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CORRESPONDENCE

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COVID-19 pandemic-altered epidemiology of respiratory syncytial virus and human metapneumovirus infections in young children

Masayuki Nagasawa[1,2,*], Tomohiro Udagawa[1], Mari Okada[1], Ryuichi Nakagawa[1], Haruna Yokoyama[1], Tomoyuki Kato[2,3], Maki Furuya[4], Hayato Sakaguchi[2,4]

[1] Department of Pediatrics, Musashino Red Cross Hospital, Tokyo, Japan;
[2] Department of Infection Control, Musashino Red Cross Hospital, Tokyo, Japan;
[3] Department of Pharmacy, Musashino Red Cross Hospital, Tokyo, Japan;
[4] Department of Laboratory, Musashino Red Cross Hospital, Tokyo, Japan.

Abstract: To evaluate the impact of the COVID-19 pandemic on the epidemiology of respiratory viral infections, we examined the prevalence of respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) infections for pediatric patients admitted to our hospital before and after the COVID-19 pandemic from January 2015 to June 2023. During the COVID-19 pandemic, no outbreaks of RSV infections were seen in 2020, and no outbreaks of hMPV infections were seen in 2020 and 2021. Before the pandemic, the two epidemics did not overlap, but after the pandemic, the two epidemics almost overlapped for the second year in a row. The average age of patients with both RSV and hMPV infection after the pandemic was significantly older than before the pandemic by approximately one year.

***Keywords*:** COVID-19, viral interference, respiratory syncytial virus, human metapneumovirus

Introduction

Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) are closely related viruses belonging to pneumovirinae subfamily and cause bronchiolitis and pneumoniae in infants and young children, resulting in hospitalization, which becomes a major health problem in pediatric care (*1,2*). To evaluate the impact of the COVID-19 pandemic on the epidemiology of these viral infections, we investigated and compared the epidemic patterns of RSV and hMPV infections in children admitted and diagnosed at our hospital before and after COVID-19 pandemic from January 2015 to June 2023. The pathogenic diagnosis was made by antigen test before 2020 and by Filmarray® respiratory panel (ver2.1) test thereafter.

Our hospital is a tertiary emergency medical facility in the North Tama area of Tokyo, Japan. It has 611 beds, more than 20,000 annual admissions, more than 10,000 annual emergency transfers, and approximately 2,000 outpatients per day.

This study was approved by the Ethical Committee of Musashino Red Cross Hospital (approval number 4061). Informed consent was secured by opt-out method. It was performed in compliance with the ethical treatment policy of human and animal research participants and the latest Declaration of Helsinki.

Trends of RSV or hMPV infected patients under 10 years old who admitted in our hospital

In the reports so far, the epidemics of both virus infections have not completely overlapped in Japan (*3,4*), and the epidemic peaks of both infections in our hospital from 2015 to 2019 did not overlap as well as shown in Figure 1. These phenomena are referred to as social viral interference and have been mentioned in several viral infections (*5-7*). COVID-19, which emerged at the end of 2019, quickly spread around the world and became a pandemic (*8,9*). Japan also implemented a semi-social lockdown from April to May 2020. As a result, social activity restrictions continued, and no epidemics of RSV or hMPV were observed in 2020. After that, a large-scale epidemic of RSV was seen in the summer of 2021 due to the easing of restrictions on social activities and movements and the reopening of nursery schools, but no hMPV epidemic was observed. In 2022 and 2023, epidemics of both RSV and hMPV were seen.

Interestingly, both outbreaks occurred around the same time, unlike before the COVID-19 pandemic (Figure 1). More interestingly, when comparing the age distribution of infected children, the age distribution in post-COVID-19 epidemic shifted nearly one year older than that before COVID-19 epidemic (Figure 2). Prior to the COVID-19 pandemic, the age distribution during the

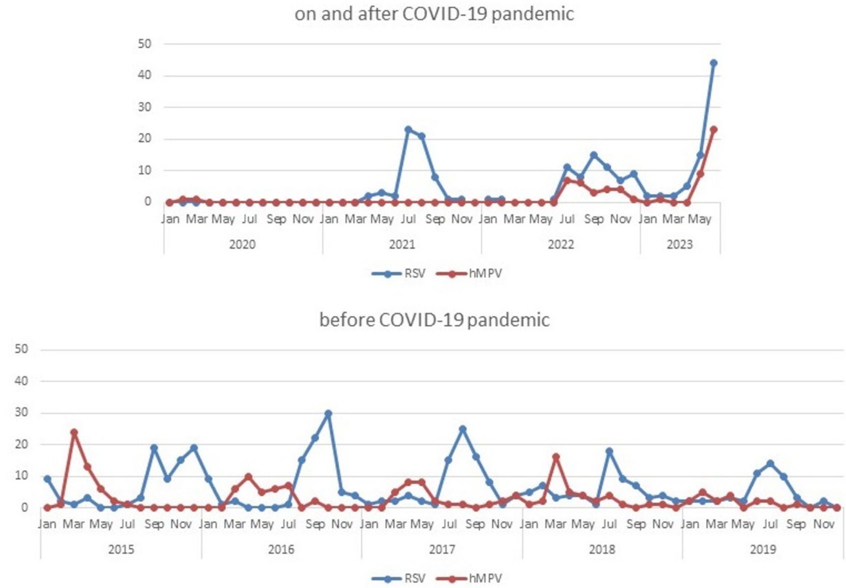

Figure 1. Trends of RSV or hMPV infected patients under 10 years old who admitted in our hospital were shown. Before COVID-19 pandemic, the epidemic peaks of RSV and hMPV infections did not overlap in each year. In 2022 and 2023, the epidemic peaks of both infections completely overlapped.

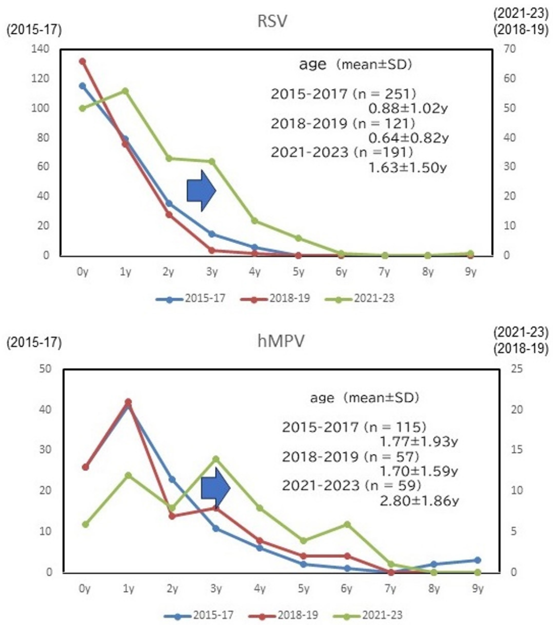

Figure 2. The age distribution of RSV (upper graph) and hMPV (lower graph) infected patients in three different periods (2015-2017, 2018-2019, and 2021-2023) were presented. The age distribution of 2021-2023 period is shifted to right (arrows) compared to that of 2015-2017 and 2018-2019 and the mean age of 2021-2023 is significantly older ($p < 0.001$: Mann-Whitney *U* test) than that of 2015-2017 and 2018-2019 in both RSV and hMPV infections.

epidemic of both viral infections was almost similar from year to year (data not shown).

COVID-19 pandemic-altered epidemiology of RSV or hMPV infections in young children

The periodic prevalence of epidemic respiratory viral infections in children can be attributed to several factors.

First is viral evolution. Viruses have the ability to mutate and evolve rapidly. These new strains can lead to recurrent outbreaks as the population lacks immunity to the modified virus. Second is host susceptibility. In a population, individuals may gain immunity to a specific viral infection through prior exposure or vaccination. However, over time, the immunity acquired through natural infection or vaccination can wane. Third are changes in population density and mobility. Population dynamics, including changes in population density and mobility, can influence the transmission of viral infections. Increased travel, urbanization, and global connectivity facilitate the rapid spread of viruses across regions and continents. Fourth are environmental factors. Certain viral infections exhibit seasonal patterns due to environmental factors. For instance, respiratory viruses like influenza tend to peak during the colder months when people spend more time indoors in close proximity, providing favorable conditions for viral transmission. Additionally, changes in climate patterns or ecological disturbances can affect the distribution and prevalence of vector-borne infections such as dengue or Zika virus. Fifth is lack of universal vaccination or treatment. The absence of effective vaccines or treatments against a particular viral infection can contribute to its periodic prevalence.

RSV and hMPV spread through similar routes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the measures taken to control COVID-19 have inevitably limited the transmission of both respiratory viruses among children. Furthermore, the reduced exposure to common respiratory viruses during the pandemic may affect the development of natural immunity in children, potentially leading to a susceptible population when restrictions ease and social interactions increase. One of the reasons why children aged 3 to 4 years became more susceptible to RSV and hMPV after the COVID-19 pandemic may be that immunity was not stimulated due to the decrease in epidemic viral diseases during the COVID-19 pandemic. Also, the possibility that the virus mutated during the COVID-19 pandemic cannot be completely ruled out.

It is unlikely that the difference in virus detection sensitivity between antigen testing and PCR testing would have an impact on this observation. FA testing was performed at the time of admission for acute lower respiratory tract infection, and the clinical symptoms were all characteristic of RSV and hMPV infections. Furthermore, it is also unlikely that an increase in detection sensitivity would result in matching the timing of epidemics from the same reason. Between January 2021 and June 2023, there were only two cases in which both RSV and hMPV were positive by FA testing, and significant interference was observed between the two virus infections (odds ratio = 0.221, 95% CI: 0.053-0.916, $p < 0.05$ by Fisher's exact test).

Viral interference at the individual level has been verified in animal experiments (*10,11*). However, virus interference at the population level is observed as an indirect phenomenon and its causes are complicated. From this perspective, a detailed examination of the trends in infectious diseases, especially in children before and after the rare COVID-19 pandemic will provide very important suggestions for considering the mode of transmission of viral infections in society, the maturation process of immunity to viruses, and countermeasures against acute viral infection epidemics.

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**Address correspondence to*:
Masayuki Nagasawa, Department of Pediatrics, Musashino Red Cross Hospital, 1-26-1, Kyonan-cho, Musashino-city, Tokyo 180-8610, Japan.
E-mail: mnagasawa.ped@tmd.ac.jp