CHANGES IN EXANTHEMA SUBITUM INCIDENCE AND PATIENT AGE DISTRIBUTION DURING THE COVID-19 PANDEMIC IN JAPAN

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Abstract: Incidences of community-acquired infectious diseases other than COVID-19 decreased during the coronavirus disease 2019 pandemic; however, exanthema subitum incidence before (2016–2019) and during the pandemic (2020) in Niigata, Japan, did not substantially differ, although the proportion of age less than 1-year-old was lower in 2020. These findings suggest that exanthema subitum is transmitted mainly among family members, not in the community.

Key Words: incidence, exanthema subitum, COVID-19, Japan, children

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INTRODUCTION

Preventive measures implemented since the beginning of the coronavirus disease 2019 (COVID-19) pandemic have decreased incidences of many viral respiratory infections other than COVID-19.[1] People in Japan have been encouraged to wear face masks even if they were asymptomatic when they have a conversation with others or cannot maintain physical distance in indoors or even outdoors since May 2020. Most Japanese have been very faithfully wearing face masks because they have gotten used to wearing face masks in the winter period annually to prevent influenza before the COVID-19 pandemic. As an exception, children younger than 2 years of age have not been recommended to wear face masks because of the risk of suffocation.

Exanthema subitum (ES) is usually caused by human herpesvirus type 6 or 7 (HHV-6/7) and is a common disease in young children. The proportions of primary HHV-6B and HHV-7 infection that lead to the typical clinical course of ES in Japanese children are high, 79.6% and 93.3%, respectively.[2,3] HHV-6/7 persists in the body and can be detected in saliva after primary infection.[4] Most children probably acquire HHV-6/7 from the saliva of siblings or adults in their family.[4]

Cases of ES have consistently been reported in epidemiologic surveillance since the beginning of the COVID-19 pandemic in Niigata Prefecture, Japan, although the incidence of other viral infections has decreased.[5] To investigate the change in ES incidence in Niigata, Japan, this study aggregated surveillance data from Niigata with national data for Japan and compared the periods before (2016–2019; prepandemic period) and during the pandemic (2020).

METHODS

Subjects and Methods

This retrospective, descriptive study used datasets from the sentinel surveillance in Niigata, Japan. To determine the impact of childhood population change, we collected age-stratified demographic data from the official publications in Niigata.[6] The numbers of children <1 year, 1–4 years and 5–14 years of age were compared for the periods 2016–2019 and 2020.

The Japanese National Institute of Infectious Diseases (NIID) administers the National Epidemiological Surveillance of Infectious Disease Program. Ten infectious diseases, including ES, are monitored as part of pediatric sentinel surveillance. There are 142 pediatric clinics and hospitals in Niigata Prefecture and approximately 40% (57/142) of these were designated as pediatric sentinel medical institutions (SMI). Physicians at SMI are required to report the numbers of ES patients weekly by age group (<1, 1–4, 5–9, 10–14, 15–19, and ≥20 years) when cases are diagnosed based on clinical symptoms.

After collecting data for 2016–2020, we compared the mean number of ES cases and the proportion of cases in children younger than 1 year (which were collected every week), and the cases/population, between 2016–2019 and 2020. We also compared the data from Niigata Prefecture with nationwide data. The total number of cases for each infectious disease under surveillance in each prefecture are publicly available in the Infectious Disease Weekly Report presented by NIID.[7]

This study was approved by the Ethics Committee of Niigata University (2021-0063). The requirement for consent was waived because the data are anonymous.

Statistical Analyses

Statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R. The unpaired t-test was used to compare mean case numbers, and Fischer's exact test was used to compare the change in the proportion of cases younger than 1 year and cases/population. A two-sided P-value of <0.05 was considered to indicate statistical significance.

RESULTS

The weekly numbers of ES in 2016–2019 and 2020 are shown in Fig. 1A. In Japan, nationwide school closures started in week 10 (2 March) in 2020, and the government declared a nationwide state of emergency on April 16 (week 16). Both continued until week 22 (end of May). When we compared the number of ES cases by the 4-week period between 2016–2019 and 2020, it was significantly lower during weeks 9 through 12 in 2020 than during the same period in 2016–2019 (0.28 cases/site vs. 0.48 cases/site, $P = 0.02$) (Table S1, Supplemental Digital Content 1 http://links.lww.com/INF/E607). During the remaining weeks, the reported numbers of cases did not significantly differ between the periods ($P \geq 0.24$, Table S1, Supplemental Digital Content 1, http://links.lww.com/INF/E607).

In our analysis of the age distribution of patients, the proportion of cases younger than 1 year was lower in the second half of 2020 than in 2016–2019 (18.8% vs. 31.6%, $P < 0.0001$) (Fig 1B), and there were significant differences between 2020 and 2016–2019 during weeks 29–32, 37–40 and 41–44 ($P < 0.01$) when we compared by 4-week period (Table S2, Supplemental Digital Content 2, http://links.lww.com/INF/E607). The proportion of cases younger than 1 year in 2020 (23.2%) was significantly lower than in 2016–2019 ($P < 0.01$), during which the proportion gradually decreased, as follows: 36.3% in 2016, 32.8% in 2017, 29.0% in 2018 and 28.5% in 2019.

Trends in ES cases per week in 2016–2019 and 2020 in nationwide data for Japan are shown in Fig. 1C. ES incidence was lower during the school closure period in 2020 but did not significantly differ between the second half of 2020 and the same period in 2016–2019.

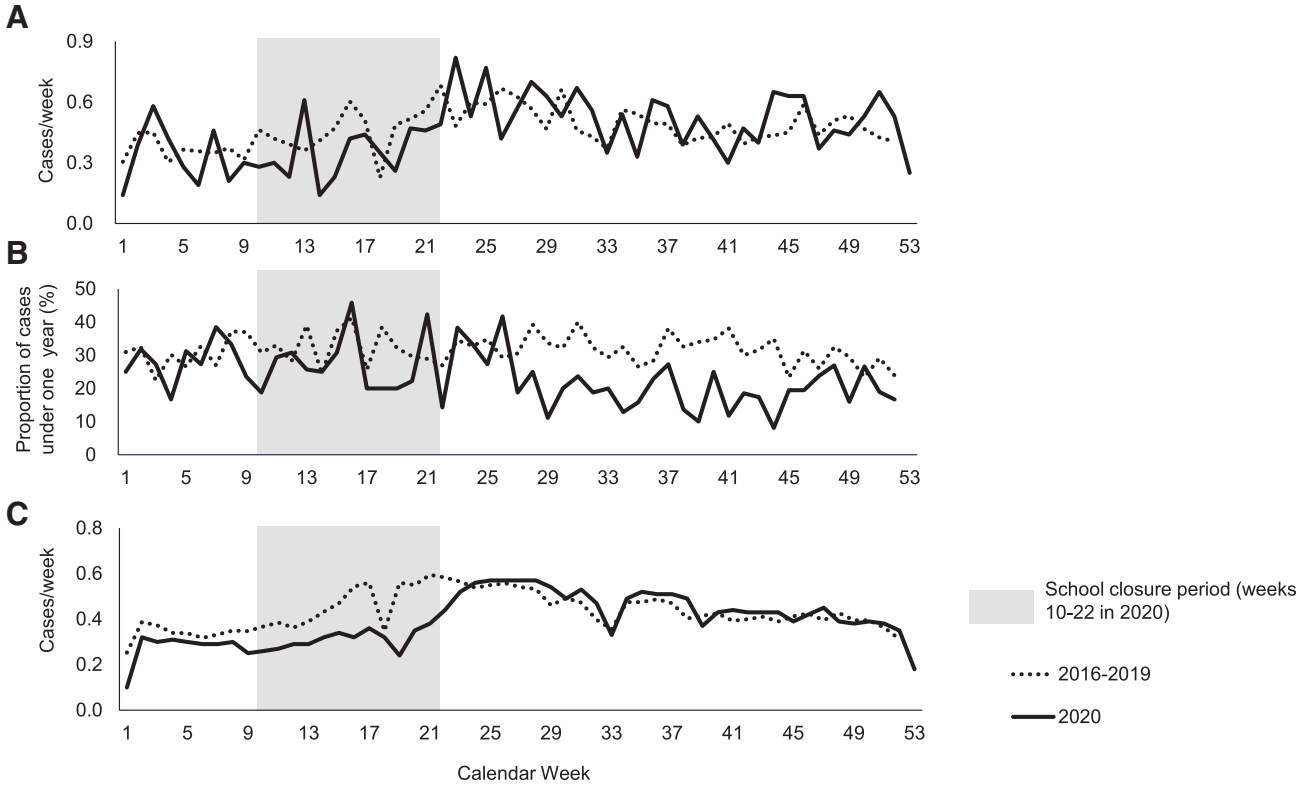

FIGURE 1. A: Number of exanthema subitum cases in Niigata, Japan, in 2016–2019 and 2020. The solid line shows the number of reported cases per sentinel medical institution per calendar week in 2020. The dotted line shows average numbers during 2016–2019. (B) Proportion of exanthema subitum patients younger than 1 year in Niigata, Japan, in 2016–2019 and 2020. The solid line shows the proportion of patients younger than 1 year to the total number of cases per calendar week in 2020. The dotted line shows the corresponding values for 2016–2019. Age data were missing in weeks 4–7 in 2016 and for weeks 2–3 in 2018. (C) Number of exanthema subitum cases in Japan in 2016–2019 and 2020. The solid line shows the number of reported cases per sentinel medical institution per calendar week in 2020. The dotted line shows average numbers during 2016–2019. The period of the nationwide school closure (week 10 to around week 22 in 2020) is shown in gray.

We analyzed population changes in ES cases, specifically, changes in the proportions of patients <1 year, 1–4 years and 5–14 years old, during 2016–2019 and 2020 in Niigata, Japan. The mean population was lower in 2020 than in 2016–2019 in all age groups (Table S3, Supplemental Digital Content 3, http://links.lww.com/INF/E607), and the decline was greatest in patients younger than 1 year. When we calculated the number of cases in relation to population in each age group, ES cases/population (%) was significantly lower in 2020 than in 2016–2019 for cases younger than 1 year ($P < 0.01$) and was higher in those aged 1–4 years ($P < 0.01$) (Table S4, Supplemental Digital Content 4, http://links.lww.com/INF/E607).

DISCUSSION

The incidence of ES in Niigata, Japan, did not significantly change during the COVID-19 pandemic (2020), as compared with the prepandemic period (2016–2019), although the patients in the second half of 2020 were older than those in 2016–2019.

The exact modes of HHV-6/7 transmission remain unknown.[4] However, infants are believed to acquire HHV-6/7 from the saliva of their family members because the virus was detected in the saliva of patients and their family members, including older siblings and parents.[4,8] Our findings suggest that COVID-19 preventive measures did not affect the overall number of ES cases, which supports the hypothesis that infants acquire HHV-6/7 mainly from family members, not from the community.

The proportion of cases younger than 1 year was lower in the second half of 2020 than in 2016–2019. Recently, the age of patients with primary HHV-6 infection appears to have increased in Japan.[2] In the present study, the proportion of cases younger than 1 year decreased over time. A reduction in saliva-sharing behaviors, such as mouth-to-mouth food transfer from adults to infants, may, in part, explain this finding. It is unclear why the proportion of cases younger than 1 year was lower during the second half of 2020. From week 10 to 22 in 2020, that is, during the first half of 2020, all schools were closed, work from home was encouraged and people were asked to stay home. Infants and young children thus had more opportunities for close contact with parents and older siblings at home, which increased the risk of primary HHV-6/7 infection early in life. This may explain why fewer infants were susceptible to HHV-6/7 during the second half of 2020 and the consequent older age distribution. Additionally, we observed the same trend in 2021; The proportion of cases younger than 1 year in the first half (week 1–26) of 2021 was 22.5%, which did not significantly differ compared with the second half of 2020 ($P = 0.10$). Based on these findings and the change of ES age distribution in recent years, the first half of 2020 was exceptional due to the increase in contact with infants and their parents or older siblings at home.

The decrease in the population of children in Niigata might have affected the total number of ES cases. However, there was no significant difference between 2016–2019 and 2020 in the cases/population ≤4 years with the shift to older age distribution. Therefore, the effect of the decrease in population appears to be negligible.

The number of ES cases was significantly lower during weeks of 9–12 of 2020, most likely because guardians of infants were concerned about COVID-19 and hesitated to visit clinics or hospitals. Indeed, the number of vaccine doses administered was also lower in March and April 2020 in Japan because parents avoided leaving their homes to decrease the risk of COVID-19 exposure.[9]

Japan has a universal health care system, thus Japanese children have easy access to clinics or hospitals when they have symptoms even if they are not sick; they visit 2.5 times higher than those of the United States.[10] Thus, parents in Japan usually bring their children to their clinics or hospitals when they have high fever or rash. Therefore, we strongly believe the number of ES reported in the surveillance would be close to the actual numbers of HHV-6/7 infected cases.

In the Japanese national data, the trend was similar to that in Niigata, that is, ES incidence did not change during the COVID-19 pandemic, except during the school closure period. This suggests that the trend was applicable to the entire country. We were unable to compare age trends because the relevant data were not included in the national dataset. Trends in other regions of the world warrant investigation.

This study has a few limitations. First, diagnosis of ES was solely based on patients' clinical symptoms and signs; virologic investigation for HHV-6/7 was not performed. However, the diagnosis of ES is usually correct for patients with febrile illness followed by a typical rash, and most Japanese physicians are familiar with the diagnosis. Second, we used sentinel surveillance data, and the diagnosis was only possible when guardians sought medical care. Thus, the potential for undiagnosed ES cases or atypical ES cases by HHV-6B or HHV-7 is a concern. Finally, many guardians avoided leaving their homes during the COVID-19 pandemic because they sought to reduce the risk of infection. Therefore, the diagnosis of ES at SMI could have been affected by the pandemic. However, even in these circumstances, the unchanged incidence of ES between 2016–2019 and 2020 indicates that the system was active.

In conclusion, the overall incidence of ES did not significantly change in Niigata, Japan, during the COVID-19 pandemic. This suggests that intimate contact with family members is responsible for the transmission of ES.

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