Updates on Coronavirus Disease 2019 in Children in Japan

Yuta Aizawa, MD, PhD, Sayaka Takanashi, MD, PhD,† and Chikara Ogimi, MD, PhD‡*

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

(*Pediatr Infect Dis J* 2022;41:e461–e467)

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,[1] 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.[4–6] Case fatality rates among children are higher in low- and middle-income versus high-income countries,[7] 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.[8] 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).[9,10] In mid-February 2020, the first pediatric patients with COVID-19 were diagnosed in Hokkaido, the northernmost island of Japan.[12] 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.[9] On February 1, 2020, COVID-19 was classified as a designated infectious disease, and medical expenses began to be publicly funded.[13]

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.[14] 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%).[14] 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).[15] 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 trending down of infection among adults due to cases averted by vaccination[18] (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.[20] 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

Accepted for publication June 24, 2022

From the *Department of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; and †Immunization Group, Center for Surveillance, Immunization, and Epidemiologic Research, National Institute of Infectious Diseases, and ‡Division of Infectious Diseases, Department of Medical Subspecialties, National Center for Child Health and Development, Tokyo, Japan.

Financial support for this study was provided by the Grant of National Center for Child Health and Development (30E-1).

The authors have no conflicts of interest to disclose.

Address for correspondence: Yuta Aizawa, MD, PhD, Department of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan. E-mail: yaizawa@med.niigata-u.ac.jp.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/22/4111-e461
DOI: 10.1097/INF.0000000000003641

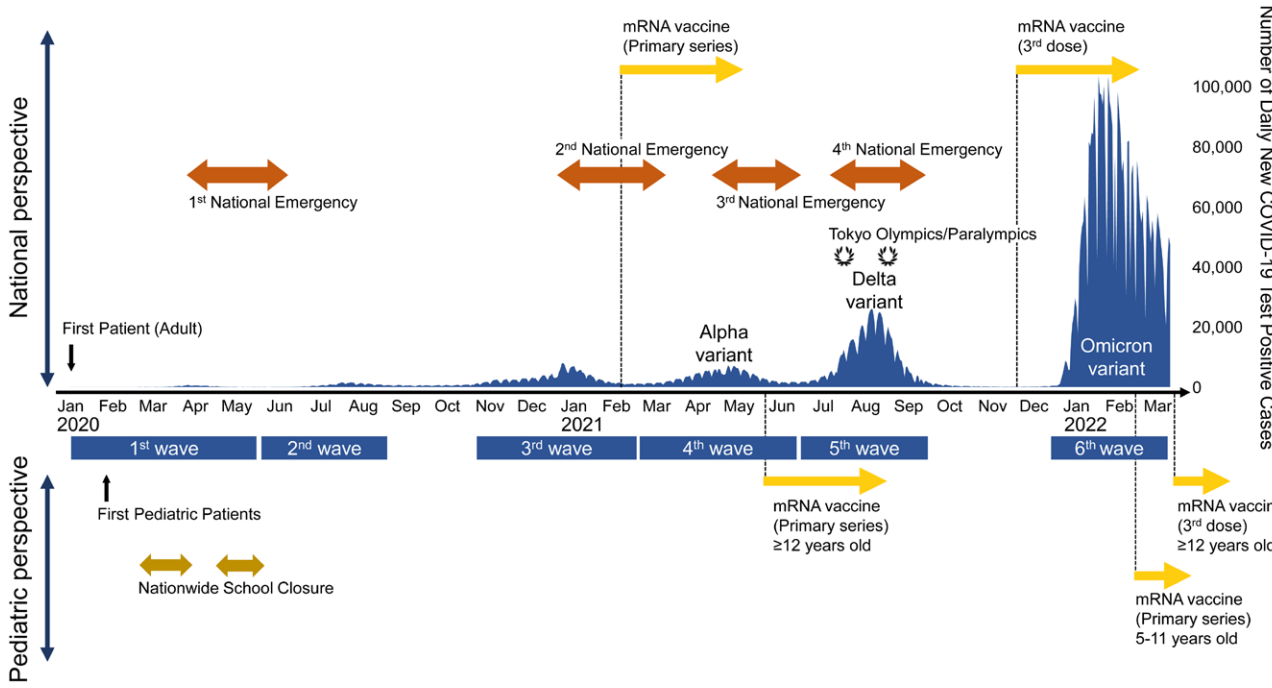

FIGURE 1. Timeline of COVID-19 events in Japan. Milestones for COVID-19 in Japan are described from both national and pediatric perspectives. Daily new COVID-19 test positive cases were derived from the database of the Ministry of Health, Labour and Welfare in Japan as of March 25, 2022.[11] mRNA indicates messenger RNA.

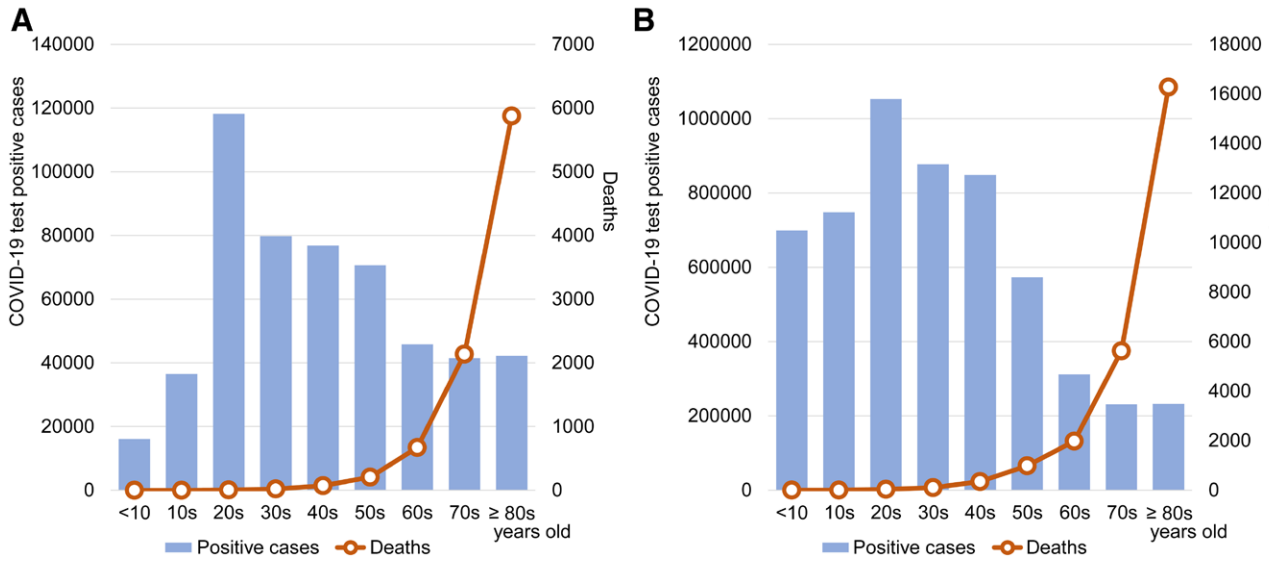

FIGURE 2. Number of COVID-19-positive cases and deaths by age group. Cumulative numbers were used for cases as of April 21, 2021 (A: at start of the fourth wave by the Alpha variant)[15] and March 15, 2022 (B: amid the sixth wave by the Omicron variant).[16]

children with COVID-19 were asymptomatic or mildly symptomatic,[21] possibly due to the differences in host immune status and response between children and adults.[22] 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).[23,24] This death rate among pediatric population was lower than those in France (0.43),[25] England and Wales (0.85)[26,27] and the United States (2.06) as of April 23, 2022.[28,29]

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

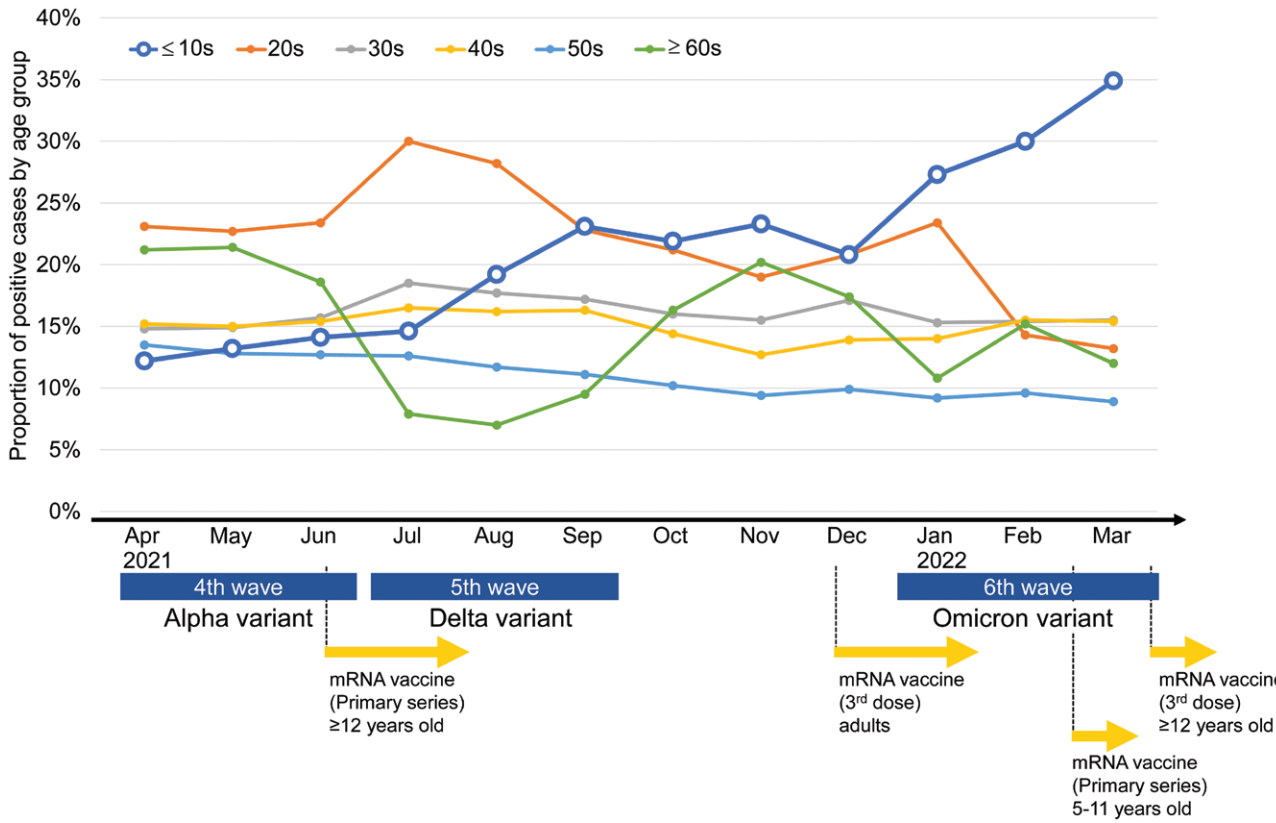

FIGURE 3. Proportion of new COVID-19-positive cases by age group between April 2021 and March 2022. Data are as of March 13, 2022. Cases were excluded if their ages were unknown. The ratio for each month was calculated by age group based on the cumulative number of positive cases using a 7-day moving average.[19] mRNA indicates messenger RNA.

and inpatients,[30,31] and the other extracted pediatric data[32,33] 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.[31]

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]

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.[37,38] Although some cases of MIS-C in Japan were reported,[41–45] the incidence was far lower than that in the other countries, such as the United Kingdom,[46] Spain,[47] Poland[48] and the United States,[49] contrary to the higher incidence of Kawasaki disease in Japan.[20] The susceptibility to MIS-C is likely multifactorial, including genetic predisposition.[50]

Factors contributing to the favorable outcomes in Japanese children are likely in part due to lower incidences of MIS-C and obesity.[33] 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),[56] behavioral problems (eg, irritability),[57] social development issues,[58] weight gain,[57] later bedtimes,[59] longer internet use[59] and increased parental stress.[60] Although the number of suicides among students did not increase during the school closure,[61] it significantly increased after school reopening.[62] Schools and nurseries closed intermittently when COVID-19 cases were identified within the institutions to balance children's health protection with learning opportunities.[63]

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.[63]

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.[63] 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.[69] 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).[70] Adverse events following immunization were reported by hospitals or manufacturers to the Pharmaceuticals and Medical Devices Agency.[71] The reporting criteria include specified 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.[72] 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.[73]

Two internet surveys have assessed the parents' COVID-19 vaccine hesitancy before pediatric vaccination in Japan.[74,75] Multiple 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[74]; uncertainty about vaccine safety; potential adverse effects and mistrust in vaccine efficiency.[75] 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 infections[77,78] 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.[77] 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.[78] 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.[84] In contrast, the COVID-19 pandemic did not change the exanthema subitum incidence,[77,85] suggesting causative agents, such as human herpesvirus types 6 or 7, are transmitted primarily among family members, not in the community.[85]

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.

ACKNOWLEDGMENTS

The authors thank Dr. Tatsuki Ikuse, the Department of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences, for helping with the figure design. The authors also thank Dr. Hiroyuki Moriuchi, the Department of Pediatrics, Nagasaki University Graduate School of Biomedical Sciences, and Dr. Akihiko Saitoh, the Department of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences, for the critical review of our article.

REFERENCES

1. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382:1199–1207.
2. World Health Organization. WHO Coronavirus (COVID-19) dashboard. 2022. Available at: https://covid19.who.int/. Accessed May 23, 2022.
3. UNICEF. COVID-19 confirmed cases and deaths. 2022. Available at: https://data.unicef.org/resources/covid-19-confirmed-cases-and-deaths-dashboard/. Accessed May 25, 2022.
4. Li Z, Lewis B, Berney K, et al. Social vulnerability and rurality associated with higher SARS-CoV-2 infection-induced seroprevalence: a nationwide blood donor study, United States, July 2020 - June 2021 [published online ahead of print February 7, 2022]. *Clin Infect Dis*. doi:10.1093/cid/ciac105.
5. Hsiang S, Allen D, Annan-Phan S, et al. The effect of large-scale anti-contagion policies on the COVID-19 pandemic. *Nature*. 2020;584:262–267.
6. Buonsenso D, Roland D, De Rose C, et al. Schools closures during the COVID-19 pandemic: a catastrophic global situation. *Pediatr Infect Dis J*. 2021;40:e146–e150.
7. Kitano T, Kitano M, Krueger C, et al. The differential impact of pediatric COVID-19 between high-income countries and low- and middle-income countries: a systematic review of fatality and ICU admission in children worldwide. *PLoS One.* 2021;16:e0246326.
8. UNICEF. COVID-19 and children. 2022. Available at: https://data.unicef.org/covid-19-and-children/. Accessed May 25, 2022.
9. Furuse Y, Ko YK, Saito M, et al; National Task Force for COVID-19 Outbreak in Japan. Epidemiology of COVID-19 outbreak in Japan, from January-March 2020. *Jpn J Infect Dis*. 2020;73:391–393.
10. Ko YK, Furuse Y, Ninomiya K, et al. Secondary transmission of SARS-CoV-2 during the first two waves in Japan: demographic characteristics and overdispersion. *Int J Infect Dis*. 2022;116:365–373.
11. Ministry of Health, Labour and Welfare, Japan. Open data (in Japanese). 2022. Available at: https://www.mhlw.go.jp/stf/covid-19/open-data.html. Accessed March 26, 2022.
12. Kakuya F, Okubo H, Fujiyasu H, et al. The first pediatric patients with coronavirus disease 2019 (COVID-19) in Japan: risk of co-infection with other respiratory viruses. *Jpn J Infect Dis*. 2020;73:377–380.
13. Ministry of Justice, Japan. Act on the prevention of infectious diseases and medical care for patients with infectious diseases. 2014. Available at: https://www.japaneselawtranslation.go.jp/en/laws/view/2830. Accessed April 29, 2022.
14. Imamura T, Saito M, Ko YK, et al; National COVID-19 Cluster Response Taskforce. Roles of children and adolescents in COVID-19 transmission in the community: a retrospective analysis of nationwide data in Japan. *Front Pediatr*. 2021;9:705882.
15. Ministry of Education, Culture, Sports, Science and Technology, Japan. New lifestyle at school Ver.6 (in Japanese). 2021. Available at: https://www.mext.go.jp/content/20210428-mxt_kouhou01-000004520_1.pdf. Accessed May 23, 2022.
16. Ministry of Health, Labour and Welfare, Japan. The 77th COVID-19 advisory committee (in Japanese). 2022. Available at: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00333.html. Accessed March 25, 2022.
17. Zhang Y, Zhang H, Zhang W. SARS-CoV-2 variants, immune escape, and countermeasures. *Front Med*. 2022;16:196–207.
18. Ledford H. How severe are Omicron infections? *Nature*. 2021;600:577–578.
19. Ministry of Health, Labour and Welfare. The 76th COVID-19 advisory committee (in Japanese). 2022. Available at: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000121431_00333.html. Accessed March 25, 2022.
20. Ministry of Health Labour and Welfare, Japan. Clinical guidance of COVID-19 version 7.1 (in Japanese). 2022. Available at: https://www.mhlw.go.jp/content/000923423.pdf. Accessed April 6, 2022.
21. Yasuhara J, Kuno T, Takagi H, et al. Clinical characteristics of COVID-19 in children: a systematic review. *Pediatr Pulmonol*. 2020;55:2565–2575.
22. Yoshida M, Worlock KB, Huang N, et al; NU SCRIPT Study Investigators. Local and systemic responses to SARS-CoV-2 infection in children and adults. *Nature*. 2022;602:321–327.
23. Ministry of Health Labour and Welfare, Japan. The preliminary figures in the updates of COVID-19 in Japan as of April 19, 2022 (in Japanese). 2022. Available at: https://www.mhlw.go.jp/content/10906000/000931620.pdf. Accessed April 24, 2022.
24. Statistics Bureau of Japan. Population estimates (in Japanese). 2022. Available at: https://www.stat.go.jp/data/jinsui/new.html. Accessed May 23, 2022.
25. Ined. The demography of COVID-19 deaths. 2022. Available at: https://dc-covid.site.ined.fr/en/data/france/. Accessed May 23, 2022.
26. Office for National Statistics. Dataset deaths registered weekly in England and Wales, provisional, as of April 15, 2022. 2022. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/weeklyprovisionalfiguresondeathsregisteredinenglandandwales. Accessed May 1, 2022.
27. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2020. 2021. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2020#age-structure-of-the-uk-population. Accessed May 24, 2022.
28. Centers for Disease Control and Prevention. Demographic trends of COVID-19 cases and deaths in the US reported to CDC. 2022. Available at: https://covid.cdc.gov/covid-data-tracker/#demographics. Accessed April 24, 2022.
29. United States Census Bureau. Population under age 18 declined last decade. 2021. Available at: https://www.census.gov/library/stories/2021/08/united-states-adult-population-grew-faster-than-nations-total-population-from-2010-to-2020.html#:~:text=By%20comparison%2C%20the%20younger%20population,from%2074.2%20million%20in%202010. Accessed May 25, 2022.
30. Katsuta T, Shimizu N, Okada K, et al. The clinical characteristics of pediatric coronavirus disease 2019 in 2020 in Japan. *Pediatr Int*. 2022;64:e14912.
31. The Committee on Immunization and Infectious Diseases, Japan Pediatric Society. Third interim analysis of pediatric database on COVID-19 in Japan (in Japanese). 2022. Available at: http://www.jpeds.or.jp/modules/activity/index.php?content_id=385. Accessed March 29, 2022.
32. Shoji K, Akiyama T, Tsuzuki S, et al. Clinical characteristics of hospitalized COVID-19 in children: report from the COVID-19 registry in Japan. *J Pediatric Infect Dis Soc*. 2021;10:1097–1100.
33. Shoji K, Akiyama T, Tsuzuki S, et al. Comparison of the clinical characteristics and outcomes of COVID-19 in children before and after the emergence of Delta variant of concern in Japan. *J Infect Chemother*. 2022;28:591–594.
34. Matsunaga N, Hayakawa K, Terada M, et al. Clinical epidemiology of hospitalized patients with coronavirus disease 2019 (COVID-19) in Japan: report of the COVID-19 registry Japan. *Clin Infect Dis*. 2021;73:e3677–e3689.
35. Murata Y, Tomari K, Matsuoka T. Children with croup and SARS-CoV-2 infection during the large outbreak of Omicron. *Pediatr Infect Dis J*. 2022;41:e249.
36. Brewster RC, Parsons C, Laird-Gion J, et al. COVID-19-associated croup in children. *Pediatrics.* 2022;149:e2022056492.

37. The Japanese Society of Intensive Care Medicine, Japan Pediatric Society. Preliminary report of severe and moderate cases in children with COVID-19 as of November 1, 2021 (in Japanese). 2021. Available at: https://www.jpeds.or.jp/modules/members/index.php?content_id=140. Accessed April 6, 2022.
38. The Japanese Society of Intensive Care Medicine, Japan Pediatric Society. Preliminary report of severe and moderate cases in children with COVID-19 as of March 27, 2022 (in Japanese). 2022. Available at: https://www.jpeds.or.jp/modules/members/index.php?content_id=140. Accessed March 31, 2022.
39. Ministry of Health Labour and Welfare, Japan. The 31st meeting of committee on immunization on March 24, 2022 (in Japanese). 2022. Available at: https://www.mhlw.go.jp/stf/shingi2/0000192554_00021.html. Accessed May 4, 202 2022. 2.
40. The Japanese Society of Intensive Care Medicine, Japan Pediatric Society. Preliminary report of severe and moderate cases in children with COVID-19 as of April 4, 2022 (in Japanese). 2022. Available at: http://www.jpeds.or.jp/modules/members/index.php?content_id=140. Accessed April 6, 2022.
41. Yamaguchi Y, Takasawa K, Irabu H, et al. Infliximab treatment for refractory COVID-19-associated multisystem inflammatory syndrome in a Japanese child. *J Infect Chemother*. 2022;28:814–818.
42. Baba T, Maruyama T, Katsuragi S, et al. Multisystem inflammatory syndrome associated with SARS-CoV-2 in a Japanese girl. *Pediatr Int*. 2022;64:e14704.
43. Ogihara A, Miyata Y, Hosaki A, et al. A Japanese case of multisystem inflammatory syndrome in children. *Pediatr Int*. 2021;64:e14869.
44. 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;5:442-447.
45. 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;85:948–952.
46. Swann OV, Holden KA, Turtle L, et al; ISARIC4C Investigators. Clinical characteristics of children and young people admitted to hospital with Covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ*. 2020;370:m3249.
47. García-Salido A, de Carlos Vicente JC, Belda Hofheinz S, et al; Spanish Pediatric Intensive Care Society working group on SARS-CoV-2 infection. Severe manifestations of SARS-CoV-2 in children and adolescents: from COVID-19 pneumonia to multisystem inflammatory syndrome: a multicentre study in pediatric intensive care units in Spain. *Crit Care*. 2020;24:666.
48. Ludwikowska KM, Okarska-Napierała M, Dudek N, et al; MOIS CoR Study Group. Distinct characteristics of multisystem inflammatory syndrome in children in Poland. *Sci Rep*. 2021;11:23562.
49. Miller AD, Zambrano LD, Yousaf AR, et al. Multisystem inflammatory syndrome in children-United States, February 2020-July 2021 [published online ahead of print December 5, 2021]. *Clin Infect Dis*. doi:10.1093/cid/ciab1007.
50. Dennis-Heyward EA. Disparities in susceptibility to multisystem inflammatory syndrome in children. *JAMA Pediatr*. 2021;175:892–893.
51. Harwood R, Yan H, Talawila Da Camara N, et al. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: a systematic review and individual patient meta-analysis. *EClinicalMedicine*. 2022;44:101287.
52. Woodruff RC, Campbell AP, Taylor CA, et al. Risk factors for severe COVID-19 in children [published online ahead of print December 22, 2021]. *Pediatrics*. doi:10.1542/peds.2021-053418.
53. Bundle N, Dave N, Pharris A, et al. COVID-19 trends and severity among symptomatic children aged 0-17 years in 10 European Union countries, 3 August 2020 to 3 October 2021. *Euro Surveill*. 2021;26:2101098.
54. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384:766–781.
55. Fukumoto K, McClean CT, Nakagawa K. No causal effect of school closures in Japan on the spread of COVID-19 in spring 2020. *Nat Med*. 2021;27:2111–2119.
56. Kishida K, Tsuda M, Waite P, et al. Relationships between local school closures due to the COVID-19 and mental health problems of children, adolescents, and parents in Japan. *Psychiatry Res*. 2021;306:114276.
57. Ueno C, Yamamoto S. The relationship between behavioral problems and screen time in children during COVID-19 school closures in Japan. *Scand J Child Adolesc Psychiatr Psychol*. 2022;10:1–8.
58. Hagihara H, Yamamoto N, Meng X, et al. COVID-19 school and kindergarten closure relates to children's social relationships: a longitudinal study in Japan. *Sci Rep*. 2022;12:814.
59. Nakayama H, Matsuzaki T, Mihara S, et al. Change of internet use and bedtime among junior high school students after long-term school closure due to the coronavirus disease 2019 pandemic. *Children (Basel)*. 2021;8:480.
60. Takaku R, Yokoyama I. What the COVID-19 school closure left in its wake: evidence from a regression discontinuity analysis in Japan. *J Public Econ*. 2021;195:104364.
61. Isumi A, Doi S, Yamaoka Y, et al. Do suicide rates in children and adolescents change during school closure in Japan? The acute effect of the first wave of COVID-19 pandemic on child and adolescent mental health. *Child Abuse Negl*. 2020;110(pt 2):104680.
62. Kobayashi J, Takeuchi R, Toyama Y, et al. Urgent need to strengthen school health in Asia and the Pacific islands. *Pediatr Int*. 2021;63:1419–1423.
63. Ministry of Education, Culture, Sports, Science and Technology, Japan. New lifestyle at school Ver.8 (in Japanese). 2022. Available at: https://www.mext.go.jp/a_menu/coronavirus/mext_00029.html. Accessed April 10, 2022.
64. Ministry of Education, Culture, Sports, Science and Technology, Japan. New lifestyle at school Ver.7 (in Japanese). 2021. Available at: https://www.mext.go.jp/content/20211122-mxt_kouhou01-000004520_4.pdf. Accessed May 23, 2022.
65. Ministry of Health, Labour and Welfare, Japan. The situation of temporary closure of nurseries by novel coronavirus (in Japanese). 2022. Available at: https://www.mhlw.go.jp/content/11920000/000919748.pdf. Accessed April 10, 2022.
66. Aizawa Y, Shobugawa Y, Tomiyama N, et al. Coronavirus disease 2019 cluster originating in a primary school teachers' room in Japan. *Pediatr Infect Dis J*. 2021;40:e418–e423.
67. Furuse Y, Tsuchiya N, Miyahara R, et al. COVID-19 case-clusters and transmission chains in the communities in Japan. *J Infect*. 2022;84:248–288.
68. Japan Pediatric Society, Japan Pediatric Association. The activities at school during COVID-19 pandemic as of March 2022 (in Japanese). 2022. Available at: http://www.jpeds.or.jp/modules/guidelines/index.php?content_id=141. Accessed March 31, 2022.
69. Prime Minister's Office of Japan. Schedule of novel coronavirus vaccine (in Japanese). 2022. Available at: https://www.kantei.go.jp/jp/headline/kansensho/vaccine_supply.html. Accessed April 11, 2022.
70. Prime Minister's Office of Japan. Novel coronavirus vaccine as of April 27, 2022 (in Japanese). 2022. Available at: https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html?msclkid=0a05e160c5f811ec958f57ce695e8f2b. Accessed April 29, 2022.
71. Katsuta T, Moser CA, Feemster KA, et al. Comparison of immunization systems in Japan and the United States - what can be learned? *Vaccine*. 2020;38:7401–7408.
72. Ministry of Health, Labour and Welfare, Japan. Request for reporting suspected adverse events following COVID-19 immunization (in Japanese). 2021. Available at: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/vaccine_hukuhannou_youshikietc.html. Accessed May 24, 2022.
73. Ministry of Health, Labour and Welfare, Japan. The 78th meeting on adverse effects of vaccination on April 13, 2022 (in Japanese). 2022. Available at: https://www.mhlw.go.jp/stf/shingi2/0000208910_00040.html. Accessed April 24, 2022.
74. Horiuchi S, Sakamoto H, Abe SK, et al. Factors of parental COVID-19 vaccine hesitancy: a cross sectional study in Japan. *PLoS One*. 2021;16:e0261121.
75. Yoda T, Katsuyama H. Parents' hesitation about getting their children vaccinated against COVID-19 in Japan. *Hum Vaccin Immunother*. 2021;17:4993–4998.
76. Szilagyi PG, Shah MD, Delgado JR, et al. Parents' intentions and perceptions about COVID-19 vaccination for their children: results from a national survey. *Pediatrics*. 2021;148:e2021052335.
77. Ae R, Shibata Y, Kosami K, et al. Kawasaki disease and pediatric infectious diseases during the coronavirus disease 2019 pandemic. *J Pediatr*. 2021;239:50-58.e2.
78. Takashita E, Kawakami C, Momoki T, et al. Increased risk of rhinovirus infection in children during the coronavirus disease-19 pandemic. *Influenza Other Respir Viruses*. 2021;15:488–494.
79. Shichijo K, Takeuchi S, Tayama T, et al. Patient attendance at a pediatric emergency referral hospital in an area with low COVID-19 incidence. *PLoS One*. 2021;16:e0258478.

80. DeLaroche AM, Rodean J, Aronson PL, et al. Pediatric emergency department visits at US children's hospitals during the COVID-19 pandemic. *Pediatrics*. 2021;147:e2020039628.

81. Dopfer C, Wetzke M, Zychlinsky Scharff A, et al. COVID-19 related reduction in pediatric emergency healthcare utilization - a concerning trend. *BMC Pediatr*. 2020;20:427.

82. Ujiie M, Tsuzuki S, Nakamoto T, et al. Resurgence of respiratory syncytial virus infections during COVID-19 pandemic, Tokyo, Japan. *Emerg Infect Dis*. 2021;27:2969–2970.

83. Li Y, Wang X, Cong B, et al. Understanding the potential drivers for respiratory syncytial virus rebound during the coronavirus disease 2019 pandemic. *J Infect Dis*. 2022;225:957–964.

84. Dee K, Goldfarb DM, Haney J, et al. Human rhinovirus infection blocks severe acute respiratory syndrome coronavirus 2 replication within the respiratory epithelium: implications for COVID-19 epidemiology. *J Infect Dis*. 2021;224:31–38.

85. Tachikawa J, Aizawa Y, Ikuse T, et al. Changes in exanthema subitum incidence and patient age distribution during the COVID-19 pandemic in Japan. *Pediatr Infect Dis J*. 2022;41:e90–e92.