PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2022) **64**, e14912 doi: 10.1111/ped.14912

Original Article

The clinical characteristics of pediatric coronavirus disease 2019 in 2020 in Japan

Tomohiro Katsuta,[1,2] Naoki Shimizu,[1,2] Kenji Okada,[1,3] Keiko Tanaka-Taya,[1,4] Takashi Nakano,[1,5] Hajime Kamiya,[1,6] Kiyoko Amo,[1,7] Naruhiko Ishiwada,[1,8] Satoshi Iwata,[1,9] Makoto Oshiro,[1,10] Nobuhiko Okabe,[1,11] Ryutaro Kira,[1,12] Seigo Korematsu,[1,13] Shigeru Suga,[1,14] Takeshi Tsugawa,[1,15] Naoko Nishimura,[1,16] Haruka Hishiki,[1,17] Masashi Fujioka,[1,18] Mitsuaki Hosoya,[1,19] Yumi Mizuno,[1,20] Mahito Mine,[1,21] Isao Miyairi,[1,22] Chiaki Miyazaki,[1,23] Ichiro Morioka,[1,24] Tsuneo Morishima,[1,25] Tetsushi Yoshikawa,[1,26] Taizo Wada,[1,27] Hiroshi Azuma,[1,28] Koichi Kusuhara,[1,29] Kazunobu Ouchi,[1,5] Akihiko Saitoh[1,30] and Hiroyuki Moriuchi[1,31]

[1]The Committee on Immunization and Infectious Diseases, Japan Pediatric Society, [4]Center for Surveillance, Immunization, and Epidemiologic Research, [6]Center for Field Epidemic Intelligence, Research and Professional Development, National Institute of Infectious Diseases, [9]Department of Infectious Diseases, National Cancer Center Hospital, [22]Division of Infectious Diseases, National Center for Child Health and Development, [24]Department of Pediatrics and Child Health, Nihon University School of Medicine, Tokyo, [2]Department of Pediatrics, St. Marianna University School of Medicine, Kawasaki, [3]Department of Nursing, Fukuoka Nursing College, [12]Department of Pediatric Neurology, Fukuoka Children's Hospital, [20]Department of Pediatric infectious diseases and immunology, Fukuoka Children's Hospital, Fukuoka, [5]Department of Pediatrics, Kawasaki Medical School, Okayama, [7]Department of Pediatric emergency, Osaka City General Hospital, [18]Fujioka Pediatric Clinic, Osaka, [8]Department of Infectious Diseases, Chiba University, Medical Mycology Research Center, [17]Department of Pediatrics, Chiba University Hospital, Chiba, [10]Department of Pediatrics, Japanese Red Cross Nagoya First Hospital, [16]Department of Pediatrics, Konan Kosei Hospital, [25]Department of Pediatrics, Aichi Medical University, [26]Department of Pediatrics, Fujita Health University School of Medicine, Aichi, [11]Kawasaki City Institute for Public Health, Kanagawa, [13]Department of Pediatrics, Nakatsu Municipal Hospital, Oita, [14]Infectious Disease Center and Department of Clinical Research, National Hospital Organization Mie National Hospital, Mie, [15]Department of Pediatrics, Sapporo Medical University School of Medicine, Hokkaido, [19]Department of Pediatrics, Fukushima Medical University, Fukushima, [21]Mine Pediatric Clinic, Saitama, [27]Department of Pediatrics, Kanazawa University, Ishikawa, [28]Department of Pediatrics, Asahikawa Medical University, Hokkaido, [29]Department of Pediatrics, University of Occupational and Environmental Health, Kitakyushu, [30]Department of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, [31]Department of Pediatrics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Abstract

***Background*:** The COVID-19 pandemic has affected the lives of people of all ages. Most reports on pediatric cases suggest that children experience fewer and milder symptoms than do adults. This is the first nationwide study in Japan focusing on pediatric cases reported by pediatricians, including cases with no or mild symptoms.

***Methods*:** We analyzed the epidemiological and clinical characteristics and transmission patterns of 840 pediatric (<16 years old) COVID-19 cases reported between February and December 2020 in Japan, using a dedicated database which was maintained voluntarily by members of the Japan Pediatric Society.

***Results*:** Almost half of the patients (47.7%) were asymptomatic, while most of the others presented mild symptoms. At the time of admission or first outpatient clinic visit, 84.0% of the cases were afebrile (<37.5°C). In total, 609 cases (72.5%) were exposed to COVID-19-positive household members. We analyzed the influence of nationwide school closures that were introduced in March 2020 on COVID-19 transmission routes among children in Japan. Transmission within households occurred most frequently, with no significant difference between the periods before and after declaring nationwide school closures (70.9% and 74.5%, respectively).

***Conclusions*:** COVID-19 symptoms in children are less severe than those in adults. School closure appeared to have a limited effect on transmission. Controlling household transmission from adult family members is the most important measure for prevention of COVID-19 among children.

Key words COVID-19, epidemiology, household contact, pediatrics, school closure.

Correspondence: Tomohiro Katsuta, MD PhD, Department of Pediatrics, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki-shi, Kanagawa, 216-8511, Japan. Email: katsuta-7-@marianna-u.ac.jp

Received 28 April 2021; revised 10 June 2021; accepted 14 June 2021.

© 2021 Japan Pediatric Society.

Since the beginning of 2020, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide and become a global threat. Most reports on pediatric COVID-19 cases suggested that children experienced fewer or milder symptoms than did adults.[1–3] However, there have also been some reports on critically ill pediatric patients.[4,5] In Japan, despite the large number of asymptomatic COVID-19 patients who were diagnosed using an application-based contact tracing system or cluster survey by healthcare centers, the number of COVID-19 patients is lower than those in other countries. This study aimed to analyze the epidemiology, clinical manifestations, and outcomes of pediatric COVID-19 in Japan, using a dedicated database in which physicians, most of them were members of the Japan Pediatric Society (JPS), registered their cases voluntarily. This is the first nationwide study that has focused on all pediatric COVID-19 cases, including patients with no or mild symptoms, reported by all pediatricians in Japan.

Methods

Study population

We included pediatric patients aged <20 years old who were diagnosed with COVID-19 by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) or loop-mediated isothermal amplification (LAMP) tests, conducted at the local healthcare center or commercial laboratories. Although we started our study in May 2020, the first pediatric COVID-19 case in Japan had been reported in February 2020. Thus, the study period was from February to December 2020, and some of the cases were registered retrospectively. This registry was based on the COVID-19 case report form that was established by the World Health Organization and International Severe Acute Respiratory and Emerging Infection Consortium.[6] Physicians input the patient's data, including epidemiological characteristics, clinical symptoms and signs, laboratory findings at the first hospital or clinic visit, treatment, hospitalization status, complications, and prognosis at the time of discharge from the hospital, into a dedicated database. We defined asymptomatic cases as those with positive SARS-CoV-2 PCR or LAMP test results "without any clinical symptoms of acute respiratory infection including fever, cough, dyspnea, or tachypnea at any time throughout the course." In asymptomatic cases, we assumed that the date of onset was when the test result was confirmed. The results obtained from the database were automatically presented as charts (graphs) by the dedicated software, swiftly published on the JPS website, and updated daily.[7] Initially, 907 laboratory-confirmed pediatric COVID-19 cases (patients aged <20 years old) were reported. As of 29 December 2020, which almost coincided with the end of our study period, there were 18 605 confirmed COVID-19 cases among patients aged <20 years old in Japan.[8] We excluded all patients aged between 16 and 19 years old from this study because we assumed that most patients in this age group visit internists rather than pediatricians. Ultimately, 840 pediatric COVID-19 patients aged <16 years old were included in this study.

In Japan, nationwide school closures were introduced in March 2020. Thereafter, some children, mainly living in large cities, were prohibited from attending school until 31 August 2020 when the summer vacation ended. Most schools resumed their regular schedule in September. Hence, we divided the study periods into the pre-reopen period (February–August 2020) and the post-reopen period (September– December 2020). The source of infection with SARS-CoV-2 was compared between the respective study periods.

Statistical analysis

Statistical analysis was performed using R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria); statistical significance ($P < 0.05$) was assessed using the Fisher's exact test.

Ethics approval

This study was approved by the Ethics Review Committee of the Japan Pediatric Society (approval number: 32).

Results

Background

A national emergency was declared on April 7 in seven urban prefectures, including Tokyo, which became nationwide on April 16. Since then, pediatric cases were reported daily with two peak periods at week 17 and 34.

Baseline characteristics

In total, 907 of 18 605 (49%) nationwide pediatric COVID-19 cases aged <20 years old in Japan were registered in the dedicated database. A total of 840 pediatric COVID-19 patients who were <16 years old were enrolled during the study period (Table 1). The median age was 6 years (interquartile range [IQR]: 2–11). Among them, 440 cases (52.4%) were males. Almost a half of the patients in this study were asymptomatic (Fig. 1). Nevertheless, during the study period, the Japanese government recommended hospitalization for all COVID-19 patients for monitoring and quarantine even if their symptom was not severe, thus, the hospitalization threshold for COVID-19 patients in Japan was extremely low. As a result, among the 840 cases, 709 (84.4%) were hospitalized, including four patients who were admitted to the intensive care unit (ICU) (Fig. 2, Table 4). The admission rates among patients aged <1, 1–5, 6–10, and 11–15 years were 92.4%, 80.1%, 80.4%, and 90.3%, respectively. The mean ± standard deviation length of hospital stay was 9.3 ± 5.2 days.

Vital signs and symptoms

Most of the pediatric patients had mild clinical symptoms and 401 (47.9%) were asymptomatic (Table 2). At the time of admission or the first outpatient clinic visit, only 130 patients

© 2021 Japan Pediatric Society.

(16.0%) had fever (≥37.5°C). Other vital signs, including heart rate, respiratory rate, and oxygen saturation on room air, were within normal ranges in 90% of cases. Additionally, only 300 patients (35.8%) had a history of fever at any time during the clinical course. The common symptoms at the onset of the illness were runny nose and dry cough (194 and 166; 23.1% and 19.8%, respectively). Forty-two patients (median age: 12 years, range 5-16 years) and 33 (median age: 13 years, range 6-16 years) had dysgeusia and dysosmia, respectively.

Laboratory results and imaging findings

Few patients had leukopenia with neutropenia and lymphopenia (14.0%, 4.5%, and 2.6%, respectively) (Table 3). The levels of most inflammatory markers, interleukin-6, liver enzymes, biochemical markers of myocardial damage, and the coagulation function markers were within the normal ranges.

Chest X-rays and computed tomography (CT) scans were examined in 316 and 85 cases, respectively; 92.4% and 80.0%, respectively, had normal results, (Table 3). The most frequently recognized abnormal CT findings were ground-glass opacities (GGOs) and consolidation; eight cases (9.4%) had either or both.

Treatment

Antiviral drugs were not administered to any of the patients (Table 4). Inhaled ciclesonide, and intravenous and oral steroids were administered to one (0.1%), five (0.6%), and one (0.1%) of the patients, respectively. As supportive care, oxygen therapy was administered to 11 cases. Invasive ventilation, inotropes/vasopressors, and placement in the prone position were introduced to a single infant case. Neither

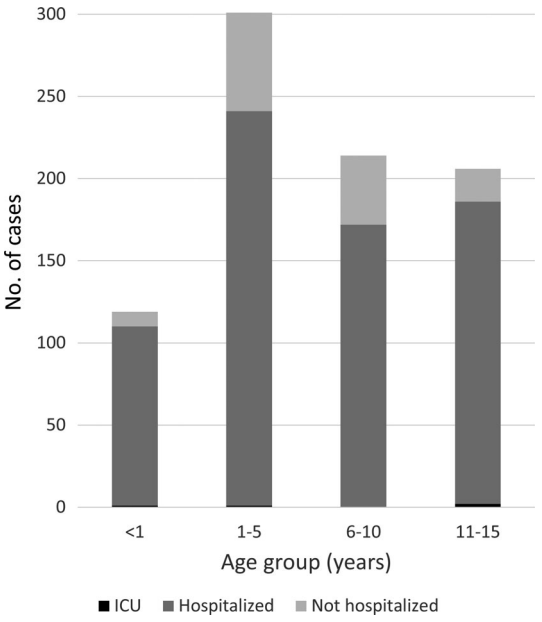

Fig. 2 The hospitalization threshold for pediatric COVID-19 patients in Japan had been extremely low. As a result, 84.4% of pediatric cases were hospitalized. The hospital admission rates among pediatric COVID-19 patients aged <1, 1–5, 6–10, and 11–15 years were 92.4%, 80.1%, 80.4%, and 90.3%, respectively. ICU: intensive care unit. (■), ICU; (■), hospitalized; (■), not hospitalized.

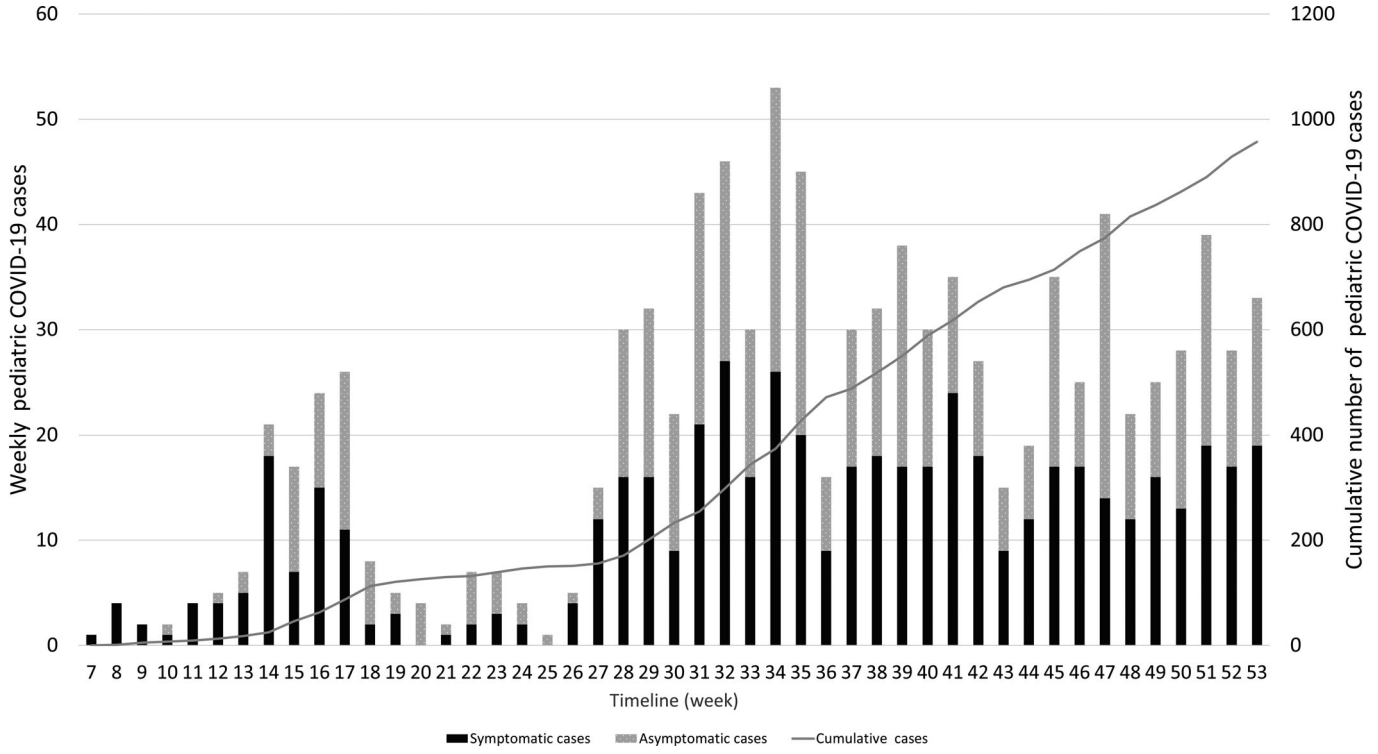

Fig. 1 Pediatric COVID-19 cases in Japan were reported with two peak periods. Almost a half of the patients were asymptomatic. (■), symptomatic cases; (■), asymptomatic cases; (—), cumulative cases.

© 2021 Japan Pediatric Society.

Table 1 Epidemiological characteristics of the pediatric COVID-19 patients aged <16 years

Characteristics	[*n* = 840]
Age, median (IQR)	6 (2–11)
Sex at birth, *n* (%)	
Male	440 (52.4)
Co-morbidities, *n* (%)	
Asthma	34 (4.0)
Obesity	17 (2.0)
Chronic cardiac disease	8 (1.0)
Chronic neurological disorder	6 (0.7)
Chronic liver disease	2 (0.2)
Chronic kidney disease	1 (0.1)
Diabetes	1 (0.1)
Tuberculosis	1 (0.1)
Malignant neoplasm	1 (0.1)
Collagen disease	1 (0.1)
Past history of Kawasaki disease[†]	5 (0.6)
Overseas travel history within 14 days of symptom onset, *n* (%)	22 (2.6)
Attending nursery, kindergarten, or school, *n* (%)	527 (62.7)

[†]This does not include complications of COVID-19, such as multisystem inflammatory syndrome in children.
IQR, interquartile range.

extracorporeal membrane oxygenation (ECMO) support, renal replacement therapy (RRT), nor dialysis was used in this study population.

Complications and outcomes

Ten (1.3%) and five (0.6%) cases were clinically diagnosed as pneumonia and bronchitis, respectively (Table 5). Shock and cardiac arrhythmias were confirmed in a single case. Encephalopathy and cardiac arrest were confirmed in another single case. There was no fatal case in this study.

Prior contact with a COVID-19 patient

Among all 840 pediatric cases aged <16 years old, 778 cases (92.6%) had recent contact with a SARS-CoV-2-positive person (Table 6). Of the total, 609 cases (72.5%) were exposed to infected household members. The most frequent index case in the family was the father (31.8%). SARS-CoV-2 was transmitted less frequently from siblings in the household (2.6%) or members of the same school (6.2%), kindergarten/nursery (6.2%), and private tutoring school (0.9%). Among the 449 patients who were infected with SARS-CoV-2 during the nationwide school closures and summer vacation period, who were categorized into the pre-reopen period group, 318 (70.9%) contracted it from their family members, especially adults. Of the 391 patients in the post-reopen period group, 291 (74.5%) contracted it from family members. The transmission rate from mothers increased significantly from 18.3% in pre-reopen period to 25.6% in post-reopen period ($P < 0.05$). Transmission rate at school increased from 4.2% in pre-reopen period to 8.4% in post-reopen period ($P < 0.05$). Contrarily, the transmission rate from members of the same kindergarten/nursery decreased significantly from 9.8% to 2.0% ($P < 0.05$) in the same periods.

Table 2 Vital signs and symptoms on admission or first outpatient clinic visit

Vital signs	*n* (%)
Fever (*n* = 813) (°C)	
<37.0	480 (59.0)
37.0–37.4	203 (25.0)
37.5–37.9	70 (8.6)
38.0–38.4	31 (3.8)
38.5–-38.9	13 (1.6)
≧39.0	16 (2.0)
Normal heart rate (age dependent) (*n* = 727)	646 (88.9)
Normal respiratory rate (age dependent) (*n* = 523)	474 (90.6)
Oxygen saturation on room air (*n* = 751)	
<90	0 (0.0)
90–94	5 (0.7)
95–100	746 (99.3)
Glasgow Coma Scale (*n* = 840)	
15	835 (99.4)
14	4 (0.5)
9	1 (0.1)
Symptoms	
Asymptomatic (*n* = 838)	401 (47.9)
History of fever (*n* = 839)	300 (35.8)
Cough (*n* = 838)	
Dry	166(19.8)
With sputum production	95 (11.3)
Sore throat (*n* = 806)	52 (6.5)
Runny nose (*n* = 839)	194 (23.1)
Wheezing (*n* = 840)	14 (1.7)
Dysgeusia (*n* = 783)	42 (5.4)
Dysosmia (*n* = 782)	33 (4.2)
Chest pain (*n* = 797)	3 (0.4)
Muscle aches (myalgia) (*n* = 798)	4 (0.5)
Joint pain (arthralgia) (*n* = 798)	9 (1.1)
Fatigue/Malaise (*n* = 803)	45 (5.6)
Shortness of breath (*n* = 825)	13 (1.6)
Inability to walk (*n* = 821)	1 (0.1)
Lower chest wall indrawing (*n* = 838)	8 (1.0)
Headache (*n* = 804)	59 (7.3)
Seizures (*n* = 840)	2 (0.2)
Abdominal pain (*n* = 814)	16 (2.0)
Vomiting/Nausea (*n* = 838)	31 (3.7)
Diarrhea (*n* = 838)	64 (7.6)
Conjunctivitis (*n* = 839)	6 (0.7)
Skin rash (*n* = 837)	12 (1.4)
Lymphadenopathy (*n* = 837)	1 (0.1)
Chilblains (*n* = 839)	1 (0.1)
Bleeding (hemorrhage) (*n* = 840)	2 (0.2)
Dehydration (*n* = 838)	12 (1.4)
Sternal capillary refill time >2 s (*n* = 776)	2 (0.3)
Malnutrition (*n* = 837)	4 (0.5)

Discussion

This is the first nationwide study of pediatric COVID-19 cases based on pediatricians' reports of all SARS-CoV-2 positive cases under the condition that the comprehensive PCR examinations were carried out by the public health centers as a cluster survey for people who had close contact with any COVID-19 patient, regardless of their clinical symptoms.

© 2021 Japan Pediatric Society.

Table 3 Laboratory results and imaging findings on patient admission or first outpatient visit

Laboratory results	Mean ± standard deviation	(Reference values)	Abnormal findings,† %
White blood cell count (n = 279)	7.1 ± 4.4 x 10^9/L	(4–11)	14.0 (Leukopenia)
Neutrophils (n = 268)	3.0 ± 2.7 x 10^9/L	(1–7)	4.5 (Neutropenia)
Lymphocytes (n = 268)	3.4 ± 2.6 x 10^9/L	(0.8–4)	2.6 (Lymphopenia)
Hemoglobin (n = 279)	133 ± 14.3 g/L	(110–160)	10.8
Hematocrit (n = 277)	39.1 ± 4.8 %	(25–43)	15.9
Platelet count (n = 276)	284 ± 148.8 x 10^9/L	(150–400)	10.1
Prothrombin time (n = 102)	12.0 ± 1.1 sec	(9–14)	4.9
Prothrombin time-international normalized ratio (n = 161)	0.99 ± 0.09	(0.85–1.15)	8.7
Activated partial thromboplastin time (n = 164)	33.6 ± 4.7 s	(25–40)	9.1
Aspartate aminotransferase (n = 278)	31.5 ± 15.2 U/L	(0–50)	7.2
Alanine aminotransferase (n = 278)	18.9 ± 13.1 U/L	(0–40)	6.1
Lactate dehydrogenase (n = 274)	250.3 ± 76.7 U/L	(120–580)	1.5
Creatine kinase (n = 246)	110.7 ± 64.4 U/L	(26–310)	0.8
Blood urea nitrogen (n = 277)	4.0 ± 1.3 mmol/L	(1.8–8.2)	2.5
Creatinine (n = 279)	36.3 ± 16.5 μmol/L	(21–65)	4.3
Uric acid (n = 201)	4.1 ± 1.3 mg/dL	(1.8–8.0)	1.5
Sodium (n = 279)	139.6 ± 2.1 mEq/L	(133–146)	0.0
Potassium (n = 279)	4.2 ± 0.4 mEq/L	(3.3–6.1)	0.4
Procalcitonin (n = 123)	0.067 ± 0.117 ng/mL	(0–0.1)	16.3
C-reactive protein (n = 276)	3.6 ± 10.3 mg/L	(0–9)	9.1
Troponin-T (n = 30)	0.007 ± 0.004 ng/mL	(0–0.014)	6.7
D-dimer (n = 164)	0.60 ± 0.33 mg/L	(0–1.0)	8.5
Ferritin (n = 121)	51.6 ± 43.0 ng/mL	(10–300)	5.8
Interleukin-6, median (interquartile range) (n = 20)	1.55 (1.15) pg/mL	(0–7)	5.0

Imaging findings‡	n (%)
Chest X-Ray (n = 316]	
Normal finding	292 (92.4)
Consolidation	14 (4.4)
Air bronchogram	7 (2.2)
Overinflation	2 (2.2)
Reticular shadow	1 (0.3)
Opacity	1 (0.3)
Atelectasis	1 (0.3)
Pleural effusion	1(0.3)
Chest computed tomography, (n = 85]	
Normal finding	68 (80.0)
Ground-glass opacity	8 (9.4)
Consolidation	8 (9.4)
Air bronchogram	2 (2.4)
Atelectasis	1 (1.2)
Pleural effusion	1 (1.2)

†Out of reference value rate.
‡All that apply were checked.

Japan has been experiencing the third peak epidemic period, which is larger than the preceding two, since the third week in November 2020.[8] Limiting the statistics to pediatric cases, however, as of December 2020, the third epidemic peak was yet to be confirmed.

Notably, almost half of the patients in this study were asymptomatic throughout the course. In Japan, public health centers conduct extensive retrospective contact tracing of COVID-19 patients and comprehensive PCR tests of the people who had close contact with them. Thus, we assumed that many asymptomatic COVID-19 cases, including pediatric cases, were confirmed through this nationwide study.

In this study, patients aged <1 year old had the highest hospitalization rate (91.6%). A previous study suggested that young children, particularly infants, are vulnerable to infection.[2,9] However, there was no simple way to evaluate the difference in COVID-19 severity by hospitalization rate because COVID-19 patients, especially younger patients, are generally recommended to be hospitalized for observation and quarantine in Japan, even when they are asymptomatic or mildly symptomatic.

Although underlying health conditions, including chronic respiratory diseases, obesity, and neurological diseases, were common in hospitalized pediatric COVID-19 patients,[1,10,11] it is unclear whether these conditions influenced the severity and actual hospitalization rate among the children in this study because only a few of them had underlying health conditions. A previous study suggested that existing chronic conditions are independently associated with severe COVID-19 in children.[12]

© 2021 Japan Pediatric Society.

Table 4 Treatment administered

	n (%)
Hospitalization status (*n* = 840)	
Outpatient	131 (15.6)
Inpatient	709 (84.4)
General ward	705 (83.9)
Intensive care unit	4 (0.5)
Length of hospital stay	9.3 ± 5.2days
Length of intensive care unit stay	4, 8, 9, 14 days
Medication (*n* = 791)	
Intravenous fluids	49 (6.2)
Antiviral drug†	0 (0.0)
Hydroxychloroquine	0 (0.0)
Corticosteroid	12 (1.5)
Ciclesonide (inhaled steroid)	1 (0.1)
Other inhaled steroid‡	5 (0.6)
Oral steroid	1 (0.1)
Intravenous steroid	5 (0.6)
Antibiotics	25 (3.2)
Acetaminophen	61 (8.1)
Non-steroidal anti-inflammatory	1 (0.1)
Supportive care (*n* = 780)	
Oxygen therapy	11 (1.4)
Non-invasive ventilation	0 (0.0)
Invasive ventilation	1 (0.1)
Extracorporeal membrane oxygenation support	0 (0.0)
Inotropes/vasopressors	1 (0.1)
Prone position	1 (0.1)
Renal replacement therapy or dialysis	0 (0.0)

†Including ribavirin, lopinavir/ritonavir, neuraminidase inhibitor, favipiravir, remdesivir, interferon-α, and interferon-β.

‡All 5 cases had started to use inhaled steroids before they were infected. with COVID-19.

Table 5 Complications and outcomes

Complications (*n* = 786)	*n* (%)
Pneumonia	10 (1.3)
Bronchiolitis	5 (0.6)
Seizures	2 (0.3)
Cardiac arrhythmia†	2 (0.3)
Shock†	1 (0.1)
Encephalopathy‡	1 (0.1)
Cardiac arrest	1 (0.1)
Acute Respiratory Distress Syndrome	1 (0.1)
Bleeding	1 (0.1)
Acute renal injury	1 (0.1)
Liver dysfunction	1 (0.1)
MIS-C/PIMS Outcomes (*n* = 758)	
Discharged alive	665 (87.7)
Improved without admission	74 (9.8)
Transferred to another facility	19 (2.5)
Death	0 (0.0)

†Shock and cardiac arrhythmia were confirmed in one case.

‡Encephalopathy and cardiac arrest were confirmed in one case.

MIS-C/PIMS, multisystem inflammatory syndrome in children/pediatric inflammatory multisystem syndrome.

Multinational systematic reviews reported that 15–60% of pediatric COVID-19 cases were asymptomatic,[13] and the most commonly described symptoms in the pediatric age group were fever, cough, and sore throat (51.6%, 47.3%, and 17.9%, respectively).[1] In this study, almost half of our cases (47.9%) were asymptomatic. In addition, vital signs were also generally stable at the first hospital or clinical visit, and 84% of them were afebrile (<37.5°C). These results suggest that body temperature measurement is not sensitive to screen pediatric COVID-19 cases. In this study, other clinical symptoms in children were also less common than those reported in the previous reviews; even the most frequent symptoms such as runny nose and cough were present in approximately only 20% of the cases in this study.

In this study, similar to a previous review,[1] some patients experienced extra-respiratory symptoms such as diarrhea, headache, fatigue/malaise, dysgeusia, dysosmia, and vomiting. In particular, dysgeusia and dysosmia have been recognized as unusual symptoms that have a high likelihood of being related to COVID-19. However, both are reported less commonly in children.[14,15] Studies have not yet clarified why the clinical symptoms in most pediatric COVID-19 cases are mild. Previous reports hypothesized that children are less sensitive to SARS-CoV-2 because the maturity and function of angiotensin-converting enzyme 2, the receptor that SARS-CoV-2 uses for host cellular entry, may be lower than those in adults.[2,16]

Multisystem inflammatory syndrome in children (MIS-C) or pediatric inflammatory multisystem syndrome (PIMS), a severe inflammatory complication resembling Kawasaki disease, has been reported among African and Hispanic children in Europe and North America.[17–20] In Japan, as of December 2020, only one case of Kawasaki disease following COVID-19 was reported; however, it did not meet the diagnostic criteria for MIS-C/PIMS and improved with no coronary artery lesion.[21] Subsequently, as of June 2021, some suspected cases of MIS-C/PIMS were reported in Japan.[22–24] The mechanism of the epidemiological and clinical differences related to MIS-C/PIMS among children from different racial/ethnic background globally has not yet been clarified.

Lymphopenia had been found in 31–40% of pediatric COVID-19 cases,[9,25] and in approximately 80% of critically ill adult cases.[26] Contrarily, similar to the findings in other previous surveys,[27,28] abnormalities in the laboratory tests, such as the lymphocyte count and levels of inflammatory markers, cytokines, liver enzymes, biochemical markers of myocardial damage, and coagulation function markers, have been less frequently observed in this study.

Such a difference in laboratory test abnormalities may be explained by the difference in the COVID-19 severity found in our study population.

Previous studies have suggested that chest radiography might range from normal findings to the sign of SARS type appearance[29] and might fail to identify mild pediatric COVID-19 cases without significant clinical symptoms.[1,30] In this study, 92.4% of the pediatric COVID-19 cases had normal chest X-ray findings. Some previous studies reported that the most common CT finding was bilateral GGOs, which was detected in 30–60% of the pediatric cases.[3,30] However, routine CT scans in the pediatric setting causes unnecessary

© 2021 Japan Pediatric Society.

Table 6 Prior contact with a COVID-19 patient

	Entire period (n = 840)	Pre-reopen period (n = 449)	Post-reopen period (n = 391)	P-value
Age: mean ± standard deviation (years)	6.8 ± 4.8	6.6 ± 4.7	6.8 ± 4.9	0.42
Sex at birth, n (%)				
Male	440 (52.4)	244 (54.3)	196 (50.1)	0.52
Prior contact with a coronavirus disease 2019 patient, n (%)				
No	62 (7.4)	28 (6.2)	34 (8.7)	0.42
Yes	778 (92.6)	421 (93.8)	357 (91.3)	
Family members, n (%)	609 (72.5)	318 (70.9)	291 (74.5)	0.25
Father	267 (31.8)	144 (32.1)	123 (31.5)	0.88
Mother	182 (21.7)	82 (18.3)	100 (25.6)	<0.05
Parents	35 (4.2)	25 (5.6)	10 (2.6)	0.06
Sibling	22 (2.6)	11 (2.4)	11 (2.8)	0.83
Grandfather[†]	37 (4.4)	20 (4.5)	17 (4.3)	1.00
Grandmother[†]	39 (4.6)	21 (4.7)	18 (4.6)	1.00
Other family member	27 (3.2)	15 (3.3)	12 (3.1)	1.00
Members of the same school, n (%)	52 (6.2)	19 (4.2)[‡]	33 (8.4)	<0.05
Adult cases (teachers, etc.)		1 (0.2)	16 (4.1)	<0.05
Child cases (friends, etc.)		12 (2.7)	15 (3.8)	0.43
Unconfirmed cases		6 (1.3)	2 (0.5)	0.29
Members of the same kindergarten/nursery, n (%)	52 (6.2)	44 (9.8)[†]	8 (2.0)	<0.05
Adult cases (teachers, nurses, etc.)		29 (6.5)	6 (1.5)	<0.05
Child cases (friends, etc.)		13 (2.9)	2 (0.5)	<0.05
Unconfirmed cases		2 (0.4)	0 (0.0)	0.50
Members of the same private tutoring school, n (%)	8 (0.9)	3 (0.7)[†]	5 (1.3)	0.48
Others	57 (6.8)	37 (8.2)	20 (5.1)	0.08

[†]Including grandparents living with or without the index pediatric cases.
[‡]Children had a few opportunities to meet with their friends even pre-reopen period because not all schools, kindergartens and nurseries had closed completely.

exposure to radiation. In this study, only 85 cases (10.1%) underwent CT, and most of them (68 cases, 80.0%) had normal findings. This is also consistent with the hypothesis that we included more mild or asymptomatic cases, due to the study design, than other studies.

In this study, 709 cases (84.4%) were hospitalized, which was much higher than the percentages of hospitalized children <18 years of age in the US (5.7%).[31] As mentioned earlier, this result reflects the fact that most pediatric cases in Japan were hospitalized for quarantine and observation, even though they had no or mild clinical symptoms. However, medical resources are limited because of the increase in the number of cases among the elderly. Further discussion is required to determine the conditions for COVID-19 childhood admission.

We could not evaluate the efficacy of antiviral drugs because no child case was administered antiviral drugs in this study. The Pediatric Infectious Diseases Society guidelines suggest that antiviral therapy for COVID-19 is not necessary for most pediatric patients.[32]

A multinational, systematic review reported that severe and critically ill COVID-19 cases accounted for 2% and 0.6% of the total pediatric cases, respectively.[1] In this study, no fatal case was reported. Although four cases (0.5%) required ICU admissions, only one of them required invasive ventilation, and none of them required more aggressive supportive care such as ECMO, RRT, or dialysis. These data are consistent with those of previous studies, which reported that most pediatric COVID-19 cases are not severe. In addition, as of December 2020, there was no confirmed MIS-C/PIMS case in this study. Although the exact reason has not yet been clarified, MIS-C/PIMS has been reportedly rare in Asian countries,[33] compared with the US and European countries.

Previous studies reported that SARS-CoV-2 transmission to children mainly involves household contact, and adult family members are the most common primary source of infection.[1,3,13,34–36] Similarly, 72.5% of the cases in this study contracted the infection through household contact, most of which were adult-to-child transmission.

During the early period of COVID-19 pandemic, many countries implemented national school closures, despite the lack of data on the relative contribution of school closures to transmission control. A previous study reported that school closure was temporally associated with decreased COVID-19 incidence and mortality.[37] However, another study reported that school closures alone would prevent only 2–4% of the deaths,[38] which is much lower than that for other social distancing interventions, and that school closures alone hardly changed the epidemic curve.[39] Instead, some reviews have noted the disadvantages of school closures, including economic damage to working parents; loss of education; negative effect on child welfare, particularly among the most vulnerable pupils; and nutritional problems, especially in children for whom free school meals are an important source of nutrition.[38,40] In Japan, nationwide school closures were

© 2021 Japan Pediatric Society.

also implemented in March 2020, and most children had difficulty attending school until the normal school schedule was resumed in September 2020. Household transmission rates were similar between the pre- and post-reopen periods (70.9% and 74.5%, respectively). Although the transmission rate at school was significantly higher (33 cases, 8.4%) in post-reopen period than that in the pre-reopen period (19 cases, 4.2%) ($P < 0.05$), 16 cases (4.1%) contracted SARS-CoV-2 from adults (e.g., teachers). Child-to-child transmission among schoolmates occurred in 12 cases (2.7%) during the pre-reopen period and in 15 cases (3.8%) during the post-reopen period, and the difference was not statistically significant. These results suggest that SARS-CoV-2 transmission to children is mainly from family members, regardless of whether school is open or closed. Using an age-structured mathematical model, Davies *et al*. found that there was limited effectiveness in school closures.[41] Some academics, including members of the JPS and the American Academy of Pediatrics, advocated that opening schools does not significantly increase SARS-CoV-2 transmission in the community in general.[42,43]

The reason why the transmission rate from mothers increased significantly between pre-reopen period and post-reopen period is unknown. However, regarding all COVID-19 cases in Japan, the ratio of female COVID-19 cases in pre-reopen period (male:female = 1.3:1 as of 5 August 2020)[44] was lower than that of post-reopen period (male:female = 1.1:1 as of 29 December 2020).[8]"

This study had a few limitations. First, we were unable to assess the secondary infection rate from the reported pediatric cases, including transmission to family members, friends, and teachers. Second, only 4.9% of the nationwide pediatric cases in Japan were included in this study. We have been considering simplifying the survey content to improve the response rate. Third, each condition or complication, including pneumonia, bronchitis, shock, encephalopathy, and acute respiratory distress syndrome, was not clearly defined during the survey. These judgements were made by each physician, so there might be a bias for diagnosing the condition or complication, depending upon the reporting physicians. Fourth, recently, new variants of COVID-19 have been reported worldwide. However, no case due to new variants has been reported during the period of this study in Japan, and we could not evaluate the influence of such variants of SARS-CoV-2. Finally, it is difficult to generalize the results from this study as it included more mild or asymptomatic cases.

Conclusion

COVID-19 in children is less severe than in adults. Approximately half of the SARS-CoV-2-positive children were asymptomatic. School closure was had a limited effect on COVID-19 prevention among children. Household transmission, especially from adult family members, contributed the most to pediatric COVID-19 cases, even with schools being open.

Acknowledgments

We thank all the Japan Pediatric Society members who participated in this study.

Financial support

This work was supported by the Health and Labor Sciences Research Grants from the Ministry of Health, Labour and Welfare in Japan.

Disclosure

The authors declare no conflicts of interest.

Author contributions

T.K., S.N., K.T., A.S. and H.M. designed the study; T.K. and S.N. collected and analyzed data; T.K., S.N., A.S., and H.M. wrote the manuscript; N.S, K.O., K.T, T.N., H.K., K.A., N.I., S.I., M.O., N.O, R.K., S.K., S.S., T.T, N.N, H.H, M.F., M.H, Y.M., M.M., I.M., C.M., I.M., T.M., T.Y., T.W., H.A., K.K., K.O., A.S., and H.M. gave conceptual advice. All authors read and approved the final manuscript.

References

1 Liguoro I, Pilotto C, Bonanni M *et al*. SARS-COV-2 infection in children and newborns: a systematic review. *Eur. J. Pediatr.* 2020; **179**(7): 1029–46.
2 Dong Y, Mo X, Hu Y *et al*. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020; **145**: e20200702.
3 Lu X, Zhang L, Du H *et al*. SARS-CoV-2 infection in children. *N. Engl. J. Med.* 2020; **382**(17): 1663–5.
4 Derespina KR, Kaushik S, Plichta A *et al*. Clinical manifestations and outcomes of critically ill children and adolescents with coronavirus disease 2019 in New York City. *J. Pediatr.* 2020; **226**: 55–63.
5 Gaborieau L, Delestrain C, Bensaid P *et al*. Epidemiology and clinical presentation of children hospitalized with SARS-CoV-2 infection in suburbs of Paris. *J. Clin. Med.* 2020; **9**: 2227.
6 International Severe Acute Respiratory and Emerging Infection Consortium. *Clinical Data Collection – The COVID-19 Case Report Forms*. [Cited: 2020 Dec 31].Available from: https://isaric.org/research/covid-19-clinical-research-resources/covid-19-crf/
7 Japan Pediatric Society. *Information about epidemiology and clinical manifestation about pediatric COVID-19 cases in Japan using a national database (in Japanese)*. [Cited: 2020 Dec 31].Available from: http://www.jpeds.or.jp/modules/activity/index.php?content_id=350
8 Ministry of Health Labour and Welfare. *Epidemiology of COVID-19 in Japan*. [Cited: 2020 Dec 31].Available from: https://www.mhlw.go.jp/content/10906000/000713230.pdf
9 Zheng F, Liao C, Fan QH *et al*. Clinical characteristics of children with coronavirus disease 2019 in Hubei, China. *Curr. Med. Sci.* 2020; **40**: 275–80.
10 Stokes EK, Zambrano LD, Anderson KN *et al*. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. *MMWR Morb. Mortal Wkly. Rep.* 2020; **69**: 759–65.

© 2021 Japan Pediatric Society.

11 Shekerdemian LS, Mahmood NR, Wolfe KK *et al*. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr.* 2020; **174**: 868–73.
12 Preston LE, Chevinsky JR, Kompaniyets L *et al*. Characteristics and disease severity of US children and adolescents diagnosed with COVID-19. *JAMA Netw. Open.* 2021; **4**: e215298.
13 Rajmil L. Role of children in the transmission of the COVID-19 pandemic: A rapid scoping review. *BMJ Paediatr. Open.* 2020; **4**: e000722.
14 Kainth MK, Goenka PK, Williamson KA *et al*. Early experience of COVID-19 in a US Children's Hospital. *Pediatrics* 2020; **146**: e2020003186.
15 Shane AL, Sato AI, Kao C *et al*. A pediatric infectious diseases perspective of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and novel coronavirus disease 2019 (COVID-19) in children. *J. Pediatr. Infect. Dis. Soc.* 2020; **9**: 596–608.
16 Bunyavanich S, Do A, Vicencio A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. *JAMA* 2020; **323**: 2427–9.
17 Davies P, Evans C, Kanthimathinathan HK *et al*. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet. Child Adolesc. Health.* 2020; **4**: 669–77.
18 Feldstein LR, Rose EB, Horwitz SM *et al*. Multisystem inflammatory syndrome in U.S. children and adolescents. *N. Engl. J. Med.* 2020; **383**: 334–46.
19 Dufort EM, Koumans EH, Chow EJ *et al*. Multisystem inflammatory syndrome in children in New York State. *N. Engl. J. Med.* 2020; **383**: 347–58.
20 Jiang L, Tang K, Levin M *et al*. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet. Infect. Dis* 2020; **20**: e276–88.
21 Uda K, Okita K, Soneda K, Taniguchi K, Horikoshi Y. Kawasaki disease following coronavirus disease 2019 with prolonged fecal viral shedding. *Pediatr. Int.* 2020; **63**(5): 597–99. https://doi.org/10.1111/ped.14452
22 Fukuda S, Kaneta M, Miyake M *et al*. A case of multisystem inflammatory syndrome in children in a japanese boy: With discussion of cytokine profile. *Mod. Rheumatol. Case Rep.* 2021. https://doi.org/10.1080/24725625.2021.1920140. Online ahead of print.
23 Uchida M, Kashima Y, Mochizuki K *et al*. Multisystem inflammatory syndrome in children- a new syndrome complicated with acute heart failure following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *Circ. J.* 2021; **85**: 948–52. https://doi.org/10.1253/circj.CJ-21-0243
24 Baba T, Maruyama T, Katsuragi S *et al*. Multisystem inflammatory syndrome associated with SARS-CoV-2 in a Japanese girl. *Pediatr. Int.* 2021. https://doi.org/10.1111/ped.14704. Online ahead of print.
25 Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: An observational cohort study. *Lancet. Infect. Dis.* 2020; **20**: 689–96.
26 Guan WJ, Ni ZY, Hu Y *et al*. Clinical characteristics of coronavirus disease 2019 in China. *N. Engl. J. Med.* 2020; **382**(18): 1708–20.
27 Du W, Yu J, Wang H *et al*. Clinical characteristics of COVID-19 in children compared with adults in Shandong Province,China. *Infection.* 2020; **48**: 445–52.
28 Cui X, Zhang T, Zheng J *et al*. Children with coronavirus disease 2019: A review of demographic, clinical, laboratory, and imaging features in pediatric patients. *J. Med. Virol.* 2020; **92**(9): 1501–10.
29 Romberg EK, Menashe SJ, Kronman MP *et al*. Pediatric radiologic manifestations of COVID-19. *Clin. Imaging.* 2021; **75**: 165–70.
30 Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatr. Pulmonol.* 2020; **55**(5): 1169–74.
31 CDC Covid- Response Team. Coronavirus disease 2019 in children - United States, February 12-April 2, 2020. *MMWR Morb. Mortal Wkly. Rep.* 2020; **69**: 422–6.
32 Chiotos K, Hayes M, Kimberlin DW *et al*. Multicenter initial guidance on use of antivirals for children with COVID-19/SARS-CoV-2. *J. Pediatr. Infect. Dis. Soc.* 2020; **9**: 701–15.
33 Choe YJ, Choi EH, Choi JW *et al*. Surveillance of COVID-19-associated multisystem inflammatory syndrome in children, South Korea. *Emerg. Infect. Dis.* 2021; **27**(4): 1196–200.
34 Chang TH, Wu JL, Chang LY. Clinical characteristics and diagnostic challenges of pediatric COVID-19: A systematic review and meta-analysis. *J. Formos. Med. Assoc.* 2020; **119** (5): 982–9.
35 Posfay-Barbe KM, Wagner N, Gauthey M *et al*. COVID-19 in children and the dynamics of infection in families. *Pediatrics* 2020; **146**: e20201576.
36 Jiehao C, Jin X, Daojiong L *et al*. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin. Infect. Dis.* 2020; **71**(6): 1547–51.
37 Zimmerman FJ, Anderson NW. Association of the timing of school closings and behavioral changes with the evolution of the coronavirus disease 2019 pandemic in the US. *JAMA Pediatr.* 2020; **175**: 501.
38 Viner RM, Russell SJ, Croker H *et al*. School closure and management practices during coronavirus outbreaks including COVID-19: A rapid systematic review. *Lancet. Child Adolesc. Health* 2020; **4**: 397–404.
39 Wang X, Pasco RF, Du Z *et al*. Impact of social distancing measures on coronavirus disease healthcare demand, Central Texas, USA. *Emerg. Infect. Dis.* 2020; **26**: 2361–9.
40 Bin Nafisah S, Alamery AH, Al Nafesa A, Aleid B, Brazanji NA. School closure during novel influenza: A systematic review. *J. Infect. Public Health.* 2018; **11**: 657–61.
41 Davies NG, Klepac P, Liu Y *et al*. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat. Med.* 2020; **26**(8): 1205–11.
42 American Academy of Pediatrics. *COVID-19 Guidance for Safe Schools*. [Cited: 2021 Jan 29]. Available from: https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/covid-19-planning-considerations-return-to-in-person-education-in-schools/
43 Japan Pediatric Society. *Current status of medical findings regarding pediatric coronavirus disease 2019 (in Japanese)*. [Cited: 2021 Jan 29]. Available from: http://www.jpeds.or.jp/modules/activity/index.php?content_id=342
44 Ministry of Health Labour and Welfare. *Guideline for coronavirus disease 2019 (COVID-19)*, 3rd edn. [Cited: 2020 Dec 31].Available from: https://www.mhlw.go.jp/content/000668291.pdf

© 2021 Japan Pediatric Society.