Saitoh Akihiko (Orcid ID: 0000-0002-2404-1128)

ORIGINAL STUDIES

Decline in Pediatric Admission on an Isolated Island in the COVID-19 Pandemic

Takuya Fuse, MD,[1] Tatsuki Ikuse, MD,[2] Yuta Aizawa, MD, PhD,[2] Michiko Fuse, MD,[1] Fumihiro Goto, MD,[1] Minoru Okazaki, MD,[1] Atsushi Iwaya, MD,[3] Akihiko Saitoh, MD, PhD[2]

Running Title

Pediatric Admission in the COVID-19

Author affiliations

[1]Department of Pediatrics, JA Niigata Kouseiren Sado General Hospital, Niigata, Japan

[2]Department of Pediatrics, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

[3]Department of Pediatrics, Ryotsu Hospital, Niigata, Japan

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ped.15326

Corresponding author

Akihiko Saitoh, M.D., Ph.D.

Department of Pediatrics

Niigata University Graduate School of Medical and Dental Sciences,

Permanent address: 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan

Phone number: +81-25-227-2222

Fax number: +81-25-227-0778

E-mail address: asaitoh@med.niigata-u.ac.jp

Word counts

32 pages; Abstract 238 words; Text 2,725 words; 2 Tables; 4 Figures; 2 Supplementary Figures; 2 Supplementary Tables

Funding

The authors received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

None declared.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, AS. The data are not publicly available due to restrictions e.g. their containing information that could compromise the privacy of research participants.

ABSTRACT

Background

A decrease in pediatric hospitalizations during the coronavirus disease 2019 (COVID-19) pandemic has been reported worldwide; however, few studies examined areas with a limited number of COVID-19 cases, where influenced by viral interference by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is minimum.

Methods

We conducted an epidemiological study of pediatric hospitalizations on Sado, an isolated island in Niigata, Japan, that was unique environment with few COVID-19 cases and reliable pediatric admissions monitoring. We compared numbers of monthly hospitalizations and associated diagnoses for the periods April 2016 through March 2020 (pre-pandemic period) and April 2020 through March 2021 (pandemic period).

Results

Data were analyzed for 1,144 and 128 patients in the pre-pandemic and pandemic periods, respectively. We observed only 3 adults and no pediatric COVID-19 cases during the pandemic period. The number of monthly

admissions was significantly lower in the pandemic period (median [interquartile ranges(IQR)]: 11.0 [7.0-14.0]) than in the pre-pandemic period (23.0 [20.8-28.3]) ($P < 0.001$). Similar decreases were observed for hospitalizations due to respiratory tract infection ($P < 0.01$), but not for asthma exacerbation ($P = 0.15$), and gastrointestinal tract infection ($P = 0.33$).

Conclusions

Pediatric hospitalizations during the pandemic significantly decreased on an isolated Japanese island where COVID-19 was not endemic and all pediatric admissions were ascertainable. This observation highlights the impact of decreased travel and increased awareness of infection control measures on pediatric hospitalizations due to infectious diseases, not by the SARS-CoV-2 viral interference.

Keywords

COVID-19; hospitalization; Japan; pediatrics; viral interference

INTRODUCTION

After the initial report in Wuhan, China, in December 2019, the first case of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was reported in Japan on January 16, 2020. Since then, the number of COVID-19 cases has been increasing, with periodic waves. To limit movement of people and promote basic infection preventive measures, the Japanese government twice declared a state of emergency: from April 7 to May 25, 2020, and from January 8 to March 21, 2021.

During the current COVID-19 pandemic, pediatric hospitalizations were reported to have decreased worldwide (1, 2). A previous meta-analysis suggested that this reduction was due to decreased movement of people and increased awareness of hygiene, particularly basic infection prevention measures such as hand hygiene, masking, and physical distancing (3). However, most studies were conducted in areas where COVID-19 incidence was high (1,4–6). Viral interference, a virus-virus interaction in which the infection and/or replication of one virus is altered by the presence of another virus within the same host, has been shown between SARS-CoV-2 and H3N2 influenza virus in an animal

model (7). Thus, SARS-CoV-2 itself might affect incidences of other infectious diseases by viral interference (8) or other mechanisms.

Sado Island, Niigata Prefecture, is located in the Sea of Japan and is one of the largest remote islands in Japan (**Supplementary Figure 1**). The total population was 52,467 in 2020, and the population less than 15 years was 5,090 in 2020, ie, approximately 10% of the total population of the island. Sado Island is a popular tourist destination, and approximately 500,000 tourists visited the island annually before the COVID-19 pandemic. The island is only accessible by ship; thus, it is easy to count the number of tourists and understand the flow of people to/from the island. There are 2 sea routes between the island and mainland, and ferries operate approximately 3 to 5 round trips per day, depending on the season. The island has only 2 hospitals (Sado General Hospital and Ryotsu Hospital) that care for inpatient and outpatient pediatric patients (**Supplementary Figure 1**). Therefore, almost all children who need medical care visit one of these hospitals, and the combined number of pediatric hospitalizations for these 2 hospitals is the total number of pediatric hospitalizations on the island. In contrast to other regions of Japan, COVID-19 incidence was limited on Sado Island, and no SARS-CoV-2 outbreak

was reported until April 2021, 1 year after the first declaration of emergency status in Japan. Although no case was reported on Sado Island, a state of emergency was declared in Niigata Prefecture, where the island is located, on April 21, 2020.

We conducted an epidemiological survey of pediatric hospitalizations before and during the COVID-19 pandemic among children living on Sado Island, which had few COVID-19 cases, to clarify the effects of travel limitations and increased awareness of infection control.

MATERIALS AND METHODS

Patients

This retrospective cohort study investigated the records of pediatric patients less than 15 years admitted to Sado General Hospital or Ryotsu Hospital on Sado Island before and during the COVID-19 pandemic, ie, between April 1, 2016 and March 31, 2021. April was set as the beginning of the study period because the COVID-19 pandemic started in Japan in April 2020. We counted the monthly numbers of pediatric hospitalizations for both hospitals and analyzed the number of pediatric hospitalizations in relation to diagnoses

associated with common infections and related conditions at admission, namely respiratory tract infection (pneumonia, bronchitis, and bronchiolitis, etc.), asthma exacerbation, and gastrointestinal tract infection (viral gastroenteritis, infectious colitis, etc.) by using the data from the Diagnosis Procedure Combination (DPC) under the national health insurance system. In terms of indication for hospitalization in two hospitals, a board-certified, senior pediatrician in each hospital had been in charge of pediatric hospitalization during the study periods. There had been no difference in indications for hospitalization in the two hospitals during the study period.

Data Collection

To determine the effects of diminished travel and promotion of basic infection control strategies attributable to the state of emergency declaration in Japan, we classified patients by date of admission as those admitted before and after the first declaration, namely, patients admitted from April 1, 2016 through March 31, 2020 (pre-pandemic period: 4 years) and from April 1, 2020 through March 31, 2021 (pandemic period: 1 year). We collected the following information for these periods: 1) clinical data from the medical records of each facility, including age, gender, diagnosis, and days of hospitalization, 2) numbers of positive

SARS-CoV-2 PCR and antigen tests in the pediatric departments of the 2 hospitals, 3) numbers of monthly passengers on ferries traveling between mainland Japan and Sado Island during the study period (data obtained from the ferry company), 4) numbers of COVID-19 patients in Japan and number of school and nursery closures in Sado Island (data obtained from the websites of the ministry of Health, Labor and Welfare of Japan and Sado City, respectively) (9,10), and 5) numbers of the general population in each age group less than 15 years in Sado Island, obtained from the Sado City Office. This study used the opt-out method and was approved by the Ethics Committee of Sado General Hospital (approval number: sgh20211020-0274). No informed consent was obtained from patients.

Statistical Analysis

Monthly mean numbers of total pediatric admissions and disease-specific pediatric admissions were compared between the pre-pandemic and pandemic periods. Descriptive statistics are reported as medians with interquartile ranges (IQR) or as means with standard deviations (SD), as appropriate. Continuous variables were compared with the Mann-Whitney U test, and categorical

variables were compared with the chi-square test. Total and disease-specific hospitalizations per month during the 2 periods were compared by using odds ratios (ORs) and 95% confidence intervals (CIs). The ORs were adjusted by calculating the number of hospitalization numbers per 1,000 children each year. Furthermore, we calculated the ORs for the patients less than 5 years because this age group was the majority of the patients. Furthermore, we divided the patients less than 5 years into the following; 1) less than 1 year, 2) 1 year, and 3) 2-4 years. A two-sided, P-value of less than 0.05 was set as the cutoff value for a significant difference. Statistical analysis was performed by using EZR on R commander software version 1.54 (11).

RESULTS

In Sado Island, the populations of children less than 15 years each year were 5,765 in 2016, 5,591 in 2017, 5,391 in 2018, 5,228 in 2019, and 5,090 in 2020, respectively. The population of children less than 5 years each year has decreased year by year; 1,744 in 2016, 1,638 in 2017, 1,558 in 2018, 1,461 in 2019, and 1,314 in 2020. The number of children less than 5 years significantly decreased by approximately 25% in 2020 compared to 2016 (**Supplementary**

Table 1). We collected data from 1,272 pediatric patients hospitalized in the 2 hospitals during the period from April 1, 2016 through March 31, 2021. Of the 1,272 patients, 1,144 (89.9%) were hospitalized in the pre-pandemic period (median age [IQR], 1.9 [0.7-5.5] years; 610/1,144 males [53.3%]), and 128 (10.1%) were hospitalized in the pandemic period (median age [IQR], 1.6 [0.3-5.2] years; 68/128 males [53.1%]). There was no significant difference in age, gender, or the number of days of hospitalization between the 2 periods (P > 0.23) (**Table 1, 2**).

The number of hospitalized patients (**Supplementary Table 2**) and general population (**Supplementary Table 1**) in each age on Sado Island in the pre-pandemic and pandemic periods are shown. These demonstrated that the majority of the hospitalization was children less than 5 years in pre-pandemic (72.6%) and pandemic periods (71.9%). The average number of monthly pediatric admissions was significantly lower in the pandemic period (median [IQR], 11.0 [7.0-14.0]) than in the pre-pandemic period (23.0 [20.8-28.3]) (adjusted OR (aOR) 0.47, 95% CI 0.29-0.71, P < 0.001). When we classified patients by admission diagnosis, the monthly number of hospitalized patients with respiratory tract infections was significantly lower in the pandemic period

(median [IQR], 6.5 [5.0-9.0]) than in the pre-pandemic period (1.0 [0-1.3]; aOR 0.20, 95% CI 0.04-0.61, P < 0.01). However, the monthly number of hospitalized patients with asthma exacerbation was not significantly lower in the pandemic period than in the pre-pandemic period (1.0 [0.8-3.0]/month vs. 0 [0-0.3]/month, respectively; aOR 0.23, 95% CI 0.01-1.50, P = 0.15). The trend was similar for patients with gastrointestinal tract infections (1.0 [0-2.0]/month vs. 0 [0-0.3]/month, respectively; aOR 0.29, 95% CI 0.01-1.88, P = 0.33) (**Table 1, Figure 1-3**).

When we compared the admission rates in children less than 5 years, decreases in the number of total hospitalizations (P < 0.001) and hospitalizations for respiratory tract infections (P < 0.001) were observed (**Table 2**). When we divided the patients 1) less than 1 year, 2) 1 year, and 3) 2-4 years, the monthly number of hospitalization due to respiratory tract infections was significantly lower during the pandemic period in all age groups, especially in patients at 1 year (aOR 0.06, 95% CI 0.03-0.13) (**Table 2**). Other diagnoses included urinary tract infections, Kawasaki disease, febrile convulsions, epilepsy, and respiratory diseases in newborns such as transient tachypnea of the newborn and respiratory distress syndrome, etc.

There were 475,241 COVID-19 cases during the study period in Japan (**Figure 4**) and only 3 adult COVID-19 cases during the study period on Sado Island: the first was confirmed in July 2020 and the other 2 in January 2021. No COVID-19 patient less than 15 years was reported on Sado Island during the study period (**Figure 4**). The average annual number of passengers on ferries between Sado Island and mainland Japan was 1,470,305 in the pre-pandemic period and 701,155 in the pandemic period (**Figure 4**). No school or nursery closure was reported on Sado Island during the study period.

DISCUSSION

During the SARS-CoV-2 pandemic, the total number of pediatric hospitalizations was significantly lower in the pandemic period than in the pre-pandemic period, although a few COVID-19 cases were reported in Sado Island. The decrease was most likely due to reduced travel and increased awareness of infection control among the island's residents. The number of pediatric admissions attributable to infectious diseases and related conditions was significantly lower in the pandemic period than in the pre-pandemic period.

Although several studies reported decreases in pediatric

hospitalizations during the SARS-CoV-2 pandemic (1,4–6), almost all examined pediatric hospitalizations in areas with a high prevalence of COVID-19. A study in Kobe, Japan, identified 3,417 COVID-19 cases during the study period, and 307 (9.0%) of the patients were younger than 20 years (5). In children, the prevalence of a viral disease might be affected by the presence of other viral diseases, because of viral interference (12–14) or cross-reactivity of existing antibodies against related viruses (15). This possibility has been suggested for SARS-CoV-2 infection (15–17). In the present study, only a few adults were diagnosed with COVID-19, and no pediatric COVID-19 case was reported during the study period. Thus, the present results were probably not directly affected by the SARS-CoV-2 infection by SARS-CoV-2 viral interference, which could have potentially influenced the epidemiologic characteristics of other viral diseases.

This study was unique because it was performed on an isolated island with limited medical resources. Almost all pediatric patients visited 1 of the 2 hospitals studied; thus, all pediatric hospitalizations on the island were identified. A study of a tertiary referral hospital in a non-endemic area in Japan reported similar results for outpatient and inpatient settings (18); however, the

number of pediatric cases identified might not have accurately reflected the numbers in the area, as pediatric patients might refrain from visiting a tertiary hospital because of fear of exposure to COVID-19 or because they visited another pediatric clinic or hospital. Thus, the number of pediatric patients identified might be underestimated.

Interestingly, the influenza endemic has been completely suppressed in Japan during the COVID-19 pandemic (19), whereas RSV endemics among Japanese children have surged since 2021 (20). The increase started at the beginning of 2021 and peaked in June of that year when incidence was roughly double that of the highest incidence before the pandemic (**Supplementary Figure 2**). During the previous decade, the peak of the RSV endemic moved toward early autumn, so the pattern differs from those of previous years (**Supplementary Figure 2**). In Japan, viral infections other than rhinoviral infection in children have been suppressed during the COVID-19 pandemic (21). Rhinovirus interferes with the influenza A virus at the host and population level (13, 21); thus, this increase in rhinoviral infection is likely attributable to the absence of influenza viruses in the population. These interesting, and complicated, observations suggest that through a similar mechanism, SARS-

CoV-2 interacts differently with each virus through viral interference or cross-reactivity against other viruses.

There are 2 possible reasons for the decrease in pediatric hospitalizations, especially those due to infectious diseases and related conditions, on Sado Island during the SARS-CoV-2 pandemic. First, the decrease in travel has resulted in a general reduction in infectious disease spread. The prevention of infectious disease importation by quarantine was reported to be a reason for Hong Kong's early success in controlling the spread of the SARS-CoV-2 pandemic (23), and control of domestic travel may be effective in preventing the spread of the SARS-CoV-2 pandemic (24). Thus, controlling the flow of people is important in reducing the spread of infectious diseases. Like SARS-CoV-2, other respiratory infectious diseases are affected by a decrease in travel. In other countries, the number of pediatric infections by influenza, RSV, and other respiratory viruses decreased after travel restrictions were imposed during urban lockdowns (25,26). Similarly, in Japan, a decrease in the number of passengers on domestic and international airlines might have contributed to a reduction in RSV cases (27). After the declaration of a state of emergency in spring 2020, the number of ferry passengers traveling from

mainland Japan to Sado Island decreased (**Figure 4**), and this restriction in travel may have contributed to the reduction in respiratory infections among children.

Second, increased awareness of infection control may have affected the spread of infectious diseases. In addition to declaring a state of emergency, the Japanese government requested people to avoid the “3 Cs” (closed spaces, crowded places, and close-contact settings) as part of a new lifestyle that emphasized physical distance between people, masking, and hand hygiene as basic infection control measures (10). Since the first emergency declaration in Japan, awareness of infection control among the population has significantly improved (10). Besides, in a survey conducted by Sado City regarding changes in the health awareness and awareness of infection control measures (28), the residents of Sado Island have significantly increased their awareness of infection control measures after the start of the COVID-19 pandemic. A previous study showed that improved hand hygiene reduced the rate of infections requiring hospitalization (29), and a meta-analysis of randomized controlled trials of suppression of SARS-CoV-2 infection by masking, hand hygiene, and physical distancing showed that these infection control measures helped reduce

COVID-19 incidence (3). Thus, a consensus developed that masking and hand hygiene are effective ways to prevent the spread of infectious diseases (3,30–34).

This study has several limitations that warrant mention. First, because it focused on pediatric hospitalizations and not on outpatients, we were unable to capture the entire picture of pediatric infectious diseases and related conditions. Second, we were unable to assess disease severity. However, the duration of hospital stay was similar before and during the SARS-CoV-2 pandemic, which suggests that disease severity was similar in these periods. Third, we were not able to identify detailed disease conditions and causative microorganisms in the respiratory tract and gastrointestinal infections, due to the limited numbers of subjects and the use of diagnosis registered for DPC under the national health insurance system, which does not provide detailed disease conditions. Fourth, the population number of cases was small in the study, and the ORs of hospitalizations with bronchial asthma exacerbations and gastrointestinal tract infections were not significant due to the beta-error; however, a larger epidemiological analysis is impossible in the isolated region.

Conclusion

COVID-19 incidence was negligible on Sado Island, and the number of pediatric hospitalizations was lower during the pandemic than before it. These findings highlight the impact of decreased travel and increased awareness of infection control measures on pediatric hospitalization for infectious diseases and related conditions, not by the viral interference by SARS-CoV-2.

Acknowledgments

We are grateful to the patients, their parents/guardians, and family members, and to the physicians who participated in this study.

Disclosure statement

The authors declare no conflict of interest.

Authorship contribution

TF and TI designed the study. TF collected and summarized the data. TF and TI performed the statistical analyses. TI, YA, MF, FG, MO, and AI contributed to data collection and interpretation. TF, TI, and YA drafted the manuscript, and

AS, TF, TI, and YA revised the manuscript. All authors approved the final version of the manuscript.

Reference

1. Sano K, Nakamura M, Ninomiya H, Kobayashi Y, Miyawaki A. Large decrease in paediatric hospitalisations during the COVID-19 outbreak in Japan. BMJ Paediatr Open. 2021;5(1):e001013.

2. Pelletier JH, Rakkar J, Au AK, Fuhrman D, Clark RSB, Horvat CM. Trends in US Pediatric Hospital Admissions in 2020 Compared With the Decade Before the COVID-19 Pandemic. JAMA Netw Open. 2021 Feb 1;4(2):e2037227.

3. Talic S, Shah S, Wild H, Gasevic D, Maharaj A, Ademi Z, et al. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. BMJ [Internet]. 2021 Nov 18 [cited 2021 Nov 30];375. Available from: https://www.bmj.com/content/375/bmj-2021-068302

4. Reid LD, Fang Z. Changes in Pediatric Hospitalizations and In-Hospital Deaths in the Initial Period of the COVID-19 Pandemic (April–September 2020), 13 States: Statistical Brief #283. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2006 [cited 2021 Oct 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK574673/

5. Iio K, Matsubara K, Miyakoshi C, Ota K, Yamaoka R, Eguchi J, et al. Incidence of Kawasaki disease before and during the COVID-19 pandemic: a retrospective cohort study in Japan. BMJ Paediatr Open. 2021;5(1):e001034.

6. Hara T, Furuno K, Yamamura K, Kishimoto J, Mizuno Y, Murata K, et al. Assessment of Pediatric Admissions for Kawasaki Disease or Infectious Disease During the COVID-19 State of Emergency in Japan. JAMA Network Open. 2021 Apr;4(4):e214475.

7. Halfmann PJ, Nakajima N, Sato Y, Takahashi K, Accola M, Chiba S, et al. SARS-CoV-2 Interference of Influenza Virus Replication in Syrian Hamsters. The Journal of Infectious Diseases. 2021 Dec;jiab587.

8. Escobedo-Bonilla CM. Mini Review: Virus Interference: History, Types and Occurrence in Crustaceans. Frontiers in Immunology [Internet]. 2021 [cited 2022 Jun 30];12. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2021.674216

9. Niigata Prefecture Sado City Official Homepage Top Page [Internet]. [cited 2021 Dec 28]. Available from: https://www-city-sado-niigata-jp.translate.goog/?_x_tr_sl=ja&_x_tr_tl=en&_x_tr_hl=ja

10. Novel Coronavirus (COVID-19) [Internet]. [cited 2021 Dec 14]. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000164708_00079.html

11. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant. 2013 Mar;48(3):452–8.

12. Gonzalez AJ, Ijezie EC, Balemba OB, Miura TA. Attenuation of Influenza A Virus Disease Severity by Viral Coinfection in a Mouse Model. J Virol. 2018 Dec 1;92(23):e00881-18.

13. Van Leuven JT, Gonzalez AJ, Ijezie EC, Wixom AQ, Clary JL, Naranjo MN, et al. Rhinovirus Reduces the Severity of Subsequent Respiratory Viral Infections by Interferon-Dependent and -Independent Mechanisms. mSphere. 6(3):e00479-21.

14. Wu A, Mihaylova VT, Landry ML, Foxman EF. Interference between rhinovirus and influenza A virus: a clinical data analysis and experimental infection study. Lancet Microbe. 2020 Oct;1(6):e254–62.

15. Shrwani K, Sharma R, Krishnan M, Jones T, Mayora-Neto M, Cantoni D, et al. Detection of Serum Cross-Reactive Antibodies and Memory Response to SARS-CoV-2 in Prepandemic and Post-COVID-19 Convalescent Samples. J Infect Dis. 2021 Oct 28;224(8):1305–15.

16. Torres-Fernandez D, Casellas A, Mellado MJ, Calvo C, Bassat Q. Acute bronchiolitis and respiratory syncytial virus seasonal transmission during the COVID-19 pandemic in Spain: A national perspective from the pediatric Spanish Society (AEP). J Clin Virol. 2021 Dec;145:105027.

17. Borrelli M, Corcione A, Castellano F, Fiori Nastro F, Santamaria F. Coronavirus Disease 2019 in Children. Front Pediatr. 2021 May 28;9:668484.

18. Shichijo K, Takeuchi S, Tayama T, Takei M, Fujioka K, Ono A, et al. Patient attendance at a pediatric emergency referral hospital in an area with low COVID-19 incidence. PLOS ONE. 2021 Oct 14;16(10):e0258478.

19. Fukuda Y, Tsugawa T, Nagaoka Y, Ishii A, Nawa T, Togashi A, et al. Surveillance in hospitalized children with infectious diseases in Japan: Pre- and post-coronavirus disease 2019. J Infect Chemother. 2021 Nov;27(11):1639–47.

20. Ujiie M, Tsuzuki S, Nakamoto T, Iwamoto N. Resurgence of Respiratory Syncytial Virus Infections during COVID-19 Pandemic, Tokyo, Japan. Emerg Infect Dis. 2021 Nov;27(11):2969–70.

21. Takashita E, Kawakami C, Momoki T, Saikusa M, Shimizu K, Ozawa H, et al. Increased risk of rhinovirus infection in children during the coronavirus disease-19 pandemic. Influenza Other Respir Viruses. 2021 Jul;15(4):488–94.

22. Nickbakhsh S, Mair C, Matthews L, Reeve R, Johnson PCD, Thorburn F, et al. Virus–virus interactions impact the population dynamics of influenza and the common cold. PNAS. 2019 Dec 26;116(52):27142–50.

23. To KKW, Sridhar S, Chiu KHY, Hung DLL, Li X, Hung IFN, et al. Lessons learned 1 year after SARS-CoV-2 emergence leading to COVID-19 pandemic. Emerg Microbes Infect. 10(1):507–35.

24. Murano Y, Ueno R, Shi S, Kawashima T, Tanoue Y, Tanaka S, et al. Impact of domestic travel restrictions on transmission of COVID-19 infection using public transportation network approach. Sci Rep. 2021 Feb 4;11:3109.

25. Diesner-Treiber SC, Voitl P, Voitl JJM, Langer K, Kuzio U, Riepl A, et al. Respiratory Infections in Children During a Covid-19 Pandemic Winter. Frontiers in Pediatrics. 2021;9:1132.

26. Wan WY, Thoon KC, Loo LH, Chan KS, Oon LLE, Ramasamy A, et al.

Trends in Respiratory Virus Infections During the COVID-19 Pandemic in Singapore, 2020. JAMA Network Open. 2021 Jun;4(6):e2115973.

27. Wagatsuma K, Koolhof IS, Shobugawa Y, Saito R. Decreased human respiratory syncytial virus activity during the COVID-19 pandemic in Japan: an ecological time-series analysis. BMC Infectious Diseases. 2021 Aug;21(1):734.

28. Results of Questionnaire Survey and Workshop on Sado City Comprehensive Plan - Official Website of Sado City, Niigata Prefecture [Internet]. [cited 2022 Jun 20]. Available from: https://www.city.sado.niigata.jp/site/plan/26004.html

29. Lin Huang GK, Stewardson AJ, Lindsay Grayson M. Back to basics: hand hygiene and isolation. Curr Opin Infect Dis. 2014 Aug;27(4):379–89.

30. Esposito S, Marchetti F, Lanari M, Caramelli F, De Fanti A, Vergine G, et al. COVID-19 Management in the Pediatric Age: Consensus Document of the COVID-19 Working Group in Paediatrics of the Emilia-Romagna Region (RE-CO-Ped), Italy. Int J Environ Res Public Health. 2021 Apr 8;18(8):3919.

31. Nanda A, Hung I, Kwong A, Man VC, Roy P, Davies L, et al. Efficacy of surgical masks or cloth masks in the prevention of viral transmission: Systematic review, meta-analysis, and proposal for future trial. J Evid Based Med. 2021 Feb 9;10.1111/jebm.12424.

32. Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, et al. Physical interventions to interrupt or reduce the spread of respiratory viruses. Cochrane Database Syst Rev. 2020 Nov 20;11:CD006207.

33. Kampf G, Brüggemann Y, Kaba HEJ, Steinmann J, Pfaender S, Scheithauer S, et al. Potential sources, modes of transmission and effectiveness of prevention measures against SARS-CoV-2. J Hosp Infect. 2020 Dec;106(4):678–97.

34. Katsumata N, Harama D, Toda T, Sunaga Y, Yoshizawa M, Kono Y, et al. The Prevention Measures for COVID-19 and Changes in Kawasaki Disease Incidence. J Epidemiol. 2021 Sep 4;

Table 1. Comparison of patients' characteristics and number of hospitalization between pre-pandemic and pandemic periods in children less than 15 years

	Pre-pandemic period April 2016 - March 2020 (N = 1,144)	**Pandemic period April 2020 – March 2021 (N = 128)**	
Patients' characteristics			**P-value**
Age, years (median, [IQR])	1.9 [0.7-5.5]	1.6 [0.3-5.2]	P = 0.24†
Gender, Male, n (%)	610 (53.3%)	71 (53.8%)	P = 0.93‡
Average numbers of days in hospital (median, [IQR])	3.0 [1.0-4.0]	2.0 [1.0-5.0]	P = 0.58†
Number of hospitalizations			**Adjusted Odds Ratio¶ (95%CI, P-value)**
Monthly average number of total hospitalizations (median, [IQR])	23.0 [20.8-28.3]	11.0 [7.0-14.0]	0.47 (0.29-0.71) P < 0.001*†
Monthly average number of respiratory tract infection (median, [IQR])	6.5 [5.0-9.0]	1.0 [0-1.3]	0.20 (0.04-0.61) P < 0.01*†
Monthly average number of asthma exacerbation (median, [IQR])	1.0 [0.8-3.0]	0 [0-0.3]	0.23 (0.01-1.50) P = 0.15†
Monthly average number of gastrointestinal infection (median, [IQR])	1.0 [0-2.0]	0 [0-0.3]	0.29 (0.01-1.88) P = 0.33†

* Statistically significant.

†Mann-Whitney U test, ‡Chi-square test

¶Odds ratio was adjusted by calculation of the hospitalization per 1000 pediatric population on Sado Island.

Abbreviations: IQR, interquartile range; OR, odds ratio; CI, confidence interval

Table 2. Comparison of patients' characteristics and number of hospitalization between pre-pandemic and pandemic periods in children less than 5 years

	Pre-pandemic period April 2016 - March 2020 (N = 830)	**Pandemic period April 2020 – March 2021 (N = 92)**		**Comparison in subgroups**		
				Less than 1 year	**1 year**	**2-4 years**
Patients' characteristics				**P-value**		
Age, years (median, [IQR])	1.3 [0.3-2.3]	1.0 [0.2-2.2]	P = 0.18†	P = 0.44†	P = 0.51†	P = 0.18†
Gender, Male, n (%)	459 (55.3%)	53 (55.2%)	P = 1.00‡	P = 0.89‡	P = 0.48‡	P = 1.00‡
Average numbers of days in hospital (median, [IQR])	3.0 [1.0-5.0]	3.0 [1.0-5.0]	P = 0.56†	P = 0.44†	P = 0.40†	P = 0.56†
Number of hospitalizations				**Adjusted Odds Ratio¶ (95%CI, P-value)**		
Monthly average number of total hospitalizations (median, [IQR])	17.0 [14.0-21.0]	8.5 [4.8-10.5]	0.50 (0.38-0.65) P < 0.001*†	0.52 (0.44-0.62) P < 0.001*†	0.34 (0.26-0.43) P < 0.001*†	0.50 (0.38-0.65) P < 0.001*†
Monthly average number of respiratory tract infection (median, [IQR])	6.0 [4.0-8.0]	1.0 [0-1.3]	0.20 (0.10-0.39) P < 0.001*†	0.27 (0.17-0.43) P < 0.001*†	0.06 (0.03-0.13) P < 0.001*†	0.32 (0.13-0.70) P < 0.01*†
Monthly average number of asthma exacerbation (median, [IQR])	1.0 [0-1.0]	0 [0-0.3]	0.35 (0.07-1.12) P = 0.10†	-	-	0.47 (0.15-1.20) P = 0.14†

Monthly average number of gastrointestinal infection (median, [IQR])	0 [0-1.0]	0 [0-0]	0.21 (0.01-1.32) P = 0.16†	-	-	0.22 (0.01-1.41) P = 0.15†

* Statistically significant.

†Mann-Whitney U test, ‡Chi-square test

¶Odds ratio was adjusted by calculation of the hospitalization per 1000 pediatric population on Sado Island.

Abbreviations: IQR, interquartile range; OR, odds ratio; CI, confidence interval

Figure Legends

Figure 1. Average monthly numbers of pediatric hospitalizations on Sado Island, Niigata, Japan, by diagnosis at admission, before and during the pandemic.

The pre-pandemic period indicates the period from April 1, 2016 through March 31, 2020, and the pandemic period indicates the period from April 1, 2020 through March 31, 2021. Error bars indicate 95% confidence intervals. The monthly numbers of A) total pediatric hospitalizations, B) respiratory tract infections, C) asthma exacerbations, and D) gastrointestinal tract infections are shown.

Figure 2. Annual change in the number of pediatric admission by diagnosis.

Annual change in the number of pediatric admission by diagnosis are shown. The number of pediatric inpatients was corrected per 1,000 pediatric population in each year.

Figure 3. Monthly numbers of pediatric hospitalizations on Sado Island,

Niigata, Japan

The number of pediatric hospitalizations started to decrease in early 2020, even though the first case of coronavirus disease 2019 on the island was confirmed in July 2020.

Figure 4. Monthly cumulative numbers of ferry passengers to/from Sado Island, Niigata, Japan, and numbers of newly infected cases of coronavirus disease 2019 in Japan

During the study period, only 3 cases of coronavirus disease 2019 were diagnosed on Sado Island.

Supplementary Figure 1. Map of Sado Island

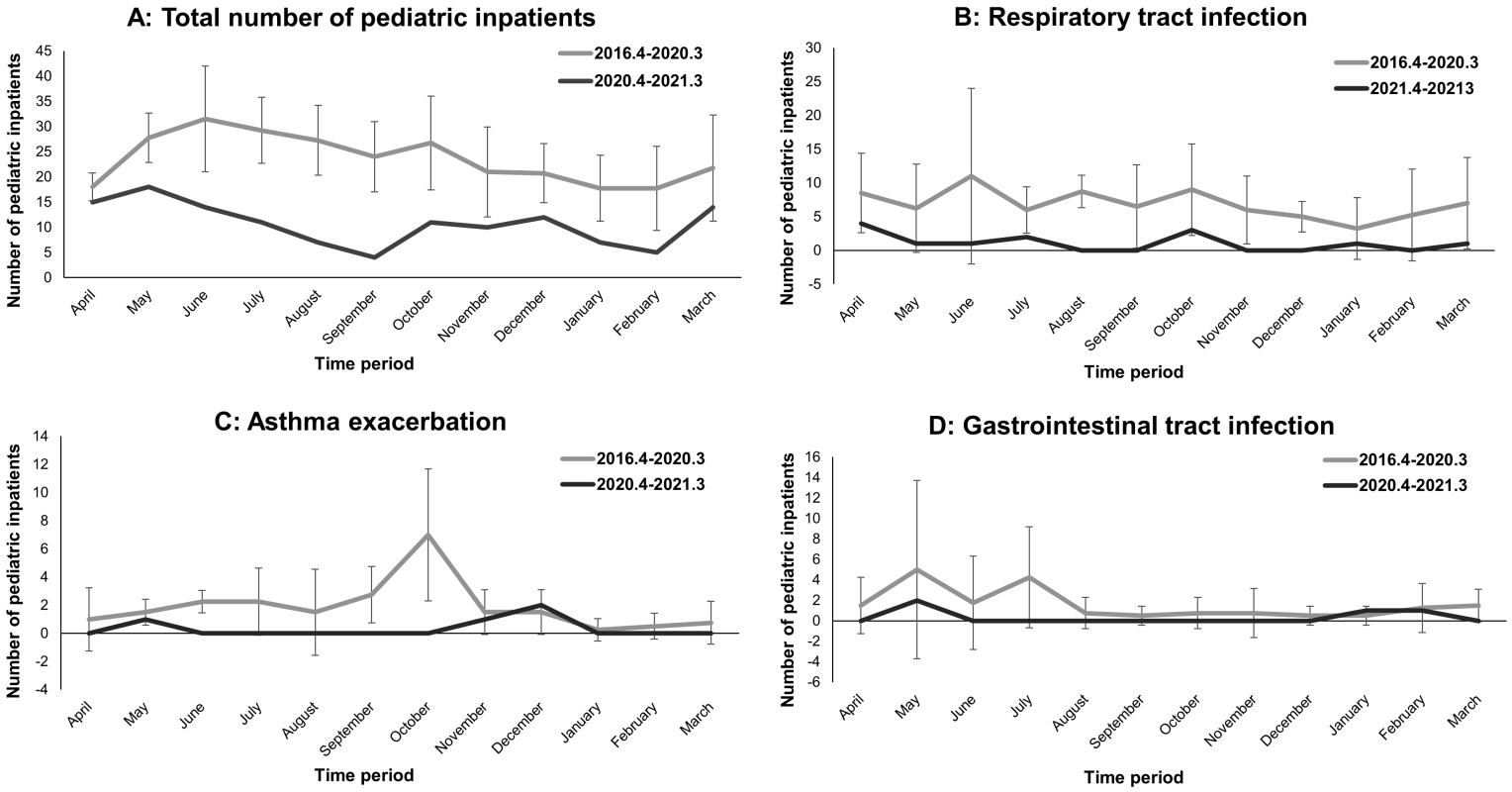
Sado Island is located in the Sea of Japan and is part of Niigata Prefecture. On the island, Sado General Hospital and Ryotsu Hospital are the 2 hospitals responsible for managing pediatric outpatients and inpatients. There are 2 sea routes to reach Sado Island from mainland Japan.

Supplementary Figure 2. Cases of influenza and respiratory syncytial

virus (RSV) reported in the Japan Infectious Disease Weekly Report

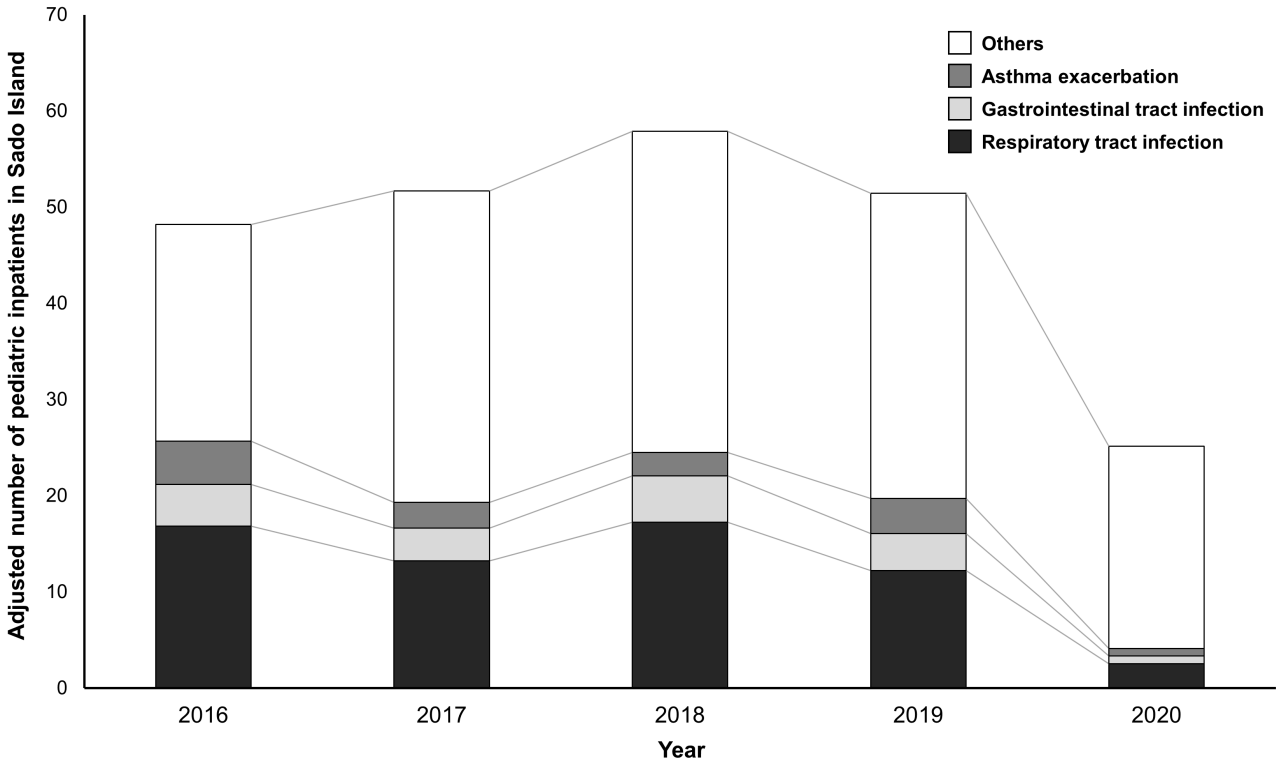
The numbers of cases of influenza and RSV reported in the sentinel weekly in Japan are shown. Reporting of the number of RSV cases began in 2018. The data are from the Infectious Disease Weekly Report Japan (IDWR) of the Ministry of Health, Labour and Welfare/National Institute of Infectious Diseases.

Figure 1



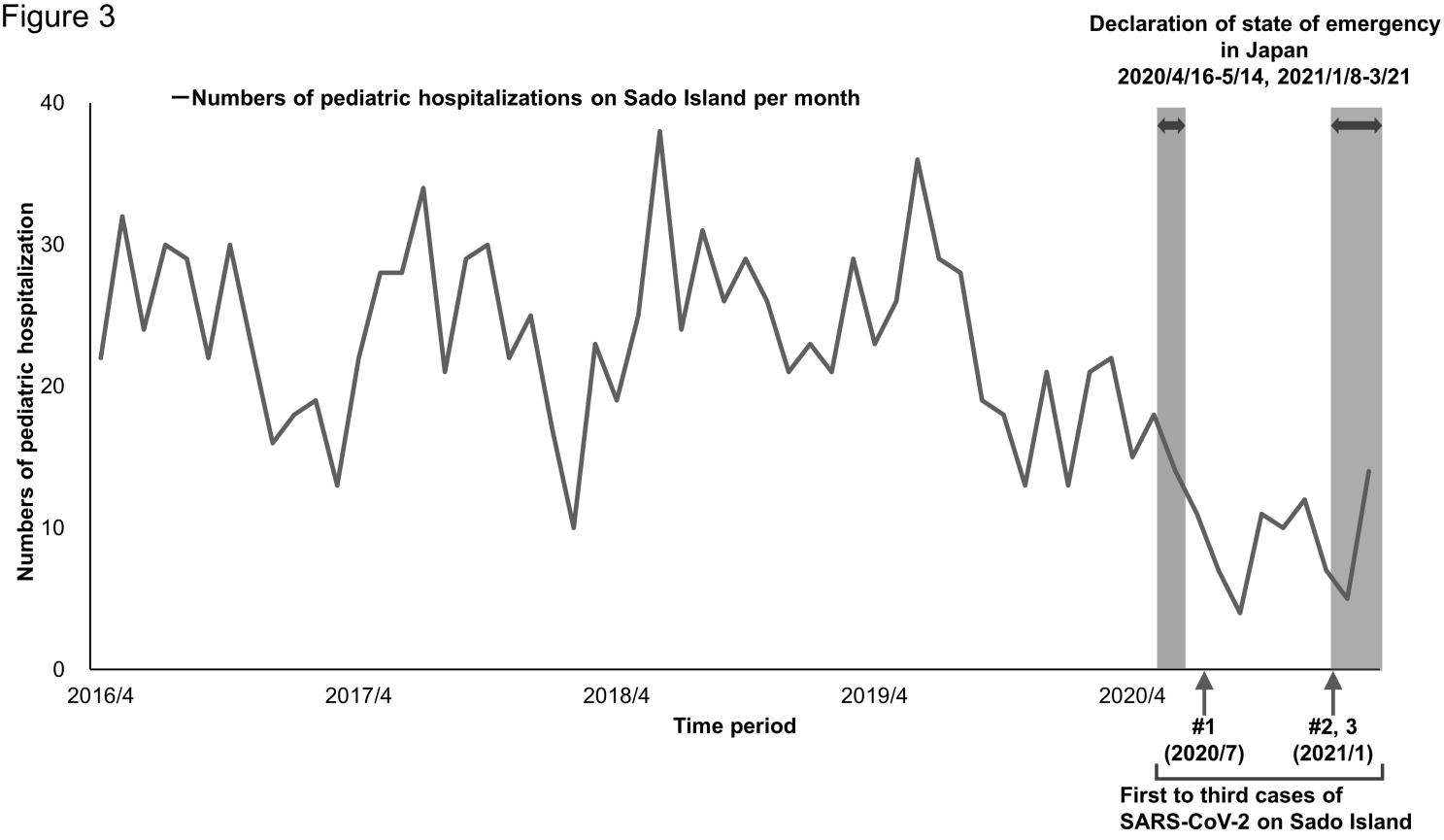
PED_15326_Takuya Fuse PI Fig.1 rev 02.tif

Figure 2



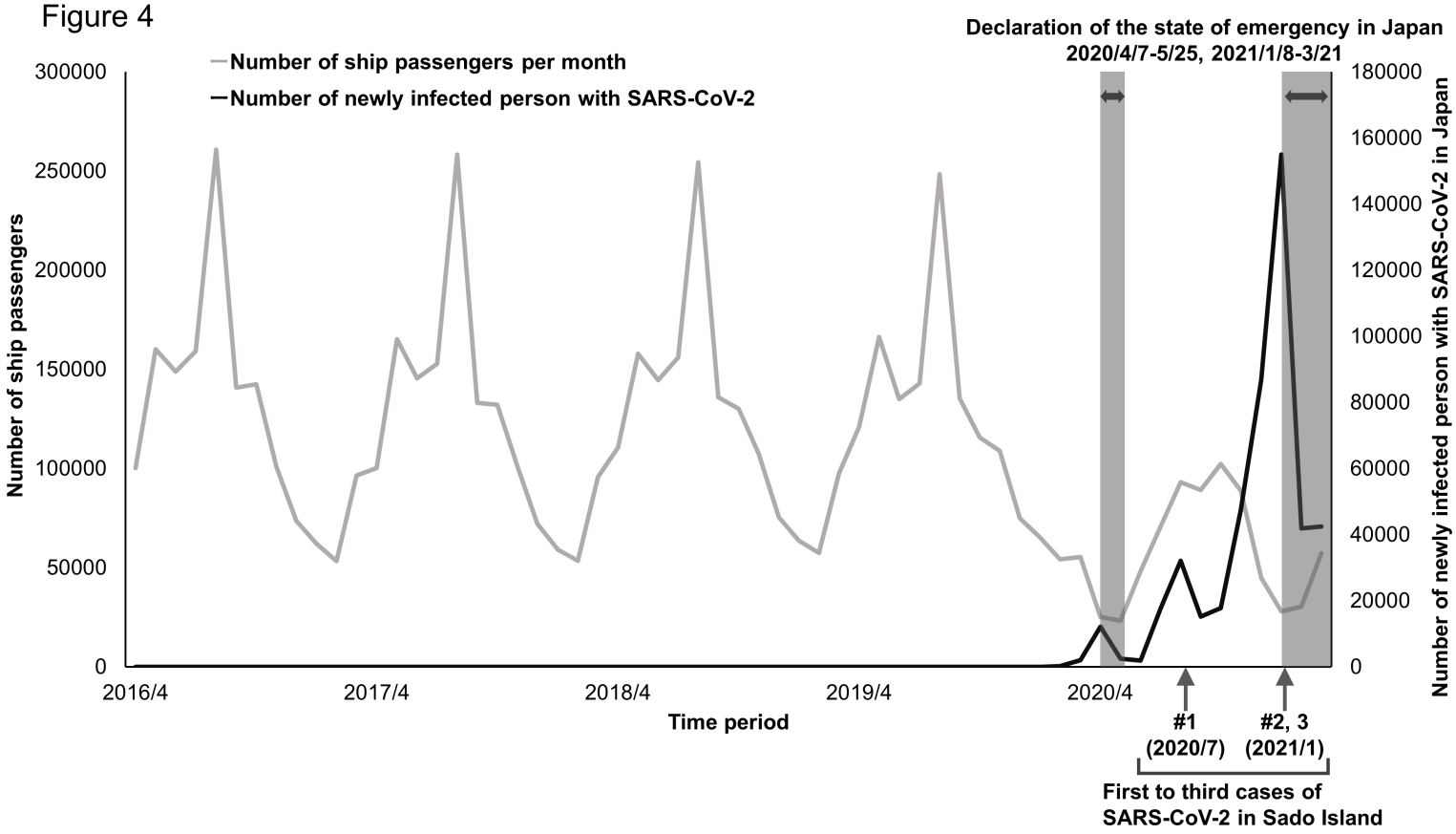
PED_15326_Takuya Fuse PI Fig 2 rev.TIF

Figure 3



PED_15326_Takuya Fuse PI Fig 3 rev.TIF

Figure 4



PED_15326_Takuya Fuse PI Fig 4 rev.TIF