

Impact of the Coronavirus Disease 2019 Pandemic on the Clinical Features of Pediatric Respiratory Syncytial Virus Infection in Japan

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Background. Mitigation measures implemented during the coronavirus disease 2019 (COVID-19) pandemic remarkably reduced the incidence of infectious diseases among children. However, a re-emergence of respiratory syncytial virus (RSV) infection was observed in 2021 in Japan. We compared the clinical characteristics of hospitalized patients with RSV infection before and during COVID-19.

Methods. We retrospectively enrolled children aged <6 years who were hospitalized with RSV infection in 18 hospitals and compared their clinical characteristics before (January 2019 to April 2020, 1675 patients) and during COVID-19 (September 2020 to December 2021, 1297 patients).

Results. The mean age of patients with RSV infection was significantly higher during COVID-19 than before (17.4 vs 13.7 months, $P < .001$). Compared with before COVID-19, a 2.6-fold increase in RSV cases in the 2–5 years age group was observed from sentinel surveillance during COVID-19, whereas a 1.2-fold increase was noted in the same age group among hospitalized patients. On average for all patients, consolidation shadows obtained on radiography were less frequently observed (26.1 vs 29.6%, $P = .04$), and reduced respiratory assistance (42.2% vs 48.7%, $P < .001$) and hospitalization stay (5.7 vs 6.0 days, $P < .001$) was required in patients with RSV infection during COVID-19.

Conclusions. Coronavirus disease 2019 and social activity restriction caused epidemiological changes in pediatric RSV infections, and a majority of patients with RSV infection aged ≥ 2 years did not develop severe symptoms requiring hospitalization. The RSV symptoms during the COVID-19 outbreak were equivalent to or milder than in the previous seasons.

Keywords. COVID-19; pediatric; RSV; SARS-CoV-2.

Respiratory syncytial virus (RSV) is a major cause of acute lower respiratory tract infections in infants, usually having a particular seasonality each year in temperate regions [1]. In Japan, respiratory syncytial virus infection used to be prevalent in autumn and winter, but the epidemic season has shifted to summer since ~2017 without precise reasons [2]. For high-risk infants of RSV infection, palivizumab, a humanized monoclonal antibody against RSV F glycoprotein, is covered by Japanese

public health insurance. Because palivizumab should be administered before the start of an epidemic, it is important to assess the timing of the seasonal epidemic and appropriately plan palivizumab administration.

Meanwhile, the mitigation measures against the coronavirus disease 2019 (COVID-19) spread, such as physical distancing, wearing face masks, and hand hygiene, have affected the transmission of respiratory pathogens simultaneously [3, 4]. The Government of Japan adopted proactive measures to control the spread of COVID-19 that included (1) restricting group activities involving children and requesting the temporary closure of schools from March 2 to May 31, 2020 and (2) the voluntary closure of daycare centers. This may have also reduced RSV transmission, with no seasonal outbreak of RSV being observed in 2020 [5]. However, a resurgence of RSV infections occurred in April of 2021, with the number of RSV cases increasing in many regions of Japan, as per sentinel surveillance [5, 6]. However, sentinel surveillance data primarily reflect outpatient visits. Therefore, the impact of the RSV resurgence on the number of hospitalizations or clinical features of

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pediatric patients with RSV infection has not been clear in Japan. In other regions, including the United States and Australia, the resurgence of RSV epidemics with different seasonalities and scales from the previous years has been observed [7, 8].

RSV affects more than 60%–70% of children aged ≤ 1 year, and almost all children acquire antibodies by the age of 3 years [9, 10]. Furthermore, an estimated 15%–40% of children with RSV infection below the age of 3 years develop bronchiolitis or pneumonia, and 1%–3% require inpatient care during the primary infection [11]. In the birth cohort study in Kenya, the highest risk of RSV diseases after primary RSV infection was seen in children aged < 6 months, but the substantial risk remained up to 18 months of age [12]. Mitigation measures implemented during the COVID-19 pandemic may have shifted the epidemic season and increased the age of the primary infection of RSV. Therefore, these differences may have affected the clinical characteristics of RSV infections. Furthermore, it is simulated that stringency of mitigation measures is associated with the increase in RSV hospitalizations in the United States [13]. Examining the timing and intensity of the resurgent RSV epidemics will lead to a reconsideration of hospital capacity management and appropriate timing and candidate to receive prophylaxis.

This multicenter study aimed to investigate the impact of the COVID-19 pandemic on the epidemiological and clinical features of pediatric patients with RSV infection in Japan. For this purpose, the clinical characteristics of hospitalized children with RSV before and during the COVID-19 pandemic were compared. Furthermore, the age distribution was compared between the hospitalized and outpatient RSV infections using regional data from the sentinel surveillance.

METHODS

Study Design, Setting, and Data Sources

From January 2019 to December 2021, we retrospectively enrolled children aged < 6 years who required hospitalization for acute respiratory tract infection due to RSV in the pediatric department of 18 general hospitals located in the Aichi and Gifu prefectures of Japan. These hospitals cover approximately 150 000 children aged < 6 years based on demographic data provided by the local governments. Medical records were reviewed to identify patients with a positive-rapid antigen detection test (RADT) for RSV.

The medical records of hospitalized patients with RSV infection were reviewed to retrieve data regarding the following: (1) demographic characteristics; (2) the presence of underlying medical conditions, such as prematurity, congenital heart disease, respiratory abnormalities, Down syndrome, and other conditions eligible for RSV prophylaxis with palivizumab; (3)

clinical presentation and findings on admission, including vital signs, auscultation, and radiography findings; and (4) the outcomes of care or parameters of disease severity, such as the duration of hospitalization, amount of oxygen supplementation, respiratory support (high-flow nasal cannula, continuous positive airway pressure support, and mechanical ventilation), intensive care unit stay, and the use of corticosteroids or antibiotics. The asymptomatic or mild RSV patients admitted to the hospitals for other medical reasons were excluded from this study. Furthermore, hospitalized mild or asymptomatic RSV patients to accompany their siblings with RSV infection were also excluded.

The sentinel surveillance data of RSV-positive cases with upper or lower respiratory tract infection in the Aichi prefecture were provided by the Aichi Prefectural Institute of Public Health. The institute gathers the number of pediatrician-diagnosed RSV infection cases weekly based on clinical symptoms and laboratory findings from 182 sentinel centers, including clinics and hospitals. The majority of RSV cases reported from the sentinel centers were considered outpatient cases. To produce an epidemiological curve of COVID-19, we obtained the number of daily COVID-19 cases from publicly available data sources provided by the Japan Broadcasting Corporation [14].

Statistical Analysis

We compared the demographic and clinical characteristics of patients with RSV infection before and during the COVID-19 pandemic. Associations between the categorical and continuous variables were analyzed using Fisher's exact test and Student's *t* test, respectively. Descriptive analyses were performed using frequency distributions or rates. Mean values \pm standard deviations or *n* (%) were used to summarize the demographic data and baseline characteristics of the patients. *P* $< .05$ were considered statistically significant. All statistical analyses were performed using the JMP version 15 (SAS Institute, Cary, NC).

Patient Consent Statement

This study was approved by the local ethics committee of Nagoya University Graduate School of Medicine (IRB No. 2021-0358, approved December 17, 2021). Patient consent was waived and not required for this study.

RESULTS

Trends of Respiratory Syncytial Virus and Coronavirus Disease 2019 Outbreaks

The study flow chart is shown in Figure 1. Of the 3107 cases, 135 were excluded (50 for reasons of hospitalization, 24 for age, and 61 for other reasons) and the remaining 2972 were classified as before COVID-19 (1675 patients) and during COVID-19 (1297 patients) groups. Considering the pediatric

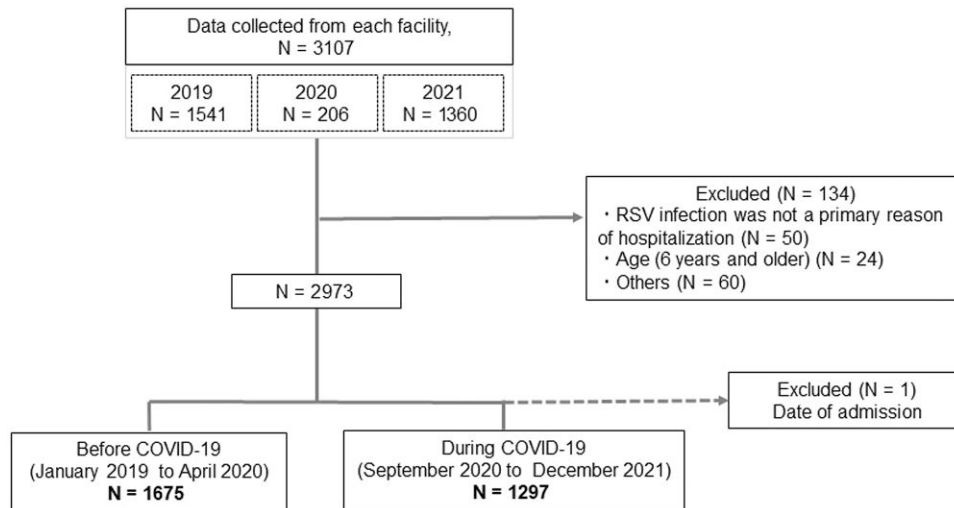


Figure 1. Patient recruitment in the respiratory syncytial virus (RSV) infection cohort. COVID-19, coronavirus disease 2019.

populations covered by the participating hospitals, the average annual rate of RSV hospitalizations among children aged <6 years in 2019 and 2021 was approximately 11.2 and 8.7 per 1000, respectively.

Figure 2 shows the timeline of COVID-19 notifications (Figure 2A), reported RSV cases from weekly sentinel surveillance in the Aichi prefecture (Figure 2B), and RSV hospitalizations (Figure 2C) from January 2019 to December 2021. In 2019, the number of patients with RSV infection sharply increased from August, and the peak was observed in September. Coronavirus disease 2019 notifications in the Aichi prefecture were recognized in January 2020. After the emergence of COVID-19, few RSV cases were observed until the end of 2020. However, the number of RSV cases gradually increased from the early spring of 2021. Thereafter, the number of cases steadily increased, peaking at the epidemiological week 25 of 2021. Based on the RSV and COVID-19 timelines (Figure 2), we defined January 2019 to April 2020 and September 2020 to December 2021 as the “before COVID-19” and “during COVID-19” periods, respectively.

Comparison of Demographic and Clinical Characteristics of Patients With Respiratory Syncytial Virus Infections Before and During the Coronavirus Disease 2019 Pandemic

We compared the demographic characteristics of hospitalized patients with RSV infection before and during the COVID-19 pandemic (Table 1). The mean age of the patients was significantly higher during the COVID-19 pandemic than before (17.4 vs 13.7 months, $P < .001$). Compared with the before-COVID-19 period, the proportion of patients aged 3–5 months and 6–11 months with RSV infection was significantly lower, and the proportion of patients aged 24–71 months with RSV infection was significantly higher

during the COVID-19 pandemic. No significant differences in underlying disease were observed between the 2 groups. Furthermore, there was no significant difference in the proportion of patients eligible to receive palivizumab in the relevant season.

The age distribution of patients with RSV infection was compared between the reported cases from the sentinel centers (mostly outpatients) and hospitalized patients. A total of 6617 and 8898 RSV cases were reported during the before-COVID-19 and during COVID-19 periods, respectively. The annual diagnosed RSV cases by RADT among children aged <6 years in 2019 and 2021 were estimated at 72.7 and 97.7 per 1000, respectively, in Aichi prefecture. However, it should be noted that patients with mild respiratory symptoms may not have been tested for RSV, especially in outpatient settings. The timeline of the reported RSV cases in each age group is shown in Figure 3. Compared with the before-COVID-19 period, a 2.6-fold increase in the number of RSV cases reported via sentinel surveillance was observed during the COVID-19 period among patients aged 2–5 years. In the same age group, there was a 1.2-fold increase in hospitalized patients during the COVID-19 period (Supplementary Figure 1).

We compared the clinical presentations and findings of the patients with RSV infection on admission before and during the COVID-19 period (Table 2). The proportion of patients presenting with wheezing at admission was significantly lower during the COVID-19 period (21% vs 25.7%, $P < .001$). Furthermore, consolidation shadows obtained on chest radiography were significantly less frequent in patients with RSV infection during the COVID-19 period (26.1% vs 29.6%, $P = .04$).

The treatment and clinical course of patients with RSV infections during hospitalization are shown in Table 3. The duration

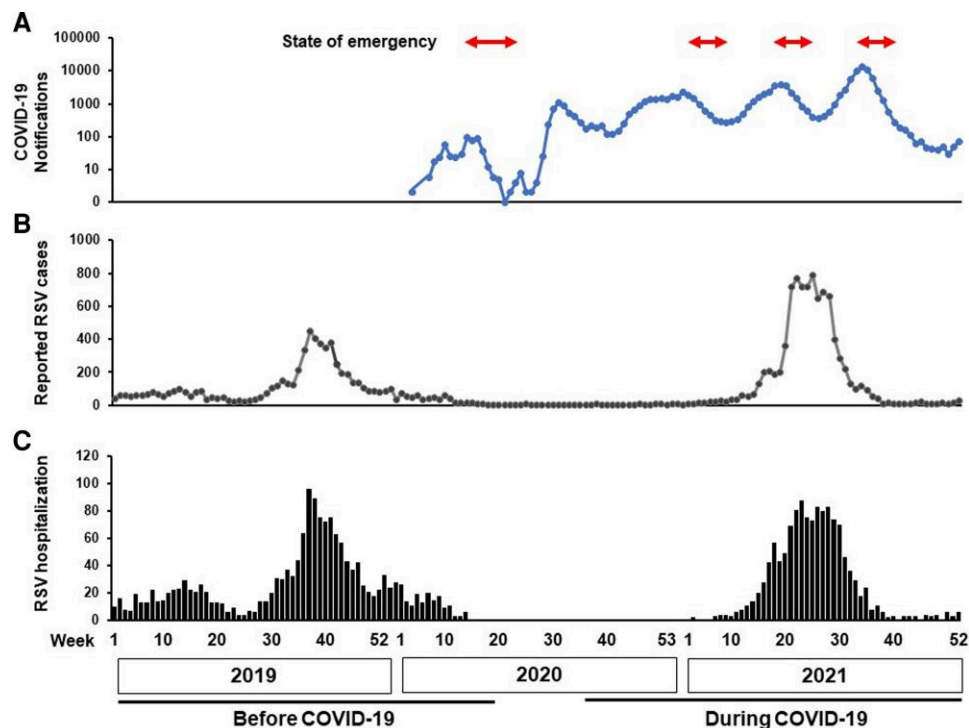


Figure 2. Timeline of coronavirus disease 2019 (COVID-19) notifications (A), reported respiratory syncytial virus (RSV) cases (mostly outpatients) from weekly sentinel surveillances in the Aichi prefecture (B), and the RSV hospitalization (C) in this study. The red bidirectional arrows indicate periods of the state of emergency, which was declared by the Japanese government. Before-COVID-19 period, January 2019 to April 2020; During COVID-19 period, September 2020 to December 2021.

of hospitalization was significantly shorter during the COVID-19 period (5.7 vs 6.0 days, $P < .001$). A significantly smaller proportion of patients required respiratory assistance and oxygenation during the COVID-19 period than before (42.2% vs 48.7% [$P < .001$] and 42.3% vs 49.3% [$P < .001$], respectively). Furthermore, corticosteroids and antibiotics were

less frequently administered during the COVID-19 period (15.3% vs 19.6% [$P < .001$] and 34.4% vs 45.1% [$P < .001$], respectively). However, there were no significant differences in the high-flow nasal cannula, continuous positive airway pressure, or intensive care unit management between the 2 groups.

Table 1. Comparison of Demographic Characteristics of Patients With RSV Infections Before and During the COVID-19 Pandemic

Demographic Characteristics	All Cases (N = 2972)	Before COVID-19 (N = 1675)	During COVID-19 (N = 1297)	P Value ^a
Females/males	1332/1640	743/932	589/708	.44
Age, months	15.3 ± 14.1	13.7 ± 12.9	17.4 ± 15.3	<.001
0–2 months	665 (22.4%)	379 (22.6%)	286 (22.1%)	.72
3–5 months	347 (11.7%)	226 (13.5%)	121 (9.3%)	<.001
6–11 months	433 (14.6%)	279 (16.7%)	154 (11.9%)	<.001
12–23 months	829 (27.8%)	479 (28.6%)	350 (26.9%)	.33
24–71 months	698 (23.5%)	312 (18.6%)	386 (29.8%)	<.001
Born at ≤28 weeks	35 (1.2%)	18 (1.1%)	17 (1.3%)	.61
Born at 29–35 weeks	73 (2.5%)	39 (2.3%)	34 (2.6%)	.63
Congenital heart disease	33 (1.1%)	19 (1.1%)	14 (1.1%)	1.0
Pulmonary abnormalities	22 (0.74%)	8 (0.48%)	14 (1.1%)	.08
Down syndrome	23 (0.77%)	15 (0.9%)	8 (0.6%)	.53
Palivizumab-eligible	41 (1.38%)	24 (1.4%)	17 (1.3%)	.87

Abbreviations: COVID-19, coronavirus disease 2019; RSV, respiratory syncytial virus.

NOTES: Before COVID-19, January 2019 to April 2020; During COVID-19, September 2020 to December 2021. Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as mean ± standard deviation.

^aComparison between the patients before COVID-19 and during COVID-19. Bold values indicate $P < .05$ (statistically significant results).

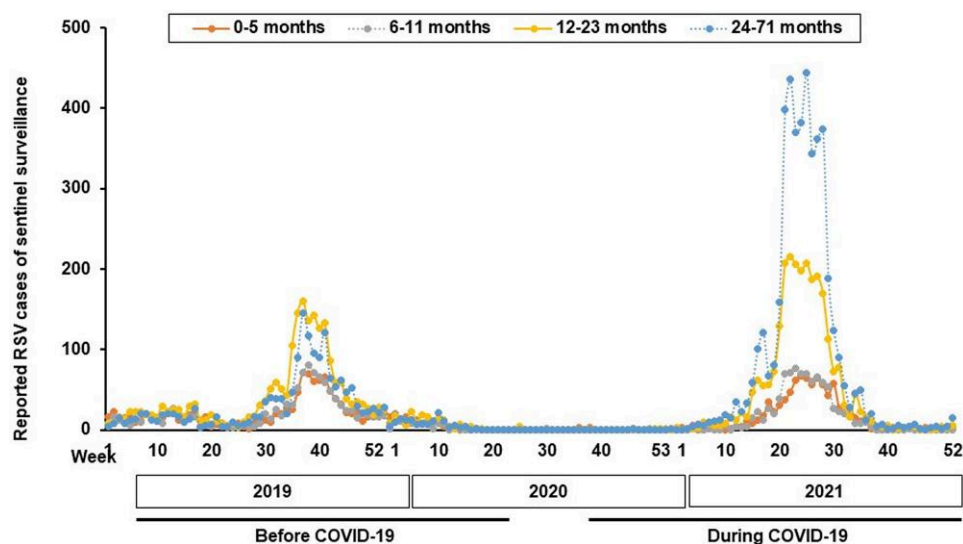


Figure 3. Respiratory syncytial virus (RSV) cases by age group based on sentinel surveillance data per week from the Aichi prefecture. Before-coronavirus disease 2019 (COVID-19) period, January 2019 to April 2020; During COVID-19 period, September 2020 to December 2021.

We also compared the treatment and clinical course of hospitalized patients with RSV infection in each age group (Supplementary Table 1). There was no significant difference in the duration of hospitalization between the 2 periods in those aged ≤ 5 months; however, the duration was significantly shorter during the COVID-19 period in those aged ≥ 6 months. A smaller proportion of patients aged < 2 months and > 12 months required respiratory assistance and oxygenation during the COVID-19 period. Corticosteroid was less frequently administered in patients aged 6–23 months, whereas antibiotics were less frequently administered in all the age groups during the COVID-19 period.

Then, the demographic characteristics and clinical course of all patients with RSV were compared. This comparison included mild or asymptomatic RSV patients admitted to the hospitals for other medical reasons or accompanying their siblings. Significant differences were observed in the same category

such as age distribution and duration of hospitalization (Supplementary Table 2).

DISCUSSION

After the emergence of COVID-19, the shift in RSV epidemic seasons and the resurgence of its infections in 2021 was reported in various countries [6, 7]. In the Aichi prefecture, the prevalence of respiratory viral infections, such as influenza and RSV infection, sharply decreased in 2020; however, the number of RSV cases from sentinel surveillance increased in 2021, probably due to the accumulation of susceptible children during the COVID-19 pandemic [15]. In contrast, compared with the previous RSV epidemic season (2019), this multicenter study revealed that a fewer number of patients with RSV infection required hospitalization during the COVID-19 pandemic. Among the hospitalized patients in 2021, the proportion of

Table 2. Comparison of Clinical Presentations and Findings of the Patients With RSV Infection on Admission Before and During the COVID-19 Pandemic

Clinical Presentations and Findings	All Cases (N = 2972)	Before COVID-19 (N = 1675)	During COVID-19 (N = 1297)	P Value ^a
Body temperature, Celsius	38.0 \pm 1.0	38.1 \pm 1.1	38.0 \pm 1.0	.007
Labored breathing	796 (26.8%)	459 (27.4%)	337 (26.0%)	.4
Wheeze	703 (23.7%)	431 (25.7%)	272 (21.0%)	<.001
Findings on chest X-ray				
Consolidation	833 (28.0%)	495 (29.6%)	338 (26.1%)	.04
Hyperinflation	776 (26.1%)	456 (27.2%)	320 (24.7%)	.12

Abbreviations: COVID-19, coronavirus disease 2019; RSV, respiratory syncytial virus.

NOTES: Before COVID-19, January 2019 to April 2020; During COVID-19, September 2020 to December 2021. Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as mean \pm standard deviation.

^aComparison between the patients before COVID-19 and during COVID-19. Bold values indicate $P < .05$ (statistically significant results).

Table 3. Comparison of Treatment and Clinical Course of Patients With RSV Infections During Hospitalization Before and During the COVID-19 Pandemic

Treatment and Clinical Course	All Cases (N = 2972)	Before COVID-19 (N = 1675)	During COVID-19 (N = 1297)	P Value ^a
Duration of hospitalization, days	5.9 ± 2.4	6.0 ± 2.3	5.7 ± 2.5	<.001
Any respiratory support	1363 (45.9%)	816 (48.7%)	547 (42.2%)	<.001
Oxygenation	1374 (46.2%)	825 (49.3%)	549 (42.3%)	<.001
Duration of oxygenation, days	3.9 ± 2.4	4.1 ± 2.5	3.6 ± 2.2	<.001
High-flow nasal cannula	224 (7.5%)	133 (7.9%)	91 (7.0%)	.36
Continuous positive airway pressure support	5 (0.17%)	2 (0.12%)	3 (0.23%)	.66
Mechanical ventilation	26 (0.87%)	14 (0.84%)	12 (0.93%)	.84
ICU admission	32 (1.1%)	20 (1.2%)	12 (0.93%)	.59
Corticosteroids	528 (17.8%)	329 (19.6%)	199 (15.3%)	<.001
Antibiotics	1201 (40.4%)	755 (45.1%)	446 (34.4%)	<.001

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; RSV, respiratory syncytial virus.

NOTES: Before COVID-19, January 2019 to April 2020; During COVID-19, September 2020 to December 2021. Categorical variables are expressed as numbers and percentages, and continuous variables are expressed as mean ± standard deviation.

^aComparison between the patients before COVID-19 and during COVID-19. Bold values indicate $P < .05$ (statistically significant results).

children aged ≥ 2 years was higher, whereas the overall symptom severity was equivalent to or milder than that in patients in the previous season. To the best of our knowledge, this is the first study to compare in detail the clinical characteristics of hospitalized patients with RSV infection on a large scale before and during the COVID-19 pandemic in Japan. This study demonstrated that the COVID-19 pandemic and restriction of social activity led to epidemiological changes in pediatric RSV infection, and a majority of patients with RSV infection aged ≥ 2 years did not develop severe symptoms that required hospitalization.

In this study, few patients were diagnosed with RSV infection using multiplex polymerase chain reaction (PCR) panels for respiratory pathogens because they were not available in most clinics. Furthermore, multiplex PCR panels have been only covered in intensive care patients by Japanese public health insurance as of July 2022. Therefore, it is considered that using multiplex PCR panels had minimal effect on the opportunity to test RSV in Japan. In contrast, some children with respiratory symptoms might have been only tested for COVID-19 in outpatient settings during the COVID-19 pandemic. It might be possible that several RSV cases from sentinel surveillance were underestimated during the COVID-19 pandemic.

In Australia, reports indicated that increased susceptibility to RSV may be associated with increased morbidity among patients aged 2–4 years, including outpatients [16]; a similar trend was observed in the present study as well. Primary RSV infections cause severe illness in the early stages of infancy [17], and the majority of children are considered to have been infected before the age of 2 years [10]. Reinfection of RSV is common, but particularly among otherwise healthy older children, recurrent RSV infection seldom involves the lower respiratory tract. However, primary RSV infection at older ages has not been described in detail. Regarding the large increase in the number of RSV cases derived from sentinel surveillance

(mostly outpatients) among children aged ≥ 2 years reported in 2021, it is speculated that more children in this age group experienced primary RSV infection in 2021 than in the previous seasons. However, most of them may not have developed severe symptoms because the increase in the number of hospitalized children aged ≥ 2 years was moderate. These results suggested that the majority of primary RSV infections among children aged ≥ 2 years may not lead to severe illness requiring hospitalization, thereby emphasizing the importance of preventing primary RSV infection during infancy.

It is interesting to note that the clinical symptoms of hospitalized RSV cases during the COVID-19 outbreak appeared to be less severe in this study. Although there was no difference in patient background-related risk factors for severe RSV infection [17], respiratory support and oxygenation were less frequently required in patients during the COVID-19 period. Respiratory syncytial virus outbreaks typically occur from autumn to winter in the northern hemisphere. However, RSV epidemics in Japan currently occur earlier, and seasonal RSV outbreaks have been observed during summer since 2017 for unknown reasons [2, 18]. In 2021, the RSV epidemic peak was observed in spring, which was even earlier than that in 2019. It is possible that the epidemic season may have affected RSV disease severity, and further studies are needed to clarify this theory.

As of July 2022, respiratory virus infection epidemics other than COVID-19 and RSV have not been observed since 2020 in Japan. For example, few influenza cases have been reported in 2 consecutive seasons. A state of emergency for COVID-19 was declared several times to restrict social and business activities. Furthermore, mitigation measures, such as wearing masks, physical distancing, and restrictions on mass gatherings, were maintained even after lifting the state of emergency. However, an increase in the number of RSV cases was observed even during the state of emergency. Although RSV may be

transmitted by the droplet route, it is considered that RSV transmission predominantly occurs through inoculation of nasopharyngeal or ocular mucous membranes after direct contact with virus-containing secretions or fomites. To prevent RSV transmission, contact precautions in addition to standard precaution are necessary. Therefore, the high transmissibility of RSV and difficulty in implementing mitigation measures among infants were related to the resurgences.

This study has several limitations. First, the details regarding outpatients with RSV infection were not analyzed. Therefore, the disease severity in outpatients could not be compared between the seasons. Second, primary or reinfection with RSV was not assessed serologically in this study. Third, RSV is broadly classified into 2 subgroups (RSV-A and RSV-B) based on differences in G protein characteristics, and each subgroup is further classified into multiple genotypes [19]. Reports based on regional surveillance data indicated that RSV-B BA9 was more predominant during the 2021 epidemic than in the previous seasons [20]. Previous reports have shown that the severity of the disease is similar among the RSV subtypes [21, 22, 23], whereas others have indicated that RSV-A causes a more severe disease than RSV-B [24]. Therefore, the difference in the dominant RSV subgroups may have affected the disease severity. Finally, the presence of coinfections in hospitalized patients was not considered. Antibiotics were less frequently administered in patients with RSV infection during the COVID-19 period, which suggested a reduction in bacterial coinfections. Therefore, the reduction of coinfections with other respiratory pathogens due to the mitigation measures might be associated with RSV hospitalization rate and disease severity in hospitalized patients with RSV infection during the COVID-19 period. The use of antibiotics and corticosteroids was decided by the attending physicians; however, the use of these agents may not necessarily be linked to disease severity [25]. In the United Kingdom and Ireland, a prospective observational study to monitor RSV disease in children attending emergency departments is currently underway to examine the effects of social activity restriction on the transmission and disease dynamics of RSV [26].

CONCLUSIONS

In conclusion, mitigation measures implemented during the COVID-19 pandemic were associated with marked reductions in RSV infections in children in 2020 in Japan. However, the accumulation of susceptible children may have resulted in a large RSV epidemic in 2021, especially among children ≥ 2 years of age. RSV resurgence during the COVID-19 pandemic did not result in an overall increase in the number of hospitalized patients, and RSV symptoms in hospitalized cases during the COVID-19 outbreak might have been less severe than in the previous seasons. These results suggested that the

majority of patients with primary RSV infection aged ≥ 2 years do not develop severe symptoms.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Author contributions. S. O. conceptualized and designed the study, acquired data, analyzed and interpreted the data, produced figures, and drafted the initial manuscript. J.-i. K. conceptualized and designed the study, interpreted the data, produced figures, and reviewed and revised the manuscript. D. Y., C. Y., T. A., M. K., K. S., C. T., K. M., S.-h. M., and A. M. conceptualized and designed the study and collected data. Y. Y. provided the sentinel surveillance data. N. N., H. K., Y. T., and Y. S. supervised the study and critically reviewed the manuscript.

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