becoming a pandemic worldwide
Host animal	Human	Horseshoe bat (Rhinolophus ferrumequinum)	Dromedary camel	Unknown
Number of infected patients	Account for 10% to 15% of the causes of common cold	8,098 patients (by end of epidemic)	2,494 patients (as of April 16, 2020)	1,991,562 patients (as of April 16, 2020)
Mortality rate	Very rare	9.4%	34.4%	6.1%
Route of transmission	Droplets and contact	Droplets, contact, and stool	Droplets and contact	Droplets and contact
Basic reproduction number	Many from 1 person	2 to 5 from 1 person	Less than 1 from 1 person	2.6 from 1 person
Incubation period	2 to 4 days	2 to 10 days	2 to 14 days	Estimated to be 1 to 14 days
Infectious Diseases Control Law	None	Infectious Diseases Category II	Infectious Diseases Category II	Designated Infectious Disease

Figure 1. Phylogenetic analysis of SARS-CoV-2 and other beta-coronavirus genomes (Orthocoronavirinae subfamily) (*11*).

an animal sold in the seafood market is the host animal for this virus. Phylogenetic analysis indicates that SARS-CoV-2 is closely related to coronaviruses harbored by bats. Bats are thus likely to be the primary host of SARS-CoV-2; however, it is unknown whether the virus was transmitted to humans directly from bats or via another intermediate host (*13*).

Epidemiology

On December 31, 2019, cases of unidentified pneumonia that occurred in Wuhan City, Hubei Province, China were reported to the WHO Office in China (*14*). Seven of 27 patients were severe and many of these patients were associated with a seafood market. By January 8, 2020, many of these patients were diagnosed as having pneumonia caused by a novel coronavirus (SARS-CoV-2) infection (*15*). According to reports on 41 confirmed cases, 66% of all patients were associated with the seafood market (for example, they worked there) (*12*). However, as early as December 2019, there were several cases not related to the seafood market, and human-to-human infection may already have occurred at this point.

Subsequently, the number of patients in Wuhan City continued to increase gradually, with 4 patients on January 18, 17 patients on January 19, and 136 patients on January 20. Cases imported from Wuhan City were reported in Thailand on January 12 and Japan on January 16 (*16*). In China, infected patients were reported in Guangdong Province and Beijing City, and the infection subsequently spread throughout China. On January 30, World Health Organization (WHO) declared a "Public Health Emergency of International Concern (PHEIC)".

As of March 30, 2020, there have been 693,224 reported patients with COVID-19 worldwide. Of these, 392,757 patients were in Europe (*17*). In Japan, as of March 30, there were 1,446 infected patients (1,420 domestic patients, 11 returnees on charter flights, and 15 patients under airport quarantine), 210 asymptomatic pathogen carriers (190 domestic patients, 4 returnees on charter flights, and 16 patients under airport quarantine), and 210 persons confirmed to be positive for coronavirus and under observation for the presence or absence of symptoms (210 domestic cases); based on data from the Tuberculosis and Infectious Disease Control Division, Ministry of Health, Labour and Welfare (Figure 2). On categorization by prefecture, urban regions such as Tokyo, Osaka, Aichi, Hokkaido, Chiba, Hyogo, Kanagawa, and Saitama account for 70% or more of infected patients.

The greatest numbers of nosocomial infections have been reported from Tokyo and Oita. In Chiba, an outbreak in a welfare facility for the disabled has also been reported.

Mode of transmission

In Wuhan City, many of the infected patients were associated with a seafood market in the early epidemic period, suggesting that spread of infection had occurred from animals to humans (*16*). However, current transmission is mainly due to human-to-human infection.

At present, although there are some unknown aspects of human-to-human infection, infection by contact and by droplet inhalation is considered to be the dominant transmission route. The virus can also be detected in stool (*18*) and saliva (*19*); it is however unclear at present how much these route contribute to transmission of infection.

A substantial issue since the start of the epidemic is that few infected patients were identified on surveying contact persons. In China, just a few percent of close

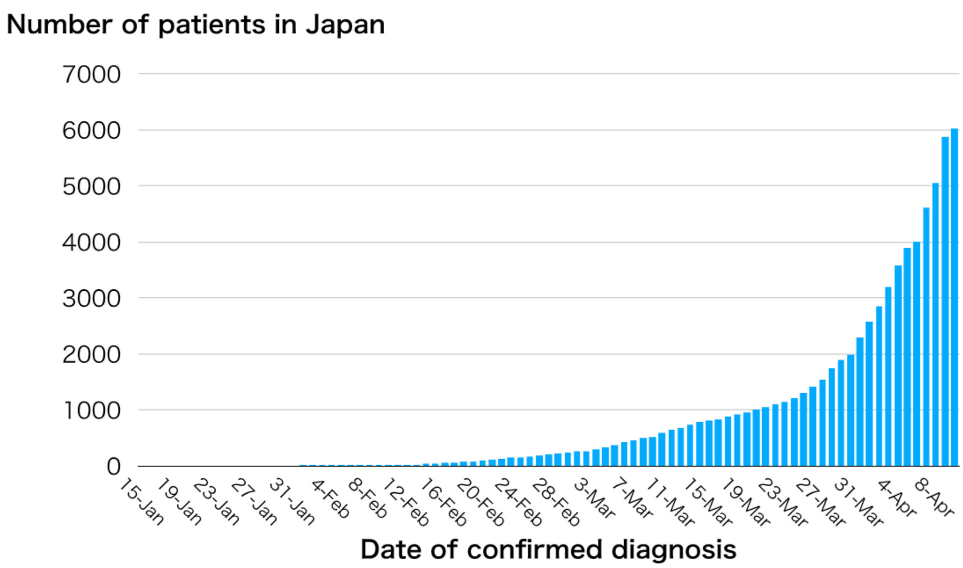

Figure 2. Change in the number of patients infected with a SARS-CoV-2 in Japan (published by the Ministry of Health, Labour and Welfare).

contacts were infected. Similarly, in USA, onset was seen in just 0.45% of 445 persons in contact with 10 confirmed patients (*20*). How therefore is infection spread?

One possibility is that infection may be spread from asymptomatic infected patients. Some cases of infection from asymptomatic infected patients have already been reported (*21-23*). If infection from such asymptomatic infected patients occurs, spreading infection can be explained even if persons are not infected through contact with symptomatic, infected patients. According to data from 44,672 Chinese patients infected with SARS-CoV-2, there are fewer infected patients under the age of 20, in comparison with the Chinese population distribution (*24*). As most infection in younger persons is asymptomatic or mild, it is possible that these individuals may not have been diagnosed. There is thus a possibility that infection may spread from younger persons with few symptoms. In addition, according to the calculations of Nishiura *et al.*, the serial interval (the interval from the onset of infection in the first person to the onset of infection in the second person) is shorter than the incubation period, suggesting that persons in the pre-onset phase or those with onset but minimal symptoms may spread the infection (*25*).

It is also known that outbreaks occur more easily in certain circumstances. In Japan, outbreaks have been reported in "confined spaces with poor ventilation" such as buses, houseboats, live music clubs, and fitness centers. The outbreak on the Diamond Princess cruise ship can be considered representative of COVID-19 (*26*). In such specific circumstances, the super-spreading phenomenon is considered to occur.

With SARS and MERS, the existence of super-spreaders has been known (*27*). In 2015, when MERS became epidemic in Korea, the existence of super-spreaders was confirmed, with spread of infection from 1 person to 29 persons and from 1 person to 86 persons (*28*). With these infectious diseases, it is epidemiologically known that although approximately 80% of patients rarely infect others, infection spreads from 1 person to many in the remaining 20%. This "20/80 rule" (*29*) may be applicable to COVID-19. According to a survey of 110 domestic patients up to February 26, performed by the Cluster Response Team of the Novel Coronavirus Response Headquarters within the Ministry of Health, Labour and Welfare, about 80% of infected patients did not infect other persons and 20% did spread the infection (Figure 3). These 20% of infected patients spread the infection in "confined spaces with poor ventilation". Therefore, it is important to prevent such clusters in order to avoid the spread of infection (*30*).

Clinical manifestations

The incubation period is 14 days or less; in many cases the onset occurs about 5 days after exposure (*15,24*).

Many symptomatic patients have symptoms such as fever, respiratory symptoms (coughing and pharyngodynia), headache, and malaise. The frequency of runny nose and nasal congestion seems to be low (*24*). The frequency of digestive symptoms such as diarrhea and vomiting is less than 10% in many reports, which seems to be lower than that in SARS and MERS. The clinical manifestations are similar to those of influenza and the common cold, but some patients complain

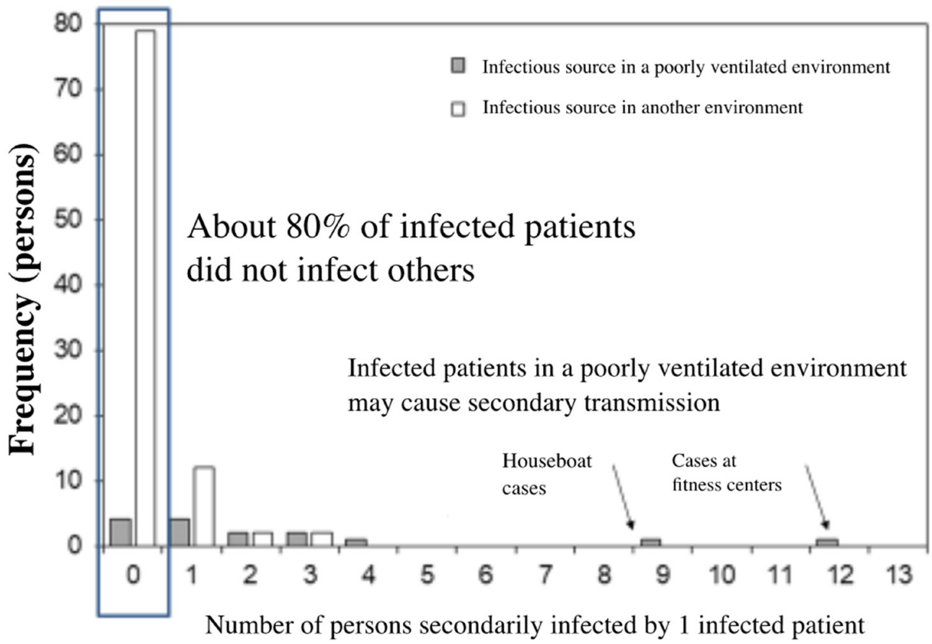

Figure 3. Number of persons secondarily infected by 1 infected patient (as of February 26, analytical result of 110 domestic patients) (Cluster Response Team of the Novel Coronavirus Response Headquarters within the Ministry of Health, Labour and Welfare).

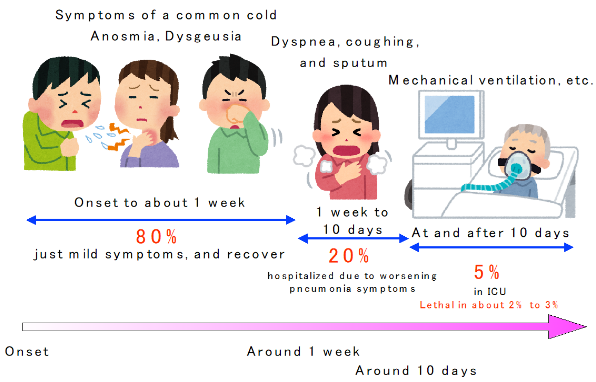

Figure 4. Typical course of the COVID-19.

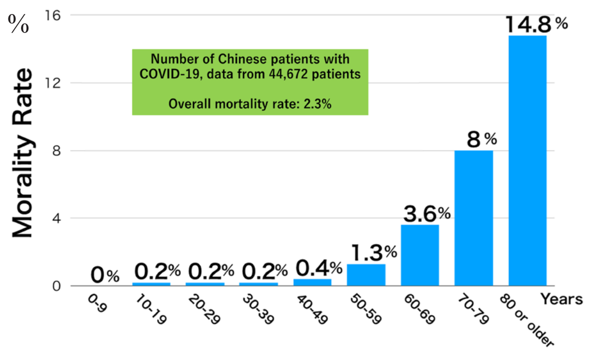

Figure 5. Mortality rate of the COVID-19, by age (*24*).

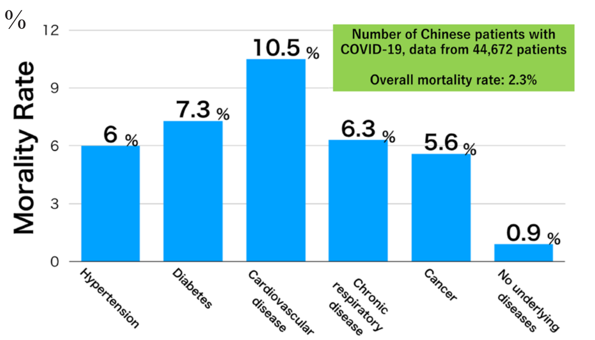

Figure 6. Mortality rate of the COVID-19, by underlying disease (*24*).

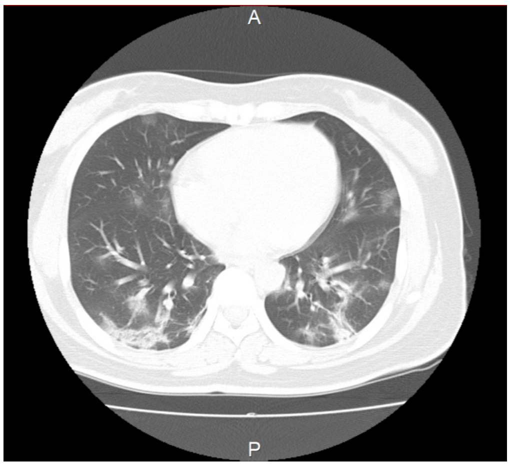

Figure 7. Chest CT image of the patient with the COVID-19 (case at the author's hospital).

of dysosmia and taste abnormality. According to Giacomelli *et al.* (*31*), in a survey conducted on 59 of 88 patients with COVID-19, who could be interviewed, 33.9% of infected patients had either dysosmia or taste abnormality and 18.6% had both. With dysosmia and taste abnormality in addition to influenza-like symptoms, the possibility of COVID-19 may be higher.

In China, it was reported that the interval from onset to visiting hospital and to hospitalization was about 5 and 7 days, respectively (*15*). In some cases, the disease is thought to become severe over the course of about 1 week. In more severe cases, patients are likely to be admitted to ICU after Day 10 (*12*) (Figure 4). According to the data of 44,672 Chinese patients, severity was mild (no pneumonia or mild pneumonia) in 81% of infected patients, severe (dyspnea, hypoxemia, opacities caused by pneumonia appearing in 50% or more of the lungs, within 24 to 48 hours) in 14%, and very severe (respiratory failure, shock, and multi-organ failure) in 5%. Of these, 2.8% died, so the lives of nearly half of these most severe patients can be saved.

Risk factors for severity are known to include advanced age and underlying diseases (cardiovascular disease, diabetes, malignancy, and chronic respiratory disease) (*24,32*).

The disease is less severe in patients aged less than 50 years, and the mortality rate increases with age in those aged 50 years or older. According to the data of 44,672 Chinese patients, the mortality rate is 14.8% in those aged 80 years or older (*24*) (Figure 5). The mortality rate is also clearly higher in patients with underlying diseases, compared with those without these diseases (Figure 6).

Severe cases have so far not been reported in pregnant women, nor has there been congenital infection (*33,34*). As SARS-CoV-2 was not detected in cord blood, amniotic fluid, and neonates (*34,35*), vertical transmission is considered not to occur. There are no reports of severe cases in infants (*36*).

Asymptomatic infected patients are known to occur at a certain rate. When the passengers of the Diamond Princess cruise ship were screened by PCR, about 17% were positive, and almost half of the positive passengers were asymptomatic (*26*).

Chest imaging findings are characterized by bilateral, peripheral infiltrative shadows, with ground glass attenuation (Figure 7). There are cases where despite pneumonia on chest CT, this cannot be diagnosed on chest X-ray. Chinese reports show that pneumonia was diagnosed on chest X-ray in just 59.1% of those with pneumonia, whereas chest CT provided a diagnosis in 86.2% (*24*). Although the author cannot directly extrapolate, because different patients may have undergone CT and X-ray, chest X-ray may miss 20% to 30% of patients with pneumonia. In cases where the pre-test probability is high (such as those with a history of contact with an infected person), even if pneumonia image is not observed on chest X-ray, a chest CT should be considered. After onset, the pneumonia image expands over time. However, the pneumonia image can be observed on chest CT even in asymptomatic infected patients (*37*). A significant pneumonia image may be observed even in asymptomatic infected patients without fever or respiratory symptoms, a characteristic of this disease.

Blood tests may show decreased lymphocytes, especially in severe cases (*24*).

Test and diagnosis

In Japan, the diagnosis is generally made by detecting SARS-CoV-2 using a PCR test.

The PCR test used to detect SARS-CoV-2 received insurance coverage from March 6. Consequently, in the Outpatient Services for Returnees and Contact Persons of approximately 800 medical institutions, the PCR test was covered by insurance when physicians wanted to investigate if the COVID-19 was present.

As PCR test samples, throat swabs or sputum, if available, was used until February 27. However, the viral load was demonstrated to be higher in the nasopharynx than in the pharynx (*38*). At present, a nasopharyngeal swab and sputum are the recommended samples (*39*). The WHO recommends that when an initial PCR test result is negative but infection is still strongly suspected, multiple samples should be collected and tested repeatedly (*40*). Many cases where an initial test result was negative despite a strong suspicion of COVID-19 based on CT findings have shown a positive result on repeated testing, including the case the author reported (*41,42*).

Because COVID-19 was designated in March as an infectious disease according to the Infections Diseases Control Law, if a diagnosis of COVID-19 is confirmed, the patient should in principle be hospitalized into an infectious disease bed at a designated medical institution for infectious diseases. In addition, the doctor who made the diagnosis must immediately report the case to a public health center.

Treatment

The CDC and WHO have their own treatment guidelines, the basis of which is to provide supportive treatment as needed, with appropriate prevention measures (*43,44*). In China, 1,099 reported patients received antimicrobial agents (58%), oseltamivir (35.8%), antifungal agents (2.8%), and glucocorticoids (18.6%) (*24*). They also received oxygen (41.3%), mechanical ventilation (6.1%: invasive 2.3% and non-invasive 5.1%), renal-replacement therapy (0.8%), and ECMO (extra-corporeal membrane oxygenation, 0.5%). Overall, 5% of patients were admitted to ICU.

Currently, there is no effective drug treatment for this COVID-19, but several candidate drugs are under investigation.

Lopinavir/Ritonavir (brand name: Kaletra) was believed to be effective for SARS and MERS, also caused by similar coronaviruses (*45,46*). In China, Kaletra has been used for this indication since the beginning of the epidemic of COVID-19. However, in a randomized, controlled study of 199 patients, lopinavir/ritonavir was not found to be effective (*47*). Because of interactions, many drugs cannot be used in combination with Kaletra. Therefore, cautionary notes include the needs for prior confirmation of the types of medicine being taken, and an HIV test (if a patient is infected with HIV, there is a risk of resistance occurring).

Remdesivir has so far been used as a candidate therapeutic agent for Ebola hemorrhagic fever in other clinical trials. With Ebola hemorrhagic fever, where there is an ongoing epidemic in the Democratic Republic of the Congo, remdesivir was administered in a randomized controlled trial but was found to be less effective than two other drugs, MAb114 and REGN-EB3. Administration of remdesivir for Ebola hemorrhagic fever has been stopped at present (*48*). However, some have suggested that remdesivir may be an effective treatment for COVID-19. The Wuhan Institute of Virology has reported the efficacy of remdesivir for COVID-19 in Cell Research (*49*). On examination of the inhibitory effect of remdesivir on virus replication, 48 hours after cultured cells were infected with the SARS-CoV-2, marked inhibition was observed. In the first diagnosed case of COVID-19 in the United States, remdesivir was also administered (*50*). This patient recovered following administration, but it is unknown whether this was due to the efficacy of remdesivir. In Japan, a global investigator-initiated registration-directed trial of remdesivir has been started primarily at the National Center for Global Health and Medicine, from late March.

Favipiravir (brand name: Avigan) is a drug developed by FUJIFILM Toyama Chemical Co., Ltd. (Japan). In Japan, Avigan is approved as an anti-influenza drug and is stockpiled for outbreaks of a novel type of influenza. However, this drug is teratogenic and is not used for seasonal influenza. Since Avigan inhibits RNA polymerase, it is expected to be effective against a wide range of RNA viruses apart from influenza. As with remdesivir, Avigan has also been used for Ebola hemorrhagic fever. On examination of the results of treatment using Avigan for Ebola hemorrhagic fever in West Africa during outbreaks in 2014 to 2015, clear efficacy could not be shown (*51,52*). Based on a clinical trial that was conducted in Japan (unpublished results), Avigan may be effective for SFTS (Severe fever with thrombocytopenia syndrome), which has a high mortality rate of 27%, with approximately 80 infected patients being reported per year in Japan. Its efficacy for the SARS-CoV-2 is unknown. However, as a result of evaluation of Avigan in the above study of remdesivir published in Cell Research, which demonstrated a virus inhibitory effect of remdesivir, a certain virus inhibitory effect of Avigan was also exhibited at a level of laboratory. According a Chinese clinical trial registration site, clinical trials of Avigan to examine its efficacy for COVID-19 (ChiCTR2000029600 and ChiCTR2000029548) are currently underway (unpublished results). A Chinese report states that when interferon-α inhalation + lopinavir/ritonavir and interferon-α inhalation + Avigan were administered for 14 days to patients with COVID-19 in a non-randomized comparative study, the latter combination was superior in terms of time to virus negativity and improvement of pneumonia on CT on Day 14 (*53*).

The National Institute of Infectious Diseases reports that ciclesonide, an inhaled steroid agent for the treatment of asthma also indicated for bronchial asthma, has a specific anti-viral effect in COVID-19 (*54*). In Japan, 3 patients were reported to improve with ciclesonide (brand name: Alvesco) (*55*). There were however just 3 patients and the efficacy of ciclesonide for COVID-19 is not yet established. Ciclesonide is a steroid that is administered topically rather than systemically; therefore, it is less invasive and has fewer side effects. Since systemic administration of ciclesonide is not currently recommended (*56*), if efficacy is observed, ciclesonide will become a promising drug.

In China, the antimalarial drug chloroquine is used in addition to these drugs. Chloroquine was once used worldwide as a therapeutic agent for malaria. However, as chloroquine-resistant malaria has recently become more common, its use for the treatment of malaria is decreasing (*57*). In Japan, chloroquine is an unapproved drug. However, hydroxychloroquine (Plaquenil), which has a similar structure to chloroquine and has anti-inflammatory and immune regulatory effects, is used for systemic lupus erythematosus (SLE). Since chloroquine has the same effect, it may be effective for COVID-19. According to the report in Cell Research by Wuhan Institute of Virology, chloroquine shows the same inhibitory effect on SARS-CoV-2 at the laboratory level as remdesivir (*49*). In China, chloroquine was administered to 100 or more patients and was superior to the control treatment in suppressing progression of pneumonia, improving lung image findings, time to virus negativity, and disease duration (*58*). In addition, in a non-randomized controlled trial that included 36 French patients with COVID-19, the viral load 6 days after participating in the trial was significantly lower in the hydroxychloroquine group (*59*).

The use of convalescent plasma is one treatment option for emerging/reemerging infectious disease (*60*). This has been administered for SARS (*61*) and MERS (*62*). Convalescent plasma contains neutralizing antibody against SARS-CoV and MERS-CoV. Therefore, if administered to a patient, it would be expected to exert an antiviral effect. However, in using convalescent plasma there are issues that need to be addressed, including the procedures required to collect plasma from recovered patients, confirmation that they are negative for SARS-CoV-2, methods for confirming the production of sufficient antibody, and the need to screen for infection, as with blood transfusion. In the United States, it was reported that when convalescent plasma was administered to 5 patients with the COVID-19, all of these patients recovered (*63*).

Although there are various candidate therapeutic drugs, their efficacies have not been confirmed. Since most patients recover spontaneously, the use of effective drugs in all cases, or of a drug where the efficacy is unknown, is considered to be disadvantageous for patients. Therefore, it is believed that administration of drugs should be limited to severe cases or cases that have a high risk of becoming severe. In "Concept of Antiviral Drugs for COVID-19, first version (February 26, 2020)", proposed by the Japanese Association for Infectious Diseases, the following points are made:

I. Generally, if patients under 50 years of age develop pneumonia, they recover as part of the natural course of the disease. Therefore, follow-up may be performed without necessarily administering an antiviral drug.
II. Generally, patients aged 50 years or older have a high likelihood of developing serious respiratory failure and their mortality rates are high. Therefore, when hypoxemia occurs and oxygen administration is required, administration of an antiviral drug should be considered.
III. Patients with diabetes, cardiovascular disease, chronic lung disease, chronic obstructive pulmonary disease, or immunosuppression, etc. should also be treated according to Item 2 above.
IV. Regardless of age, administration of an antiviral drug should be considered in cases that exhibit respiratory failure that worsens when treated with oxygenation and symptomatic measures alone.

Conditions for discharge are as follows: On confirmation that a fever of 37.5°C or higher has not been observed for 24 hours or more and that respiratory symptoms are improving, a PCR test is conducted. For this, samples are collected 48 hours (first test) after the patient condition described above is confirmed, and a further 12 hours later (second test). If the results of both tests are negative, patients are able to leave the hospital (*64*). In asymptomatic infected patients, a PCR test is conducted using samples collected 48 hours (first test) after the day on which they were found to be positive and a further 12 hours later (second test). If the results of both tests are negative, patients are able to leave the hospital. There have been cases where SARS-CoV-2 is detected again by PCR testing in patients who have recovered from the COVID-19 and were confirmed to be negative by two PCR tests (*65*). At the present time, it is unknown what proportion of patients becomes PCR positive again following a negative test, or how long positivity lasts.

Measures for infection prevention

Protecting healthcare professionals from infection is one of the most important aspects of clinical practice for COVID-19. Among 138 patients reported from China, 43% were considered to be due to infection in hospital (*66*). Other coronavirus diseases, SARS and MERS, are known to be transmitted easily by nosocomial infection (*67,68*) and constitute a risk for healthcare professionals, who often have close contact with patients in confined spaces, in other words in hospital.

The route of transmission is considered to be infection by contact and inhaling droplets. The implementation of measures for airborne infection control is recommended in environments where aerosols are present. The WHO recommends implementation of measures for prevention

Table 2. Personal protective equipment recommended for each target and activity (WHO. Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19). *https://apps.who.int/iris/bitstream/handle/10665/331215/WHO-2019-nCov-IPCPPE_use-2020.1-eng.pdf***)**

Hospitalized patients			
Ward	Healthcare professionals	Healthcare professionals who provide medical care	Surgical mask, gown, gloves, goggles or eye shield
		Procedure that causes virus aerosolization	N95 mask, gown, gloves, goggles or eye shield
	Sanitary workers	Entering a patient's room	Surgical mask, gown, thick gloves, goggles or eye shield (in case of a risk of inhaling droplets), boots
	Visitors	Entering a patient's room	Surgical mask, gloves
Other areas patients may move to (hospital ward, hallway, *etc.*)	All staff	All activities except for contact with patients	Personal protective equipment is not needed
Triage	Healthcare professionals	Screening that does not necessitate direct contact with patients	Keep a distance of at least 1 m. Personal protective equipment is not needed
	Patients with respiratory symptoms	All cases	Keep a distance of at least 1 m. Wear mask
	Patients without respiratory symptoms	All cases	Personal protective equipment is not needed
Laboratory	Laboratory technician	Handling of respiratory specimens	Surgical mask, gown, gloves, goggles or eye shield (if there is a risk of inhaling droplets)
	Target	Activity	Personal protective equipment
Outpatients			
Doctor's office	Healthcare professionals	Examination of patients with respiratory symptoms	Surgical mask, gown, gloves, protection of eyes
	Healthcare professionals	Examination of patients without respiratory symptoms	Standard preventive measures
	Patients with respiratory symptoms	All cases	Wear surgical mask
	Patients without respiratory symptoms	All cases	Personal protective equipment is not needed
	Sanitary workers	After examination or between the examinations of patients with respiratory symptoms	Surgical mask, gown, thick globes, goggles or eye shield (if there is a risk of inhaling droplets), boots
Waiting room	Patients with respiratory symptoms	All cases	Wear mask. Move immediately to an isolated room or a place distant from other patients. If this is impossible, keep a distance of at least 1 m from other patients
	Patients without respiratory symptoms	All cases	Personal protective equipment is not needed
Triage	Healthcare professionals	Screening that does not necessitate direct contact with patients	Keep a distance of at least 1 m. Personal protective equipment is not needed
	Patients with respiratory symptoms	All cases	Keep a distance of at least 1 m. Personal protective equipment is not needed
	Patients without respiratory symptoms	All cases	Personal protective equipment is not needed

of infection by contact and droplet inhalation, in addition to standard preventive measures. If a procedure is used that causes aerosolization of the virus, measures that prevent airborne infection should also be implemented (*69*). The personal protective equipment recommended for each activity is shown in Table 2.

The CDC recommendations are similar, except for always implementing measures that prevent airborne infection (CDC. Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings. *https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Finfection-control.html*). A point of similarity is that eye protection is emphasized and the use of eye guards is recommended.

In "Infection Control for COVID-19", proposed by the National Institute of Infectious Diseases and Disease Control and Prevention Center, National Center for Global Health and Medicine (*https://www.niid.go.jp/niid/images/epi/corona/2019nCoV-01-200305.pdf*), the followings are described (the contents are same as that those of the WHO):

I. Preventive measures for infection by contact and inhaled droplets should be implemented, in addition to the standard preventive measures.
II. Single rooms are desirable for doctors' offices and hospital rooms.
III. Doctors' offices and hospital rooms do not need a negative-pressure setting, but should be adequately ventilated.
IV. If a procedure is used that causes virus aerosolization, (for example, tracheal aspiration, endotracheal intubation, and lower respiratory tract specimen collection), an N95 mask (or DS2, equivalent mask), eye protector (goggles or face shield), long-sleeved lab coat, and gloves should be worn.
V. Patient movement should be limited to movement for essential purposes. Staff (information desk, attendant, and security guard) should comply with standard preventive measures.

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COVID-19 in China: the role and activities of Internet-based healthcare platforms

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Abstract: In the fight against the COVID-19 epidemic, the Chinese Government has enhanced its use of Internet-based healthcare. A large number of online medical platforms designed for COVID-19 have emerged in China. These platforms can be categorized according to the entity operating them, mainly the government, hospitals, and companies. Online medical platforms run by public hospitals provide follow-up consultations for common ailments and frequent ailments based on the hospital's offline services. Online diagnosis and treatment platforms provided by companies cover most of the regions in China. In terms of offering pandemic-related services, corporate platforms provide at least 1,636,440 doctors for online care, 1.685 billion consultations, and 109 million remote consultations. In terms of regular medical care, those platforms provide at least 940,182 doctors for online care and 13.7 million remote consultations; more than 84,916 specialists have provided online care during this period. During the prevention and control of this epidemic, online diagnosis and treatment has filled the gap of family doctors in epidemic prevention and control, it has reduced the chance of cross-infection of patients with a mild infection, and it has overcome the geographical limitations of medical resources. However, online diagnosis and treatment still faces challenges in terms of resource allocation and industry supervision.

***Keywords*:** COVID-19, SARS-CoV-2, China, Internet-based healthcare, online medical platforms

Introduction

As of March 31, 2020, the WHO reported a total of 750,890 confirmed cases of COVID-19 worldwide, of which 82,545 were diagnosed in China; 36,405 people died worldwide, of which 3,314 died in China (*1*); there are still 20,314 individuals who had close contact with SARS-CoV-2 who are still under medical observation in China (*2*).

Since the end of 2019 when pneumonia caused by SARS-CoV-2 spread in Wuhan, Hubei, the central government and the regional governments prioritized this issue, and the healthcare industry has stood at the forefront of the battle against the epidemic (*3*). In order to prevent the spread of the virus, the government and disease prevention and control departments have joined forces with multiple departments to raise citizens' awareness of self-protection from the disease. All provinces have implemented a primary public health emergency response, requiring people to stay at home as much as possible, travel less, cancel mass gatherings, and avoid crowds. Even during the Chinese Spring Festival, the country's most revered tradition, the government explicitly suggested canceling New Year's greetings (*4*). In the face of the panic brought about by this unknown disease, online medical platforms designed for COVID-19 have emerged, providing online care and information like updates on the epidemic, scientific articles and videos, dispelling rumors, clinic maps, online psychological assessments, tools to test for symptoms of pneumonia, instruction manuals, drug delivery services, free clinics for COVID-19, observation of at-home quarantine, psychological counseling and hot lines, and health insurance information (*5-9*).

In addition to pneumonia caused by coronavirus, many patients have chronic diseases, common ailments, seasonal diseases, or need tumor treatment, immunization, *etc*. Medical needs of these groups of patients may not be satisfied due to the fear of cross-infection in hospitals or travel restrictions. They may not receive timely treatment or medication for long-term treatment (*10*). In order to support Hubei, numerous teams of doctors and nurses from Respiratory Medicine, Infection Control, ICUs, ENT, Dentistry, and traditional Chinese medicine (TCM) departments across the country have set out to assist Wuhan, resulting in a shortage of medical resources in hospitals outside Hubei. Certain departments in some hospitals have suspended services (*11*). In addition, clinics in medical facilities around the country have overburdened with too many patients as the epidemic spread. Some hospitals have increased the proportion of online medical care (*12*). In this context, Internet-based healthcare has regained its significance.

Concept behind and operation of Internet-based healthcare

Concept behind Internet-based healthcare

Internet-based healthcare is the combination of the Internet and complete medical care. It involves seven main entities: the Internet, doctors, patients, hospitals, pharmaceutical companies, logistics companies, and insurance providers. It uses the Internet as a conduit and technical means to provide health and medical care including health education and medical information, electronic health records, assessment of disease risk, online disease consultation and diagnosis, remote consultation, remote rehabilitation, electronic prescribing, and drug delivery.

The core of the Internet is interconnected information. For patients, the Internet can solve the problem of insufficient communication between patients and doctors due to time limits, and it can fix the problem of having to go to the hospital in person for medical care in terms of appointments. For doctors, it can extend their available hours, increase the work experience of young doctors, increase their income, and highlight the value of their profession. For hospitals, operational efficiency can be improved, appointments and registrations can be made online, thereby improving patient satisfaction; for administrative departments, consulting or prescribing medicine online can provide a massive amount of medical data, which can facilitate disease management, drug development, hospital management, and medical insurance adjustment. The process of Internet-based healthcare is shown in Figure 1.

A description of the mode of operation of typical online diagnosis and treatment platforms in China

At present, online medical platforms can be categorized into government-based, hospital-based, and corporate platforms.

Online diagnosis and treatment platforms built by the government are mainly led by local governments. They commission Internet companies to develop, design, and/or operate and maintain the platform. They also organize doctors at hospitals in the region to provide patients with free information, science education, and online consulting services. A typical representative of this type of platform is an online consultation platform in Beijing.

Online diagnosis and treatment platforms built by hospitals can be divided into two categories according to the extent of the part played by hospitals and Internet companies in the platforms. The first type is a platform launched and built by a hospital, which is actually an online extension of a hospital, as exemplified by the Online Hospital of Shanghai Children's Hospital (*13*). The second type is jointly launched by one or several hospitals and Internet companies. In this type, the Internet companies build third-party platforms and the hospitals arrange medical staff to provide online care on the platform and perform continuous diagnosis and treatment offline. The two parties reach an agreement on the rights and obligations in relation to the operation of the online hospital. Online hospitals including the

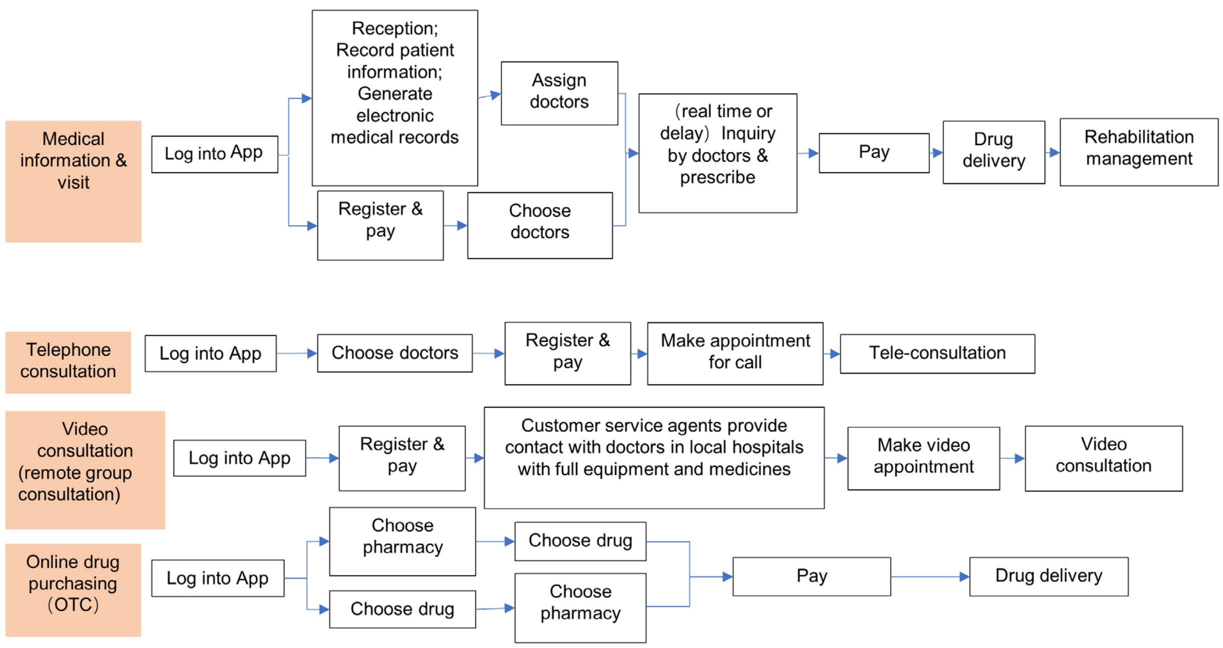

Figure 1. Flow chart for Internet-based healthcare.

Ningxia Yinchuan Online Hospital, Shanghai Xuhui District Central Hospital Guanzhong Online Hospital, and Tianjin We Doctor Online Hospital exemplify this type of platform (*14-17*).

Online diagnosis and treatment platforms built by companies are often launched by Internet companies. This type of platform establishes or purchases a private hospital depending on its online medical platform. In a few cases, they also rely on public hospitals to assemble doctors in various places. Doctors provide services such as diagnosis and treatment by working with multiple sites on the platform. In principle, the doctor's work is regarded separately from his or her work at a facility. Wuzhen Online Hospital, Ali Health, Tencent Penguin Hospital, Good Doctor, Ping An Good Doctor, and Lilac Garden exemplify this type of platform (*18-22*).

Services and effectiveness of Internet-based medical care during the COVID-19 outbreak

When fighting the epidemic, the online diagnosis and treatment platforms run by the government and by hospitals provide care similar to that offline. Table 1 lists some of the services provided by some of the relatively large online diagnosis and treatment platforms operated by companies.

Treatment of COVID-19 has affected normal care at high-level hospitals (tertiary general hospitals and specialized hospitals) since these hospitals are usually designated to treat COVID-19 patients in most areas of China. Such an arrangement also leads to failure to meet routine medical needs for chronic diseases, common ailments, seasonal diseases, tumor treatment, immunization, *etc.* (*23*). Table 2 describes the activities the online diagnosis and treatment platforms run by companies in terms of diagnosis and treatment of conventional diseases.

Support and promotion of national policies related to online diagnosis and treatment in the prevention and control of the COVID-19 epidemic

China issued policies to use the Internet to combat the COVID-19 epidemic within one month of its outbreak. On February 7, 2020, the Government issued polices "to capitalize on the advantages of online medical care and to vigorously develop online diagnosis and treatment services, and especially online diagnosis and treatment consulting services for patients with a fever." All provincial health and administrative departments are directed to establish a uniform online medical care platform, to organize certified medical facilities in the province, and to organize doctors from Respiratory Medicine, Infection Diseases, Emergency Medicine, ICUs, Mental Health, and general departments to provide online consultation services for patients with a fever. According to these policies, certified medical facilities

Table 1. Services provided by online diagnosis and treatment platforms run by Internet companies in response to the outbreak

No.	APP Name	Service Category				Service Provider	Service Category		FAQ
		Information	Tool	Daily information update	COVID-19 consultation		Consulting services Amount (million)	Remote Consultation Amount (million)	
1	We Doctor	√	√	√	√	38,952 doctors online; 1,788 psychologists online	110.0	1.7	1.Determine whether the symptoms are caused by coronavirus; 2.Prevention and treatment of COVID-19; 3.Mask purchase choices and wearing methods; 4.Low fever treatment methods, Maternal protection consultations, etc.
2	Ali Health	√			√	10,000+ doctor	1.6	2.8	
3	Dingxiang Doctor	√	√	√	√	150,000 doctors	341.0	83.0	
4	Pingan Good Doctor	√			√	10,000+doctors	1110.0	15.7	
5	Chunyu Doctor	√	√	√	√	10,000 stuff members	62.6	0.5	
6	Weimai	√			√	20,000+ doctor	58.0	0.9	
7	Haodaifu			√	√	47,488 doctors	1.4	4.3	

Note: Statistics as of 4:00 PM, March 30, 2020.

Table 2. General medical care provided by online diagnosis and treatment platforms run by Internet companies

Disease category	Services	App	Service Provider	Target population	Result	
					Remote consultation Amount	Number of Specialists who provided online care during this period
Chronic disease	Online follow-up consultation Prescribing Health consulting Medication reminder Risk screening	Medlinker	700,000+ doctors; 35,000+ signed doctors; 10,000+ cloud pharmacy drug types	Patients with a chronic disease	6,002,101	50,422
Common ailments	Telemedicine Online family physician	We Doctor	6,700 subject leader, 200,000+ physicians	Patients with general ailments	6,477,310	2,164
	Online health management Online registration	Pingan Good Doctor	10,000+ physicians		330,000 daily	10,000+
Immunization	Scientific knowledge on vaccines Information on stock, appointment, and payment Inoculation reminder Electronic Vaccination Certificate Search	Little bean	Vaccination assistance system	Children needing immunization	NA	NA
Tumor treatment	Surgery appointment Personal physician	Pingan Good Doctor	10,000+ physicians	Patients with a tumor	879,994	2,148
	Online and off-line follow-up consultation Multidisciplinary remote consultation	We Doctor	10,000+ physicians		2,951	10,000+
Medical cosmetology	Free consultation AI skin test	Xinyang We Doctor	10,182 physicians	Patients with a skin ailment	3,663,670+	10,182

Note: Statistics as of 4:00 PM, March 30, 2020.

Table 3. China's policies on online diagnosis and treatment in response to the COVID-19 outbreak

No.	Release time	Policy	Department
1	February 7, 2020	Notice on the Hard Work of Online Diagnosis and Consultation Services to Prevent and Control Epidemics (General office of the National Health Commission Doc No. [2020] No. 112) (*24*)	National Health Commission of the People's Republic of China
2	February 21, 2020	Notice on National Tele-Consultation Services at the National Telemedicine and Connected Health Center for Severe or Critical Patients with COVID-19 (General office of the National Health Commission Doc No. [2020] No. 153) (*25*)	National Health Commission of the People's Republic of China
3	February 26, 2020	Notice on Launching Online Services to Further Enhance Epidemic Prevention and Control in Hubei (Comprehensive Prevention and Control Mechanism [2020] No. 85) (*26*)	Leading Group of the CPC Central Committee for COVID-19 Prevention and Control
4	February 28, 2020	Guiding Opinions on Promoting "Internet +" Medical Insurance Services during the Prevention and Control of the COVID-19 Outbreak (*29*)	National Health Care Security Administration, National Health Commission of the People's Republic of China
5	March 13, 2020	(Tentative) Notice on the Formulation of a Health Management Plan for Newly Discharged Patients with COVID-19 (General office of the National Health Commission Doc No. [2020] No. 225) (*27*)	National Health Commission of the People's Republic of China

need to fully utilize their in-house platform, online medical platforms, their website, social media platforms, and other platforms to fast-track consultations for patients with COVID-19 or a fever, to provide free online consultations for COVID-19, to provide guidance for home-based medical observation and health assessment, and to provide other services to guide patients to receive medical care in an orderly and precise manner (*24*).

On February 21, the Chinese Government clarified the fact that the National Telemedicine and Connected Health Center (China-Japan Friendship Hospital) would take charge of operating a national teleconsultation platform for patients with severe COVID-19. Provincial health and administrative departments are required to guide designated hospitals in their jurisdictions to provide remote consultations for patients with severe COVID-19 to aid in their recovery (*25*). On February 26, the Government put forward specific requirements in terms of standardizing online diagnosis and treatment services and it made specific suggestions for national medical resources to support Wuhan, Hubei via the Internet (*26*). On March 13, the Government emphasized Internet-based health management of discharged patients with COVID-19 (*27*).

In terms of medical insurance, the emergency code "RA01.0", which represents COVID-19, was added to the ICD-11 codes (*28*). Designated medical facilities that have been approved to establish an online hospital or online diagnosis and treatment by the health administrative department can be reimbursed for the cost of "Internet +" follow-up consultations by insured patients for common ailments and chronic diseases (*29*). Table 3 shows the Chinese national policies related to Internet-based healthcare during the outbreak.

The state has put forward a series of policies and measures supporting and promoting online diagnosis and treatment to prevent and control the COVID-19 epidemic, thus providing new opportunities for the development of online diagnosis and treatment. However, a point worth mentioning is that online diagnosis and treatment still faces obstacles such as a lack of medical and IT personnel (*30*), failure to connect patient information (*31*), unnecessary repetition and omission due to multi-sector supervision (*32*), regulatory obstacles such as whether online diagnosis and treatment should have the same standards as those of public hospitals (*33*), as well as challenges in terms of the security of patient information and medical ethics (*34,35*).

Conclusion

During the prevention and control of this epidemic, online diagnosis and treatment has played three vital roles. First, it fills the gap of family doctors in epidemic prevention and control, including giving local residents timely medical consultations, performing triage, and providing emotional comfort and psychological counseling. Second, it reduces the chance of cross-infection of patients with a mild infection, that is, it physical isolates patients through remote diagnosis of disease. Third, it overcomes the limitation of medical resources in terms of space; tens of thousands of doctors have participated in epidemic prevention and control at different times and in different places (*36*). During the epidemic, some of the medical insurance payment problems that have long troubled the development of online diagnosis and treatment have been partially solved, but there are still many problems in terms of technology, supervision, and insurance that need to be fixed systematically.

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Major ongoing clinical trials for COVID-19 treatment and studies currently being conducted or scheduled in Japan

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Abstract: The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a serious threat to global public health and economies. Currently, hundreds of clinical trials on a wide variety of treatments against COVID-19 are being conducted around the world. Here, we conducted a search for ongoing clinical trials for the treatment of COVID-19 at the clinicaltrials.gov database on April 2, 2020. In total, 48 clinical trials were identified, and of these, 41 trials adopted drug intervention and the other 7 trials utilized biological intervention. The number of trials stratified by a chief country conducting the investigation were 18 in China, 5 in the United States, 4 in Canada, 3 in Italy, 2 in France and Brazil, and 4 trials are being performed multinationally. The drugs utilized in more than one trials were remdesivir (6 trials), lopinavir/ritonavir (6 trials), hydroxychloroquine (6 trials), interferon (5 trials), methylprednisolone (3 trials), nitric oxide gas (3 trials), oseltamivir (2 trials), arbidol (2 trials), and vitamin C (2 trials). We also described the Japanese trials which are now being conducted or scheduled, utilizing lopinavir/ritonavir, remdesivir, favipiravir, ciclesonide and nafamostat.

***Keywords*:** COVID-19, SARS-CoV-2, coronavirus disease 2019, clinical trial, Japan

Introduction

The outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a serious threat to global public health and economies (*1*). The SARS-CoV-2 belongs to Betacoronavirus which also contains severe acute respiratory syndrome coronavirus (SARS-COV-1) spread in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) spread in 2012 (*2*). As of April 5, 2020, over 2,845 cases have been confirmed in Japan, including 69 deaths as well as over 1,169,217 confirmed cases including 63,437 deaths all over the world. Such huge numbers of infected and dead people call for an urgent demand of effective, available, and affordable treatments to control and diminish the pandemic SARS-CoV-2 infection. Currently, hundreds of clinical trials on a wide variety of treatments against COVID-19 are being conducted around the world. Here, we summarize major ongoing clinical trials registered to ClinicalTrials.gov database as of April 2, 2020, and describe the trials which are now being conducted or scheduled in Japan.

Methods

A search for ongoing clinical trials for the treatment of COVID-19 was conducted at the clinicaltrials.gov database on April 2, 2020. The search words were "COVID-19", "SARS-CoV-2", "2019-nCoV" and "2019 novel coronavirus", and they were entered to the simple search field "conditions or disease", with "Status" being "All studies" and without any restrictions in other search windows. The subsequent filter conditions for identifying the eligible studies were as follows: recruitment is "Recruiting", "Active, not recruiting", "Enrolling by invitation", or "Completed"; study type is "Interventional"; study phase is "Phase I-IV"; and primary purpose is "treatment". The other conditions including sex, age, study results, funder type, and study documents were not restricted.

The severity of COVID-19 infection was defined according to the previous report as follows (*3*).

Mild: asymptomatic or symptomatic (*i.e.*, with fever, cough, or myalgia), but might not require hospitalization for treatment.

Severe: tachypnoea (≥ 30 breaths per min) or oxygen saturation 93% or higher at rest, PaO_2/FiO_2 ratio less than 300 mm Hg, and requiring hospitalization for treatment.

Critical: requiring mechanical ventilation, septic shock, or other organ dysfunction or failure that requires intensive care.

Results And Discussion

Summary of the identified trials

We identified 48 clinical trials in total. Of these, 41 trials adopted drug intervention (Table 1) and the other 7 trials utilized biological intervention (Table 2).

The number of trials stratified by a chief country conducting the investigation were 18 in China, 5 in the United States, 4 in Canada, 3 in Italy, 2 in France and Brazil, and 4 trials performed multinationally. The drugs utilized in more than one trial were remdesivir (6 trials), lopinavir/ritonavir (6 trials), hydroxychloroquine (6 trials), interferon (5 trials), methylprednisolone (3 trials), nitric oxide gas (3 trials), oseltamivir (2 trials), arbidol (2 trials), and vitamin C (2 trials). The other pharmaceutical interventions included danoprevir, darunavir, ritonavir, ribavirin, cobicistat, chloroquine, bevacizumab, sarilumab, meplazumab, baricitinib, tocilizumab, anakinra, sargramostim, fingolimod, corchicine, sildenafil citrate, tetrandrine, DAS181, ASC09F, and traditional Chinese medicines.

As for the 7 clinical trials utilizing biological intervention, almost all the trials were conducted in China except one in Jordan. The biological interventions included MSCs, NK cells, aAPC vaccine and synthetic minigene vaccine. All the trials are clinical phase I or II with a relatively small target number of patients.

Clinical trials conducted or scheduled in Japan

The clinical trials which are now being conducted or scheduled in Japan for the treatment of COVID-19 are as follows, and the details of the drugs utilized in the trials are briefly summarized.

Lopinavir/ritonavir

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, and ritonavir is combined with lopinavir to increase its plasma half-life through the inhibition of cytochrome P450. Because lopinavir/ritonavir has been reported to have a benefit treating both SARS-CoV-1 (*4*) and MERS-CoV infection (*5*), similar effectiveness for COVID-19 is expected and several clinical studies using lopinavir/ritonavir are currently being conducted for COVID-19 around the world as mentioned above. However, a latest report published from China on March 18, 2020 reported no benefit of lopinavir/ritonavir treatment beyond standard care in hospitalized adult patients with severe COVID-19 (*6*). In Japan, lopinavir/ritonavir was administered to patients with COVID-19 from February 21, 2020 as part of an observational study. To confirm or exclude the treatment benefit of lopinavir/ritonavir, the results of the ongoing studies should be carefully observed in the future.

Remdesivir

Remdesivir is a broad-spectrum antiviral agent and was developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection (*7*). The antiviral mechanism of remdesivir is a delayed chain cessation of nascent viral RNA by obscuring viral RNA polymerase and evading proofreading by viral exonuclease (*7*). Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses including SARS-CoV-1 and MERS-CoV infection in cultured cells, mice and non-human primate models (*8-10*). Based on the broad-spectrum anti-corona virus activity of remdesivir that were demonstrated in pre-clinical studies, several multinational, randomized, placebo controlled, double-blind clinical trials are currently being conducted. Of these, Japan is participating in Adaptive COVID-19 Treatment Trial, in which remdesivir (200 mg on day 1, then 100 mg/day up to 10 days) or placebo was administered to patients with severe or critical COVID-19 infection. Remdesivir is one of the most expectant and frequently investigated treatment for COVID-19 around the world, and accumulation of cases and analysis of results are awaited.

Favipiravir

Favipiravir is an antiviral compound that selectively and potently inhibits the RNA-dependent RNA polymerase of influenza and many other RNA viruses (*11*). Wan *et al.* revealed the antiviral effect of favipiravir to COVID-19 *in vitro* although a high concentration was required to reduce the viral infection (*12*). A randomized clinical trial from Wuhan, although the report has not been evaluated critically, reported that favipiravir has a higher 7 day's clinical recovery rate and more effectively reduced incidence of fever and cough compared with arbidol in ordinary COVID-19 patients untreated with antiviral previously (*13*). Although another clinical study comparing favipiravir with lopinavir/ritonavir for COVID-19 was published from Shenzhen on *Engineering*, it was thereafter withdrawn for some unknown reason. In Japan, Fujita Health University launched a multi-institutional, open-label, phase II study using favipiravir for asymptomatic or mild COVID-19 patients on March 2, 2020. The patients are assigned into immediate and delayed favipiravir arm, and favipiravir is administered orally for 10 days. The administration of favipiravir is scheduled as follows: immediate favipiravir arm, 1,800 mg twice a day on Day 1 followed by 800 mg twice a day from Day 2; delayed favipiravir arm, 1,800 mg twice a day on Day 6 followed by 800 mg twice a day from Day 7 to Day 15. Primary outcome is a proportion of subjects with clearance of COVID-19 virus in nasopharyngeal swab on Day 6. The collection of cases is going to be initiated in the near future.

Ciclesonide

Ciclesonide is an inhaled corticosteroid originally used in

Table 1. Clinical trials identified at Clinicaltrials.gov related to drug intervention for COVID-19 treatment

Study	Study Start	Interventions	Severity	Target Number	Phase	Status	Country
Safety and Efficacy of Hydroxychloroquine Associated With Azithromycin in SARS-CoV2 Virus (Coalition Covid-19 Brasil II)	28-Mar-20	hydroxychloroquine +/- azithromycin	Severe/Critical	440	III	Recruiting	Brazil
Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients - Sarilumab Trial - CORIMUNO-19 - SARI	27-Mar-20	sarilumab *vs.* control	Severe/Critical	240	II/III	Recruiting	France
Sargramostim in Patients With Acute Hypoxic Respiratory Failure Due to COVID-19 (SARPAC)	24-Mar-20	sargramostim *vs.* control	Severe	80	IV	Recruiting	Belgium, Italy
Chloroquine Diphosphate for the Treatment of Severe Acute Respiratory Syndrome Secondary to SARS-CoV2	23-Mar-20	chloroquine diphosphate (high dose *vs.* low dose)	Severe/Critical	440	II	Recruiting	Brazil
Efficacy of Methylprednisolone for Patients With COVID-19 Severe Acute Respiratory Syndrome	23-Mar-20	methylprednisolone	Severe/Critical	104	II/III	Recruiting	Italy
Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA)	23-Mar-20	colchicine *vs.* control	Mild	6,000	III	Recruiting	Canada
Trial of Treatments for COVID-19 in Hospitalized Adults	22-Mar-20	remdesivir *vs.* lopinavir/ritonavir +/- interferon β-1A *vs.* hydroxychloroquine *vs.* control	Severe/Critical	3,100	III	Recruiting	France
Nitric Oxide Gas Inhalation Therapy for Mild/Moderate COVID-19	21-Mar-20	nitric oxide gas *vs.* control	Mild	240	II	Recruiting	United States
Nitric Oxide Gas Inhalation in Severe Acute Respiratory Syndrome in COVID-19	21-Mar-20	nitric oxide gas *vs.* control	Severe/Critical	200	II	Recruiting	United States
Tocilizumab in COVID-19 Pneumonia (TOCIVID-19)	19-Mar-20	tocilizumab	Critical	330	II	Recruiting	Italy
Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial	18-Mar-20	lopinavir/ritonavir *vs.* control	Severe/Critical	440	II	Active not recruiting	Canada
Post-exposure Prophylaxis / Preemptive Therapy for SARS-Coronavirus-2	17-Mar-20	hydroxychloroquine *vs.* control	Mild	3,000	III	Recruiting	United States
Evaluation of the Efficacy and Safety of Sarilumab in Hospitalized Patients With COVID-19	16-Mar-20	sarilumab *vs.* control	Severe/Critical	400	II/III	Recruiting	United states
Baricitinib in Symptomatic Patients Infected by COVID-19: an Open-label, Pilot Study.	16-Mar-20	baricitinib *vs.* control	Mild	60	III	Recruiting	Italy
Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment	15-Mar-20	remdesivir *vs.* control	Mild	600	III	Recruiting	Multinational*
Comparison of Lopinavir/Ritonavir or Hydroxychloroquine in Patients With Mild Coronavirus Disease (COVID-19)	11-Mar-20	lopinavir/ritonavir *vs.* hydroxychloroquine sulfate *vs.* control	Mild	150	II	Recruiting	Korea
Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19)	6-Mar-20	remdesivir *vs.* control	Severe	400	III	Recruiting	Multinational†
Tetrandrine Tablets Used in the Treatment of COVID-19	5-Mar-20	tetrandrine *vs.* control	Mild/Severe	60	IV	Enrolling by invitation	China
Yinhu Qingwen Decoction for the Treatment of Mild / Common CoVID-19	27-Feb-20	YinHu QingWen Decoction *vs.* Chinese medicine treatment *vs.* standard western medicine treatment	Mild	300	II/III	Active not recruiting	China
Fingolimod in COVID-19	22-Feb-20	fingolimod *vs.* control	Mild/Severe	30	II	Recruiting	China
Adaptive COVID-19 Treatment Trial (ACTT)	21-Feb-20	remdesivir *vs.* control	Severe/Critical	440	III	Recruiting	Multinational‡

*United States, China, Germany, Hong Kong, Italy, Korea, Singapore, Spain, Switzerland, Taiwan, United Kingdom, †United States, Germany, Hong Kong, Italy, Korea, Singapore, Spain, Switzerland, Taiwan, United Kingdom, ‡United States, Japan, Korea, Singapore.

Table 1. Clinical trials identified at Clinicaltrials.gov related to drug intervention for COVID-19 treatment (continued)

Study	Study Start	Interventions	Severity	Target Number	Phase	Status	Country
Evaluation of Ganovo (Danoprevir) Combined With Ritonavir in the Treatment of Novel Coronavirus Infection	17-Feb-20	danoprevir + ritonavir +/- interferon nebulization	Mild	11	IV	Completed	China
Treatment of Pulmonary Fibrosis Due to 2019-nCoV Pneumonia With Fuzheng Huayu	15-Feb-20	N-acetylcysteine +/- Fuzheng Huayu Tablet	Mild/Severe	136	II	Recruiting	China
Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia	14-Feb-20	vitamine C *vs.* control	Severe/Critical	140	II	Recruiting	China
Mild/Moderate 2019-nCoV Remdesivir RCT	12-Feb-20	remdesivir *vs.* control	Mild	308	III	Recruiting	China
Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment	10-Feb-20	lopinavir/ritonavir + ribavirin + lnterferon β-1B *vs.* control	Mild/Severe/ Critical	70	II	Recruiting	Hong Kong
A Pilot Study of Sildenafil in COVID-19	9-Feb-20	sildenafil citrate	Mild/Severe	10	III	Recruiting	China
Severe 2019-nCoV Remdesivir RCT	6-Feb-20	remdesivir *vs.* control	Severe	453	III	Recruiting	China
Efficacy and Safety of Hydroxychloroquine for Treatment of Pneumonia Caused by 2019-nCoV (HC-nCoV)	6-Feb-20	hydroxychloroquine *vs.* control	Mild/Severe/ Critical	30	III	Completed	China
Clinical Study of Anti-CD147 Humanized Meplazumab for Injection to Treat With 2019-nCoV Pneumonia	3-Feb-20	meplazumab	Mild/Severe	20	I/II	Recruiting	China
Bevacizumab in Severe or Critical Patients With COVID-19 Pneumonia	Feb-20	bevacizumab	Severe/Critical	20	II/III	Recruiting	China
A Randomized, Open, Controlled Clinical Study to Evaluate the Efficacy of ASC09F and Ritonavir for 2019-nCoV Pneumonia	1-Feb-20	ASC09F + oseltamivir *vs.* ritonavir + oseltamivir *vs.* oseltamivir	Mild	60	III	Recruiting	China
A Prospective/Retrospective, Randomized Controlled Clinical Study of Antiviral Therapy in the 2019-nCoV Pneumonia	1-Feb-20	arbidol hydrochloride *vs.* oseltamivir *vs.* lopinavir/ritonavir *vs.* control	Mild/Severe/ Critical	400	IV	Recruiting	China
A Prospective/Retrospective, Randomized Controlled Clinical Study of Interferon Atomization in the 2019-nCoV Pneumonia	1-Feb-20	arbidol hydrochloride +/- lnterferon atomization	Mild/Severe/ Critical	100	IV	Recruiting	China
The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia	1-Feb-20	methylprednisolone (< 40 mg/day *vs.* 40-80 mg/day)	Severe	100	IV	Recruiting	China
Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-nCoV	30-Jan-20	darunavir + cobicistat *vs.* control	Mild/Severe/ Critical	30	III	Recruiting	China
Glucocorticoid Therapy for Novel Coronavirus Critically Ill Patients With Severe Acute Respiratory Failure	26-Jan-20	methylprednisolone *vs.* control	Severe/Critical	80	II/III	Recruiting	China
STOP PIV - Phase III DAS181 Lower Tract PIV Infection in Immunocompromised Subjects	23-May-19	DAS181	Severe	250	III	Recruiting	United States
Lessening Organ Dysfunction With Vitamin C	8-Nov-18	vitamin C *vs.* control	Critical	800	III	Recruiting	Canada
Inhaled Gaseous Nitric Oxide (gNO) Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections	24-Oct-17	nitric oxide gas	Mild	20	II	Active not recruiting	Canada
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia	11-Apr-16	lopinavir/ritonavir +/- hydroxychloroquine *vs.* lnterferon β-1A *vs.* Anakinra *vs.* control	Severe/Critical	6,800	IV	Recruiting	Multinational§

§Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, United Kingdom

Table 2. Clinical trials identified at Clinicaltrials.gov related to biological intervention for COVID-19 treatment

Study	Study Start	Interventions	Severity	Target Number	Phase	Status	Country
Immunity and Safety of Covid-19 Synthetic Minigene Vaccine	24-Mar-20	LV-SMENP-DC vaccine + antigen-specific CTLs	Mild/Severe	100	I/II	Recruiting	China
A Phase I/II Study of Universal Off-the-shelf NKG2D-ACE2 CAR-NK Cells for Therapy of COVID-19	21-Mar-20	NK cells *vs.* IL15-NK cells *vs.* NKG2D CAR-NK cells *vs.* ACE2 CAR-NK cells *vs.* NKG2D-ACE2 CAR-NK cells	Mild/Severe	90	I/II	Recruiting	China
Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	16-Mar-20	WJ-MSCs	Mild/Severe/Critical	5	I	Recruiting	Jordan
Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	5-Mar-20	MSCs *vs.* control	Severe	90	II/II	Recruiting	China
NK Cells Treatment for Novel Coronavirus Pneumonia	20-Feb-20	NK Cells *vs.* control	Mild/Severe/Critical	30	I	Recruiting	China
Safety and Immunity of Covid-19 aAPC Vaccine	15-Feb-20	Pathogen-specific aAPC	Mild/Severe	100	I	Recruiting	China
Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus	27-Jan-20	MSCs *vs.* control	Mild/Severe/Critical	20	I	Recruiting	China

the continuous treatment of mild-to-severe asthma (*14*). A recent report from National Institute of Infectious Diseases (Tokyo, Japan) revealed that ciclesonide blocks coronavirus RNA replication by targeting viral NSP15, and therefore, has an antiviral effect on COVID-19 (*15*). Thereafter, the efficacy of ciclesonide on three cases with early to middle-stage COVID-19 pneumonia has been reported from Kanagawa Prefectual Ashigarakami Hospital (Kanagawa, Japan). Based on these findings, a clinical trial to investigate the efficacy of ciclesonide for patients with COVID -19 pneumonia commenced on March 2, 2020 in National Center for Global Health and Medicine (Tokyo, Japan) and Fujita Health University (Aichi, Japan). After arrangement of the details, collection of the cases is going to be initiated in the near future.

Nafamostat

Nafamostat mesylate is a low molecular weight (539.6 kD) protease inhibitor that has been shown to inhibit serine proteases, such as trypsin, kallikrein, C1r and C1s, thrombin, and plasmin (*16*). Based on this inhibitory profile, nafamostat mesylate has been widely used in Asia to treat acute pancreatitis, disseminated intravascular coagulation, and extracorporeal circulation (*17*). In 2016, Yamamoto *et al.* revealed that nafamostat mesylate also blocked MERS-CoV infection *in vitro* by inhibiting the activity of TMPRSS2 and subsequent membrane fusion to the attached cell (*18*). In addition, Hoffmann *et al.* recently reported a similar effect on COVID-19 by camostat mesylate, an analogous drug to nafamostat mesylate (*19*). According to these reports, the effectiveness of nafamostat mesylate on COVID-19 was evaluated in Institute of Medical Science, The University of Tokyo (Tokyo, Japan), and they reported successful inhibition of COVID-19 infection in cultured human airway epithelial cells (Calu-3) at a lower concentration, which was around 10% compared with camostat (not published). Based on the results, a clinical trial for COVID-19 using nafamostat mesylate is scheduled in Institute of Medical Science, The University of Tokyo (Tokyo, Japan), The University of Tokyo Hospital (Tokyo, Japan) and National Center for Global Health and Medicine (Tokyo, Japan).

In conclusion, we summarized 48 major ongoing clinical trials registered to ClinicalTrials.gov database as of April 2, 2020, and presented the trials which are now being conducted or scheduled in Japan. Special attention must be paid to the results of these clinical trials to prevent further disease spread and fatal outcomes of COVID-19.

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Epidemiology and quarantine measures during COVID-19 outbreak on the cruise ship Diamond Princess docked at Yokohama, Japan in 2020: a descriptive analysis

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Abstract: The outbreak of coronavirus disease 2019 (COVID-19) on the cruise ship Diamond Princess docked at Yokohama, Japan was highlighted due to its number of cases in the early stage of the global epidemic when the picture of the virus itself, as well as epidemiological characteristics, were being established. We conducted an observational epidemiological study of the outbreak, focusing on a total of 403 individuals who developed a fever of ≥ 37.5°C from 20 January to 22 February 2020. Quarantine measures are also discussed with a descriptive method. Of a total of 3,711 individuals (2,031 males) from 57 countries, 2,666 (71.8%) and 1,045 (28.2%) were passengers and crew with mean age of 66.0 (range: 2-98) and 36.6 (range: 19-64), respectively. Among 403 febrile individuals, 165 passengers and 58 crew members were diagnosed as laboratory-confirmed COVID-19 cases. Until 6 February, the number of confirmed cases was three or less per day. However, distribution of thermometers on 7 February revealed 43 confirmed cases, and it then started decreasing. The outbreak was initiated from decks for passengers and expanded to areas for crew. As of 17 March, when more than14 days had passed after disembarkation of all passengers and crew, there was no report of forming a cluster of infections in Japan from them. At the time of the initiation of quarantine, the outbreak had already expanded to most of the decks from those for passengers, and the results might suggest the contribution of the set of quarantine measures in unprecedented challenges of the control operation.

***Keywords*:** COVID-19, disease outbreaks, ships, quarantine, Japan

Introduction

An ongoing international outbreak of coronavirus disease 2019 (COVID-19) started from Wuhan, China has rapidly expanded worldwide, and the World Health Organization declared a pandemic on 11 March 2020. Asian neighboring countries that have close human and economic relations with China were first affected. The case of the cruise ship Diamond Princess was highlighted due to its number of cases in the early stage of the global epidemic when the picture of the virus itself, as well as epidemiological characteristics, were being established.

In February 2020, a cruise ship named Diamond Princess, under the flag of the United Kingdom and operated by an American company, was quarantined at Yokohama city, Kanagawa, Japan. The cruise ship departed from Yokohama on 20 January 2020 and was scheduled to return to Yokohama after calling at Kagoshima (Japan), Hong Kong, Chan May (Vietnam), Cai Lan (Vietnam), Keelung (Taiwan), and Okinawa (Japan). During this voyage, a passenger who had been coughing since 23 January disembarked in Hong Kong on 25 January and was confirmed positive for COVID-19 on 1 February. This information was immediately notified to Japan through International Health Regulations as early as 2 February after the ship left Okinawa. Hence, when the ship reached Yokohama in the evening of 3 February, the Japanese government adopted an anchorage quarantine approach by sending quarantine officers to the ship for health evaluation of all passengers and crew members as well as collecting specimens from the individuals with fever or respiratory symptoms, their close contacts, and close contacts of the index case for reverse transcriptase-polymerase chain reaction (RT-PCR) tests. The first reports of the tests revealed ten positive cases (*1*), and isolation in cabins was initiated from 5 February.

This study aims to elucidate the epidemiology of COVID-19 during an outbreak on the cruise ship and discuss the contribution of quarantine strategies, including isolation in cabins for passengers and crew members.

Materials and Methods

Study design and data collection

We conducted an observational epidemiological study of the COVID-19 outbreak on the cruise ship Diamond Princess, covering the period from 20 January (start of the cruise voyage) to 22 February, 2020 (completion of disembarkation of almost all of the passengers). In addition to this, the follow-up information of the passengers and crew after disembarkation was assessed on 17 March, 2020. Age, sex, nationality, room size, deck number, date of fever onset, and results of RT-PCR tests of passengers and crew members were compiled for analysis. Information on the follow-up and assessment of disembarked persons was collected from the official press release of the Ministry of Health, Labour and Welfare (MHLW), and local governments.

This study was approved by the Human Research Ethics Committee of the National Center for Global Health and Medicine (NCGM), Tokyo, Japan (NCGM-G-003505-00). Written informed consent was waived as only anonymized data was used.

Definitions of study cases

During this voyage and quarantine starting from 20 January to 22 February, a total of 403 passengers and crew members developed a fever of ≥ 37.5°C, and this study focused on them. Confirmed cases in this study were defined as cases with a fever of ≥ 37.5°C and RT-PCR positive by pharyngeal swab specimen. Close contact is defined as those cabinmates of the confirmed cases and their family members or partners staying in other cabins.

Laboratory confirmation

Pharyngeal swab specimens were placed in plastic containers and transported to the laboratories under 4°C. Laboratory confirmation by RT-PCR test for COVID-19 was performed following the protocol established by the National Institute of Infectious Diseases (NIID), Tokyo, Japan (*2*). The tests were conducted at NIID, quarantine stations in Tokyo, Yokohama and Narita, prefectural or city institutes of public health, medical universities, and a commercial laboratory.

Quarantine measures

First, starting from 5 February, all passengers were isolated in their cabins for 14 days. Second, crew members were given instructions on appropriate infection prevention and control practice, and minimum services for passengers were provided by the crew. Third, all RT-PCR positive patients, regardless of symptoms, were promptly sent to hospitals outside the ship for isolation and care, and their close contacts were tested. In addition, those with health conditions that do not allow quarantine on the ship were sent to appropriate facilities. Fourth, on 7 February, thermometers were distributed and self-monitoring of body temperature twice a day was requested from all passengers and crew. Fifth, to separate routine health services for chronic conditions of the large population of senior passengers on board from those for possible infections, in addition to the existing Medical Center, a dedicated Fever Call Center (FCC) was also established on the ship to manage calls from passengers who had a fever of ≥ 37.5°C and other suspicious symptoms. The FCC was opened on 7 February and closed on 22 February after disembarkation of almost all passengers. Sixth, for COVID-19 testing, RT-PCR test was initially performed only for symptomatic cases until 10 February, but systematic screening was started from 11 February as testing capacity was expanded. The priority of the screening was based on age and comorbidities. Passengers aged ≥ 80 years and their cabinmates were tested first; followed by those in the seventies and their cabinmates; and those in the sixties and their cabinmates. Those who had comorbidities (including diabetes, chronic pulmonary diseases, and cardiac diseases) were also prioritized. Then, all other passengers were tested by visiting all remaining cabins. Seventh, the 14-day quarantine period was completed after confirming a negative RT-PCR test, no fever, or other physical conditions.

Statistical analysis

Categorical variables were counted and presented as proportion. Continuous variables were expressed as mean and range. All statistics are analyzed descriptively with the Stata IC version 16.1.

Results

A total of 3,711 individuals (2,031 males and 1,680 females) were on board at the beginning of quarantine. Of these, 2,666 (71.8%) were passengers with mean age of 66.0 (range: 2-98) and 1,045 (28.2%) were crew members with mean age of 36.6 (range: 19-64). Passengers accounted for 99.2% (2,144/2,162) of those aged ≥ 60 years, whereas 82.1% (669/815) of those aged < 40 years were crew members. For the nationalities of all individuals on board from 57 countries, Japanese occupied the largest proportion (36.1% [1,341/3,711]), followed by nationals of the Philippines (14.5% [538/3,711]), United States (11.5% [428/3,711]), Hong Kong (7.0% [260/3,711]), Canada (6.9% [255/3,711]), and Australia (6.1% [226/3,711]).

Passengers and crew members stayed alone in a cabin or shared a cabin with 2 to 4 persons, and most of them stayed in double rooms during the voyage and quarantine (89.8% and 79.7%, respectively). Upper decks (*i.e.* deck nos. 8-12 and 14) were mostly used for passengers, while lower decks (*i.e.* deck nos. 2, 3, 5, and 7) were mainly for crew members.

Among a total of 403 febrile individuals, 223 individuals (165 passengers and 58 crew members) were diagnosed as confirmed COVID-19 cases. With regard to the proportions of the cases stratified by age group (Figure 1), they ranged from 4.3% to 7.5% consistently across age groups between 20 and 89 years. There were no confirmed febrile cases aged 19 years or younger, while the largest proportion was observed in the nineties (16.7%), although the denominator of these age groups was small compared to other groups.

Figure 2 shows the fever onset of confirmed cases defined as those with fever of ≥ 37.5°C and RT-PCR positive, and illustrates implementation dates of control measures. Until 6 February, the number of confirmed cases was three or less per day. However, immediately after distribution of thermometers for self-monitoring and open of FCC on 7 February, a substantial number of confirmed cases was revealed and it started decreasing after 8 February. On the other hand, the number of confirmed cases among crew members peaked on 9 February, and then the daily numbers of cases gradually decreased with some fluctuation.

The pattern of spread of the infection based on deck number is described in Figure 3. As illustrated, the outbreak seemed to have spread from the area of the passengers. At the time when FCC was opened, the outbreak had already expanded to most of the decks.

As of 17 March 2020 when more than 14 days had passed after disembarkation of all passengers and crew on 1 March, there were six cases whose PCR results were initially negative but turned out to be positive after returning to communities. However, there was no report

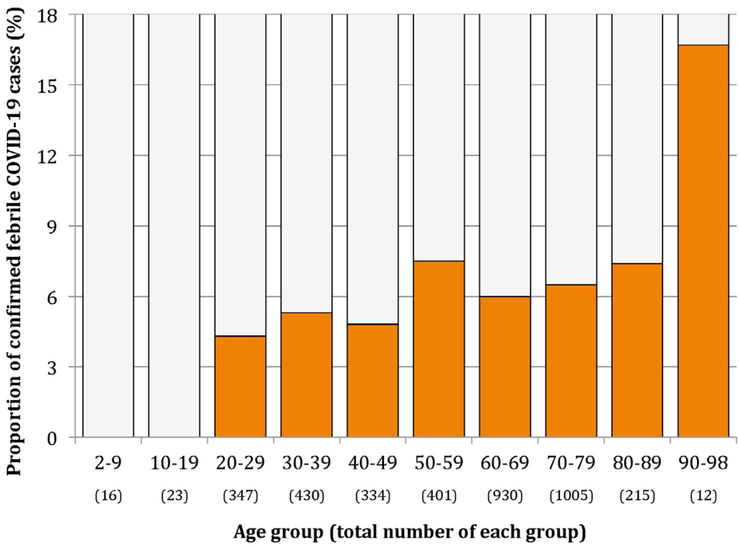

Figure 1. Proportion of confirmed febrile COVID-19 cases in each age group. The proportions of the cases ranged from 4.3% to 7.5% consistently across age groups between 20 and 89 years. No confirmed febrile case aged 19 years or younger was observed, while the largest proportion was in the nineties (16.7%), although the small denominator of these age groups should be considered.

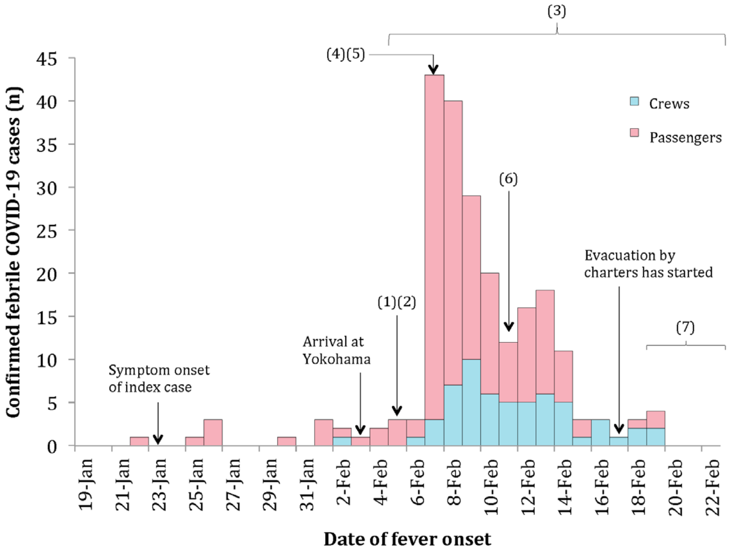

Figure 2. The number of confirmed febrile COVID-19 cases and the implementation date of quarantine measures. The numbers in the figure describes following quarantine measures implemented: (1) isolation of all passengers in their cabins for 14 days was started, (2) crew members were given instructions of appropriate infection prevention and control practice, (3) all RT-PCR positive patients regardless of symptoms are sent to hospitals or other facilities for isolation and care, (4) thermometers were distributed and self-monitoring was requested for all passengers and crew members, (5) a dedicated Fever Call Center was established on the ship, (6) systematic screening of RT-PCR test for COVID-19 was initiated, and (7) on 19 February, disembarkation was started after confirming negative RT-PCR test, no fever, or other physical conditions.

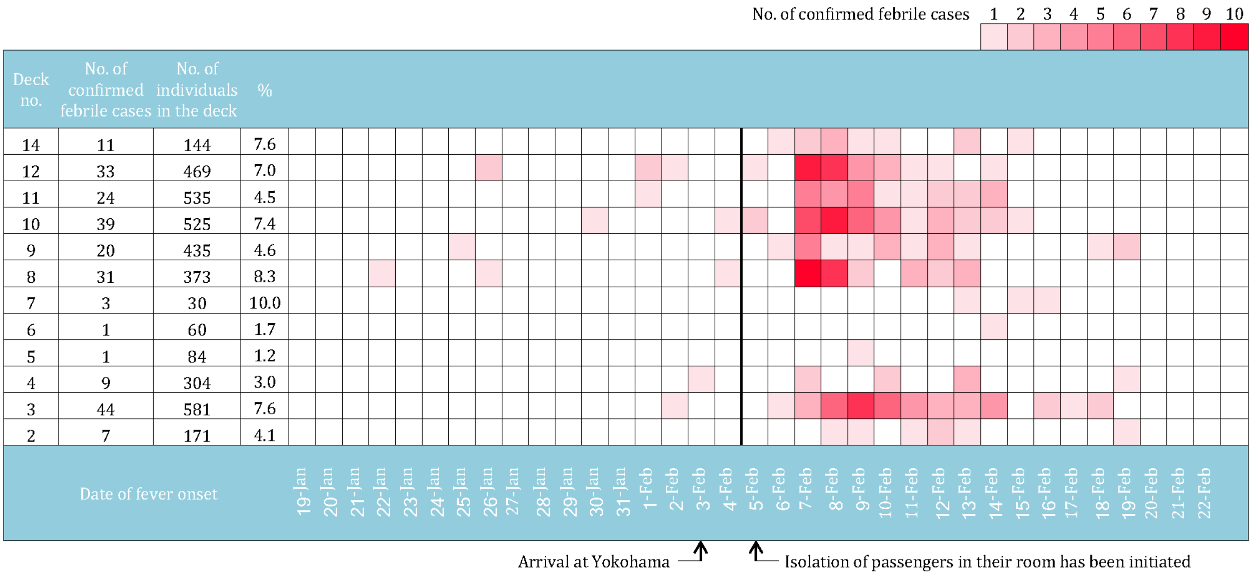

Figure 3. Outbreak dynamics of confirmed febrile COVID-19 cases stratified by deck numbers. This figure shows the association between the fever onsets of the confirmed febrile COVID-19 cases and the deck where the cases stayed during travel and quarantine. Passengers' cabins were located on deck nos. 4, 6, 8-12, and 14, whereas crew members' cabins were located on deck nos. 2-7, 12, and 14. This revealed that COVID-19 had already spread to most of the decks before arrival at Yokohama and initiation of isolation strategy in cabins.

of forming a cluster of infections in Japan from those passengers.

Discussion

This is the first comprehensive epidemiological report of COVID-19 outbreak on the cruise ship Diamond Princess in 2020 covering the period from the beginning of the cruise voyage to disembarkation of passengers with follow-up information of passengers after disembarkation, further to earlier publications from the NIID for the shorter period (*3-5*). When Japan faced this challenge in early February 2020, there was extremely scarce information available for dealing with outbreaks of infectious diseases on cruise ships. Indeed, we found some information about other infections such as gastrointestinal infections, influenza, and measles (*6-9*), but there is no report of a huge outbreak on a cruise ship caused by an emerging infectious disease.

The epidemic curve reveals that the COVID-19 outbreak on the cruise ship had already expanded before the initiation of quarantine (Figure 2). Since some previous studies reported mean and median incubation periods of 5.2 days (95% confidence interval [CI] 4.1-7.0) and 4 days (interquartile range [IQR] 2-7), respectively (*10,11*), many of the cases confirmed on 7 February should have been contracted before initiation of isolation measures on 5 February. In addition, the peak of infection among the confirmed cases could be before 7 February because the number of confirmed cases sharply decreased then. Moreover, the cases had been distributed in most of the decks by 5 February (Figure 3), possibly through recreational activities and facilities shared by all on board that were available to some extent before the isolation was initiated on 5 February.

The number of confirmed cases decreased substantially shortly after the initiation of quarantine. This might suggest the contribution of the set of countermeasures implemented to overcome this outbreak. To control an epidemic, the passengers were isolated into their cabins immediately after the initiation of quarantine. Cabins were selected as the isolation place because there were no available facilities on shore to isolate all passengers and crew members from 57 countries, and some suitable facilities were occupied with people who were evacuated from Wuhan by another national operation. For early detection of the cases and suspected cases, thermometer distribution, FCC establishment, and systematic screening with RT-PCR were implemented to improve detection of cases with mild symptoms and asymptomatic cases. In addition, once their diagnoses were confirmed, cases including asymptomatic patients were promptly transported to outside facilities for isolation and care, and their close contacts were tested. The effectiveness of these measures is supported by two small studies reporting that COVID-19 viral load peaked within 5-6 days after symptom onset (earlier than that of severe acute respiratory syndrome: 6-11 days after illness onset) and high viral loads were detected shortly after symptom onset (*12,13*). However, at the same time, these studies also indicated the difficulty of controlling COVID-19. Moreover, to avoid transmission between passengers and crew during quarantine period, instruction for personal protective equipment was performed for crew members. Thus, these control measures seemed to contribute to reduction of transmission, although additional studies are required to determine with confidence the degree of contribution.

Another point is the outcome of quarantine exercise to protect the inflow of epidemics into Japan. Considering no report of formation of clusters in Japanese communities despite the follow-up of the passengers and crew for two weeks after disembarkation and careful monitoring of the close contacts of the cases whose PCR result turned out to be positive after disembarkation (*14*), this might suggest the contribution of the quarantine exercise on board.

The present study has some limitations. First, individuals who have only respiratory symptoms without fever were not included in the epidemic curve because of the lack of such information. This was due to best allocate limited resources, such as laboratory capacity for the novel pathogen. Second, it was possible that some crew members were reluctant to report mild symptoms in order to maintain minimum function on the huge cruise ship. This was suspected from the fluctuation pattern of the epidemic curve of crew members, although there was no solid evidence.

Acknowledging the above limitations, the authors believe that this study provides some insight on COVID-19 and similar events in the future including a clear and detailed description of the epidemiology of an outbreak in a unique environment of a cruise ship in terms of physical environment and a predominantly older high-risk population, and possibly effective quarantine exercises to protect inflow of epidemics into a country. Furthermore, the importance of collaboration among various teams such as the ministry of health, quarantine stations, and medical and pharmaceutical support units, and effective management of a massive amount of information using a systematically constructed integrated data platform accessible to each team should be highlighted to overcome unprecedented challenges of control operations in a very limited timeframe.

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SARS-CoV-2 infection among returnees on charter flights to Japan from Hubei, China: a report from National Center for Global Health and Medicine

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Abstract: Due to the significant spread of a new type of coronavirus (SARS-CoV-2) infection (COVID-19) in China, the Chinese government blockaded several cities in Hubei Province. Japanese citizens lost a means of transportation to return back to Japan. The National Center for Global Health and Medicine (NCGM) helped the operation of charter flights for evacuation of Japanese residents from Hubei Province, and this article outlines our experiences. A total of five charter flights were dispatched, and the majority of returnees (793/829 [95.7%]) were handled at NCGM. A large number of personnel from various departments participated in this operation; 107 physicians, 115 nurses, 110 clerical staff, and 45 laboratory technicians in total. Several medical translators were also involved. In this operation, we conducted airborne precautions in addition to contact precautions. Eye shields were also used. The doctors collecting the pharyngeal swab used a coverall to minimize the risk of body surface contamination from secretions and droplets. Enhanced hand hygiene using alcohol hand sanitizer was performed. Forty-eight persons were ultimately hospitalized after the triage at NCGM operation, which was more than the number of persons triaged at the airport (n = 34). Of those hospitalized after NCGM triage, 8.3% (4/48 patients) ultimately tested positive for SARS-CoV-2, significantly higher than the positive rate among subjects not triaged (4/48 [8.3%] *vs.* 9/745 [1.2%]: p = 0.0057). NCGM participated in a large-scale operation to evacuate Japanese nationals from the COVID-19 epidemic area. We were able to establish a scheme through this experience that can be used in the future.

***Keywords*:** charter flight, Japan, airborne precautions, contact precautions, SARS-CoV-2, COVID-19

Introduction

Since the end of 2019, an accumulation of severe pneumonias of unknown cause was reported in Wuhan City, Hubei Province, China, which was subsequently found to be a new type of coronavirus (SARS-CoV-2) infection (COVID-19) (*1*). Due to the significant spread of the infection in China, especially in Wuhan City and Hubei Province, the Chinese government blockaded several cities in Hubei Province including Wuhan on January 23, 2020 (*2*). Due to the blockade, Japanese citizens lost a means of transportation to return back to Japan. The National Center for Global Health and Medicine (NCGM) helped the operation of charter flights for evacuation of Japanese residents from Hubei Province, and this article outlines our experiences.

Operational Methods and Results

Summary of the number of persons returning from charter flights

A total of five charter flights were dispatched, and the majority of returnees were handled at NCGM. The number of persons returning from charter flights are summarized in Table 1 (*3-6*). Among the returnees, 2~6.7% of the returnees on each flight were transported directly from the airport to other hospitals from the initial triage at the Haneda Airport. NCGM took care of the remaining returnees.

NCGM's response system

Under the direction of the Ministry of Health, Labour and Welfare, NCGM helped the screening of COVID-19 infection among returnees, in collaboration with the National Institute of Infectious Diseases. Because returnees had been having a hard time to come back to Japan during the emergent situation, we also provided care for the persons who felt sick as well as provided food and drinks for them. A large number of personnel from various departments participated in this operation; infectious disease doctors, support doctors from other departments, the nursing department, the medical professions division, the department of clinical laboratory, and the infection control team. The approximate number of staff members who participated in the operation at NCGM is summarized in Table 2.

After arrival of the buses, which carried returnees from Haneda Airport, we were divided into the following groups, with nurses and clerical staff guiding the returnees between each section. Large sightseeing buses were chartered to transport about 15 to 25 people per bus, with about 5 to 6 buses per flight.

1. *Bus triage*

ICNs (Certified Infection Control Nurses) and other nurses (3 to 5 nurses) triaged symptomatic patients in the bus. Returnees were also asked to fill out a questionnaire inside the bus as much as possible.

2. *Guidance*

Symptomatic persons who were triaged on the bus were directed by the clerical staff to the Infectious Diseases department, where a physician provided medical care to the patients thereafter. The remainder were directed by the clerk to a site for questioning and specimen collection.

Table 1. Summary of the number of persons returning from charter flights

Flight	Date	Number of returnees	Symptomatic patients triaged at airport[a]	Returnees screened at NCGM	Numbers of patients admitted after NCGM triage[d,e]
No.1	29/Jan/2020	206	5 (2.4%)	199[b] (96.6%)	7 (3.4%)
No.2	30/Jan/2020	210	13 (6.2%)	197 (93.8%)	13 (6.2%)
No.3	31/Jan/2020	150	10 (6.7%)	140 (93.3%)	15 (10%)
No.4	7/Feb/2020	198	4 (2%)	194[c] (98%)	8[c] (4%)
No.5	17/Feb/2020	65	2 (3.1%)	63 (96.9%)	5 (7.7%)
Total		829	34 (4.1%)	793 (95.7%)	48 (5.8%)

[a]Transferred to other hospitals from Haneda airport; [b] Two persons rejected screening and were not screened at NCGM; [c] Including three family members for attending purpose; [d] People who were not admitted were quarantined for 14 days at public facilities; [e] % was calculated using the denominator of total numbers of returnees.

Table 2. The number of staff members who participated in the operation at NCGM

Flight	Date	Number of returnees	Physicians	Nurses	Clerical staff	Laboratory technicians	Total
No.1	29/Jan/2020	206	25	19	28	5	77
No.2	30/Jan/2020	210	25	26	19	6	76
No.3	31/Jan/2020	150	20	24	23	5	72
No.4	7/Feb/2020	198	22	27	21	6	76
No.5	17/Feb/2020	65	15	19	19	2	55
Total		829	107	115	110	24	356

Table 3. Summary of the questionnaire

- Age, sex and date of birth
- Address (where you will be staying in Japan) and telephone number
- Area of stay in Hubei Province of China within the past 14 days
- History of contact with a person with fever or cough symptoms in the past 14 days
- History of contact (or possible contact) with patients with COVID-19 infection within the past 14 days
- The presence or absence of any abnormality in physical condition and its symptoms
- Taking any antipyretic, cold medicine or pain medication.
- Body temperature (measured by NCGM)

3. *Reception*

Clerical staff assigned reception numbers and handed over specimen containers and performed other reception duties.

4. *Interview*

The doctors confirmed the contents of the questionnaire (Table 3). Those with additional symptoms or suspected unprotected exposure to COVID-19 confirmed patients identified at this stage were referred to the infectious disease outpatient clinic. Nurses and clerical staff guided the patient from the interview to blood collection and pharyngeal swab collection.

5. *Blood collection*

The nurse and pediatrician drew blood samples to test for SARS-CoV-2 PCR testing as well as antibodies for SARS-CoV-2.

6. *Pharyngeal swab specimen collection*

Pharyngeal swab specimens were collected for SARS-CoV-2 PCR testing by a physician.

7. *Specimen confirmation and collection*

The specimens and medical questionnaires were collected. The average number of returnees per staff member in each occupation was as follows; 9-10 doctors, 5-8 nurses, 8-14 clerical staff, and 28-40 laboratory technicians (For flights 4 and 5, the percentage of children was particularly high, therefore, it is not included in the above average calculation because we needed more staff members than other flights). In the real operation, one doctor who collected pharyngeal swab samples handled about 40-50 specimens by himself. For nurses, the number of personnel needed could have been reduced if there was no need for blood draws. In addition, many Japanese families with Chinese nationality were included in the latter half of the flights (flights 4 and 5), and several Chinese interpreters were assigned from the International Health Care Center to assist with operations. Although there were children under six years old on each flight, the number of children was particularly high on the fourth and fifth flights, and pediatrician support was important throughout. In addition, although not included in the above, there was a need for personnel to timely communicate with airport quarantine and the Ministry of Health and Welfare.

In terms of response locations, it was necessary to choose locations that did not intersect with the hospital's patients. Triage was conducted in a room with a capacity of about 100 people, using a dedicated elevator from the backside parking lot. For the collection of pharyngeal swab specimens, a dedicated staff member was assigned to a separate room with an open window (a separate room was available for flights 4 and 5).

Infection control

In this operation, we conducted airborne precautions in addition to contact precautions (Figure 1). Eye shields were used according to the recommendations of the CDC and WHO (*7,8*).

In addition to the above, the doctor collecting the pharyngeal swab used a coverall to minimize the risk of body surface contamination by secretions and droplets (Figure 2). The doctor of the Department of Infectious Diseases instructed the staff of each section in the donning of personal protective equipment (PPE) prior to the start of the operation, and periodically checked for inappropriate use during the operation. Alcoholic hand sanitizers were placed in various locations for hand hygiene.

Number of symptomatic patients and summary of SARS-CoV-2 test results

A summary of the number of NCGM cases that resulted in hospitalization is shown in Table 1. Although quarantine triage was conducted at the airport upon arrival of the charter flight (34 persons in total), 48 persons were ultimately hospitalized due to fever or symptoms (those with strong symptoms or relatively high probability of exposure) during the NCGM operation, which was more than the number of persons triaged at the airport. Of those hospitalized (NCGM or other hospital) after NCGM triage, 8.3% (4/48 patients) ultimately tested positive, which was significantly higher than the positive rate among subjects not triaged,

Figure 1. Personal protective equipment used in this operation.

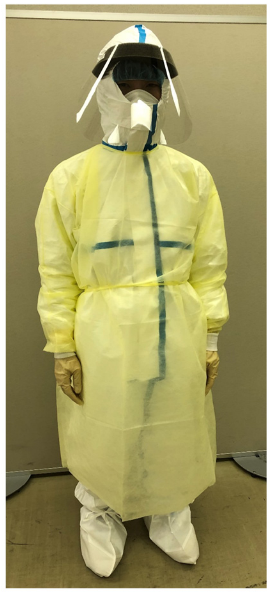

Figure 2. Personal protective equipment used in this operation to obtain pharyngeal swab samples.

and suggested the effectiveness of triage at NCGM (4/48 [8.3%] *vs.* 9/745 [1.2%]: $p = 0.0057$ [Fisher's exact test]).

Discussion

NCGM had an extremely valuable experience in operating a mass return from an emerging infectious disease epidemic area. Although this was the first time for such a large scale evacuation of Japanese people, we were able to complete the operation without any major problems.

With regard to the evacuation of its own citizens from China, where the spread of COVID-19 infection was initially recognized, the United States, Germany, and other countries, as well as Japan, had responded. Due to geographical proximity and economic ties, the number of Japanese staying in China was large (*9*), and indeed, it was much larger than Germany (126 people), with more than 800 evacuations, which was on a par with the United States (*10,11*).

In a paper on evacuation from Wuhan in Germany (*11*), of 126 people, 10 (7.9%) were triaged in an airplane (*e.g.*, symptomatic or suspected exposure to COVID-19 cases) and an additional 1/116 (0.9%) were triaged in a subsequent physician's assessment at a medical assessment center. However, as a result, 2/114 (1.8%) PCR-positive individuals with SARS-CoV-2 were from people who were not triaged. The positive rate among asymptomatic patients was similar to that in Japan, where the rate was 1.2%, while the Japanese operation had a relatively high positive rate of 5.9% (2/34) among symptomatic patients at the airport and 8.3% (4/48) among those hospitalized after triage at NCGM. One of the reasons for this high rate of positive triage at our center, even though it was secondary triage, was the use of screening by experienced physicians, experienced nurses including ICNs, and Infectious Diseases physicians. The fact that the population of the Japanese cohort had a higher prevalence of symptoms than the German cohort may also have played a role.

Information on the number of staff members, location, means of transportation, and infection control in this operation is considered to be extremely important when conducting similar operations in the future. The hospital is a designated medical institution for specified infectious diseases, and many of the staff were more familiar with infection control measures even in ordinary times because the hospital routinely treats patients with infectious diseases and promotes infection control measures. However, the time to prepare for this operation was extremely limited, and we did not have enough time to train clerical staff for donning and doffing PPE in advance. We changed PPE to draw blood from pediatric patients from contact and droplet precautions (Figure 1) to coverall with N95 (Figure 2) for the latter half of the flights expecting that coverall might protect the staff members better in this circumstance. Although no positive results were reported this time from children, special care and preparation were considered necessary for infection control for this population. Although a few staff members visited the department of infectious diseases for respiratory tract symptoms within 2 weeks after participation in this operation, no one was confirmed to be infected with COVID-19; a detailed evaluation using serum antibodies is being planned in the future. In addition, central government officials, airline company employees, bus drivers, and others involved in this operation were screened for possible COVID-19 infection at the NCGM; none of them tested positive for SARS-CoV-2 by pharyngeal swab specimen PCR tests (data not shown).

Various studies are currently underway, and new evidence related to the pathogenesis of COVID-19 and effective infection control measures is awaited in the future from this operation cohort.

In conclusion, NCGM with a mission for infectious diseases, participated in a large-scale operation to evacuate Japanese nationals from the COVID-19 epidemic area. We were able to establish a scheme through this experience that can be used in the future.

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Epidemiological features after emergency declaration in Hokkaido and report of 15 cases of COVID-19 including 3 cases requiring mechanical ventilation

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Abstract: The ongoing spread of coronavirus disease (COVID-19) is a worldwide crisis. Hokkaido Prefecture in Japan promptly declared a state of emergency following the rapid increase of COVID-19 cases, and the policy became an example to mitigate the spread of COVID-19. We herein report 15 cases of COVID-19 including 3 cases requiring mechanical ventilation. Based on review of our cases, among patients over 50 years of age with underlying diseases such as hypertension and diabetes mellitus, and those who required oxygen administration tended to deteriorate. These cases highlight the importance of understanding the background and clinical course of severe cases to predict prognosis.

***Keywords*:** COVID-19, SARS-CoV-2, emergency declaration, mechanical ventilation, risk factor

Introduction

Starting in Wuhan, China in December 2019, the number of coronavirus disease (COVID-19) has been increasing worldwide especially since the World Health Organization (WHO) declared a pandemic on March 11. As of April 12, 2020, there were a total of 6,748 laboratory confirmed cases in Japan (excluding the cruise ship) and 267 cases in Hokkaido where the first outbreak occurred in Japan. The Mayor of Hokkaido independently declared a state of emergency on February 28 that was 5 weeks earlier than the Prime Minister of Japan did. In this report, we reviewed our first consecutive 15 cases of COVID-19 in which three cases required mechanical ventilation.

Patients and Methods

Sapporo City General Hospital

Our hospital is designated as the Category I Infectious Diseases Medical Facility in Hokkaido. In addition to two private rooms for patients with Category I Infectious Diseases, there are three rooms for two patients with Category II Infectious Diseases. Then, we can treat the 8 patients at the same time period. As of April 4, our hospital has treated a total of 31 adult cases of COVID-19. In this study, we presented the first consecutive 15 cases. Among them, three cases required mechanical ventilation.

Three cases required mechanical ventilation

Case 1: Man in his 60's

Chief complaint: general fatigue, fever.

Past medical history: diabetes mellitus, hypertension, atrial fibrillation.

History of present illness: On Day X (Hereinafter, date of symptom onset is defined as X in each patient), patient presented to medical institution A (1st visit) with fever of 37.5°C. First influenza antigen test was negative. He was sent home with symptomatic treatment. On X + 1 day, he visited the same medical institution A (2nd visit) for persistent fever of 37 to 38°C. The second influenza antigen test was negative. He was sent home with symptomatic treatment. On X + 5 days, he visited the same medical institution A (3rd visit) for persistent fever of 38°C and higher. The third influenza antigen test was negative. He denied shortness of breath and SpO_2 was 95% in room air. He was sent home with cefcapene. He started to have a higher fever of 40°C, cough, and rhinorrhea after returning home.

On X + 6 days, he visited the same medical institution A (4th visit), then he was referred to our hospital by the Sapporo City Public Health Center for suspected COVID-19. Nasopharyngeal specimen was obtained for SARS-CoV-2 PCR. Vital signs at initial consultation was temperature 37.7°C, heart rate 70 beats per minute, respiratory rate 14 breaths per minute, and SpO_2 97% (room air). The patient was in good physical condition without any respiratory distress. Chest CT showed ground glass opacity bilaterally. Clinical course and imaging study were considered to be consistent with COVID-19 (Figure 1, A1,A2). He was sent home until the PCR result available. On X + 8 days, nasopharyngeal SARS-CoV-2 PCR was confirmed positive, and he was admitted to our hospital.

Review of systems: Positive for fever, general fatigue, cough, rhinorrhea. Negative for headache, nausea, sore throat, shortness of breath, abdominal pain, diarrhea, arthralgia, rash.

Physical examination on admission: Alert and oriented. Temperature 39.3°C, heart rate 82 beats per minute, blood pressure 141/62 mmHg, respiratory rate 12 breaths per min, SpO_2 97% (room air). A fine crackle was heard on bilateral lower lobe. Abdomen soft and flat, non-tender.

Blood test on admission: WBC 2,900/μL (Seg 72%, Lym 21%), CRP 11.6 mg/dL, PCT 0.08 ng/mL, AST 44 U/L, ALT 25 U/L.

Culture test: Blood culture 2 sets negative on X + 8 days, sputum culture negative on X + 8 days.

Hospital course: On admission (X + 8 days), fever around 39°C and cough were noted. He denied shortness of breath and no hypoxia was observed. Due to drug interactions with rivaroxaban and other medication, lopinavir/ritonavir was not initiated. On X + 9 days, although his symptoms remained relatively mild, his oxygenation level decreased, and 3 L/min of oxygen was started. Chest X-ray on the same day showed bilateral upper lobe infiltration (Figure 1, B1). Ampicillin sulbactam 3 g every 8 hours was added for possible concomitant bacterial pneumonia. On X + 10 days, chest X-ray and chest CT showed worsening of bilateral pneumonia (Figure 1, C1-C3). Blood pressure dropped the same night, antibiotics was changed to meropenem 1 g every 8 hours for possible septic shock. On X + 11 days, oxygenation status became worse and nasal high flow therapy was initiated, however, his SpO_2 remained around 90% with FiO_2 of 1.0. Because of the rapid deterioration of oxygenation, favipiravir was started after accelerated approval by hospital ethics committee regarding its off-label and compassionate use. Favipiravir was given 1,800 mg twice every 12 hours on day 1, then 800 mg once every 12 hours from day 2. In addition, ciclesonide 200 μg inhalation four times a day was also started on the same day. On X + 12 days, respiratory condition became worse, and mechanical ventilation was started after intubation.

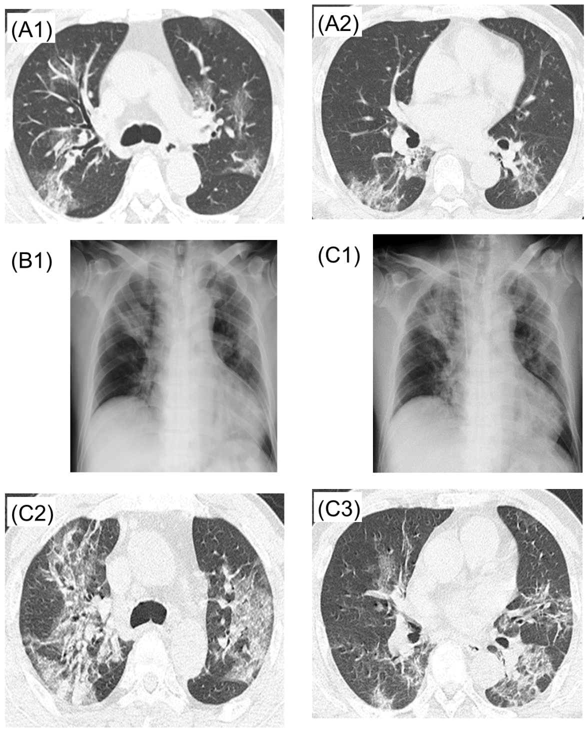

Figure 1. Case 1. A1, A2: X + 6 days, B1: X + 9 days, C1, C2, C3: X + 10 days.

On X + 13 days, due to lack of improvement, he was transferred to another hospital for ECMO management.

Case 2: Man in his 70's

Chief complaint: fever.

Past medical history: hypertension, emphysema, benign prostatic hyperplasia.

History of present illness: On Day X, patient started to have fever of 37.6°C, then fever of 37 to 38°C persisted thereafter. On X + 2 days, he visited medical institution B (1st visit). He was sent home with garenoxacin. On X + 5 days, he visited the same medical institution B due to persistent fever (2nd visit). Chest X-ray did not show any obvious pneumonia. On X + 8 days, he visited the same medical institution B (third visit). Chest X-ray showed pneumonia (Figure 2, A1), and he was referred to medical institution C. Vital signs at that time showed temperature 38.8°C, SpO_2 87% (room air). He was admitted with 2 L/min oxygen. Chest CT showed diffuse ground-glass opacities bilaterally (Figure 2, A2-A4). For possible COVID-19, sputum and throat swab specimens were obtained for SARS-CoV-2 PCR testing. Respiratory condition worsened, endotracheal intubation was performed and mechanical ventilation was started. Levofloxacin and ciclesonide were started. On X + 9 days, SARS-CoV-2 PCR was found to be positive. On X + 10 days, patient was transferred to our hospital.

Vital signs on admission: temperature 37.7°C, heart rate 71 beats per minutes, blood pressure 83/54 mmHg, respiratory rate 20 breaths per minute, SpO_2 90%.

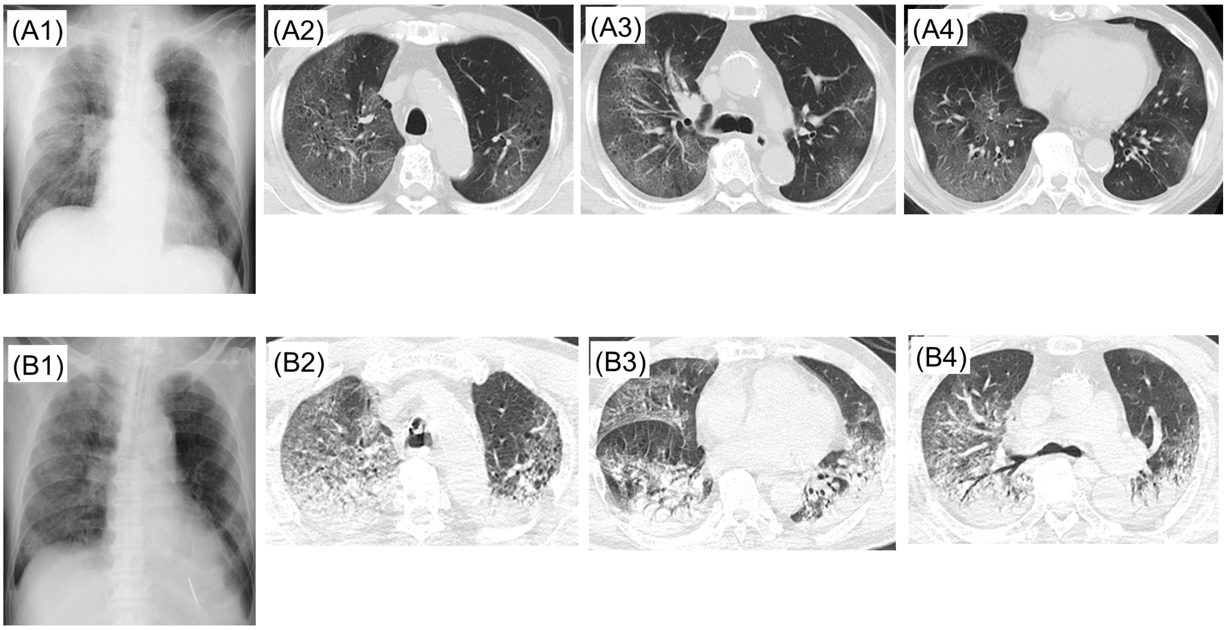

Figure 2. Case 2. A1, A2, A3, A4: X + 8 days, B1, B2, B3, B4: X + 10 days.

Ventilator settings on admission: SIMV + PS, FiO_2 1.0, PEEP12, PC15, PS8.

Blood test on admission: WBC 8,600/μL (Seg 87%, Lym 5%), CRP 10.68 mg/dL, PCT 0.08 ng/mL, AST 53 U/L, ALT 25U/L.

Culture test: Blood culture 1 set negative on X + 10 days, urine culture negative on X + 10 days, endotracheal aspiration sputum culture positive only with normal flora on X + 10 days.

Hospital course: Patient was in severe respiratory failure on admission to our hospital transfer (X + 10 days) and he was transferred to the ICU. Chest X-ray and chest CT on the same day showed rapid progression of bilateral ground-glass opacities (Figure 2, B1-B4). Ciclesonide was increased to 400 μg three times a day for severe COVID-19, and lopinavir/ritonavir 5 mL (400 mg/100 mg) twice daily was started. Since no improvement of pneumonia was confirmed, ceftriaxone 2 g daily was added for possible complication with bacterial pneumonia. On the same day, right chest tube was inserted for pneumothorax. Medical condition did not improve, and he died on day X + 15 days due to COVID-19 associated respiratory failure.

Case 3: Man in his 50's

Chief complaint: fever, general fatigue, cough.

Past medical history: diabetes mellitus, hypertension, dyslipidemia, hyperuricemia, sleep apnea syndrome.

History of present illness: On Day X, patient started to have fever, malaise, and cough. On X + 3 days, he visited medical institution D (1st visit), and first influenza antigen test for influenza was negative. On Day X + 4 days, he visited the same medical institution D (2nd visit), and the 2nd influenza antigen test was negative. Chest X-ray showed pneumonia in upper right lung field (Figure 3, A1). He was referred to medical institution E where chest CT was obtained (Figure 3, A2,A3). He was sent home for pneumonia after ceftriaxone administration and azithromycin prescription. On X + 7 days, he visited the same medical institution E (3rd visit). Ceftriaxone was given and he was sent home with garenoxacin. On X + 11 days, he visited medical institution F due to persistent fever and shortness of breath. His vital signs were temperature 38.7°C and SpO_2 around 80% (room air). Chest X-ray and CT showed worsening pneumonia bilaterally (Figure 3, B1-B3). After admission, nasal high flow oxygen therapy, steroid pulse therapy for ARDS, and meropenem and minocycline for possible concomitant bacterial pneumonia were started. On X + 12 days, since respiratory condition did not improve, he was intubated, and mechanical ventilation was started in the ICU. On X + 14 days, although respiratory status improved, cause of severe pneumonia was unknown, SARS CoV-2 PCR test was performed on sputum and throat swab specimens, which came back positive. On X + 15 days, he was transferred to our hospital. Vital signs and physical examination on admission: temperature 37.4°C, heart rate 60 beats per minute, blood pressure 170/80 mmHg, respiratory rate 15 per minute, SpO_2 98%. Fine crackles were noted on bilateral posterior lower lobe diffusely.

Ventilator settings on admission: SIMV + PS, FiO_2 0.6, PEEP10, PS10, RR15.

Blood test at admission: WBC 8,600/μL (Seg 90%, Lym 3%), CRP 2.6mg/dL, PCT 0.11ng/mL, AST 185 U/L, ALT 442 U/L.

Culture test: sputum culture *Klebsiella oxytoca* on X

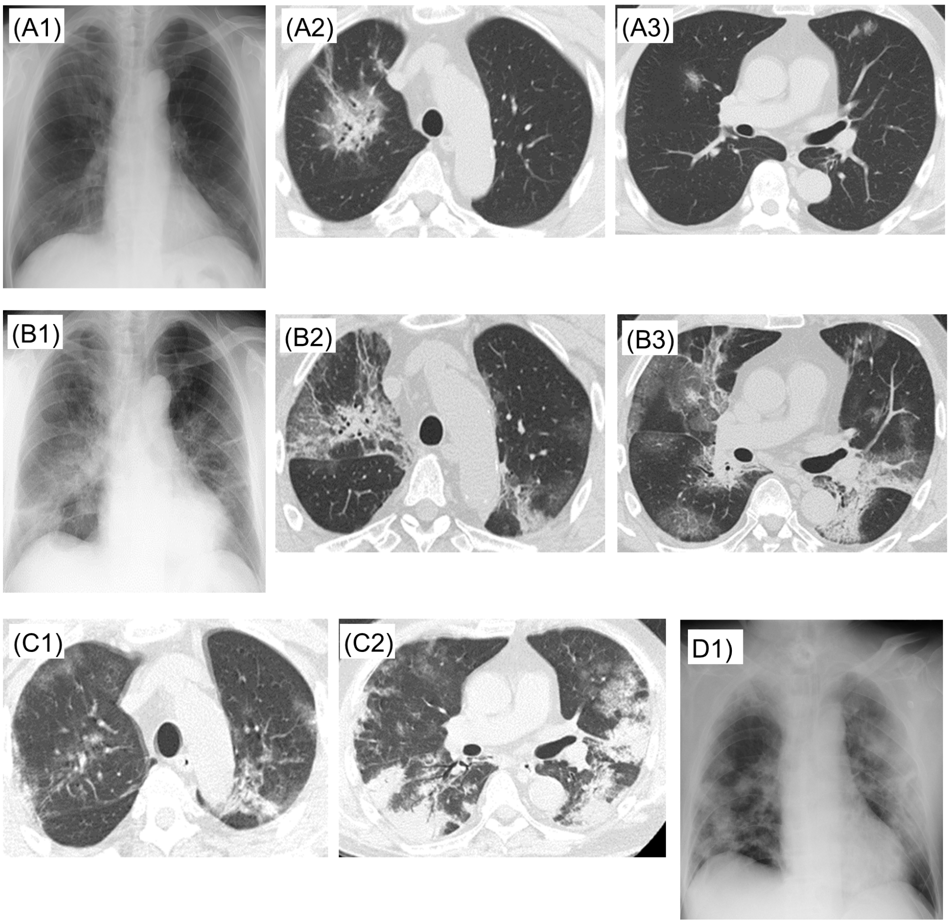

Figure 3. Case 3. A1, A2, A3: X + 4 days, B1, B2, B3: X + 11 days, C1, C2: X + 22 days, D1: X + 23 days.

+ 11 days, endotracheal aspiration sputum with normal flora on X + 15 days. Blood culture 2 sets negative on X + 17 days.

Hospital course: We did not give systemic steroid based on available recommendations for COVID-19 management (*1*). There was no established evidence of antiviral effectiveness at that time. Of clinical trials conducted in China on lopinavir/ritonavir, inclusion criteria were within 7 days of onset (NCT04261907), or within 72 hours after confirmation of abnormal chest X-Ray or symptom onset (NCT04251871). Since patient was transferred to our hospital 15 days after symptom onset, we initially did not give lopinavir/ritonavir. We discontinued minocycline due to elevated liver function tests, and continued meropenem 1 g every 8 hours for possible concomittant bacterial pneumonia. After admission to our hospital, fever above in 39°C continued every day, and respiratory condition did not improve. Although there was no clear evidence of benefit at that time, we started lopinavir/ritonavir (400/100 mg twice daily) from X + 18 days after accelerated approval by hospital ethics committee regarding its off-label and compassionate use. On X + 19 days, the intubation tube was blocked due to clogged sputum, it was emergently exhanged. After this event, respiratory status worsened and there was a continuing high risk of re-occlusion of endotracheal tube due to viscous sputum, emergency tracheostomy was performed on the same day. Thereafter, his respiratory condition gradually improved to the point he could participate in a rehabilitation program in the ICU. Meropenem was discontinued on X + 21 days. On X + 22 days, chest CT showed organizing process of ground-glass infiltration bilaterally (Figure 3, C1,C2). On X + 23 days, chest X-ray showed bilateral consolidation process possibly due to effect of scarring (Figure 3, D1). After X + 25 days, fever resolved, and a total of two SARS-CoV-2 PCR were negative on X + 25 days and X + 26 days. On X + 27, he was transferred to the High Care Unit. Lopinavir/ritonavir was discontinued on X + 27 days.

Results and Discussion

Declaration of a state of emergency in Hokkaido on Feb 28

The number of COVID-19 had increased in mid-February in Hokkaido (Figure 4). This was the first outbreak of COVID-19 in Japan. According to the

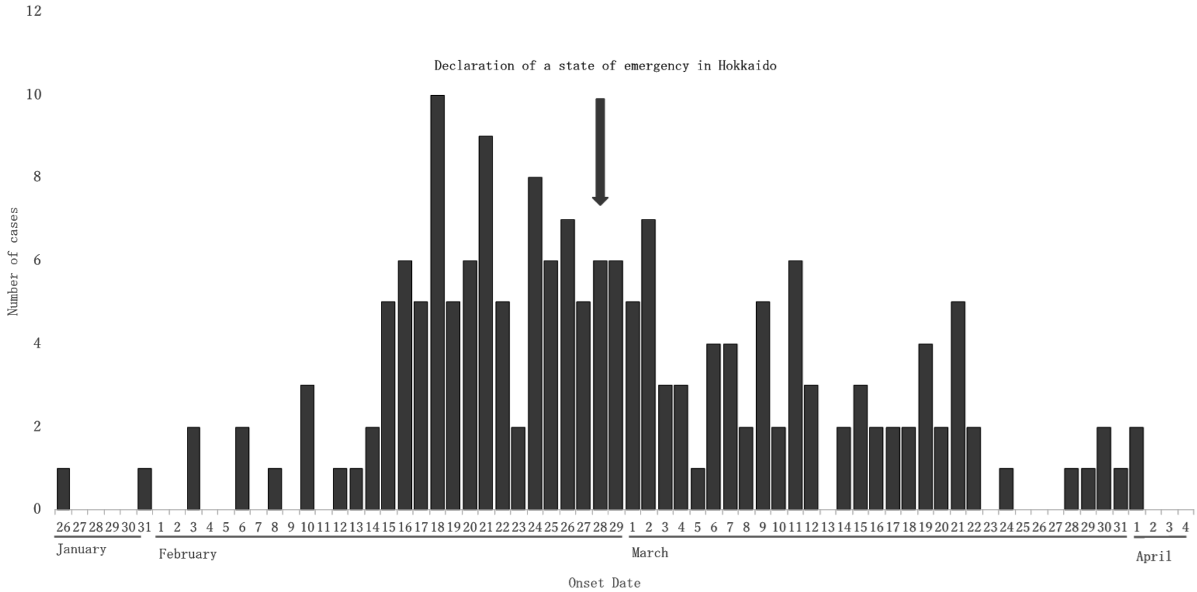

Figure 4. COVID-19 epidemic curve in Hokkaido. (Based on information from the Hokkaido Government website as of 12:00 on April 4, 2020.)

bad situation, the Mayor of Hokkaido independently declared a state of emergency on February 28 when the number of COVID-19 was 141 cases. At that time, the number was the largest in Japan. After the declaration, the number of new cases has decreased and the outbreak was successfully mitigated, although social distancing policy in Hokkaido was not as strict as lockdowns conducted in France, Italy, and the United States. Strong political commitment has been clearly demonstrated in Hokkaido. The Prime Minister of Japan declared a state of emergency at Tokyo, Kanagawa, Saitama, Chiba, Osaka, Hyogo, and Fukuoka prefectures on April 7 for one month, due to the steep increase of COVID-19 in these areas. The number of COVID-19 was over 3,000 cases around Tokyo area, and over 1,000 cases around Osaka area. There are some arguments that the declaration of Japan might be delayed. We need to watch and observe the trend of new cases during April 7 to May 6. In contrast, the number in Hokkaido was still stable at around 250 cases with some new cases in mid-April. The declaration of Hokkaido has been successful so far. However, further and intense social distancing is urgently needed to prevent a surge of patients.

The first consecutive 15 cases

We treated 15 cases until March 11. A summary of the cases is listed in Table 1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=3*). As described in case reports, 3 cases of COVID-19 who required endotracheal intubation and mechanical ventilation intubation experienced relatively mild symptom until just before admission. Eight to 11 days after the onset, oxygen therapy was started, and endotracheal intubation was required 1-3 days afterwards. As previously reported (*2*), our patients also rapidly deteriorated after oxygen administration became necessary. Risk factors for severe disease are elderly, underlying diseases (hypertension, diabetes mellitus, cerebrovascular diseases, *etc.*), lymphopenia, and increased inflammatory markers (*3,4*). In our hospital, all intubated patients were over 50 years of age, and had risk factors for severe disease such as hypertension or diabetes. In all three cases, lymphopenia and elevated inflammatory markers were seen. Based on clinical course of 15 cases in our hospital, among patients over 50 years of age, those who required oxygen administration tended to deteriorate.

At the time of this writing, antiviral drugs and ciclesonide are treatment options in Japan. In our cases, with the approval of the hospital ethics committee, and consent from patients or patients' family, antiviral drugs lopinavir/ritonavir and favipiravir were given based on guideline from The Japanese Association for Infectious Diseases and reports from China (*5,6*) until a subsequent study from China which revealed lopinavir/ritonavir might not be effective for COVID-19 (*7*). According to the guideline, antiviral therapy is indicated mainly for those who are older than 50 years of age and who require oxygen. Since patients who require mechanical ventilation usually progress rapidly, timing to give antivirals for patients with risk factors for severe disease should be further discussed. In addition, it has been reported that ciclesonide is also effective (*8*). We will use ciclesonide in patients with risk factors such as diabetes mellitus until further study results are available. According to package insert, combination of ciclesonide and lopinavir/ritonavir is not recommended due to drug interactions. Care must be taken when choosing drug combination therapy. Further studies are needed in safety, efficacy, and timing of those treatments.

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Early cases of COVID-19 in Tokyo and occupational health

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Abstract: The coronavirus disease 2019 (COVID-19) has spread rapidly across the globe, presenting severe challenges to societies. Gaining a better understanding of patient demographics is essential to develop measures to counteract such spreading. In this context, from a viewpoint of occupational health, we analyzed the publicly available data on patients diagnosed with COVID-19 in Tokyo, which reported the highest number of cases in Japan. A total of 243 cases aged 20 years or older (excluding students) were recorded between January 14 and March 27, 2020. Of 233 cases excluding 10 cases of the first cluster, 162 were men and 176 were of working age (20 to 69 years). Of 203 cases with valid information on employment status, 151 (74%) were workers: 114 employees, 31 self-employed, and 6 medical staff. Of the working patients, the majority were male: 72% in employed and 87% in self-employed. These data suggest the importance of occupational health in controlling the spread of COVID-19. In April 2020, a state of emergency was declared in response to a surge in the number of cases, especially in metropolitan areas. A working schedule associated with lower risks of infection, including telework and flexible working hours, should be rigorously promoted to minimize human-to-human contact. Such policies, along with the implementation of effective measures to protect essential workers from infection, overwork, and stigma, would ensure the smooth running of society amidst the present crisis.

***Keywords*:** COVID-19, emerging infectious disease, Tokyo, occupational health, infection prevention and control

Introduction

In December 2019, China reported a cluster of pneumonia cases of unknown cause in Wuhan, Hubei (*1*). Patients with this illness, now known as coronavirus disease 2019 (COVID-19), showing a wide range of symptoms such as fever, cough, and shortness of breath (*2*). As of March 31, 2020, World Health Organization announced 750,089 confirmed cases of COVID-19 globally, including 36,405 deaths (*3*).

In Japan, the first case of COVID-19 was reported by the Ministry of Health, Labour and Welfare on January 16, 2020, with the second case on January 24 (*4*). These two cases had visited or come from Wuhan. Then, the number of confirmed cases in Japan has been steadily increasing since the end of January (*5*), adding up to 1,953 cases and 56 deaths as of March 31, (*6*) and 6,656 cases and 171 deaths as of April 20 (*7*). The majority (over 70%) of the patients in Japan, as of March 30, 2020, were aged 20 to 69 years (*8*); the number of cases aged less than 20 years were relatively few (n = 46). In terms of the geographical distribution, the highest number of cases were recorded in Tokyo, which has high population density and mobility, both of which are possible risk factors of transmission (*9,10*).

Considering the important role of Tokyo in national and global economy (*11*), a better understanding of patient characteristics is needed for the implementation of effective infection prevention and control measures. The Tokyo Metropolitan Government has made basic data (*e.g.*, age, sex, residence, characteristics including employment status) of each confirmed case available on its website, uploading in a daily basis. However, to date, a detailed analysis of these basic patient characteristics is not available. In this report, we analyzed the publicly available characteristics of COVID-19 patients from Tokyo. Since the accumulating data suggest that the majority of these patients were of working age, we focused on adults and their employment status and discussed potential strategies to protect workers during the COVID-19 pandemic from the viewpoint of occupational health.

Methods

Study settings

We collected publicly available data on confirmed

Table 1. Characteristics of confirmed cases of COVID-19 in Tokyo between January 14 and March 27, 2020 (n = 243)

Characteristics	Employment status (n = 203)				Employment status unknown or missing (n = 30)	Cases in the first cluster* (n = 10)
	Employed† (n = 114, 56.2%)	Self-employed (n = 31, 15.3%)	Medical staff (n = 6, 3.0%)	Non-employed (n = 52, 25.6%)		
Age						
20 to 29 years	11 (9.7)	1 (3.2)	1 (16.7)	2 (3.9)	2 (6.7)	0 (0)
30 to 39 years	15 (13.2)	4 (12.9)	1 (16.7)	4 (7.7)	4 (13.3)	1 (10.0)
40 to 49 years	31 (27.2)	10 (32.3)	1 (16.7)	4 (7.7)	6 (20.0)	1 (10.0)
50 to 59 years	29 (25.4)	6 (19.4)	3 (50.0)	3 (5.8)	4 (13.3)	2 (20.0)
60 to 69 years	18 (15.8)	5 (16.1)	0 (0)	10 (19.2)	1 (3.3)	3 (30.0)
70 to 79 years	7 (6.1)	5 (16.1)	0 (0)	16 (30.8)	10 (33.3)	2 (20.0)
80 to 89 years	0 (0)	0 (0)	0 (0)	8 (15.4)	2 (6.7)	1 (10.0)
90 years or older	1 (0.9)	0 (0)	0 (0)	4 (7.7)	1 (3.3)	0 (0)
Missing	2 (1.8)	0 (0)	0 (0)	1 (1.9)	0 (0)	0 (0)
Sex						
Men	82 (71.9)	27 (87.1)	3 (50.0)	24 (46.2)	26 (86.7)	8 (80.0)
Women	32 (28.1)	4 (12.9)	3 (50.0)	28 (53.9)	4 (13.3)	2 (20.0)
Residence						
Tokyo	109 (95.6)	30 (96.8)	5 (83.3)	48 (92.3)	11 (36.7)	0 (0)
Not Tokyo	5 (4.4)	1 (3.3)	1 (16.7)	4 (7.7)	1 (3.3)	0 (0)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	18 (60.0)	10 (100)
Visited abroad	15 (13.2)	2 (6.5)	0 (0)	5 (9.6)	0 (0)	NA
Major symptoms‡						
Fever	103 (90.4)	28 (90.3)	4 (66.7)	41 (78.9)	7 (23.3)	1 (10.0)
Cough	62 (54.4)	20 (64.5)	6 (100)	27 (51.9)	2 (6.7)	1 (10.0)
Fatigue	39 (34.2)	5 (16.1)	0 (0)	12 (23.1)	0 (0)	1 (10.0)
Sore throat	8 (7.0)	2 (6.5)	0 (0)	2 (3.9)	0 (0)	0 (0)

Data are shown as number (%). NA, not available. *One medical staff was classified into this category, not in the category of "medical staff". 5 cases were taxi drivers and one was a worker of the houseboat. †Four executives were included in this category. ‡Persons with missing data on symptoms are included as denominator in each analysis.

cases of COVID-19 in Tokyo, Japan for the present descriptive analysis. Data for the period of January 14 to March 27, 2020 were collected. The source of the data is summarized in Supplementary Table 1. We also referred to a chronological list of patients in Tokyo that provides data on age, sex, and residence (*12*). The present study did not include the cases on the cruise ship "Princess Diamond" (*13*) and airport quarantine. Since we used publicly available anonymous data, ethical approval was not required for this work.

Official consultation process for COVID-19 diagnosis in Tokyo

The Tokyo Metropolitan Government announced the following procedures for patients to be tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using PCR. If a person who has family physician exhibited common-cold like symptoms, fever, and extreme fatigue or shortness of breath, or anxiety about COVID-19, he/she was advised to consult the family physician by phone. If COVID-19 was suspected, the patient was then referred to a specialized outpatient facility, where PCR testing was performed, if deemed appropriate. For people without a family physician, there were two options available for consultation. Those with common cold-like symptoms, fever, extreme fatigue, and shortness of breath lasting 4 days or more (2 days or more for high-risk individuals) could make a phone call to the consultation desk at a public health center. Then, the patient would be referred to an outpatient facility for PCR testing if necessary. Alternatively, anyone who feels anxious about COVID-19 due to light symptoms could call to the COVID-19 call center. If professional advice was required, he/she would then be referred to the consultation desk at a public health center. Detailed information on the consultation process for COVID-19 diagnosis in Tokyo is available at the official website of the Tokyo Metropolitan Government (*14,15*).

Variables

The age data were binned and reported as age groups (*e.g.*, <10 years, 10s, 20s, and so on). Since the original information on patient characteristics consisted of a mixture of employment status and occupation, we reclassified cases into the following five categories: employed, self-employed, medical staff, non-employed, and unknown or information missing. Company executive (n = 4) was classified into the category of employed. Medical staff was treated as a separate category as they are at a higher risk of infection.

For most cases, information on symptoms were concisely summarized; in some cases, the chronological development of symptoms was recorded. For such cases, we extracted information on the symptoms from the narrative description accompanying each case.

Information on close contact was available for the cases reported March 25, 2020 onward. Data on the travel history, particularly of visits abroad, were also extracted. It is to be noted here that definition of abroad (countries and areas) has been changed appreciably over time, based on the expansion of epidemic areas.

Data analysis

We conducted a descriptive analysis of the case characteristics (*e.g.*, age, sex, residence, and travel history, and symptoms) according to the employment status. As data on employment status or job were not available for some cases in the first cluster that occurred in mid-February, we counted this group separately. As a sensitivity analysis, we repeated the main analysis excluding cases resulting from close contact with COVID-19 patients because such cases were identified by active surveillance and may be different from those that were identified by other means.

Results and Discussion

Between January 14 and March 27, 2020, a total of 259 confirmed cases (179 men, 79 women, and 1 unknown) were officially reported in Tokyo, Japan (corresponding to 13.3% of the total COVID-19 case in Japan during that time period). The rate of increase in the cases in Tokyo accelerated after March 4 (see Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=4*); 219 cases (84.6%) were reported from that day onward. Of the 259 cases, we excluded 12 patients who were either aged less than 20 years or were students. We further excluded 4 cases: first 3 cases who lived in China and had traveled directly from there; and another case with no data on age, sex, and employment status, leaving a total of 243 adult cases for analysis.

As shown in Table 1, the ten cases were from the first cluster including five taxi drivers, one worker of a houseboat, and one medical staff. Of 233 cases excluding those in the first cluster, 162 (69.5%) were men and 176 (75.5%) were of working age (20 to 69 years). Out of the 203 cases with information on employment status, 151 (74.4%) were workers. Of these, 114 (56.2%) were employed, 31 (15.3%) were self-employed, and 6 (3.0%) were medical staff. The majority of patients with a job were men: 82 (71.9%) of employed and 27 (87.1%) of self-employed, respectively. Twenty-two cases had a recent history of visits abroad; of these, 19 cases were reported after March 21, 2020. The characteristics of 197 cases without close contact to other COVID-19 patients were similar to those in the entire group of adult cases (Supplementary Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=4*).

The present data showed that 74% of adult patients diagnosed with COVID-19 in Tokyo until March 27, 2020 were workers, indicating the importance of occupational health in controlling COVID-19 spread. This figure may reflect the proportion of workers in Tokyo (*11*). Nevertheless, workers in the metropolitan area were expected to have a greater chance of close human contact while working in offices and other settings, commuting to work, and doing activity on leisure; therefore, they were deemed to be at a higher risk of the infection and transmission. According to a nationwide online survey among 24,097,701 LINE users aged 15 years or more conducted in the period ranging from March 31 to April 1, 2020 (*16*), individuals in occupations with high risk of infection (*e.g.*, jobs with difficulties in avoiding crowded or enclosed spaces, or close contact with people) reported having fever more frequently than those in other occupations.

On April 7, 2020, the Government of Japan declared a state of emergency in response to a surge in the number of COVID-19 cases, especially in the metropolitan areas. Meanwhile, the Ministry of Health, Labour and Welfare has requested the bodies of labor and management to promote preventive measures at workplace by showing examples of such measures as well as checklist (*17*), and academic societies have updated practical information on the protection of workers against COVID-19 while continuing business in essential services (*18*). In this context, both employers and employees are expected to rigorously implement multiple measures tailored for each occupation and workplace to ensure that the state of the emergency declared by the government is implemented properly.

Of measures against the spread of COVID-19, remote work can drastically decrease the human-to-human contact associated with work and commuting. Under the current emergency condition, telework is strongly recommended for workers engaging in non-essential service. A survey in March, 2020 reported that 26% of companies introduced telework (*19*), and this figure seems improved in April (*20*). In Tokyo, 99% companies comprise of small- and medium-scale (*11*), which may not have sufficient monetary and human resource to implement these measures against COVID-19. The Ministry of Health, Labour and Welfare (*21*) and the Tokyo Metropolitan Government (*22*) have initiated programs that provide financial and technical supports to encourage teleworking in small and medium enterprises. Such support schemes are expected to ensure an increase in the rate of implementation and popularization of teleworking in Japan during the course of the pandemic.

The present data included only 6 cases of medical staff. After March 27, 2020, large-scale nosocomial infections have been reported in Tokyo (*23-25*). Such outbreaks led higher risks of scaling or shutting down hospital facilities. Thus, it is crucially important to protect frontline health care workers (*26*). The basic measures include engineering controls (*e.g.*, appropriate air-handling system), administrative controls (*e.g.*, measures preventing bringing infection from outside, interval regulations for sleep hygiene, and educational [such as hand-hygiene], behavioral, and psychological support), and providing sufficient alcohol-based hand rubs and personal protective equipment (*27*). Additionally, there is an increasing concern about stigma toward health care workers, and this situation should be corrected by improving the public discourse around COVID-19 and educating the public on COVID-19 transmission, prevention, and control (*28*). These measures could be extended to workers in government sectors responsible for the response to COVID-19 and those in essential services (*e.g.*, energy, emergency services, food and agriculture, water, transportation and logistics, communication and information technology, schools, financial services, *etc*.).

In the present dataset, 19 of the 22 cases with a travel history of visits abroad were reported in late March, consistent with the global surge in infected patients during this month. This might be attributed to both business trips and sightseeing during the spring vacation. As of March 31, the Ministry of Foreign Affairs urged Japanese nationals to avoid all travel to 73 countries and regions and advised to avoid non-essential travel for the rest of the world (*29*) and the Ministry of Health, Labour and Welfare requested all individuals returning from overseas should stay at a designated place (*e.g.*, home) for 14 days (*30*). On April 24, the Ministry of Foreign Affairs further raised the travel alert in 14 countries. Careful follow-up of such updated restrictions on overseas travel is required to protect workers and our society against the forthcoming third and fourth waves of COVID-19 from overseas epicenter.

In conclusion, three-quarters of the adult COVID-19 cases in Tokyo till March 27, 2020, comprised of workers, suggesting the importance of implementing occupational health measures in protecting the national and global socioeconomic scenario from ramifications of COVID-19. Given the rapidly increasing number of infected cases in both Tokyo and other prefectures, more rigorous measures should be adopted to protect essential workers against COVID-19 infection, overwork, and stigma. This, along with the implementation of a work style, including teleworking and stay at home policies, ensuring lower risks of infection for people with other occupations, would ensure the smooth progression of society during these challenging times.

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Rapid spread of COVID-19 in New York and the response of the community

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Abstract: The first COVID-19 patient in New York (NY) was reported on March 1, 2020. Since then NY has become one of the largest epicenters in the world where the disease has been overwhelming the healthcare system. Here I report how rapidly COVID-19 spread, and how the community responded during the first 30 days in NY. Gathering reliable information quickly was important in the evolving situation. Shortage of beds, personal protective equipment, ventilators, and staffing was observed. Reducing the number of infections and increasing the efficiency of medical resource allocation have been two major strategies taken in NY. It is important for Japan to accurately analyze the current situation, refer to answers in other parts of the world, and quickly establish strategy for clear goals that will lead to a "New Normal".

***Keywords*:** COVID-19, New York, New Normal

Introduction

The global outbreak of novel coronavirus (SARS-CoV-2) was begun in Wuhan, China, in December 2019 (*1*). The first United States (U.S.) case was in Washington State (*2*), reported on January 20, 2020. The disease was named COVID-19 by World Health Organization on February 11 (*3*). In the U.S., the alertness was firstly raised on the West Coast. However, shortly thereafter, a rapid spread hit the East Coast hard, and New York City (NYC) has been one of the largest epicenters in the world where the disease has been overwhelming the healthcare system. As of April 15, total global deaths reached 137,193 and the deaths in New York State (NYS) counted 11,586, which is 43% of 26,708 U.S. deaths (*4*). Here I report how rapidly COVID-19 spread, and how the community responded during the first 30 days in New York (Figure 1). I also discuss which sources of information were useful, and what Japan should prepare.

March 2020 of New York

The first COVID-19 patient in NYS was reported on March 1, forty-one days after the disease reached the U.S.. This got widely known in the Japanese community in New York by an email from the Consulate General of Japan in New York issued at late night. That was the beginning. Three days later, on March 4, eleven people were reportedly test-positive and several schools related to the patients shut down. New Yorkers in the 5 Boroughs (Manhattan, Queens, Bronx, Brooklyn, and Staten Island, which constitute NYC) did not take the situation seriously because 10 out of 11 patients lived outside the City. At that time, NYC recommended *i*) staying home if feeling sick, *ii*) covering the sneezes and coughs with the sleeve, and *iii*) washing hands often, to prevent the spread of any virus. Mount Sinai Health System held the first town hall meeting on COVID-19 on March 4 in an auditorium of the hospital. This town hall was broadcasted via the web, but for those who could not leave their workplace, not for "social distancing". Other university hospitals in NYC banned domestic business travels of their employees.

NYS declared the State of Emergency on March 7 when test-positives tolled 11 (NYC) and 76 (NYS). Majorities of test-positives were the residents in Westchester County. New Rochelle, Westchester was designated as a containment area because there was the largest cluster of patients. The state authority seemed to try to track all contacts of patients at that time. On March 12, all Broadway theaters, Carnegie Hall, and Metropolitan Opera went dark with the State of Emergency of NYC. Museums including Metropolitan Museum closed, and all sports games after that day were canceled. This abruptly raised the alertness of people in the City. The numbers of cases were 96 (NYC) and 325 (NYS) on March 12, which were increased by more than 1.5-fold every day, and the number reached 269 (NYC) and 613 (NYS) on March 14. This rapid increase prompted me to start collecting COVID-19-related information. I supposed that Twitter (twitter.com) was the best tool because the spread should be exponential and very rapid in its nature and Twitter was a suitable channel for real-time information. Mayor of NYC Bill de Blasio tweeted on Sunday, March 15 – "We need to treat this like wartime – and we have a simple mission: protect the people most vulnerable and protect our health care system" (*5*). There were 329 (NYC) and 729 (NYS) patients, and the deaths were reported for the first time – 5 in NYS. NYS Governor Andrew Cuomo stated that there was an urgent need for more ICU beds. NYS urgently expanded the testing capacity of SARS-CoV-2 nucleic acid for COVID-19. The wartime began in NYS only after two weeks from the first case.

In the week of March 16, several key measures were announced in a flash. All public schools were shut down on Monday. Bars and eating-in at all restaurants were prohibited from Monday night, earlier than originally announced. Icahn School of Medicine at Mount Sinai announced that all non-essential researches should be ramping down by Friday. By the end of this week, Cuomo stated "potential staffing shortages (*6*)", and "critical need for Personal Protective Equipment (PPE) including gloves, gowns and masks — as well as ventilators (*7*)". The numbers of test-positives in NYC and NYS were 1,871 and 2,914 on March 18, and increased to 5,683 and 8,516 on Friday, March 20, respectively. On March 20 Cuomo announced the "New York State on PAUSE" executive order (Table 1) (*8*), a 10-point policy including "All non-essential businesses statewide will be closed by March 22", and "When in public individuals must practice social distancing of at least six feet from others", which has been considered as the beginning of so-called "lockdown" of NYS and NYC – currently ongoing.

Figure 1. Pictures of Manhattan in the evolving situation. (A), Times Square, March 16, 2019; **(B)**, Times Square, March 15, 2020; **(C)**, Times Square, March 22, 2020; **(D)**, Grand Central Terminal, March 17, 2020; **(E)**, Rockefeller Plaza, March 22, 2020. Picture (A) was before COVID-19, pictures (B-E) were after COVID-19. All pictures were taken by the author.

The last 10 days of March saw a mix of number of rumors and official annoucements fly. On March 21, NYS announced the purchase of 1 million N95 masks for NYC, 500,000 for Long Island, and an additional 6,000 ventilators statewide, and at the same time, Twitter showed that some hospitals were running out of PPE/ventilators and healthcare providers were scared. In addition, on Monday, March 23, it was reported that one emergency department in NYC was experiencing 1-2 tracheal intubations per hour, and several sources reported that the ICU beds in NYC were almost full. For staffing shortages, along with the recruitment of retired healthcare providers, New York University and Department of Defense announced that they let their medical students graduate early to help the COVID-19 frontline. Key statistics of NYS were released on March 27. To prepare for the "apex" or the maximum load in about 21 days, 140,000 COVID-19 beds and 40,000 ICU beds were needed, but only 53,000 and 3,000 were available at the moment, while needed 20 million N95 masks and 30,000 ventilators, but only about 1.5 million and several thousand respectively. These statistics provided a straightforward road map to save and maintain the local healthcare system and eventually the lives of New Yorkers. With the clear numbers, people recognized the vital items and numbers under the shortage and were facilitated to unite each other to

Table 1. New York State on PAUSE (*8*)

The 10-point NYS on PAUSE plan is as follows:	
1	Effective at 8PM on Sunday, March 22, all non-essential businesses statewide will be closed;
2	Non-essential gatherings of individuals of any size for any reason (*e.g.* parties, celebrations or other social events) are canceled or postponed at this time;
3	Any concentration of individuals outside their home must be limited to workers providing essential services and social distancing should be practiced;
4	When in public individuals must practice social distancing of at least six feet from others;
5	Businesses and entities that provide other essential services must implement rules that help facilitate social distancing of at least six feet;
6	Individuals should limit outdoor recreational activities to non-contact and avoid activities where they come in close contact with other people;
7	Individuals should limit use of public transportation to when absolutely necessary and should limit potential exposure by spacing out at least six feet from other riders;
8	Sick individuals should not leave their home unless to receive medical care and only after a telehealth visit to determine if leaving the home is in the best interest of their health;
9	Young people should also practice social distancing and avoid contact with vulnerable populations;
10	Use precautionary sanitizer practices such as using isopropyl alcohol wipes.

fight against the COVID-19 pandemic which was still going up the mountain to the apex. Clear goal setting by the leader with strong leadership was critical to the emergency situation.

What happened and what was done

In NYC, the situation progressed from the work-from-home order for non-essential workers to the shortage of ICU beds in a very short period of time, less than a week. During this time, four bad things progressed in NYC hospitals. The first was the shortage of PPE (N95 masks, surgical masks, medical gowns, *etc*.), which was supplemented by massive donations from various organizations and global companies. Extended use or even reprocessing of N95 masks was done under a policy of each hospital. Second, there has been a definite shortage of ventilators, which has been replenished by global sourcings and the establishment of new production lines. Ventilators for large animals were converted to human use. Some anesthetic machines were also utilized as ventilators. Even using one ventilator for two patients has been considered. Third, there has been a shortage of beds, mainly ICU beds. This has been supplied by both increasing the capacity and reducing the demand. The bed capacity was increased, by building eight temporary hospitals in the New York metropolitan area through a close collaboration between the NYS and the Federal Emergency Management Agency, by converting hotel rooms to beds, by constructing medical tents in such as Central Park, and by doubling the number of ICU beds of each hospital. Reducing the load to hospitals was achieved by ordering people with mild to moderate symptoms to stay home until they got severe. The fourth and last was the shortage of medical personnel. This was responded to by bringing in retired healthcare providers, recruiting healthcare providers from other States, expediting medical school graduations, and even sending research trainees and medical students to the field as auxiliary personnel. Even when a healthcare provider comes into close contact with COVID-19 patients, it has been often the policy to continue working as long as he or she is asymptomatic.

The NYS public health administration has responded to the COVID-19 outbreak in two major ways. Firstly, policies have taken place to reduce the spread of COVID-19, as summarized in "New York State on PAUSE (*8*)," intended to reduce interpersonal contacts, focusing on "social distancing." Secondly, policies to expand and replenish the health care system in response to the rapid growth in the number of patients. The policy covered facilities, beds, staffing, ventilators, PPE, COVID-19 testings, and new treatments. NYS announced that its Central Coordinating Team would manage those issues of the healthcare system of the state (*9*), seeking help from the federal government.

Living in an evolving situation

In an evolving situation, gathering reliable information quickly is important. At the same time as the press conference by Governor Cuomo, public information was tweeted from him, allowing us to quickly and accurately learn about upcoming policies and when they would come into effect. The press conferences were also sent out live on Twitter, allowing us to learn the number of patients, ICU admissions, tracheal intubation, deaths, and hospital discharges that day. It was emphasized by Cuomo that these statistics were important for health care policymaking in the evolving situations, and he gave a relatively logical explanation of how he reasoned from those statistics to make decisions. Moreover, Cuomo gave New Yorkers strong messages to encourage them in the difficult situation. I believe that this consistency has fostered an atmosphere of unity, where people cooperate with each other and appreciate the healthcare providers.

I personally gathered information to find out two things – *i*) the spread of COVID-19 and *ii*) whether the health care infrastructure was likely to collapse. For these purposes, I started to follow City of New York (@nycgov), Mayor Bill de Blasio (@NYCMayor) and Andrew Cuomo (@NYGovCuomo) because the statistics they published were also useful for my analysis of the ongoing situation. As they retweeted other useful public sources, I added those accounts to my asset. Tweets from non-medical people living in NYC area were also very helpful. They provided the atmosphere of every part of the city, and even provided the information, from a friend healthcare provider, that what was going on in the emergency department. Of course, this kind of hearsay is often inaccurate, so I checked the bio of the account and treated the information as a clue to be aware of similar observations. Importantly, at the very beginning of the surge, healthcare providers did not post much on Twitter or Facebook because they were under institutional social media policy and did not have time to post.

For the future of New York and Tokyo

The number of patients in Tokyo is still certainly on the rise, although it is difficult to predict whether Tokyo and other parts of Japan will experience medical resource depletion at a similar speed to what happened in NYC. The measures taken in NYC, such as reducing the number of infections and increasing the efficiency of medical resource allocation, are certainly necessary in Japan. Beds, PPE, ventilators, and staffing may be in short supply, thus there is a need for adequate preparation by government and administrative leadership. As of April 15, NYS appears to have reached the apex, and will someday enter a phase of cautious PAUSE mitigation. Governor Cuomo insisted that NYS on PAUSE would continue for another month or so, during which time he would work with neighboring states to *i*) control the spread of infection, *ii*) strengthen hospital functions, *iii*) establish a testing and tracking system, and *iv*) consider a "New Normal".

Fortunately, we have some answers on how to fight COVID-19 all over the world. Under strong leadership, it is important for Japan to accurately analyze the current situation, refer to those answers, and quickly establish strategy for clear goals that will lead to a "New Normal".

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Nursing care for patients with COVID-19 on extracorporeal membrane oxygenation (ECMO) support

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Abstract: In Japan, four medical facilities including our own - the National Center for Global health and Medicine (NCGM) - have been designated for the treatment of specified infectious diseases by the Minister of Health, Labour, and Welfare. Here, we report our nursing care for patients with severe COVID-19 on extracorporeal membrane oxygenation (ECMO) support. In addition to infection control measures in the form of an N95 mask, a water-repellent isolation gown, a cap, a shielded mask on top of the N95, and double-layered gloves, nurses were required to wear one-piece suits (DuPont™ Tyvek®) and use powered air-purifying respirators (PAPRs). While closed system catheters are normally changed once a day to limit aerosol exposure, they are now changed once every 4 days. Nursing care included equipment checks, monitoring of hemodynamics and respiratory status, management of anticoagulants, observation of the patient's general condition, management of sedatives and analgesics, prevention of medical device-related pressure ulcers and bedsores, and maintenance of hygiene. Fundamentally sound nursing remains the best practice for patient treatment and management. During nursing care for patients with COVID-19 on ECMO, infection control measures should be faithfully and properly followed.

***Keywords*:** COVID-19, ECMO, nursing care, personal protective equipment

Medical facilities for specified infectious diseases in Japan

In Japan, four medical facilities have been designated for the treatment of specified infectious diseases by the Minister of Health, Labour, and Welfare. Medical facilities for specified infectious diseases are hospitals that accept patients with new infectious diseases: Class 1 infectious diseases, such as Ebola hemorrhagic fever, and Class 2 infectious diseases, such as Middle East respiratory syndrome (MERS) or pandemic influenza (*1*). The National Center for Global health and Medicine (NCGM) has been designated as a medical facility for specified infectious diseases and is home to four of ten such beds available nationwide. These four beds are in the New Infectious Diseases Ward (NIDW), which is opened only when patients with the diseases in question are admitted for treatment. The NIDW is staffed by two full-time infection monitoring room nurses and 24 nurses who work there in addition to their usual ward duties. A certified infection control nurse who works full-time in the infection monitoring room is the leader of the ward, and all nurses who work there meet once per month to exchange information, review manuals, and practice putting on and removing personal protective equipment (PPE). Moreover, nurses meet with government officials and personnel from other hospitals three times a year to participate in simulations to prepare for patient admittance.

To date, the NIDW at NCGM has admitted patients with pandemic influenza, severe acute respiratory syndrome-like diseases, Ebola hemorrhagic fever, and MERS-like diseases. Reported here is the nursing care for patients with severe COVID-19 on ECMO support receiving treatment in the NIDW of our center.

ECMO

ECMO is a life-support technique that involves the use of a heart-lung machine; when used in patients with severe respiratory failure, it is called respiratory ECMO. Cases in which ECMO was used to save lives were reported during the pandemic outbreak of H1N1 influenza in 2009 (*2,3*). That same year, the CESAR Study (*4*), a randomized clinical trial of respiratory ECMO, proved its effectiveness, leading to the acceptance of ECMO worldwide.

The effectiveness of ECMO as a therapy for COVID-19 has not yet been established, but there are reports of it saving lives in severe cases (*5-7*), and emergency guidelines have been promulgated (*8,9*).

Nursing system for patients on ECMO support in NIDW

Treatment of respiratory failure *via* ECMO requires specialized knowledge and training for not only doctors but also nurses, clinical engineers, and several other staff members (*10,11*). ECMO is known to improve the prognosis for patients in facilities that have used it in more cases (*4*); this therapy requires considerable experience and skill on the part of the medical team administering it.

The NIDW opens only when necessary, the NIDW nurses are normally posted to a variety of different wards, and most do not normally oversee intensive care. Thus, ICU nurses who were experts in ECMO were asked to provide support, and they contributed in setting up the NIDW quickly. Over the several days that it took the patient to stabilize following the introduction of ECMO, these ICU nurses worked alongside NIDW nurses. They helped teach monitoring methods and nursing techniques and reviewed and updated our equipment and rules. Moreover, NIDW nurses were instructed by clinical engineers on how to use the ECMO machine and learned how the machine works and basic troubleshooting procedures.

Use of ECMO lasted three weeks, thus, the head nurse gathered all expert nurses within the hospital and adjusted their schedules so that they could rotate through the NIDW in shifts. Initially, the patient was managed by a small team to limit contact with others. However, as the situation developed and ECMO management was projected to become more long-term, work assignments were adjusted so that nurses who work in the NIDW in addition to their duties in other wards could all oversee the management of this patient. These nurses were posted alongside expert or experienced nurses who had managed many patients and who worked to ensure patient safety. This helped assuage the worries of nurses with limited experience.

Infection control measures

The entire situation was managed by a certified infection control nurse, a full-time member of the hospital infection monitoring room. Monitoring is important (*12*). Patient vital sign monitors and feeds from cameras installed in the sickroom, antechamber, and testing room were all linked to the monitoring room so that nurses could ensure that proper infection control measures were being followed. Personal protective equipment used included the following. For normal care, nurses used N95 masks, water-repellent isolation gowns, caps, a shielded mask on top of the N95, and double-layered gloves. During intubation, extubation, and insertion/removal of the ECMO cannulae, all of which are treatments likely to generate aerosols, nurses were additionally required to wear one-piece suits (DuPont™ Tyvek®) and use powered air-purifying respirators (PAPRs). Finally, while closed system catheters are normally changed once a day to limit aerosol exposure, they were changed once every 4 days. Although closed system catheter replacement can be done instantly, for safety, nurses wore PAPRs while performing this procedure (Table 1).

Nursing care for patients with COVID-19 on ECMO support

Nursing care for COVID-19 patients on ECMO support involves a wide variety of different tasks, including equipment checks, monitoring of hemodynamics and respiratory status, management of anticoagulants, observation of the patient's general condition, management of sedatives and analgesics, prevention of medical device-related pressure ulcers and bedsores, and maintenance of hygiene (Table 2). Because the nature of this case required all these tasks to be done with PPE, nurses experienced much more fatigue than usual. Water-repellent isolation gowns cause sweating with even the smallest tasks, and breathing through an N95 mask feels labored and restricted. Double-layered gloves dull one's sense of touch, requiring far more concentration than usual when performing delicate tasks. The hood that is worn when using a PAPR machine presses tightly against the head when worn for long periods. Moreover, because infections are known to most commonly occur while removing PPE, nurses rotated shifts before they became too tired to prevent them from losing concentration so that they would adhere to proper equipment removal procedures.

Because the patient's family was also quite worried about the patient's health, they met regularly with a supervising doctor (*13*). For the patient to remain connected with loved ones while in isolation, we arranged for the use of a smartphone to allow calls and the exchange of messages.

Apart from the need to use PPE at all times and to be mindful of sterile practices, there were no differences in the protocol used here from the usual ECMO management procedures, and no special care was needed to treat this patient with COVID-19.

Conclusion

Reported here is the nursing care for patients with severe COVID-19 that involved the use of ECMO. These patients require more nursing care (*14*), the patients' condition were managed while adhering to strict infection control procedures to prevent transmission of COVID-19. This work caused a significant amount of physical and mental stress. Despite the fact that patients on ECMO need a great deal of bedside nursing, at present there have been no cases of infection among the healthcare staff at our facility. A nurse is charged with providing all patients, regardless of illness or condition, with safe, comfortable care, to attend to their needs so that they can draw on their own strength, and to

Table 1. Personal protective equipment for treating patients with COVID-19 on ECMO support

Type	Normal	Special
Situation	• Normal care	• Performing invasive procedures • Performing an aerosol-generating procedure
Ex.	• Checking vital signs • Sponge bath • Changing the patient's body position • Oral care • Closed-system suctioning	• Changing the "closed suction system" (every 4 days) • Assisting with intubation & extubation • Assisting with the insertion & removal of ECMO cannulae
Photo		
Equipment	• Disposable scrub brush • N95 • Water-repellent isolation gown • Surgical mask with face shield (on the N95) • Double gloves • Cap	• DuPont™ Tyvek® • Surgical mask • Cap • Hood with integrated head suspension • Powered air-purifying respirator • Isolation gown • Double gloves • Foot cover

ECMO, extracorporeal membrane oxygenation.

Table 2. Nursing care for patients with COVID-19 on ECMO support

Items	Initiation of ECMO	Continuation of ECMO	ECMO weaning, decannulation
Nursing management	Mainly ICU nurses manage the patient Day shift: 3 nurses Night shift: 2 nurses Education for Nurses Explanation of equipment from a clinical engineer Distribution of leaflets prepared by a nurse certified in intensive care	New nurses work with experienced nurses Expert nurses work at regular intervals Day shift: 3 nurses Night shift: 2 nurses Ensure a smooth handoff with a note	Day shift: 3 nurses Night shift: 2 nurses Ensure a smooth handoff with a note
Nursing Care	Monitoring ECMO Ensuring a sufficient flow rate Monitoring ventilation Checking vital signs Management of sedation Preventing MDRPUs (medical device-related pressure ulcers) Hygiene and personal care Providing comfort care	Monitoring ECMO Ensuring a sufficient flow rate Monitoring ventilation Checking vital signs Management of sedation Preventing MDRPUs (medical device-related pressure ulcers) Hygiene and personal care Providing comfort care Mobilization	Monitoring ECMO Ensuring a sufficient flow rate Monitoring ventilation Checking vital signs Management of sedation Preventing MDRPUs (medical device-related pressure ulcers) Hygiene and personal care Providing comfort care Mobilization Preparation for removal of ECMO
Family support	Family meeting Explaining the purposes and trajectory of ECMO and its time-limited nature	Family meeting Discussing where we have been, what the present looks like, and time-limited trials Family meets with the patient *via* video call	Family meeting Explaining the likelihood of recovery risks Family meets with the patient *via* video call

ECMO, extracorporeal membrane oxygenation.

perform management and monitoring with the necessary technology and equipment; this exhortation continues to hold true for patients with COVID-19. If basic infection control measures are faithfully and properly adhered to, we believe that there is no need to be unduly afraid of COVID-19.

While there will certainly be more patients with COVID-19 in the coming months, our experience taught us that fundamentally sound nursing remains the best practice for patient treatment and management.

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LETTER

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WORLD REPORT SERIES

Japanese strategy to COVID-19: How does it work?

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Abstract: Despite substantial inflow of infected cases at the early stage of the pandemic, as of the end of April, Japan manages the outbreak of COVID-19 without systematic breakdown of health care. This Japanese paradox – limited fatality despite loose restriction – may have multiple contributing factors, including general hygiene practice of the population, customs such as not shaking hands or hugging, lower prevalence of obesity and other risk factors. Along with these societal and epidemiological conditions, health policy options, which are characteristic to Japan, would be considered as one of the contribution factors. Some health policy factors relatively unique to Japan are described in this article.

***Keywords*:** COVID-19, Japan, social distancing, "soft-landing"

Due to geographical proximity, there has been a substantial number of inflows of people from Wuhan Province, China – epicenter of COVID-19 epidemic at the early stage of pandemic – to Japan before travel restriction was imposed to Wuhan on 23 January 2020. Total of more than 18,000 visitors arrived to Japan from Wuhan by air during 30 December 2019 to 22 January 2020 by 23 scheduled air flights per week (*1*). The prevalence of COVID-19 among Japanese evacuees from Wuhan, where 14 out of 826 tested cases were positive (1.7%) (*2*), indicates that a considerable number of infections had already existed in Japan as early as January.

Despite this substantial inflow of infected cases at the early stage of the pandemic, as of the end of April, Japan manages the outbreak of COVID-19 without systematic breakdown of health care. Moreover, this has been achieved with relatively loose restriction on social activity. So far, Japan does not impose lock down as observed in many parts of Europe and the United States (U.S.). What element of Japanese policy contributed to controlling the outbreak while avoiding tough restriction on social activity, and will it continue to work?

Basically, Japan has several difficult conditions in terms of COVID-19 control, compared to other countries. In addition to geographical proximity to Wuhan that allowed inflow of infected cases at the early stage as mentioned above, Japan's population density, with its living conditions, office environments and crowded commuting trains all contributed to the transition of the disease. Japan also has smaller number of ICU and PCR laboratory capacity per population, compared to other industrialized countries (*3*). From a policy perspective, Japan has limited political options for enforcement of lock down, which has not yet been implemented as of the end of April. In addition, as COVID-19 disproportionately affects senior populations (*4*), Japanese demographic reality – one of the most aged societies in the world – makes our response more challenging.

In spite of these preconditions, the number of reported cases of deaths due to COVID-19 remains far less than other countries (413 as of 29 April 2020). While there may be a certain number of unreported cases due to lack of proper diagnosis, this would be common in all countries, and there is no reason to suspect that underreporting in Japan is higher or systemic compared to other countries. As a result, access to healthcare for those in need, especially severe cases that requires intensive respiratory care, has not yet hampered in a systematic manner.

This Japanese paradox – limited fatality despite loose restriction – may have multiple contributing factors, including general hygiene practice of the population, customs such as not shaking hands or hugging, lower prevalence of obesity and other risk factors. Along with these societal and epidemiological conditions, health policy options which are characteristic to Japan, would be considered as one of the contribution factors. While all countries take common approaches – testing, treatment, isolation, social distancing, *etc*., – there are certain health policy factors relatively unique to Japan as described below.

Firstly, practicing conventional and basic public health measures by the local health center. By law, health centers – approximately there are 600 health centers nationwide, or one per 200,000 population in average – are responsible for identification, contact tracing, arrangement of health care and reporting of each case (*5*). Through these steady and routine works at each community level by public health nurses and other front-line health professionals, they succeeded in identifying clusters of infections and taking measures to contain them.

Secondly, the political leaders provided a straightforward and clear message for all nationals. The message of what to do and why were repeatedly conveyed to citizens for their understanding and behavioral change. More specifically, a new terminology of "San-mitsu" – three concentration in terms of closed spaces, crowded places, and close-contact settings – was generated so as people to avoid it (*6*). The political leaders and experts joined efforts to repeat this simple message to reduce the social contacts by 80% to mitigate the spread of the epidemic.

This simple message was successfully reached to many citizens. For example, an expert who developed a projection model to offer the background of 80% reduction appeared frequently with the political leaders and he became a familiar and popular figure and even is called "80% uncle". The measurable 80% reduction in social contact has become a widely shared target across the society. By doing so, we are hopeful to achieve a similar effect of "lockdown", avoiding legal enforcement adopted by the U.S. and European nations.

Third and lastly, allocation and coordination of the optimal use of hospital beds at community level is functioning through the joint effort coordinated by local authorities. For example, the public health bureau of the Tokyo Metropolis, updates all admitted COVID-19 cases in about 300 hospitals and availability of hospital beds in daily bases, as an effort to monitor the demand and supply of hospital beds in the respective area. At the same time, 31 health centers report all newly infected cases with assessment of need and urgency of hospitalization. These enable the Tokyo Metropolis government to launch a coordination mechanism to request an appropriate hospital to take suitable patients, taking account of individual condition and location of residency, and then transportation is also arranged. Those who demonstrate no or mild symptoms and require no oxygen therapy, are accommodated in the hotels or facilities rented by the Tokyo Metropolis in order to monitor the health conditions of infected cases without putting unnecessary burden on the health care facilities. All these government efforts enable us to monitor the health condition of individual cases and to secure hospital beds and transportation services, resulting in the maximum use of potential capacity of local health and medical resources.

It was February when the outbreak of COVID-19 started and is expected to continue for at least several more months. We do need not to be complacent so as to continue to be successful in managing the epidemic and avoid the collapse of the health system. So far, by the end of April, the declaration of national emergency seems effective in reducing the trend of new reported cases. Therefore, the maintenance of above three measures and adjusting the degree of social distancing to balance the public health needs and maintenance of socioeconomic activities is critical. If we can achieve the optimal balance, Japan truly offers a best practice of "soft-landing" of handling this epidemic, with minimizing the adverse effects on society and economy.

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Response to the COVID-19 epidemic: a report from Shenzhen, China

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Abstract: The whole world is now facing an unprecedented pandemic with over 1.8 million confirmed cases and more than one hundred thousand deaths. To counter the pandemic, Shenzhen created a central command and control structure based on the only designated hospital- Shenzhen Third People's Hospital which is a large general hospital specialized on infectious diseases in the bay area. The hospital has taken many decisive and effective actions to respond to the epidemic. Here, we will describe and share healthcare experiences from Shenzhen and call for international cooperation and collaboration.

***Keywords*:** COVID-19, public health emergency, Shenzhen, China

Once the lockdown of Wuhan ended on April 8th, efforts to combat COVID-19 in China have earned a stage achievement. The entire process of fighting the epidemic is a huge test for the Chinese healthcare system. As an extremely large city in the Guangdong-Hong Kong-Macau Greater Bay Area, Shenzhen has a large number of residents and migrant workers from Hubei Province, and the need for epidemic prevention and control has brought enormous pressure on the city. Shenzhen Third People's Hospital is the only designated hospital for COVID-19 epidemic in the city, and it is also the "National Clinical Research Center for Infectious Diseases" (*1*). The first patient infected with COVID-19 was admitted on January 11, 2020; this was the earliest family-concentrated case in Guangdong Province. This case provided direct and solid evidence for the existence of person to person transmission and thus blew the whistle in the whole province.

As of the afternoon of April 11, 456 COVID-19 cases have been seen at the hospital, involving 225 males and 231 females (Figure 1A). A total of 423 patients were discharged from the hospital and 3 patients died, representing a mortality rate of 0.65%. That rate was significantly lower than the rate reported in other areas of China affected by COVID-19 (*2*). Moreover, there were "no infections" among medical personnel.

In order to deal with a potential epidemic, the hospital vacated 1,000 beds, and built an emergency hospital area similar to Wuhan Huoshenshan Hospital, providing more than 1,000 beds of reserves (Figure 1B); Shenzhen Health Commission and the hospital prepared seven extracorporeal membrane oxygenation (ECMO) machines to save the lives of severely ill patients. The hospital was also the first to use antibodies extracted from the plasma of recovered patients as well as lung transplantation to treat severe cases, and this approach has yielded good results (*3,4*). At the same time, Shenzhen Third People's Hospital organized and summarized its clinical experience in the Shenzhen version of COVID-19 diagnosis and treatment guidelines based on national and provincial treatment protocols for COVID-19. In addition, the Shenzhen version has been constantly updated and adjusted in accordance with changes in clinical practice. Furthermore, Shenzhen Third People's Hospital released a new version of the guidelines for newborns, infants, and children and an English version to share Shenzhen's experience with the world (Figure 1C).

Shenzhen Third People's Hospital published as many as 27 academic articles related to COVID-19, providing reliable references for colleagues around the world (*5-8*). Our hospital, the National Clinical Research Center for Infectious Diseases, was the first facility to detect live coronavirus in the stool of patients, indicating the possibility of fecal-oral transmission of COVID-19 (*9*). The hospital's experience in treating severely ill patients with plasma from recovered patients was featured in the authoritative international journal JAMA (*4*). The hospital conducted scientific research in cooperation with Tsinghua University's School of Medicine, the Chinese Academy of Medical Science, and the Southern University of Science and Technology to screen the blood of recovered patients and isolate B lymphocytes that can secrete high-affinity antibodies and to establish monoclonal antibody cell lines. The technique devised by that research can now be used clinically, and a related scientific paper has been published (*10*).

At present, China's prevention and control of COVID-19 has achieved important initial results. Outside

(A)
(B)
(C)


Figure 1. (A), A total of 456 confirmed cases admitted in Shenzhen Third People's Hospital from January 19, 2020 to April 11, 2020 (Data are from the Shenzhen CDC); (B), Photo of the newly-built emergency hospital area; (C), Video conference to share experience fighting the epidemic with colleagues overseas.

China, however, the pandemic continues to spread, and Shenzhen faces increasing risks of imported cases from overseas. Viruses have no borders, so we should enhance international cooperation and jointly combat this global pandemic.

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LETTER

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WORLD REPORT SERIES

COVID-19 outbreak and surgeons' response at a Cancer Center in the United States

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Abstract: In the pandemic of severe acute respiratory syndrome due to coronavirus-2 (SARS-CoV-2), United States (U.S.) also experienced the spread of coronavirus disease 2019 (COVID-19). Here, we report the current status of Houston, Texas and the response to COVID-19 at MD Anderson Cancer Center (MDACC) and in the Department of Surgical Oncology. MDACC has taken the institutional measures in order to prevent its employees and patients from COVID-19. Furthermore, surgeons have also responded aggressively in the outpatient setting, operating room and inpatient care. The predicted peak in Texas is on April 29 and our mitigation measures appear to be effective at the time of writing, however there still remain a lot of unknowns about SARS-CoV-2 and the performance of cancer operations remains an ongoing and delicate issue. In order to minimize the risks to patients, our healthcare system, and our community, MDACC has navigated the countering pressures through honest and open communication with patients, judicious use of alternative treatment strategies, and thoughtful selection of surgical cases.

Keywords: COVID-19, SARS-CoV-2, cancer operations, patients, healthcare system

Since the first report of severe acute respiratory syndrome due to coronavirus-2 (SARS-CoV-2) in Wuhan, China was published at the end of 2019 (*1*), this coronavirus disease 2019 (COVID-19) has rapidly spread worldwide. As of the end of March 2020, the number of patients with confirmed COVID-19 reached 900,000 in the world and was declared a pandemic by the World Health Organization (*2*). The first United States (U.S.) case of COVID-19 was documented on 21 January 2020, in a Washington state patient who had recently traveled from Wuhan. In spite of initial travel bans from China and then from Europe, the number of patients with COVID-19 has been increasing exponentially worldwide and over 10,000 patients had died so far (*2*).

Here, we report the current status of Houston, Texas and the response to COVID-19 at MD Anderson Cancer Center (MDACC) and in the Department of Surgical Oncology. Texas reported its first case of COVID-19 on March 4 and the governor declared a statewide emergency on March 13 (*3*). On that exact date of the first patient reported, MDACC declared a domestic and international travel ban for all its employees and limited in-person meetings to 15 people. All internal meetings (*e.g.* tumor boards and faculty meetings) were transitioned to virtual meetings using WebEx (Cisco, San Jose, CA). After the identification of 2 cases at the Texas Medical Center on March 5, eligible employees were asked to work at home, while all patients, visitors, and employees underwent limited screening consisting of brief questionnaire items regarding symptoms and exposure, including recent travel, and a temperature check at hospital entrances. The institution moved to a one-visitor-per-patient policy and finally to a no-visitor policy on March 24, one week before the Texas Governor issued a statewide stay-at-home order. All research laboratories were closed with only critical cell lines and animals kept alive with a skeleton crew. All clinical trials not amenable to remote consenting and remote follow-up were halted. Furthermore, MDACC also developed an algorithm to stratify patients with suspected or confirmed COVID-19 by risk factors and symptoms, which rationed the limited quantity of personal protective equipment (PPE) available, especially N95 masks. This algorithm was required to limit the burn rate of the N95 masks and the regular "ear-loop" masks until stocks were re-supplied from the limited supply chain in the U.S. At the time of manuscript drafting, the operating rooms had instituted a limited trial of using ultraviolet radiation sterilization of N95 masks for up to 5 uses per individual.

Surgeons have also responded aggressively to this situation. In the outpatient setting, clinic appointments were rescheduled to a future date for all routine post-treatment surveillance visits for patients at low risk for disease recurrence. Postoperative visits were converted to telephone (and soon video conferencing) encounters. New patients or consults were considered on a case-by-case basis to determine the urgency and timing of their visits. With regards to operating room utilization, following directions from both the governor's office and guidance from surgical societies, all elective cases were cancelled. Cancer cases, on the other hand, were carefully triaged in accordance to guidelines released by the Society of Surgical Oncology (SSO) for disease-site specific management (*4*). Nonoperative therapeutic approaches such as initiating or extending neoadjuvant chemotherapy and choosing percutaneous ablation over resection were suggested by the SSO to postpone curative intent resection in hepato-pancreato-biliary malignancies. Patients with high likelihood for blood transfusion needs or postoperative intensive care unit stay were also rescheduled for resource preservation in anticipation of the upcoming surge of COVID-19 patients in the Houston metropolitan area. Starting April 7, the remaining patients undergoing elective surgery will be tested for COVID-19 the day before surgery with same-day results. In the operating room, due to limited supply of critical PPE, N95 masks are reserved for cases where the airway is opened and remains open; cases involving the oral, nasal, or pharyngeal mucosa; esophagectomies; thoracic cases requiring double lumen intubation where one lumen remains open to air; and emergency cases where SARS-CoV-2 testing cannot be performed in a timely manner. Based on the Society of Gastrointestinal & Endoscopic Surgeons (SAGES) guidelines (*5*), MDACC mandated that all laparoscopic and robotic procedures use a filtration system such as AirSeal (ConMed, Utica, NY) devices to reduce the risk of viral particle transmission when using pneumoperitoneum. Inpatient care was streamlined by combining services to eliminate traditional surgical teaching rounds with small groups and remote technology was used for patient interactions (video calls) and orders.

At the time of writing, it appears that state- and local-level mitigation efforts may be curbing the increase of both the number of new COVID-19 cases (Figure 1A) and deaths from COVID-19 (Figure 1B) ahead of the predicted peak in Texas on April 29. Our mitigation measures appear to be effective. Our critical care and floor bed occupancy remain 30% and 60% full, respectively, with total operative volume less than 30% of normal (Figure 2). Given the unclear and unstable situation and considering the highly contagious nature of the disease and the unknown number of asymptomatic carriers of SARS-CoV-2 (*6*), there remain a lot of unknowns, including when the peak in incidence will occur in Texas and in Houston, the 4th largest city in the U.S. In areas outside of the wave of hot spots (*e.g.* New York City), much of the country remains in vigilant limbo. Each U.S. hospital is now required to conserve its resources and accumulate PPE reserves while awaiting the surge in their local area. Surgical hospitals have a societal responsibility to continue to balance the needs of urgent surgical care for the general population against the risk of being a vector of transmission amongst patients and employees until a future date when a therapy is established. The performance of cancer operations remains a fluid and delicate issue. On the one hand, delaying cancer cases has the potential to negatively impact oncologic

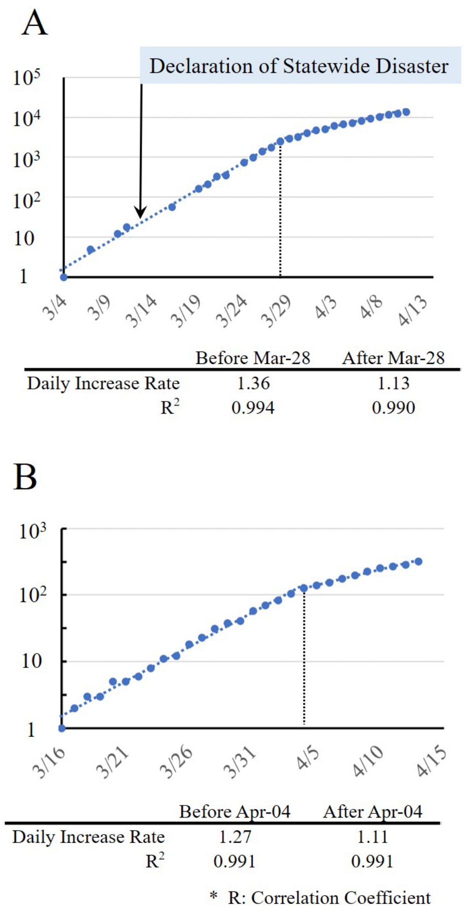

Figure 1. Trend of the Number of (A) New COVID-19 Cases and (B) Deaths from COVID-19 (from Texas Department of State Health Services, *https://txdshs.maps.arcgis.com/*). The dates of cutoffs were decided on the highest correlation coefficient of fitting line.

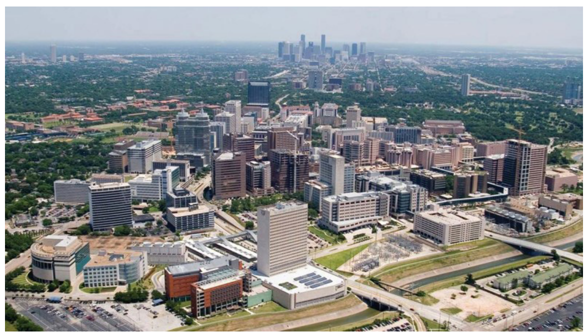

Figure 2. View of MD Anderson Cancer Center Fighting with COVID-19.

outcomes as well as patient's anxiety and quality of life. On the other, because the perioperative management of major cancer operations can be so resource intensive, these cases can place a significant strain on personnel, facility, and supplies alike, and divert them away from potential COVID-19 patients. MDACC has navigated these countering pressures through honest and open communication with our patients, judicious use of alternative treatment strategies, and thoughtful case selection to minimize the risks to patients, our healthcare system, and our community.

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The National Health Service (NHS) response to the COVID-19 pandemic: a colorectal surgeon's experience in the UK

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Abstract: The UK government was arguably slow to take action against the COVID-19 pandemic. However, since switching their policy from "mitigation" to "suppression", swift changes have been implemented to all aspects of life. In this unprecedented crisis healthcare has been on the battlefront across the globe. Every effort has been made in the UK to stop the National Health Service (NHS) from being overwhelmed, leading to the national slogan: "Stay at home. Protect the NHS. Save lives". In this article, a consultant general and colorectal surgeon in Southampton reports on the NHS response to the COVID-19 pandemic.

***Keywords*:** COVID-19, surgery, National Health Service (NHS), pelvic exenteration

Even as the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic on 11 March and neighbouring European countries implemented lockdowns, the UK appeared relatively relaxed. On 16 March, however, the tide clearly turned. The UK government's "mitigation strategy" – to delay the spread of the disease while developing herd immunity within the community – switched to a "suppression strategy". Allegedly shocked into action by an Imperial College London report predicting hundreds of thousands of deaths and a complete collapse of the UK National Health Service (NHS) (*1*), the government moved rapidly towards locking down the country. By 23 March, with the death toll at 55 and confirmed cases at 1,543, all pubs, restaurants, gyms, social venues, non-essential retailers and schools were closed. People were limited to leaving the house for a choice of only four reasons. Deepening the sense of crisis were the announcements that HRH Prince Charles (on 25 March), and the Prime Minister Boris Johnson and Health Secretary Matt Hancock (on 27 March), had all tested positive for the coronavirus.

Life has changed dramatically since then. Social distancing – remaining at least two metres away from anyone outside of your household – impacts all activities. Neighbours help each other out with supplies to limit the number of supermarket and pharmacy trips. Children are home-schooled. Everyone – even small children – socialise over video call apps such as Zoom and House Party. Exercise is limited to one hour per day. If someone develops a high fever or persistent cough – the typical COVID-19 symptoms – the entire household must remain in quarantine for 14 days. Reminded daily by the government to "Stay at Home. Protect the NHS. Save Lives", the majority of the British public appear to accept and support these extreme restrictions on their freedom.

Drastic changes have also been introduced very rapidly across the NHS. The primary focus has been on increasing ICU capacity in anticipation of a surge in critical COVID-19 patients. Hospital services were reconfigured and big field hospitals have been set up in London, Birmingham and Manchester with the help of the military. To ramp up staffing, the rules were swiftly relaxed to allow non-intensive care specialists to be paired with specialists and to make it easier for retired doctors and nurses to join the NHS workforce. All healthcare professionals are expected to be flexible in their practice, working outside of their specialty or in unfamiliar circumstances, with regulatory bodies and Trusts covering medical indemnity.

Within our organisation in Southampton, all medical training rotations were halted and junior doctors were deployed to ICU, high dependency unit (HDU) and medical wards. All surgeons were mandated to undertake ICU training, in readiness to deliver intensive care to COVID-19 ventilated patients if needed. Our surgical rota was reconfigured splitting all GI surgeons into three acute surgical care teams with each team covering all sub-specialties and rotating through acute surgery, elective surgery and virtual clinics. All endoscopy service was halted except for emergency procedures like haemostasis or colonic stenting and the endoscopy suites were converted into medical wards. All routine benign operations for gall stones, hernias, diverticulosis and pelvic floor diseases were also cancelled and, following

(A)

(B)

Figure 1. Performing pelvic exenteration in full PPE. (A) Anaesthetists prepping in theatre instead of the anaesthetic room and (B) Colorectal and urological surgeons.

guidance from the Surgical Royal Colleges (*2*), even acute conditions like appendicitis, cholecystitis and diverticulitis are treated as conservatively as possible. Meanwhile, nearby private hospitals have been acquired and designated as "clean" hospitals to allow critical elective care – primarily cancer operations – to continue to take place.

As colorectal and exenterative surgeons, my colleagues and I have had to make difficult prioritisation and adjudication decisions including to suspend complex surgery and to not accept any new regional referrals. This is particularly difficult and upsetting as deferring surgery is likely to compromise oncological outcomes and our patients' anxiety is evident. Nevertheless the current situation makes exenterative surgery all but impossible as it is a resource intensive procedure requiring multiple consultants/specialties and critical care beds postoperatively. As a result we have asked the referring local MDTs to consider possible holding measures such as additional neoadjuvant treatment and sought to have open conversations with individual patients on the waiting list.

My personal impression from this experience has been that the UK has been highly effective at making and implementing fast decisions – even as the details are still being clarified. On the other hand, the speed of change has caused confusion and anxiety in various areas. In particular, there has been concern over the lack of personal protective equipment (PPE) (Figure 1) and conflicting and confusing guidance over its use. There are also staff-shortage issues with many staff having to self-isolate when household members have symptoms. None of this is helped by the limited availability of testing – an issue the government is still struggling with.

Within our Trust, the Occupational Health team have conducted risk assessments on all staff with underlying health conditions known to be susceptible to COVID-19 leading to a large number being discouraged from coming into face-to-face contact with patients. This has had a further impact on staffing but is evidence of the difficult balance the Trust faces between staff safety and patient care at this time of crisis. All in all, however, there has been clear leadership with transparency and accountability and a strong spirit of working together.

It is often said that "the NHS is the closest thing the English have to a religion" (*3*). This has probably never been more true. Every Thursday people across the country stand on their doorsteps and clap to show their support for the healthcare workers fighting on the frontline of this "battle" against an invisible enemy. On his return home from three nights in intensive care, Boris Johnson declared, "We will win because our NHS is the beating heart of this country. It is the best of this country. It is unconquerable. It is powered by love" (*4*).

A "tsunami" of cases is expected to come to Southampton in the next two weeks and we are predicted to run out of beds. Regardless of what happens my faith in my NHS colleagues is strong.

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Can we apply lessons learned from Ebola experience in West Africa for COVID-19 in lower income countries?

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Abstract: The COVID-19 affects vulnerable groups disproportionally in a society where inequities are long-standing issue. Weak health system, especially the shortage and maldistribution of capable health workforce will be the main challenge in lower income countries to fight against the COVID-19. Applying the lesson learned and success from the Ebola outbreak in West Africa is important. International collaboration with already well functioned local mechanisms, such as the Network of Managers of Health Workforce in Francophone Africa is the key to provide prompt support. This approach contributes not only to the short-term COVID-19 control but also long-term strengthening of the sustainable and resilient health system in the lower income countries.

***Keywords*:** public health emergency, international collaboration, health system, health workforce, Francophone Africa

As of April 10, more than 1.6 million COVID-19 cases and 100,000 deaths have been globally reported. Although the virus infects everyone equally in theory, the data from New York City clearly shows the disproportion of fatality rates among race/ethnicity (Figure1) (*1*). Mayor and Governor in New York link this result to the long-standing healthcare disparities in the society due to poverty and other factors consist of the social determinants of health.

COVID-19 cases have also grown in lower income countries where social inequities are long-standing issue. Many populations are poor without social security and lack access to quality of health care services. Those who live in overcrowded condition with inadequate ventilation, limited access to clean water and sanitation, undernutrition, tuberculosis, HIV, or uncontrolled non-communicable disease are particularly vulnerable. More than 7 million forcibly displaced populations living in high density camps or similar settings shouldn't be forgotten, too. Innovative COVID-19 control measures should be implemented in those environments, such as the targeted shielding approach to protect high-risk individuals in the isolated green zone in a community (*2*). As each country is learning by trying, results should be documented and shared globally to identify better approaches.

The fundamental challenge to fight against COVID-19 in lower income countries is the weak health system, such as incomplete data collection and analysis, inadequate laboratory and health care infrastructure, and limited health workforce to deal with all these activities. The review of the Ebola outbreak in West Africa revealed that the health workforce had the most important effect on the Ebola control but also most affected among the six WHO health system building blocks (*3*). More than 8% of doctors, nurses and midwives died of Ebola in Liberia, 7% in Sierra Leone, and 1.5% in Guinea. This left the long-lasting negative health impact on the population (*4*).

Under the shortage and maldistribution of capable health workforce, any disease program does not function properly. The mobilization of limited health workforce to Ebola control caused disruption of routine health services provision in West Africa. During the Ebola outbreak, the number of deliveries with skilled health attendants dropped by 37% and fully immunized children fell by 26% in Serra Leone. In Guinea, family planning services declined by 75%. A total of 24,900 additional maternal, infant and under-five deaths, and 10,900 additional malaria deaths per year were estimated in three Ebola affected countries (*4*).

Despite the outbreak in the neighboring countries, Senegal and Cote d'Ivoire successfully quelled Ebola. The Network of Managers of Health Workforce in Francophone Africa, currently consisted of the administrators in the Ministry of Health (MoH) in 13 Francophone African countries, played a critical role in this success (*5*). The network is a peer learning and information sharing platform utilizing a comprehensive framework for health workforce, so-called "house-model" (*6*). At the very early period of the Ebola outbreak, the network declared a strong commitment to

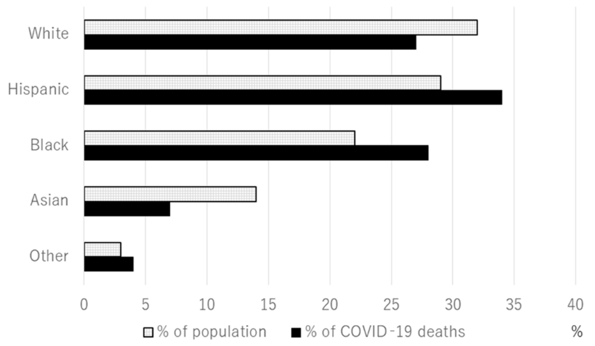

Figure 1. Population percentage and COVID-19 fatalities by race/ethnicity in New York City. Source: Department of Health, New York State. (accessed April 10, 2020)

protect health workforce in member countries. Smooth communication, coordination, and peer learning spirits in the member countries enabled effective interventions during the outbreak. MoH in Senegal quickly identified health personnel working in the border regions for effective logistical support and training to protect from Ebola. This swift action was possible thanks to the well-functioning health workforce database, which had been carefully developed by the MoH based on the lesson learned from the member countries of the network. MoH in Cote d'Ivoire quickly developed standard operational procedures for Ebola and started training for identified health workforce and local authorities with strong support from MoH in DRC through the network (*7*).

To fight against COVID-19, World Bank, WHO, Global Fund, and many other international collaboration agencies are mobilizing budget to provide financial, material and technical support for lower income countries (*8,9*). As in the case of Ebola, this influx could cause significant shifts of national health resources, including health workforce, from routine activities to COVID-19 control. The successful experience of the network during the Ebola outbreak shows that the utilization of the already existed and well functioned local mechanism is the key for prompt, effective, and efficient support to COVID-19 control without victimizing the routine health programs. Such local mechanism can identify the fundamental needs in the country, and propose a cost-effective plan to the partner agencies. This process is also a good opportunity for the local mechanism to strengthen their own capacity. Thus, this approach can contribute not only to the short-term COVID-19 control but also long-term strengthening of the sustainable and resilient health system in the country, which can prevent the loss of life due to another pandemic in the future.

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Challenges to neonatal care in Cambodia amid the COVID-19 pandemic

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Abstract: Since mid-February, 2020, coronavirus disease-2019 (COVID-19) has been spreading in Cambodia and, as of April 9, 2020, the Ministry of Health has identified 119 polymerase chain reaction (PCR)-positive cases. However, the PCR test is available in only two specialized institutes in the capital city Phnom Penh; therefore, exact and adequate identification of the cases remains still limited. Many vulnerable newborn infants have been admitted to the neonatal care unit (NCU) at the National Maternal and Child Health Center in Phnom Penh. Although the staff have implemented strict infection prevention and control measures, formidable gaps in neonatal care between Cambodia and Japan exist. Due to the shortages in professional workforce, one family member of sick newborn(s) should stay for 24 hours in the NCU to care for the baby. This situation, however, may lead to several errors, including hospital-acquired infection. It is crucial not only to make all efforts to prevent infections but also to strengthen the professional healthcare workforce instead of relying on task sharing with family members.

***Keywords*:** COVID-19, Cambodia, neonatal care, family, workforce, task sharing

In Cambodia, the index case of COVID-19 was reported on January 27, 2020. The patient was a Chinese national traveling from China to Sihanoukville, the largest port city in Cambodia. Since mid-February, infections by the causative virus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) have been spreading daily (Figure 1). As of April 9, 2020, the Ministry of Health (MOH) has reported a total of 119 polymerase chain reaction (PCR)-positive cases (*1*). According to MOH regulations, all confirmed cases should be admitted to two designated facilities in Phnom Penh, 24 provincial hospitals, or four specialized children's hospitals (*2*). In Cambodia, however, the PCR test is available in only two specialized institutes in the capital city Phnom Penh; therefore, exact and adequate identification of positive cases remains highly limited. This situation makes isolation and treatment of infected individuals difficult, similar to the situation in many low- or middle-income countries.

The National Maternal and Child Health Center (NMCHC) is a tertiary referral hospital for obstetrics, gynecology, and neonatology in Phnom Penh, Cambodia. The National Center for Global Health and Medicine (NCGM) and the Japan International Cooperation Agency (JICA) have conducted technical cooperation projects with the NMCHC since 1995. The total number of beds for parturient women and newborn infants is 154. The annual number of deliveries is approximately 7,500, one-quarter of which are by cesarean section, and approximately 10% of all newborns require admission to the neonatal care unit (NCU) for medical treatment (*3*). The main criteria for admission to the NCU include: very low birth weight (< 1,500 g); severe asphyxia; and concerning signs such as respiratory distress/disorders, fever, jaundice and convulsion, among others (*4*). Needless to say, every patient in the NCU is vulnerable to and at the highest risk for all types of infections.

Sufficient infection prevention and control measures are routinely implemented in the NCU in accordance with regulations from the Cambodian MOH. Regulations were strengthened in 2012 when the NCU experienced an outbreak of Klebsiella among newborn infants (*5*). Since then, infection prevention and control have been strictly performed in the NCU, including monthly

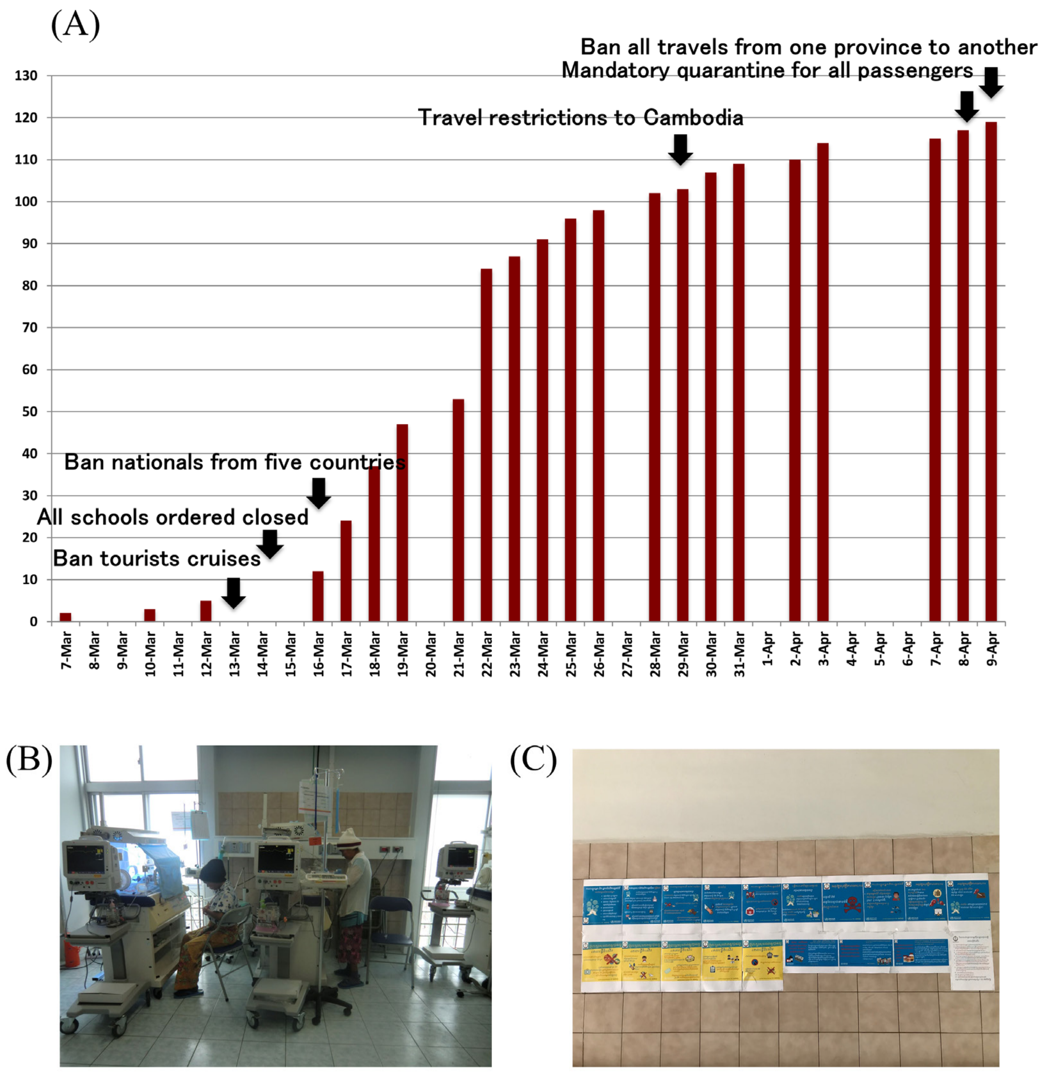

Figure 1. Amid the pandemic of COVID-19 in Cambodia. **(A)** Accumulated cases of COVID-19 and main measures in Cambodia from 7 March to 9 April in 2020 (Source: Ministry of Health, Cambodia. Press release. *http://moh.gov.kh/?lang=en* accessed from January 27 to April 9, 2020); **(B)** Care at Neonatal Care Unit; **(C)** General precautions and possible symptoms of the disease were displayed in the lobby of the National Maternal and Child Health Center on 13 February 2020.

cleaning of the facility environment using alcohol-based agents, maintaining a distance of ≥ 1 m between infant incubators, cleaning of equipment (*e.g.*, incubators, monitors), and strict hand washing and hygiene practices among family members and staff. These systematic measures have prevented the newborn patients in the NCU from hospital-acquired infections.

Nevertheless, formidable gaps in neonatal care between Cambodia and high-income countries, such as Japan, exist. Attendance of family members is essential to all inpatients in every hospital setting. In many NCUs in Cambodia, one family caregiver, it is often the father or grandmother of the newborn patient, should remain in the NCU for 24 hours. The expected roles of the family at incubator-side include provision of essential care, such as tube feeding every three hour, diaper change(s) and measurement of body temperature. Sometimes, even respiratory support using a bag and mask is performed by the family in the NCU. Due to the shortage of professional workforce, both in quantitative and qualitative aspects, neonatal care in the NCU, in reality, cannot be provided without such task sharing among healthcare professionals and family caregivers (*6*). It has been reported that participation of family members in the care of sick newborn infants has a favorable impact (*7*); however, it may also lead to several errors including hospital-acquired infection(s).

In the NMCHC, preventive measures to avoid the spread of SARS-CoV-2 infection have been gradually implemented. General precautions and possible symptoms of COVID-19 were prominently displayed in the lobby of the hospital on February 13, 2020. The staff increased the times of cleaning with alcohol for inside the building: every three day. Since March 26, 2020, screening of body temperature and hand hygiene using alcohol-based agents for all visitors has been mandated at the entrance of the hospital. Now the nurses of outpatient department interview all the patient women about their health condition with questionnaire sheets. However, the virus (*i.e.*, SARS-CoV-2) can be brought into the hospital by asymptomatic infected individuals. Because the movement of people, in large part, transmits SARS-CoV-2, family members going to and from the NCU represent the highest risk factors for its infection. An effective measure to avoid virus transmission is isolation; therefore, many hospitals have restricted family visits to the neonatal intensive care unit (NICU) in Japan (*8*). However, compared with Japanese NICUs, it is quite difficult to prohibit family caregivers from entering the NCUs in Cambodia because they have already been integrated into the hospital care system.

Therefore, we strongly recommend the implementation of a second independent screening test for COVID-19, which consists of measurement of body temperature and questions regarding other disease symptoms (*e.g.*, cough, shortness of breath), and history of close contact to confirmed cases, for all staff and family members before entering the NCU. However, if a COVID-19-positive individual is found among staff or families, temporary closure of the NCU cannot be avoided. Because delivery rooms, operation theaters, and intensive care units for parturient women are on the same floor of the building, disinfection of facilities, as well as isolation of staff, would be considered. This has a significant negative impact on maternal and neonatal health in Cambodia. Now is the time to reconsider how the professional healthcare workforce can be strengthened in Cambodia – instead of relying on task sharing with family members – to protect newborn infants and parturient women, who are among the most vulnerable patients in hospitals.

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The necessity of continuous international cooperation for establishing the coronavirus disease 2019 diagnostic capacity despite the challenges of fighting the outbreak in home countries

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Abstract: The importance of laboratory diagnostic capacity for effective infectious disease control has been widely recognized in recent years, but many of the countries still struggled to establish it when the newly discovered diseases was happened, such as coronavirus disease 2019 (COVID-19). Even in the country that the laboratory system was highly evaluated by Global Health Security Index like Myanmar, support from external partners is essential to establish the diagnostic capacity for COVID-19. WHO and other contributors, including Japan, have been supporting the establishment of a diagnostic system for SARS-CoV-2 in response to the disease outbreak. The testing laboratory was established in Myanmar on February 20, 2020. The first confirmed diagnosis was reported on March 23, and 15 positive cases as of March 31. Since it is difficult to control the outbreak in a given country without controlling it in the neighboring countries, continuous international cooperation for establishing the coronavirus disease 2019 diagnostic capacity was crucial despite the challenges of fighting the outbreak in home countries.

***Keywords*:** health security, COVID-19, international cooperation, laboratory capacity

As JICA's adviser for infectious disease control and laboratory services in Myanmar, we have been involved in the mission for strengthening the laboratory capacity, especially concerning infectious disease control (*1*). The importance of laboratory diagnostic capacity for effective infectious disease control has been widely recognized in recent years, which requires not only the ability to detect the diseases but also the introduction of new diagnostic technologies as well as the quality control schemes. The laboratory capacity is also important for global health security, as it was listed in the core capacities of the International Health Regulation 2005 (*2*). Many of the health programs, including HIV, TB, malaria, hepatitis, antimicrobial resistance, and health security, have requested the commitment of laboratories to the programs.

The laboratory capacity in Myanmar has been improved and highly evaluated in the Joint External Evaluation of IHR Core Capacities and Global Health Security Index survey (*3,4*). Table 1 shows the results of the JEE assessment and the GHS Index on the laboratory system in Myanmar. Although it mainly assessed the capacity to conduct diagnostic tests for the 10 core tests defined by the WHO, JEE found that Myanmar developed its capacity in each category, and the GHS Index score was far beyond the world average and ranked in 20th in the world.

However, in case of epidemics of newly discovered diseases such as coronavirus disease 2019 (COVID-19), it would still not be possible for such countries to establish a diagnostic system solely by themselves. Support from external partners is essential, especially for the procurement of reagents for diagnostic testing. For instance, at the time of the Zika virus outbreak in 2016, the US-CDC initially supported establishing the diagnostic capacity by providing reagents such as primers for PCR diagnosis, and the Nagasaki University and others joined the cooperation (*5*). Under the threat of the influenza epidemic in 2017, the people of Myanmar panicked, and the Myanmar Ministry of Health had to establish the diagnostic capacity in order to rule out the possibility that it was the novel influenza. The Niigata University and others helped Myanmar and found that it was a seasonal influenza epidemic (*6*).

Similarly, WHO and other contributors, including Japan, have been supporting the establishment of a diagnostic system for SARS-CoV-2 in response to the disease outbreak (*7*). In order to functionalize the testing laboratory, the national reference laboratory and its partners collaboratively worked on *i*) the procurement of necessary testing reagents including PCR primers and probes that all needed to be imported, *ii*) securing other

Table 1. Myanmar's laboratory capacity assessed by the WHO joint external evaluation and Global Health Security Index

Joint External Evaluation in May 2017 (*https://www.who.int/ihr/publications/WHO-WHE-CPI-REP-2018.5/en/*)

National Laboratory System		Score
D 1.1	Laboratory testing for detection of priority diseases	3
D 1.2	Specimen referral and transport system	3
D 1.3	Effective modern point-of-care and laboratory-based diagnostics	3
D 1.4	Laboratory quality system	3

Scores: 1 = No capacity; 2 = Limited capacity; 3 = Developed capacity; 4 = Demonstrated capacity; 5 = Sustainable capacity

2019 Global Health Security Index (*https://www.ghsindex.org/*)

Detection and Reporting	Country score*	Average of 195 countries	Ranking
Laboratory system	83.3	54.4	20/195

*Scores are normalized (0–100, where 100 = most favorable)

test-related items, such as consumables for specimen collection, *iii*) securing PCR testing devices with sufficient capacity for the estimated testing needs, *iv*) setting up the quality control scheme, *v*) arrangement of human resources, *vi*) training of the laboratory staff on testing procedures, specimen handling, testing quality, and biosafety including guidance on Personal Protective Equipment (PPE), *vii*) establishing the specimen transfer network, *viii*) establishing the laboratory data management system for this new diagnostic testing, and *ix*) resource mobilization for these processes. After all these efforts, the testing laboratory was established in Myanmar on February 20, 2020. The first confirmed diagnosis was reported on March 23, and 15 positive cases as of March 31.

In addition to direct support for establishing diagnostic capacity, indirect support for business continuity is often crucial to functionalize the laboratory. New disease epidemics will put more pressure on the already stretched human resources of the laboratories. For the sustainability of the laboratory function, external support was crucial in reducing staff workload and protecting laboratory technicians from infection, since most of the laboratory staff were involved in establishing laboratory capacity.

We have noticed some arguments over the rationale of supporting other countries while having a hard time controlling the outbreak in our own country. We strongly believe that supporting other countries where health security capacities are weak will contribute to a successful outbreak control also in the home countries of the supporters. In the case of Myanmar, although their laboratory capacity was highly evaluated by the JEE and GHS Index surveys, there was still room for improvement to establish the diagnostic capacity for the new SARS-CoV-2 strain within their country. As the WHO Director-General emphasized in his speech, diagnostic capacity is central for controlling the COVID-19 outbreak. Considering that the epidemic could spread worldwide from Wuhan, China within a few months, it is difficult to control the outbreak in a given country without controlling it in the neighboring countries. In case other counties are struggling with an outbreak, those that succeeded in controlling disease transmission would still have to close their borders. Considering the huge impact of "lockdown" on the economy and society, this would not be a sustainable option. Therefore, international cooperation is crucial under the spirit of global health security. We believe that now is the time to unite for fighting against the outbreak of COVID-19.

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Sustainable implementation of international health cooperation projects while Japanese technical experts cannot go to low- and middle-income countries because of the COVID-19 pandemic travel restrictions

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Abstract: Due to the COVID-19 pandemic, Japanese technical experts who have been supporting health in low- and middle- income countries (LMICs) are facing unprecedented travel restrictions. As of 11 April 2020, of 195 countries Japan has diplomatic relationship with, 181 countries have entry restrictions and 69 countries have post-entry movement restrictions (self-quarantine) for Japanese nationals or travellers from Japan. In order for technical experts to assist LMICs technically from Japan to meet the increased demand and needs in the health sector due to COVID-19, it is important to prioritize and reorganize the project activities in accordance with the local situation in particular to address three challenges *i*) to communicate from Japan; *ii*) to prioritize activities to match to the increased COVID-19 related tasks; and *iii*) to advocate health workers' rights and working environment.

***Keywords*:** COVID-19, international cooperation, international health cooperation, travel restrictions, low- and middle-income countries

Since 1979, the National Center for Global Health and Medicine (NCGM) has been supporting capacity development of the health sector in low- and middle-income countries (LMICs) with 4,800 Japanese experts dispatched to 140 countries (*1*). As Dr. Kokudo, the president of NCGM, expresses in the Editorial (*2*), "Viruses know no borders, races, or ideologies. International cooperation and coordination are essential to tackling this pandemic". The issue is how to do so in this global crisis.

In January 2020, before the World Health Organization (WHO) announced the Public Health Emergency of International Concern, twelve NCGM staff members were abroad on long-term assignments (over one year) in the following countries; Cambodia, Democratic Republic of the Congo, Lao People's Democratic Republic, Mongolia, Myanmar, the Philippines, and Senegal through Japan International Cooperation Agency or the WHO. After the WHO COVID-19 pandemic announcement on 11 March 2020, most of them were required to repatriate or evacuate to Japan for the following reasons: risk of COVID-19 infection and/or social instability; lock-down measures in those or transit countries; and few or no commercial flights between those countries and Japan Consequently, as of 15 April 2020, only two NCGM staff members are still abroad. Furthermore, all planned short-term assignments in April and May 2020 to LMICs from NCGM were cancelled or postponed, for the first time in over three decades of the NCGM's international cooperation.

Due to the COVID-19 pandemic, international travellers face unprecedented restrictions and difficulties worldwide. According to the Ministry of Foreign Affairs (MOFA) Japan, as shown in the Figure 1, of 195 countries Japan has diplomatic relationship with, 181 countries have entry restrictions and 69 countries have post-entry movement restrictions (self-quarantine) for Japanese nationals or travellers from Japan (*3*) as of 11 April 2020. Also, according to the Overseas Travel Safety Information (*4*) and the Warning on Infectious Diseases of MOFA Japan (*5*), 49 countries are categorized as Level 3 (Avoid all travel), and all other countries in the world are categorized as Level 2 (Avoid non-essential travel) for Japanese nationals as of 31 March 2020.

It may be difficult to identify precise projections of how long COVID-19 transmission will continue in LMICs (*6*). In the given situation with rising confirmed cases both in Japan and LMICs, it is likely that Japanese technical experts may not be able to go to LMICs for technical support at all for a number of months.

There are three challenges which repatriated Japanese technical experts have been facing and trying to address

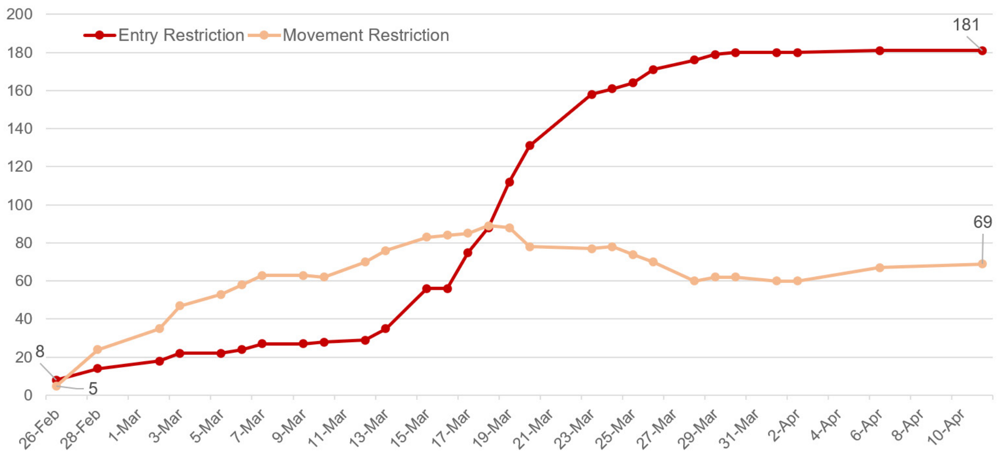

Figure 1. Number of countries (red line) entry restriction and (yellow line) post-entry movement restriction (self-quarantine) for Japanese nationals/travelers from Japan (from 26 February to 11 April 2020) of those 195 countries which Japan have diplomatic relationship (Data Source: Ministry of Foreign Affairs, Japan. *https://www.anzen.mofa.go.jp/covid19/pdfhistory_world.html*).

while implementing health projects by prioritizing and reorganizing the activities.

The first is to provide technical support to their counterparts from Japan. Using web-meetings, messenger services and email, it is possible to maintain communication with their counterparts, national staff, and development partners. Thanks to better IT infrastructure in LMICs, IT skills and smart-phone use by their counterparts, web-based communication is much easier compared to one or two decades ago. As long as the time-difference is not large, web-based meetings or training could be organized. These special circumstances could be used to develop innovative approaches or to reconsider methods of technical support to strengthen further ownership by the counterparts.

The second is their counterparts in the health sector are managing increased responsibilities in relation to COVID-19 and/or are affected by lock-down measures. This may require reprioritization and reorganization of activities planned. For example, non-urgent activities and assessments targeting health facilities or households are to be postponed because of local social distancing measures. This allows valuable health staff to prioritize COVID-19 related tasks. At the same time, Japanese repatriated experts could support the increased COVID-19 related tasks technically as a priority in line with the scope of the original project.

The third challenge is to ensure their counterparts' health workers' rights and environment. Currently, even in high income countries, it is extremely difficult to ensure goods and commodities for infection control including personal protective equipment, because of increased global demand. This could be an underlying cause of intra-hospital infection. Obviously, the issue should be solved at global, national, sub-national, and facility levels in LMICs in collaboration with the respective authorities with development partners. At the same time, as long as it is justifiable, project funds could be used to support protecting health care workers. Repatriated Japanese technical experts could advocate health workers' rights (*7*) to ensure their working environment in LMICs.

"We stand on the side of people in need" (*1*), says Dr. Kokudo. People in need include vulnerable people and health workers (*8*) in LMICs, a point emphasised by global leaders (*9,10*). While Japanese technical experts are not able to go to LMICs because of the COVID-19 pandemic travel restrictions, it is therefore imperative to implement international health cooperation projects in a sustainable manner by prioritizing and reorganizing the project activities in accordance with the local situation.

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