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National Institute of Infectious Diseases and
Tuberculosis and Infectious Diseases
Control Division,
Ministry of Health, Labour and Welfare

<THE TOPIC OF THIS MONTH>
COVID-19 as of May 2020

Coronaviruses are enveloped, positive-sense single-stranded RNA viruses. Coronaviruses known to infect humans include four causative viruses of the common cold, human coronavirus 229E, OC43, NL63, and HKU1, and severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), both of which cause severe pneumonia. SARS-CoV-2, the cause of coronavirus disease 2019 (COVID-19), which was first identified in December 2019, is classified in the same Betacoronavirus genus as SARS-CoV with high genetic homology (approximately 80%), and was reported to bind and enter human cells using the receptor ACE2.

Domestic and International Trends:

On December 31, 2019, COVID-19 was reported to the World Health Organization (WHO) from Wuhan City, Hubei Province of China, as a cluster (a group with associations found among patients) of pneumonia cases of unknown etiology (p.105 of this issue). In response to the increasing number of cases in China and confirmed human-to-human transmissions in 19 countries, including Japan, the WHO declared on January 30, 2020 that COVID-19 is a "public health emergency of international concern (PHEIC)" under the International Health Regulations (IHR). Due to the subsequent spread of infection, the WHO declared COVID-19 a "pandemic" on March 11, 2020. As at June 4, 6,287,771 cases were confirmed in 216 countries in all 6 WHO regions and there were 379,941 deaths (p.105 of this issue). As at 24:00 on May 31, according to the press release of the Ministry of Health, Labour and Welfare (https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00086.html), the domestic number of cases with positive PCR tests was 16,884 (16,679 domestic cases, 15 returnees by charter flights, and 190 cases at airport quarantine) (not including those quarantined or isolated onboard the cruise ship "Diamond Princess" (p.106 of this issue)). Of these, 892 deaths were identified, which included the results from a follow-up survey.

In Japan, the legislation to classify COVID-19 as a designated infectious disease was issued on January 28 and implemented on February 1 (Table 1). Among the cases reported to the National Epidemiological Surveillance of Infectious Diseases (NESID) since then, 16,911 cases were tested and confirmed by the local governments (15,012 case-patients, 1,868 asymptomatic virus carriers, and 31 deaths at the time of notification) as at the 22nd week of 2020. As at May 31, the largest number of cases reported to NESID was on April 9 (655 cases), while the largest number of cases by onset day was April 1 (431 cases, only cases with known onset date) (Figure in p.105). There were 9,284 males and 7,627 females (male/female ratio 1.2:1), and the median age was 49 years (range 0-104). The main symptoms at the time of reporting were fever (75%), cough (43%), acute respiratory tract symptoms other than cough (8.9%), and severe pneumonia (6.9%). In Japan, from early March, the number of cases suspected to be associated mainly with Europe and the United States increased. By mid-March, the number and percentage of cases with unknown sources of infection increased. By late March, clusters were reported mainly in urban areas (pp.110 & 111 of this issue). Of the pathogens identified from suspected COVID-19 cases reported to NESID's Infectious Agents Surveillance System from public health institutes and local public health centers nationwide from January 29 to June 16, 3,177 were SARS-CoV-2 (2,188 in April) and 24,555 were negative (Table 2 in p.105).

Transmission Route, Treatment, and Prevention:

The initial symptoms of COVID-19 are similar to those of influenza or the common cold, and it is difficult to distinguish them in the early stage of the disease. The primary transmission route is droplet infection and through direct contact. After an incubation period of 1-14 days (5-6 days is the most frequent according to the WHO, as at April 17), patients develop symptoms such as fever, respiratory tract symptoms, and general fatigue. The majority of patients (approximately 80% according to the WHO) recover without the need for hospitalization. Common cold-like symptoms often persist for approximately one week, and from around this time on, pneumonia may be diagnosed by chest radiography and computed tomography. Some patients may progress to a critical condition and develop respiratory failure. The elderly and those with underlying health conditions are particularly at high risk of developing a severe outcome.

Table 1. Management of COVID-19 patients in Japan

Infectious Diseases Control Law (implemented on 1 February 2020) As a designated infectious diseases, physicians who diagnose patients with COVID-19 must immediately notify the cases to their prefectural governors via local public health centers.
School Health and Safety Act (notification on 28 January 2020) When COVID-19 is designated as a designated infectious disease according to this government ordinance, it is considered to be a Type I infectious disease. The principal may suspend the attendance of any child or student who has contracted the disease until he/she is cured.

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(THE TOPIC OF THIS MONTH-Continued)

Effective and specific treatments for COVID-19 have yet to be established. Remdesivir, which was developed for the treatment of Ebola hemorrhagic fever, received special approval on May 7, and as at June 17, drugs, such as favipiravir and ciclesonide, are evaluated under observational studies, specific clinical studies, and corporate trials in Japan. Vaccines to prevent COVID-19 are being developed and evaluated in many countries, including Japan.

Tests, Diagnosis, and Pathological Findings:

The National Institute of Infectious Diseases (NIID) developed a real-time PCR test to detect the SARS-CoV-2 gene and published a laboratory manual for government laboratories on tests for detecting the novel coronavirus pathogen (https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/2518-lab/9403-labo-manual.html). NIID provides support to laboratory facilities, such as public health institutes, that conduct diagnostic tests for local governments, administers the distribution of SARS-CoV-2, classified as a class 4 pathogen designated under the Infectious Diseases Control Law, and develops cell culture for efficient isolation of SARS-CoV-2 (p.115 of this issue). The correlation between the number of ill days and the threshold cycle (Ct) values of real-time PCR testing has been used to inform clinical decisions (p.117 of this issue).

As for SARS-CoV-2 antigen testing, a rapid immunochromatography diagnostic kit based on enzyme immunoassay is in use and can detect patients who secrete large amounts of the virus. A rapid testing kit for the SARS-CoV-2 antibody is available. However, results should be interpreted with caution because the evaluation of its performance is not sufficient. It is also necessary to prepare reference panels for the quantitative measurement of antibody titers.

The analysis of the histopathology of COVID-19 autopsy cases is highly important to elucidate the pathology of the disease. In the first autopsy case in Japan, the lungs exhibited diffuse alveolus injury, a pathological finding of acute respiratory distress syndrome. The largest amount of SARS-CoV-2 virus detected was from the peripheral tissue of the lungs, followed by the bronchus, trachea, and nasopharynx. Low copy numbers of virus genes were also detected from blood and stool specimens (p.119 of this issue).

Public Health Countermeasures, Declaration of the State of Emergency, and its Subsequent Lifting:

On March 14, the partial revision of the National Action Plan for Pandemic Influenza and New Infectious Diseases was officially approved by the Cabinet, and COVID-19 became regarded as Pandemic Influenza and New Infectious Diseases enacted by the law. On March 28, the basic policy for COVID-19 was announced: it emphasized controlling the number of cases, and maintaining medical systems and social functions, promoting the containment of cluster events by active epidemiological investigations. It is a characteristic of COVID-19 that clusters form quickly when an infected person comes in contact with susceptible persons in settings that fulfill the 3 Cs (closed spaces, crowded places, and close-contact settings). It is important to identify these clusters and interrupt their chains of transmission (p.108 in this issue). In Japan, public health centers are conducting contact tracing, including identification of movement histories of infected persons, listing of close contacts, and monitoring health conditions (pp.113 & 114 in this issue).

As the number of cases with unknown routes of transmission was increasing and the medical system was at risk of being overwhelmed, a state of emergency was declared in 7 prefectures on April 7, and then nationwide on April 16. After the situation improved, the state of emergency was lifted in all prefectures on May 25.

Future Agenda:

Measures led by the Ministry of Health, Labour and Welfare are to publicize information needed to control infection, support the medical system, and promote research and development.

As for the information collection system, the Health Center Real-time Information-sharing System on COVID-19 (HER-SYS) was introduced to share and collect information. This system aimed to reduce the workload of public health center and simultaneously enables more rapid collection of information. Using HER-SYS, information can be shared immediately among public health centers, local municipalities (other than public health centers), and medical facilities. Furthermore, the COVID-19 Contact-Confirming Application/app (COCOA) was developed to enable each person to identify contacts quickly. Upon consent of the user, this app uses the Bluetooth function of the user's smartphone, and after the privacy of both the infected person and the contact person are ensured, the user can be notified when the user may have come in contact with an infected user. The notified users can receive support from the public health center, such as prompt testing, which is expected to prevent the spread of the virus. In this manner, in addition to rapid collection and sharing of information, and enabling changes in behavior such as social distancing, an approach that ensures that contacts can promptly consult medical facilities is being promoted.

As for the medical system, in addition to continuing border protection measures at ports and airports, and by actively testing those who have been in close contact with infected persons, early detection of infected individuals, including asymptomatic cases, and effective countermeasures against clusters, will be implemented. In addition to nasopharyngeal swab PCR testing, the following diagnostic tests have been put into practical use: PCR testing using saliva specimens, rapid antigen test using nasopharyngeal swabs, and quantitative antigen test using nasopharyngeal and saliva specimens. These tests are being implemented accordingly, based on the current capacity and state of the infection prevention measures at the testing facilities. It is important to establish a consultation system, such as one where the testing facilities cooperate with the medical association, and a system that includes care facilities tailored to accommodate the case-patients' specific symptoms, to prevent the medical system from collapsing.

Regarding research and development, the development of drugs in addition to remdesivir are being promoted, along with the development of vaccines both in Japan and overseas, in an all-out effort to realize their real-world application.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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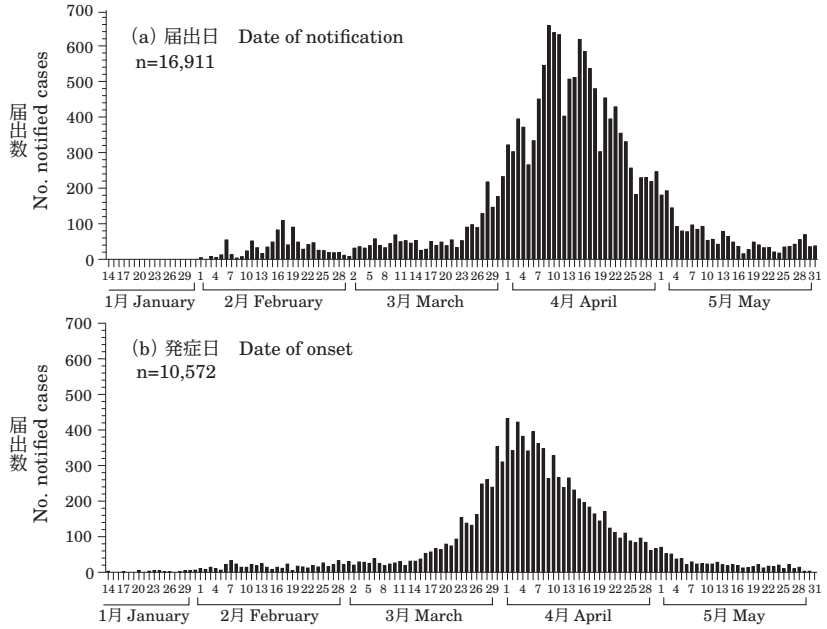
図. 届出日別，発症日別 COVID-19 届出数，2020年１月14日～５月31日
Figure. Daily number of notified COVID-19 cases, 14 January - 31 May 2020, Japan



（感染症発生動向調査：2020年６月３日現在届出数）
（National Epidemiological Surveillance of Infectious Diseases: as at 3 June 2020）

表2. 新型コロナウイルス感染症疑い例から検出された病原体，2020年１月～６月 (n=27,896)
Table 2. Reported number of pathogens isolated/detected (n) from COVID-19-suspected cases, January-June, 2020 (n=27,896)

病原体　Pathogen	検体採取月 Month of specimen collection						Total
	January	February	March	April	May	June (-15th)	
Negative	34	1,725	6,913	11,627	3,881	375	24,555
SARS-CoV-2	2	181	541	2,188	232	33	3,177
Human coronavirus 229E	-	4	15	-	-	-	19
Human coronavirus HKU1	-	2	8	-	-	-	10
Human coronavirus NL63	-	2	-	-	-	-	2
Human coronavirus OC43	-	9	22	-	-	-	31
Influenza virus AH1pdm09	-	4	1	-	-	-	5
Influenza virus B	2	-	3	-	-	-	5
Parainfluenza virus	-	2	1	-	-	-	3
Respiratory syncytial virus	-	7	6	-	-	-	13
Human metapneumovirus	-	18	19	-	-	-	37
Rhinovirus	-	13	12	-	-	-	25
Coxsackievirus B5	-	2	-	-	-	-	2
Enterovirus 68	1	-	-	-	-	-	1
Adenovirus	-	5	-	-	-	-	5
Herpes simplex virus 1	-	1	2	-	-	-	3
Human bocavirus	-	1	-	-	-	-	1
Mycoplasma pneumoniae	-	2	-	-	-	-	2
Total	39	1,978	7,543	13,815	4,113	408	27,896

(病原微生物検出情報：地方衛生研究所、保健所からの報告、2020年６月16日現在)
(Infectious Agents Surveillance System: Data based on reports from public health institutes and public health centers as at 16 June 2020)