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RESEARCH LETTER

Decreased incidence followed by comeback of pediatric infections during the COVID-19 pandemic in Japan

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During the coronavirus disease 2019 (COVID-19) pandemic, the Japanese government implemented several infection control measures, such as states of emergency (SoE) and school closures, and encouraged universal masking and hand hygiene. Initial activity restrictions and improved hygiene were found to be associated with declines in the incidence of influenza during the 2019–2020 winter season [1]. Prior studies have found that the incidence of seven pediatric infections, such as pharyngoconjunctivitis and varicella, decreased during and after the school closures in Japan [2]. As activity restrictions continue to be lifted, there is growing concern that pediatric infections may suddenly return given that the pool of susceptible children increased during the pandemic [3]. In this study, we use national infectious disease sentinel data from January 2012 to October 2021 to assess changes in the reported number of pediatric infections in Japan during the COVID-19 pandemic. We hypothesize that the reporting of many infectious diseases decreased during the early stages of the pandemic but ultimately returned to normal when activity restrictions were lifted.

Case numbers for varicella, erythema infectiosum, gastroenteritis, group A *Streptococcal* (GAS) pharyngitis, hand, foot and mouth disease (HFMD), herpangina, mumps, pharyngoconjunctivitis, respiratory syncytial virus (RSV) infection, and roseola among those aged less than 15 years are monitored under the Infectious Disease Control Law in Japan. The present study considered the aforementioned diseases with the exception of erythema infectiosum and mumps because they lack annual periodicity and thus were not suitable for the estimation method employed in this study (Supplementary Fig. 1). For ease of comparison, pediatric infections were classified as either summer viral illnesses (HFMD, herpangina, and roseola), multiseason illnesses (gastroenteritis, GAS pharyngitis, and pharyngoconjunctivitis), or fall/winter viruses (varicella and RSV) based on their peak incidence in 2019.

We performed cross-sectional analyses using national, weekly data from January 2012 (week 1: December 26, 2011 to January 1, 2012) to October 2021 (week 42: October 18–24, 2021) sourced from the National Institute of Infectious Disease (NIID), Japan (https://www.niid.go.jp/niid/ja/data.html). The NIID gathers weekly reports on the number of infections diagnosed by pediatricians or general

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practitioners based on clinical symptoms and/or laboratory findings from approximately 3150 sentinel institutions. The notification values for all pediatric illnesses shown in this study reflect the total weekly number of clinical diagnoses. Sentinels are randomly selected each year, and the number of institutions fluctuates from week-to-week. We conducted a quasi-Poisson regression to estimate the expected weekly number of reports while controlling for overdispersion, and we included an offset term to account for changes in the number of reporting sentinels each week [4]. The method and sensitivity analyses are explained further in the Supplement. The beginning of the pandemic was defined as January 16, 2020, when the first official case of COVID-19 was identified in Japan.

Weekly observed and predicted trends in the number of pediatric infection notifications are shown in Fig. 1 and Supplementary Tables 1–8. Figure 1 includes trends dating back to January 2017 to illustrate seasonality. The results of the sensitivity analyses are described in the Supplement, and they are consistent with the results of the primary analyses presented below: (1) summer viral illnesses: reporting of both HFMD and herpangina showed broad deficits beginning weeks 18–19 of 2020 and extending to weeks 51 and 40, respectively. During the 2021 season, HFMD and herpangina again showed broad deficits between weeks 22–32 and 24–33, respectively, after which both returned to within-predicted range. Reports of herpangina were in excess during week 42 of 2021. During both the 2020 and 2021 seasons, notifications of roseola largely remained within-predicted range. Though there were scattered weekly deficits in roseola reporting during this period, they resemble patterns in notifications pre-COVID-19 except for 4 weeks of consecutive deficits from weeks 18–21 of 2020; (2) multiseason illnesses: reporting of gastroenteritis showed broad deficits during weeks 11–27 and 43–51 of 2020 but remained within-predicted range during 2021. Notifications

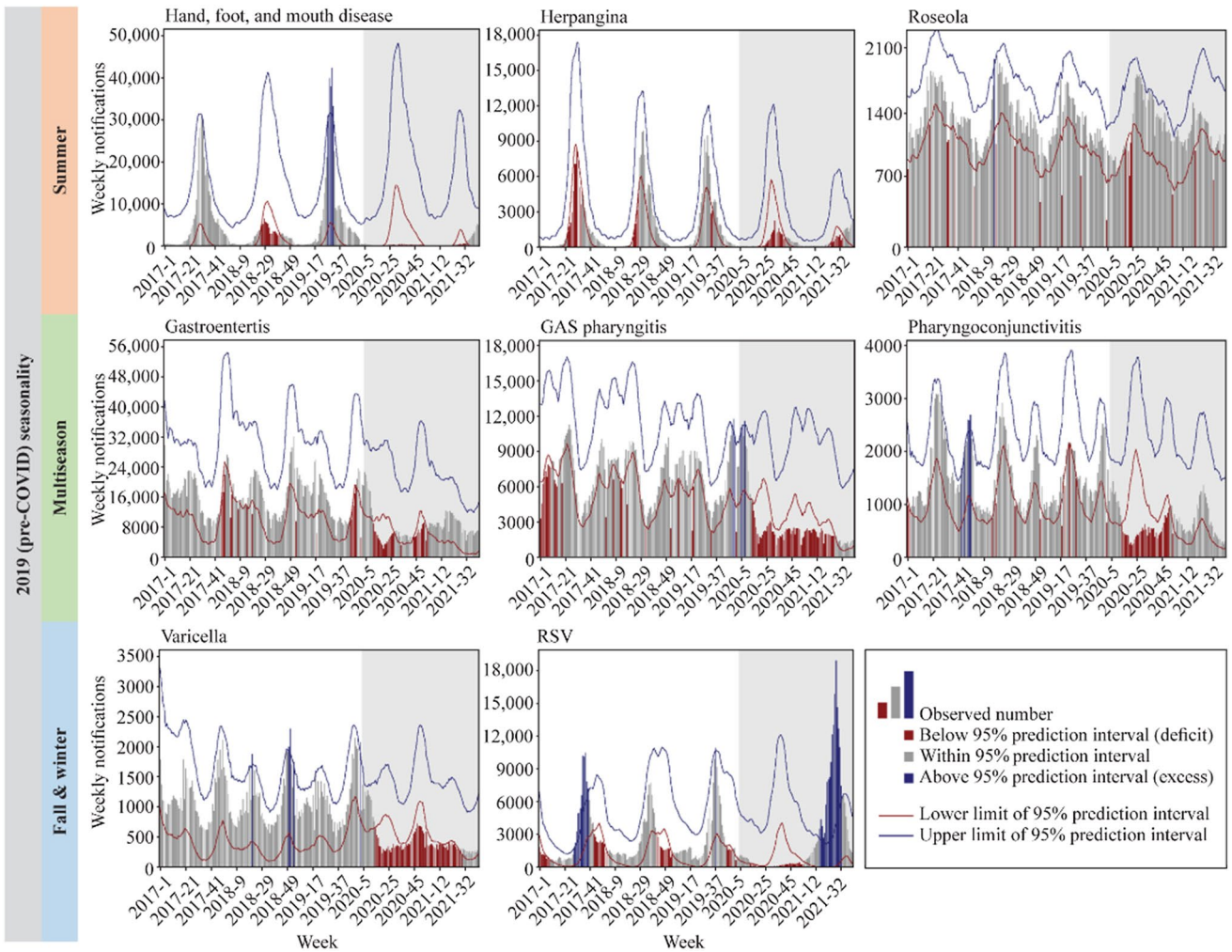

Fig. 1 Weekly observed and predicted trends in the number of pediatric infection notifications in Japan, 2017–2021. *GAS* group A *Streptococcal*, *RSV* respiratory syncytial virus

of GAS pharyngitis showed scattered weekly excesses in February 2020 (weeks 5, 6, and 8) but were followed by broad deficits between week 14 of 2020 and week 26 of 2021, after which it returned to within-predicted range. Reporting of pharyngoconjunctivitis showed evidence of broad deficits between weeks 13–50 of 2020 but returned to within-predicted range during 2021; (3) fall and winter viruses: reporting of varicella showed broad deficits during weeks 14 of 2020 to week 27 of 2021. Starting week 30, notifications of varicella remained within-predicted range for the remainder of 2021. Reporting of RSV showed broad deficits between week 13 of 2020 and week 2 of 2021, after which is returned to within-predicted range through week 14 of 2021. Notifications of RSV were found to be in excess between weeks 15–32 of 2021, after which they again returned to within-predicted range.

Using Japanese sentinel data, we investigated how the reporting of pediatric infections changed throughout the COVID-19 pandemic compared to previous years. We found evidence of broad deficits in reporting for HFMD, herpangina, gastroenteritis, GAS pharyngitis, pharyngoconjunctivitis, varicella, and RSV, followed by a normalization in disease notifications. Of the eight infections examined in this study, only roseola appeared to be relatively unaffected by the pandemic.

Our findings suggest that the incidence of seven pediatric infections declined during the pandemic, consistent with infection control measures implemented to decrease COVID-19 case-counts. Prior evidence during the early stages of the pandemic found that reporting of influenza markedly declined in Japan compared to previous years, likely due to the first SoE, increased mask-wearing, and improved hygiene practices [1]. Later analyses of pediatric hospital admissions in Japan found dramatic decreases in the number of inpatients with upper respiratory, lower respiratory, and gastrointestinal infections [5]. Another analysis of 18 hospitals in Hokkaido (northern Japan) found that the number of admissions for influenza, RSV, adenovirus, rotavirus, and norovirus decreased significantly compared to pre-COVID-19 levels [6]. Similar trends have been reported in the US [3] and France [7].

The significant decline in the reporting of pediatric infectious disease is likely due to several factors. SoEs and school closures limited contact among students, which directly decreased the number of exposures among children. Even after the lifting of school closures, mitigation measures (e.g., staggered school days) remained in place. Furthermore, improved hygiene awareness, such as increased use of masks and improved adherence to hand-washing, decreased the risk of infection even when in close proximity to infected children. With the exception of infectious gastroenteritis, all pediatric infections in this study can be transmitted by respiratory droplets. The use of masks, though intended to stymy COVID-19 infections, likely had the collateral benefit of decreasing transmission of several other infections [6]. Roseola was unique among the summer viruses in that it resisted significant changes in reporting during the pandemic. Though the reasons for this are unclear, it is possible that because many nurseries remained open even during school closures, young children (especially those under 2 years) that comprise the majority of roseola cases continued to have exposures outside the home [8].

All pediatric infections that showed evidence of reporting decreases also normalized to predicted ranges during early-to-mid 2021, though the number of notifications was still relatively lower than pre-pandemic years (excluding RSV). Given school re-openings and the gradual lifting of activity restrictions, it follows that increased contacts and socialization would eventually lead to a return to pre-pandemic disease transmission, though this trend is just beginning. RSV uniquely showed evidence of broad, excess reporting during 2021. Since the number of susceptible children increased as a result of decreased pediatric illness transmission during 2020 and 2021, excess infections are not unexpected [3]. In fact, prior research predicted a spike in Tokyo RSV cases following the pandemic, though in reality it happened earlier than expected [9]. Notably, the seasonality of RSV has been shifting to earlier months over the past several years, and the pandemic may have accelerated this trend [10]. Similar resurgences in enteric pathogens have been observed in China after nonpharmaceutical interventions were relaxed [11].

Resurgences of pediatric infection are concerning. In the case of RSV, palivizumab administration is timed based on seasonal epidemic trends, but RSV seasonality as seen in Japan during 2021 has never been observed before [12]. Furthermore, the rise of RSV in children poses risks to elderly populations [13], which are particularly large in Japan. Decreased maternal RSV antibody protection has been documented one year after the start of the pandemic, which places infants at particularly high-risk of severe illness [14]. Finally, sudden resurgences in pediatric infections threaten to overburden hospital systems, especially as COVID-19 threatens hospital bed availability.

This study has limitations. First, the regression analysis employed in this study is not designed to assess causality, but rather tests temporal associations based on historical data. Second, the regression analysis is able to capture gradual shifts in trends but cannot capture rapid changes that occur abruptly; thus, we cannot pinpoint the effect of unknown confounders that may have been present during the assessed period. Third, it is possible that parents refrained from taking their children to medical centers during the pandemic for fear of COVID-19 infection, which would have artificially lowered sentinel reporting. However, true decreases in inpatient admissions have been reported [5–7], suggesting that our findings of broad deficits in reporting are real.

We believe our findings should serve as initial evidence for the upcoming normalization of pediatric infections after the prolonged pandemic period. Given the increased number of children susceptible to pediatric infections, new outbreaks are to be expected, as has been observed with RSV already. We encourage pediatricians and hospital systems to make the necessary arrangements to handle potentially off-season influxes in clinic visits and hospital admissions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12519-022-00575-9.

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Data availability Data are openly available on the Japan National Institute for Infectious Diseases (NIID) website (https://www.niid.go.jp/niid/ja/data.html).

Declarations

Ethical approval Ethical approval was not required for this secondary analysis of publicly available data.

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. The authors have no conflict of interest to declare.

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