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Surveillance in hospitalized children with infectious diseases in Japan: Pre- and post-coronavirus disease 2019

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ABSTRACT

Introduction: The epidemic of coronavirus disease 2019 (COVID-19) rapidly spread worldwide, and the various infection control measures have a significant influence on the spread of many infectious diseases. However, there have been no multicenter studies on how the number of hospitalized children with various infectious diseases changed before and after the outbreak of COVID-19 in Japan.

Methods: We conducted a multicenter, prospective survey for hospitalized pediatric patients in 18 hospitals in Hokkaido Prefecture, Japan, from July 2019 to February 2021. We defined July 2019 to February 2020 as pre-COVID-19, and July 2020 to February 2021 as post-COVID-19. We surveyed various infectious diseases by sex and age.

Results: In total, 5300 patients were hospitalized during the study period. The number of patients decreased from 4266 in the pre-COVID-19 period to 701 (16.4%) post-COVID-19. Patients with influenza and RSV decreased from 308 to 795 pre-COVID-19 to zero and three (0.4%) post-COVID-19. However, patients with adenovirus (respiratory infection) only decreased to 60.9% (46–28) of pre-COVID levels. Patients with rotavirus, norovirus, and adenovirus gastroenteritis decreased markedly post-COVID-19 to 2.6% (38–1), 27.8% (97–27) and 13.5%...
1. Introduction

The most common conditions seen in the field of pediatrics are infectious diseases, and there are a wide variety of epidemic diseases that are often difficult to manage. Infectious disease outbreaks vary greatly depending on the season, year, region and country, and it is important to understand the epidemiology. In Japan, the National Institute of Infectious Diseases (NIID) surveys the national trends in infectious diseases [1]. National surveillance in Hokkaido Prefecture reports weekly on infectious diseases including influenza, respiratory syncytial virus (RSV) and infectious gastroenteritis [2]. However, these data do not provide information on trends in patients who require hospitalization.

From July 1, 2019, we have run a survey called Hokkaido Pediatric Infectious Diseases Surveillance (HPIDS), to gather data about inpatient children with infectious diseases in the 18 hospitals in Hokkaido Prefecture. The survey’s purpose is to share information on severe infectious diseases among hospitals and use this to alert and provide information to medical staff and patients.

The epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), rapidly spread worldwide shortly after the survey started. In Hokkaido Prefecture, Japan, COVID-19 spread from mid-February 2020. Primary, junior high, and high schools and special support schools all closed from 28 February to May 31, 2020, to prevent the spread of COVID-19 among children [3,4]. In pediatrics, we know that various infection control measures have a significant influence on the spread of many infectious diseases. However, to our knowledge, there have been no multicenter studies on how the number of hospitalized children with various infectious diseases changed before and after the outbreak of COVID-19. This paper therefore reports changes in the number and age distribution of pediatric patients with various infectious diseases, drawing on the results of surveillance up to February 28, 2021.

2. Materials and methods

2.1. Study period and institutions

We aggregated data from patients aged 0–15 years who were newly admitted to the 18 hospitals in Hokkaido Prefecture from July 1, 2019 to February 28, 2021. We defined the 8 months from July 1, 2019 to February 28, 2020 as “pre-COVID-19”, and from July 1, 2020 to February 28, 2021 as “post-COVID-19”. The staff of each hospital input the data every week using Microsoft Excel and emailed it to the central staff.

2.2. Diseases

We surveyed for measles, rubella, varicella, mumps, pertussis, influenza A, influenza B, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), mycoplasma pneumoniae, adenovirus (respiratory infection), lower respiratory tract infection (LRTI), rotavirus gastroenteritis, norovirus gastroenteritis, adenosivirus gastroenteritis, other gastroenteritis, aseptic meningitis, bacterial meningitis, encephalitis/encephalopathy, complex febrile seizure, urinary tract infection (UTI), and Kawasaki disease (KD). We aggregated each disease by sex and age (0–3 months, 4–6 months, 7–12 months, 1 year old, 2 years old, 3–6 years old, 7–12 years old and 13–15 years old).

2.3. Inclusion and exclusion criteria

For influenza, RSV, hMPV, adenovirus (respiratory infection), rotavirus gastroenteritis, norovirus gastroenteritis, and adenosivirus gastroenteritis, we included patients with positive rapid antigen detection tests. For mycoplasma pneumoniae, we included patients with mycoplasma deoxyribonucleic acid (DNA) or antibodies in the blood, or positive rapid antigen tests. We excluded patients whose symptoms or epidemiological associations suggested that they might be infected, but who either had a negative rapid test or were not tested. If the items overlapped, we aggregated both. For example, when RSV was detected in a patient with pneumonia, the patient was counted for both RSV and LRTI.

2.4. Data analysis

The data was only analyzed in a descriptive manner. Comparisons of number of patients between pre-COVID-19 and post-COVID-19 are reported as relative differences in percentages.

Ethical approval

This study was approved by the Ethics Committee of Sapporo Medical University (Institutional ethical clearance number: 312–3349).

3. Results

In total, 5300 patients were hospitalized during the study period (July 1, 2019 to February 28, 2021) (Table 1). Of these, 4266 were pre-COVID-19 and 701 post-COVID-19, or just 16.4% of the pre-COVID numbers. From 1 March to June 31, 2020, 333 patients were hospitalized. No diseases increased post-COVID-19.

The number of patients with influenza, RSV, hMPV, and mycoplasma pneumoniae, which cause respiratory symptoms, all decreased drastically by more than 98%. Diseases that decreased moderately (50–70%) were adenovirus (respiratory infection), other gastroenteritis, complex febrile seizure, and KD. UTIs decreased relatively little to 82.6% of pre-COVID-19 levels.

3.1. Influenza A and B

Pre-COVID-19, there were 269 patients with influenza A and 39 with influenza B. No patients were hospitalized post-COVID-19 (Table 1). Influenza A increased from the end of November 2019, and the largest cluster of cases was at the beginning of December (Fig. 1). After that, incidence decreased sharply, and no patients were observed after May 2020. Influenza B peaked in mid-February 2020, when influenza A cases tended to converge, but the number of hospitalizations was not as high as at the peak of influenza A. Influenza B also decreased during the school closure period (28 February to May 31, 2020), and there were no patients after April 2020.

3.2. RSV, hMPV and mycoplasma pneumoniae

In total, 795 patients had RSV, 201 hMPV and 158 mycoplasma pneumoniae pre-COVID-19. This decreased drastically to three (0.4%), zero and two (1.3%) post-COVID-19 (Table 1). RSV and mycoplasma pneumoniae increased from June to November 2019. About five to ten
In Hokkaido Prefecture, Japan, the first COVID-19 patient was recognized on January 28, 2020, and the number of patients increased rapidly 

there has been no fixed epidemic period for the past few years in Hokkaido Prefecture. This is different from other regions in Japan and Hokkaido Prefecture, the patterns of infectious disease outbreaks tend to be similar to those elsewhere, although they are usually observed in the northern part of Japan (Fig. 4). The population of Hokkaido Prefecture is about 5.4 million, around 4.2% of the total population of Japan. We found that the number of children who needed hospitalization among hospitalized children before and after the COVID-19 epidemic in Hokkaido Prefecture, Japan. The figures for some diseases decreased more than 98%, but some decreased by less than half. SARS-CoV-2 is primarily transmitted between people through droplets, aerosols or contact, and the importance of wearing a mask, securing physical distance from others, washing hands, and disinfecting hands with alcohol has become well known [5–8]. Nowadays in Japan, we wear masks when going out, and the installation and use of alcohol disinfectants is widespread in both homes and public places [9]. It seems that these infection control measures have affected not only COVID-19 but also many other infectious diseases.

Hokkaido Prefecture, which we surveyed in this study, is located in the northernmost part of Japan (Fig. 4). The population of Hokkaido Prefecture is about 5.4 million, around 4.2% of the total population of Japan, and 11.4% of population is aged <15 years old [10]. According to information about infectious diseases from the national surveillance in Japan and Hokkaido Prefecture, the patterns of infectious disease outbreaks seen in Hokkaido Prefecture are similar to those elsewhere, although RSV is most often seen nationwide around September, whereas many other infectious diseases.

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Fig. 1. Trends in the number of patients per week over the study period. A: influenza. B: RSV, hMPV, Mycoplasma pneumoniae. C: adenovirus (respiratory infection). D: lower respiratory tract infection (LRTI). The vertical axis shows the number of patients, and the horizontal axis weeks. The shaded area indicates the school closure period from 28 February to May 31, 2020.
Fig. 2. Trends in the number of patients per week over the study period. A: norovirus, rotavirus and adenovirus gastroenteritis. B: gastroenteritis (all). C: urinary tract infection (UTI). D: Kawasaki disease (KD). The vertical axis shows the number of patients, and the horizontal axis weeks. The shaded area indicates the school closure period from 28 February to May 31, 2020.
Fig. 3. Age distribution of each disease. The percentages of patients aged 0–3 months, 4–6 months, 7–12 months, 1 year old, 2 years old, 3–6 years old, 7–12 years old and 13–15 years old for each disease are shown by color. A: For influenza A/B, RSV, hMPV, mycoplasma pneumoniae, and rotavirus/norovirus/adenovirus gastroenteritis, total number of patients during the study period is listed on the right side of the bars, and the number of patients pre- and post-COVID-19 are in parentheses. B: For LRTI, gastroenteritis, UTI and KD, upper and lower rows show pre- and post-COVID-19, and the number of patients are listed on the right side of the bars.
closure period (28 February to May 31, 2020). Additionally, almost no patients with these diseases were hospitalized after the school closure period until February 28, 2021. In Hokkaido Prefecture, there is usually a higher incidence of influenza A during December to February, influenza B in February to April, hMPV in March to June, and mycoplasma pneumoniae in October to December [2]. RSV in Hokkaido Prefecture has been seen almost year-round since 2017. Considering the trends in these diseases over the past few years, the period post-COVID-19 was extremely unusual.

Infectious gastroenteritis also decreased markedly post-COVID-19. In Hokkaido Prefecture, the largest number of cases of infectious gastroenteritis have generally been seen in March to May in the last few years, and the numbers have decreased from August to October, then gradually increased toward winter [2]. Rotavirus gastroenteritis accounts for most of the March–May increase, and the increase in the number of patients in winter may be related to norovirus gastroenteritis. In our study, the number of patients with gastroenteritis overall decreased remarkably during the school closure period, and there was no increase in March to May. Even after the school closure period, the number of patients remained at about half those seen in the same period in 2019, and few patients were hospitalized with rotavirus, norovirus, and adenovirus gastroenteritis.

However, the decrease in the number of patients with infectious gastroenteritis was smaller than that for respiratory infectious diseases (overall gastroenteritis decreased to 39.6% post-COVID-19, while influenza, RSV, hMPV and mycoplasma pneumoniae decreased to almost none). This may be because of the different transmission routes for infectious gastroenteritis and respiratory infectious diseases. Influenza, RSV, hMPV and mycoplasma pneumoniae are mainly transmitted by droplets in the air from a person who coughs or sneezes [12-17].

Fig. 4. Location of Hokkaido Prefecture and the 18 hospitals in this study. The shaded area is Hokkaido Prefecture. Filled circles indicate each hospital. The filled square is Sapporo City, where five hospitals are located.

Fig. 5. Daily number of new patients with COVID-19 in 2020. The vertical axis shows the number of patients, and the horizontal axis days. The shaded area indicates the school closure period from 28 February to May 31, 2020. Figures for both Japan and Hokkaido Prefecture are shown.
Infectious gastroenteritis including rotavirus, norovirus and adenovirus are mainly transmitted through the fecal–oral route [18–20]. This suggests that the current infection control measures for COVID-19 such as wearing a mask, securing physical distance from others, washing hands, and disinfecting hands with alcohol are more effective for droplet transmission than fecal–oral transmission. Another reason why respiratory infectious diseases decreased markedly might be that children who had even slight respiratory symptoms (e.g., coughing or sneezing) were not sent to schools or nurseries, because of the possibility of COVID-19 infection.

Adenovirus (respiratory infection) decreased after the school closure period. However, the figures never dropped as low as for the other respiratory diseases. One reason may be that the adenovirus (respiratory infection) is spread by both droplet infection and by touching surfaces or objects that an infected person has touched [21]. It is also possible to be an asymptomatic carrier of adenovirus, and its incubation period is relatively long, at 2 days to 2 weeks [22,23]. Children might therefore have gone to nursery without knowing they were infected and spread the infection by touching other children, desks, doors, or toys. Another reason might be that adenovirus is a non-enveloped virus. SARS-CoV-2 is an enveloped virus and is susceptible to alcohol disinfectants. The importance and effectiveness of disinfection using alcohol is now widely known [24–26]. Influenza, RSV, and hMPV are also enveloped viruses and can be expected to be inactivated by alcohol [27]. However, adenovirus, as a non-enveloped virus, is generally considered to be more resistant to disinfectants including alcohol [27,28]. It may therefore be difficult to control adenovirus (respiratory infection) with the current infection control measures for COVID-19.

Urinary tract infections (UTIs) are common bacterial infections in childhood. The majority of febrile UTI results from the ascent of bacteria from the periurethral area, migrating in a retrograde fashion through the urethra to reach the upper urinary tract, which is often related to the congenital anomalies of the kidney and urinary tract [29]. Almost all patients with UTIs might have required inpatient treatment regardless of the COVID-19 epidemic, so our survey (HPIDS) may have shown the number of patients with UTIs. Unlike other diseases, the number of patients with UTIs was similar pre- and post-COVID-19 (109 and 90 patients) (Table 1). This suggests that UTIs were not affected by the current infection control measures, and that they are not spread directly from child to child.

The cause of KD is still unknown, but epidemiology strongly suggests the involvement of infectious factors in triggering its onset [30]. In Japan, the number of patients peaks in January every year, decreases in February, increases from spring to summer, and decreases again in September–October [31]. A similar trend was seen from HPIDS during the study period, but the number of hospitalizations after the school closure period in 2020 was lower than during the same period in 2019 (Fig. 2). Many infectious diseases decreased after the school closure period suggesting that infectious diseases may indeed be involved in triggering the onset of KD.

During the COVID-19 epidemic worldwide, there have been several reports of critically ill patients with symptoms like KD [32–34]. This was described and understood as a disease different from KD, called multi-system inflammatory syndrome in children (MIS-C) [35]. Compared with KD, MIS-C often presents with severe abdominal pain and myocardial dysfunction, and requires intensive care [36,37]. The median age for MIS-C was 9–10 years. This is in marked contrast to KD, which occurs predominantly in children ≤5 years old [35,37]. KD is often seen in Asian children, including in Japan, but MIS-C is rarely reported in Asian children, and is recorded predominantly as an issue among African children [35]. Not all the 270 patients with KD in this study underwent COVID-19 tests, but there were no reports of the severe symptoms or characteristics associated with suspected MIS-C. There had been almost no reports of MIS-C in Japan, despite many worldwide. However, Fukuda et al. reported the first case of MIS-C in a Japanese boy in April 2021 [38]. The Japanese Pediatric Society and Japanese Society of Kawasaki Disease also published notification that there have been a few patients who may be MIS-C in Japan from mid-February 2021 [39]. It is therefore likely that MIS-C may become apparent in Japan when the number of children with COVID-19 has increased.

We have therefore found that many infectious diseases decreased after the outbreak of COVID-19. We targeted patients who needed to be hospitalized, so is likely to show relatively little effect of patients refraining from seeing a medical institution for fear of being infected with COVID-19. Doctors may also have performed rapid tests (e.g., influenza, RSV, and rotavirus/norovirus/adenovirus gastroenteritis) more actively on admission than among outpatients, to improve infection control. Our study is therefore considered to be able to detect rapid test positive patients more accurately. Our findings may not only reflect changes in awareness and behavior associated with COVID-19. For example, viral interference, which is a phenomenon where one virus out-competes and suppresses the replication of other co-infecting viruses, may also be happening [40–42]. Certainly, the decrease in the number of children with many infectious diseases post-COVID-19 is surprising.

Several limitations of this study should be highlighted. First, we started the HPIDS survey from July 1, 2019, so we have only 8 months of data pre-COVID-19. It is therefore not possible to compare the post-COVID-19 period with data from several years before the pandemic. Second, to compare the number of patients between pre-COVID-19 and post-COVID-19 in the same months, we omitted patients from March to June 2020, the period shortly after COVID-19 spread. Third, for several diseases such as influenza, mycoplasma, and rotavirus/norovirus/adenovirus gastroenteritis, we included patients with positive rapid tests. Rapid antigen tests or antibody tests have problems of sensitivity and specificity, so may not be reliable for diagnosis. We also did not specify rapid tests and the 18 hospitals may therefore not have used the same products. This could have resulted in some detection bias.

In conclusion, the number of children who needed hospitalization for infectious diseases decreased markedly after the COVID-19 epidemic in Japan. We suggest that current infection control measures for COVID-19 such as wearing masks, washing hands, and disinfecting hands with alcohol are effective against various infectious diseases. However, these effects vary by disease and the result of our survey may not only reflect infection control measures for COVID-19. Further surveys are required to evaluate whether the outbreak of many infectious diseases can be suppressed in the long term.

5. Authorship statement

All authors meet the ICJME authorship criteria.

Author contributions

Yuya Fukuda drafted the manuscript and contributed to the data analysis. Takeshi Tsugawa prepared the final draft, critically revised the article for important intellectual content. Yukihiko Kawasaki critically revised the article for important intellectual content. Tomohiro Nawa, Atsuo Togashi, Jun Kunizaki, Satoshi Hirakawa, Junya Iida, Toju Tanaka, Toshitaka Kizawa, Dai Yamamoto, Ryoh Takeuchi, Yoshide Sakai, Masayoshi Kikuchi, Kazushige Nagai, Hirofumi Asakura, Rina Tanaka, Masaki Yoshida, and Ryo Hamada acquired or interpreted data. All authors contributed to the writing of the final manuscript and gave final approval for the article to be published.

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Declaration of competing interest

None.

The authors declare that they have no conflicts of interest.

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References

[1] National Institute of Infectious Diseases. Japan. Infectious diseases weekly report. https://www.niid.go.jp/niid/en/idwr-e.html. [Accessed 30 May 2021]. Accessed.

[2] Hokkaido Infectious Disease Surveillance Center. Sentinel weekly reporting diseases (in Japanese), https://www.jpff.pref.hokkaido.jp/kansen/weekuniti_infection.html. [Accessed 30 May 2021]. Accessed.

[3] Hokkaido government. Data for COVID-19 in Hokkaido prefecture (in Japanese), http://www.pref.hokkaido.lg.jp/js/df/000597148.pdf. [Accessed 25 May 2021]. Accessed.

[4] Hokkaido Government Board of Education. Information about COVID-19 (in Japanese), http://www.dokyoi.pref.hokkaido.lg.jp/hk/krk/corona.htm. [Accessed 30 May 2021]. Accessed.

[5] World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions. [Accessed 30 May 2021]. Accessed.

[6] Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19), how to protect yourself & others. https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/prevention.html. [Accessed 30 May 2021]. Accessed.

[7] Gandhi Monica, Beyer Chris, Goosby Eric. Masks do more than protect others during COVID-19: reducing the inoculum of SARS-CoV-2 to protect the wearer. J Gen Intern Med 2020;35:3063-6. doi:10.1007/s11606-020-05607-y.

[8] Ministry of Health, Labour and Welfare, Japan. Prevention measures against coronavirus disease 2019 (COVID-19). https://www.mhlw.go.jp/content/1090000/000597148.pdf. [Accessed 25 May 2021]. Accessed.

[9] Statistics Bureau of Japan. Final report of 2015 “Population and households of Japan”. https://www.stat.go.jp/english/data/kokusei/2015/final_en/pdf/s01.pdf. [Accessed 30 May 2021]. Accessed.

[10] Hokkaido government. Data for COVID-19 in Hokkaido prefecture (in Japanese), http://www.pref.hokkaido.lg.jp/js/df/000597148.pdf. [Accessed 25 May 2021]. Accessed.

[11] Weber Thomas, Stilianakis Nikolaos. Inactivation of influenza A viruses in the environment. J Hosp Infect 2018;98:30-6. https://doi.org/10.1016/j.jhin.2018.05.011.

[12] Leung Alexander KC, Wong Alex HC, Leung Amy AM, Hon Kam L. Urinary tract infection in children. Recent Pat Inflamm Allergy Drug Discov 2019;13:12-18. https://doi.org/10.2174/1872213X13666181228154940.

[13] Rowley AH, Shulman Stanford T. The epidemiology and pathogenesis of Kawasaki disease. Front Pediatr 2018;6:117. https://doi.org/10.3389/fped.2018.000374.

[14] Japanese Kawasaki Disease Research Center. 25th nationwide survey on Kawasaki disease. https://www.jpeds.or.jp/modules/guidelines/index.php?content_id=311003110366601090. [Accessed 30 May 2021]. Accessed.

[15] Rowley AH, Shulman Stanford T. Kawasaki disease: two different illnesses with overlapping clinical features. J Pediatr 2020;199:631-636. https://doi.org/10.1016/j.jpeds.2020.06.057.

[16] Rowley AH. Multi-system inflammatory syndrome in children and Kawasaki disease: two different illnesses with overlapping clinical features. J Pediatr 2020;224:129-32. https://doi.org/10.1016/j.jpeds.2020.06.057.

[17] Nakra Natasha A, Blumberg Dean A, Herrera-Guerra Angel, Angoulvant François, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 2020;369:m2094. https://doi.org/10.1136/bmj.m2094.

[18] Feldstein Leora, Rose Erica, Horwitz Steven, et al. Multi-system inflammatory syndrome in U.S. Children and adolescents. N Engl J Med 2020;383:334-46. https://doi.org/10.1056/NEJMc2012618.

[19] Verdoni Lucio, Mazza Angelo, Gervasoni Annalisa, Martelli Laura, Ruggeri Maurizio, Ciufrèda Matteo, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 2020;395:2077-84. https://doi.org/10.1016/S0140-6736(20)31103-X.

[20] Rowley AH. Multi-system inflammatory syndrome in children and Kawasaki disease: two different illnesses with overlapping clinical features. J Pediatr 2020;224:129-32. https://doi.org/10.1016/j.jpeds.2020.06.057.

[21] Nakra Natasha A, Blumberg Dean A, Herrera-Guerra Angel, Lakshminrusimha Satyan. Multi-system inflammatory syndrome in children (MIS-C) following SARS-CoV-2 infection: review of clinical presentation, hypothesis of pathogenesis, and proposed management. Children 2020;7:69. https://doi.org/10.3390/children7070069.

[22] Esposito Susanna, Nicolini Principi. Multi-system inflammatory syndrome in children related to SARS-CoV-2. Paediatr Drugs 2021;23:119-29. https://doi.org/10.1007/s40272-020-00435-x.

[23] Fukuda Sayaka, Kaneta Miyoko, Miyake Mayuko, Ohya Takashi, Miyake Kaci, Iwamoto Mari, et al. A case of multisystem inflammatory syndrome in children in a Japanese boy; with discussion of cytokine profile. Mod Rheumatol Case Rep 2021 Apr 27:1-11. https://doi.org/10.24725/mrcr.2021.190140.

[24] About severe pediatric cases of Covid-19 in Japan. Japanese pediatric society (in Japanese), http://www.jpeds.or.jp/modules/guidelines/index.php?content_id=1225. [Accessed 30 May 2021]. Accessed.

[25] Wu Anchi, Mihaylova Valia T, Landry Marie I, Foxman Ellen F. Interference between rhinovirus and influenza A virus: a clinical data analysis and experimental infection study. Lancet Microbe 2020;1:e254-62. https://doi.org/10.1016/S2666-5266(20)30011-4.

[26] Nickbakhsh Sema, Mair Colette, Matthews Louise, Reeve Richard, Johnson Paul CD, Thorburn Fiona, et al. Virus–virus interactions impact the population dynamics of influenza and the common cold. Proc Natl Acad Sci Unit States Am 2019;116: 27142-50. https://doi.org/10.1073/pnas.1910831114.

[27] Dee Kieran, Goldfarb Daniel M, Haney Joanne, Amat Julian AR, Herder Vanessa, Stewart Meredith, et al. Human rhinovirus infection blocks severe acute respiratory syndrome coronavirus 2 replication within the respiratory epithelium: implications for COVID-19 epidemiology. J Infect Dis 2021;224:1-8. https://doi.org/10.1093/infdis/jiaa147.