Updates on Coronavirus Disease 2019 in Children in Japan

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Abstract: This review provides updates on coronavirus disease 2019 (COVID-19) in children in Japan by summarizing published data. By the end of March 2022, Japan had experienced 6 waves of COVID-19 outbreaks. Over this time, the clinical features presented among children have changed in the context of the predominant variants. Although the COVID-19 pandemic affected children in terms of medical, physical and psychosocial aspects, the clinical outcomes have been favorable in Japan compared with those in some European countries and the United States, which may be partly due to a lower incidence of multisystem inflammatory syndromes in children and obesity. The COVID-19 vaccine has been available for children; however, the vaccination rate in children 5–11 years of age is lower than that in older children due to the government’s lack of an active approach in this specific population. Further action is needed to improve the overall vaccination rates in children.

Key Words: children, coronavirus disease 2019, Japan, neonates

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The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first exploded in China in December 2019, has caused more than 520 million infections and 6 million deaths worldwide as of May 20, 2022. Approximately 11% of these infections were in the Western Pacific region, including Japan, where nearly 60 million infections and 230,000 deaths have occurred.2

Globally, as of May 21, 2022, children <20 years old accounted for 21% of the reported cases and 0.4% of the deaths according to the COVerAGE database (an open-access database compiled by the Max Planck Institute for Demographic Research).3 The incidence is affected by geography, rurality, social vulnerability, race/ethnicity and nonpharmaceutical interventions by national policy, such as mask-wearing, lockdown and school closure.4,5 Case fatality rates among children are higher in low- and middle-income versus high-income countries,6 and the disease characteristics and impact on children differ among countries. Although children with COVID-19 are often asymptomatic or mildly symptomatic with favorable outcomes, the COVID-19 pandemic has negatively impacted children in terms of the loss of learning opportunities, malnutrition, poverty and disruption of health services, such as routine childhood immunization.7 This review article utilizes the published data to characterize the pediatric COVID-19 in Japan.

EPIDEMIOLOGY

The first wave of COVID-19 was recognized in Japanese adults on January 15, 2020, in Kanagawa Prefecture, near Tokyo (Fig. 1).8,9 In mid-February 2020, the first pediatric patients with COVID-19 were diagnosed in Hokkaido, the northernmost island of Japan.10 Between January and February 2020, most cases in Japan were traced to patients who traveled from China and their contacts, after which local transmission without known linkage to imported cases led to the first wave.11 On February 1, 2020, COVID-19 was classified as a designated infectious disease, and medical expenses began to be publicly funded.12 During the first and second waves of COVID-19, the epidemiologic curves were parallel for cases among children <20 years of age and the total cases in all age groups.13 Children 0–9 years old accounted for 4% of primary cases,10 and the proportion of children <20 years of age reached its peak of <15% of the total cases in early October 2020.14 The most common source of infection in children was household members (32%).15 Secondary transmission from children 0–9 years old to others was uncommon; regardless of school closure, children did not play a major role in community transmission (Fig. 1).10

At the beginning of the fourth wave, in April 2021, the proportion of children <20 years of age to the total cumulative cases was low—3% for those <10 years and 7% for those ≥10 years old (Fig. 2A).16 Following the emergence of variants of concern (VOCs) that increased transmissibility to all age groups and the widespread availability of COVID-19 vaccination for eligible age groups,17 the proportion of new pediatric cases to total new cases increased by up to 35% in March 2022, which proportionally represents the trend down of infection among adults due to cases averted by vaccination18 (Fig. 3). During the sixth wave caused by the Omicron variant, in March 2022, the proportions of both pediatric age groups (<10 and ≥10 years) increased to 13%; thus, children <20 years old accounted for approximately one-quarter of the total cumulative cases (Fig. 2B).

The main source of infection in children was their family members. As of March 22, 2022, the Japan Pediatric Society (JPS) registry showed that 73% of SARS-CoV-2 transmissions occurred within households, 10% at school and 9% at nurseries/kindergartens among 5872 patients with COVID-19 <20 years of age.19 However, during the sixth wave with the Omicron variant, a change in the common source of infection in children was observed—the proportions of infection at school and nurseries/kindergartens increased up to 19% and 11%, respectively, whereas family member transmission decreased to 49% among 1583 children with COVID-19 between January and March 22, 2022.20

CLINICAL FEATURES OF GENERAL PEDIATRIC POPULATIONS

In contrast to the older age group with higher case fatality rates throughout the COVID-19 pandemic in Japan (Fig. 2), most
children with COVID-19 were asymptomatic or mildly symptomatic, possibly due to the differences in host immune status and response between children and adults. As of April 19, 2022, 12 deaths have been reported in Japan in children <20 years of age among 20 million children of the same age group (0.06 death rate per 100,000 children of the same age group). This death rate among pediatric population was lower than those in France (0.43), England and Wales (0.85) and the United States (2.06) as of April 23, 2022.

Data for clinical characteristics of Japanese children and adolescents with COVID-19 published by the end of March 2022 are summarized (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/E776). Two major pediatric registries were included; the JPS registry included both outpatients and inpatients.
and inpatients,30,31 and the other extracted pediatric data32,33 from patients of all ages in the COVID-19 registry in Japan, which is the largest COVID-19 registry of inpatients in Japan.34 Both registries were generated from physicians’ voluntary participation. Notably, the largest registries include only a fraction of pediatric patients—the JPS registry recorded 0.5% of the national pediatric number of COVID-19 cases as of February 28, 2022.31

Even in the inpatient registry until the third wave, approximately one-third of patients were asymptomatic.32 At that time, most pediatric patients, including asymptomatic and mildly symptomatic children, were hospitalized for isolation and observation by the Japanese government’s recommendations.30 Some children were also hospitalized because their parents developed severe COVID-19, and no other family members were allowed to provide care.32 As the total number of patients increased in the community, available hospital beds decreased and the quarantine of asymptomatic or mild cases transitioned from hospitals to hotels or home settings.33

In COVID-19 registry in Japan, the fifth wave by the Delta variant led to some changes, mainly higher proportions of young patients, patients with underlying diseases, symptomatic patients and intensive care unit (ICU) admissions.33 However, because no patients underwent mechanical ventilation (MV) or died, the outcomes remained favorable. During the sixth wave by the Omicron variant, the JPS registry showed fever, vomiting/nausea and seizures were more prominent.31 Although this registry did not include croup cases, the proportion of sore throat cases was higher in the sixth wave than in the wave before it. In fact, 3 cases of Japanese infants and children with croup were reported within a short period during the sixth wave,35 consistent with the US report showing a sharp increase in croup incidence with the emergence of Omicron.36 In contrast, dysgeusia and dysosmia became less frequent during the sixth wave.31 Although VOCs, especially Delta and Omicron variants, affected the clinical features in children, the proportion of pneumonia complications was similar regardless of predominant VOCs and myocarditis/pericarditis and encephalitis/encephalopathy were even rarer.11

A collaboration between JPS and the Japanese Society of Intensive Care Medicine provided another COVID-19 registry for pediatric severe and moderate cases. Between July 2021 (fifth wave, Delta) and March 27, 2022 (sixth wave, Omicron), 176 cases were reported.37,38 Notably, 72.2% (127 cases) were after January 1, 2022, during the Omicron period. The numbers of SARS-CoV-2-positive individuals were much higher during the Omicron period (997,460 between January 1, 2022, and March 8, 2022) than those before (173,932 between April 1, 2021, and December 31, 2021).39 The proportion of infants and preschool children (1–6 years old) increased from 10.2% and 26.5% to 25.4% and 46.8% in these periods, respectively. Although the proportion of ICU admissions was approximately 50% in both Delta and Omicron periods, the proportion of seizure cases nearly doubled from 12.2% to 23.0% and croup emerged with 15.1% of cases during the Omicron period as the cause of ICU admission. Pneumonia shifted from the first (40.8%) to the second (23.0%) ranking along with seizures for the cause of admission. Extracorporeal membrane oxygenation support was used for only 1 patient during the Delta period, whereas MV was indicated for 32.7% during this period and 25.4% during the Omicron period. Compared with the Delta period, a higher proportion of respiratory support by MV or high-flow nasal cannula was noted in preschool children during the Omicron period.40

**FIGURE 3.** Proportion of new COVID-19-positive cases by age group between April 2021 and March 2022. Data are as of March 13, 2022. Cases were excluded if their ages were unknown. The ratio for each month was calculated by age group based on the cumulative number of positive cases using a 7-day moving average.19 mRNA indicates messenger RNA.
Multisystem inflammatory syndrome in children (MIS-C) was recorded in 10 children during the Delta period and 8 during the Omicron period in the registry for pediatric severe and moderate cases of COVID-19, as of March 27, 2022.²³,³⁶ Although some cases of MIS-C in Japan were reported,⁴¹-⁴³ the incidence was far lower than that in the other countries, such as the United Kingdom,⁴⁴ Spain,⁴⁵ Poland⁴⁶ and the United States,⁴⁷ contrary to the higher incidence of Kawasaki disease in Japan.⁴⁸ The susceptibility to MIS-C is likely multifactorial, including genetic predisposition.⁴⁹

Factors contributing to the favorable outcomes in Japanese children are likely in part due to lower incidences of MIS-C and obesity.⁵³ Obesity was an independent risk factor for severe disease and death among hospitalized children.⁵¹ In contrast to a 20.9% obesity rate among the US hospitalized children with COVID-19,⁵² the comparable rate was 0.8%–2.0% in Japan (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/E776),³²,³³ and the rates in some European countries were somewhere between those in Japan and the United States,⁵³ although obesity definitions vary by the data source. The national estimated prevalence of obesity in children <20 years of age was 3.4% in boys and 2.4% in girls in Japan, which was lower than that of 3.8%–13.9% (boys) and 3.4%–13.5% (girls) in European countries and 12.4% (boys) and 13.4% (girls) in the United States.⁵⁴

SCHOOLS AND NURSERIES

As true globally,⁶ Japan closed schools nationally from March 2 to the end of May 2020 (Fig. 1), except for spring break and the period from the start of the new school year through April 23 (in Japan, a school year starts in early April after a couple of weeks of spring break). School closure continued until July, when summer break began, in large cities where the numbers of COVID-19 cases remained high. In September 2020, after the summer break, schools resumed regular activities with some restrictions to avoid superspreading events. No apparent effect of school closure was found to reduce the COVID-19 spread in Japan.⁵⁵ Instead, negative impacts of school closure were reported, including but not limited to mental health problems (eg, anxiety),⁶⁶ behavioral problems (eg, irritability),⁶⁷ social development issues,⁶⁸ weight gain,⁶⁹ later bedtimes,⁷⁰ longer internet use⁷¹ and increased parental stress.⁷² Although the number of suicides among students did not increase during the school closure,⁷³ it significantly increased after school reopening.⁷⁴ Schools and nurseries closed intermittently when COVID-19 cases were identified within the institutions to balance children’s health protection with learning objectives.⁷⁵

The emergence of the Omicron variant also impacted COVID-19 epidemiology in schools and nurseries/kindergartens. The number of outbreaks including ≥5 SARS-CoV-2-positive individuals increased by 1.8 times (from 9813 as of October 31, 2021, to 18,001 as of March 7, 2022) at all school levels, especially in elementary schools (6–12 years old), with increases of 35.7% to 50.8% among all schools during this time.⁶³,⁶⁴ Temporary nursery closures showed a similar trend; the peak number increased by 4.2 times (from 185 on September 2, 2021, to 777 on February 3, 2022).⁶⁵ Between January 2022 and February 2022, schools and kindergartens were closed by the whole institutions (9.4%) for an average of 2.5 days, by school grade (19.0%) for an average of 2.3 days and by classes (71.6%) for an average of 2.5 days.⁶⁵

Notably, adults and children in the community reflect school teachers/staff and students, implying a transmission chain can begin with teachers/staff and spread to students,⁶⁶ as in the community.⁶⁷ In fact, the main source of SARS-CoV-2 infection in teachers/staff was not within-household or school transmissions before and during the Omicron wave.⁶⁸ Therefore, JPS and the Japan Pediatric Association recommend vaccination for teachers/staff not only at schools but also in extracurricular activities, such as cram school and sports or cultural clubs.⁶⁸

COVID-19 VACCINES IN CHILDREN IN JAPAN

In Japan, COVID-19 vaccination started in February 2021, targeting healthcare workers and then adults older than 65 years in April 2021.⁷⁹ For children 12 years and older, 2 messenger RNA vaccines, BNT162b2 and mRNA-1273, have been used for the first 2 doses since June 2021 and August 2021, respectively, and BNT162b2 vaccine has been used for the third dose since late March 2022. For children 5–11 years old, the BNT162b2 vaccine has been used for the 2 doses since late February 2022 (Fig. 1). The National Immunization Act did not make it compulsory to vaccinate children 5–11 years old, given the lack of enough data for this age group. As of April 27, 2022, 8.2% of children 5–11 years and 75.7% of those 12–19 years of age received 2 vaccine doses (vs. 92.6% for 2 doses and 87.4% for 3 doses in adults 65 years or older).⁸⁰ Adverse events following immunization were reported by hospitals or manufacturers to the Pharmaceuticals and Medical Devices Agency.⁸¹ The reporting criteria include specific disorders such as myocarditis and thrombosis, any symptoms leading to hospitalization, disability or death that were deemed related to COVID-19 vaccination by physicians; and other specified conditions such as seizure and Guillain-Barré syndrome, regardless of the disease severity according to the Brighton Collaboration definition.⁸² Adverse events of BNT162b2 vaccine in children 5–11 years old were rare; 1 case of suspected myocarditis/pericarditis was reported as of April 1, 2022, which resolved.⁸³ Two internet surveys have assessed the parents’ COVID-19 vaccine hesitancy before pediatric vaccination in Japan.⁷⁴,⁷⁵ Multi-ple factors were identified: social media rather than official information as the most reliable source; low perceived risk of infection; sex differences of respondents (mothers vs. fathers); lower satisfaction in social relationships during the social distancing era;⁸⁶ uncertainty about vaccine safety; potential adverse effects and mistrust in vaccine efficiency.⁸⁷ More than 40% of participants trusted public information the most in Japan,⁷⁴ and the US survey suggested more than two-thirds of parents agree with pediatricians’ recommendations for vaccination.⁷⁶ To help parental decision-making for COVID-19 vaccination, governmental organizations (eg, Ministry of Health, Labour and Welfare), academic societies (eg, JPS) and local medical associations should continue to provide updated objective data.

EPIDEMIOLOGIC CHANGES OF OTHER DISEASES DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic changed the landscape of pediatric infectious diseases and provided some insights into various infectious diseases. Strict infection prevention, such as increased awareness of hand hygiene, mask-wearing, physical distancing and activity restrictions, greatly reduced viral and bacterial infections⁷⁷,⁷⁸ and outpatient visits and hospitalizations in children in Japan,⁷⁹ similar to the United States and Europe.⁸⁰,⁸¹ The incidence of Kawasaki disease also declined, suggesting certain infections play a significant role in this disease pathogenesis.⁸² The trajectory of the respiratory syncytial virus was unique. After quite low activity in 2020,⁷⁷,⁷⁸ an unprecedented surge occurred in summer 2021,⁸² as also observed in other countries, likely due to the accumulation of susceptible populations.⁸³ The incidence of rhinovirus infection was also increased in children younger than 10 years between June 2020 and September 2020.⁷³ Interestingly, also observed were a high
incidence of rhinovirus infection and low incidence of COVID-19 in children younger than 10 years, as well as low incidence of rhinovirus infection and high incidence of COVID-19 in those 10 years or older, suggesting viral interference between rhinovirus and SARS-CoV-2. Indeed, rhinovirus suppressed SARS-CoV-2 replication in vitro.18 In contrast, the COVID-19 pandemic did not change the exanthema subitum incidence,19,20 suggesting causative agents, such as human herpesvirus types 6 or 7, are transmitted primarily among family members, not in the community.19

CONCLUSIONS
This review provided updates on COVID-19 in children in Japan. Given the emergence of VOCs, the future of the pandemic is unpredictable. The epidemiology, clinical features, vaccination rates and impact of the COVID-19 pandemic vary according to countries, depending on factors, such as geography, ethnicity, medical systems and disease control policies. Tailored measures are continuously required based on analyses of the individual COVID-19 situation in each country.

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