Journal of Patient-Centered Research and Reviews

Volume 10 | Issue 2 Article 6

4-18-2023

Exploring the Possible Phenomenon of Viral Interference Between the Novel Coronavirus and Common Respiratory Viruses

Spencer Deleveaux
Alexandria Clarke-Kregor
Xavier Fonseca-Fuentes
Essam Mekhaiel

Recommended Citation

Deleveaux S, Clarke-Kregor A, Fonseca-Fuentes X, Mekhaiel E. Exploring the possible phenomenon of viral interference between the novel coronavirus and common respiratory viruses. J Patient Cent Res Rev. 2023;10:91-7. doi: 10.17294/2330-0698.1995

Published quarterly by Midwest-based health system Advocate Aurora Health and indexed in PubMed Central, the Journal of Patient-Centered Research and Reviews (JPCRR) is an open access, peer-reviewed medical journal focused on disseminating scholarly works devoted to improving patient-centered care practices, health outcomes, and the patient experience.

Exploring the Possible Phenomenon of Viral Interference Between the Novel Coronavirus and Common Respiratory Viruses

Spencer Deleveaux, MD,[1] Alexandria Clarke-Kregor, DO,[1] Xavier Fonseca-Fuentes, MD,[2] Essam Mekhaiel, MD[2]

[1]Department of Medicine, Advocate Christ Medical Center, Oak Lawn, IL; [2]Department of Pulmonary and Critical Care, Advocate Christ Medical Center, Oak Lawn, IL

Abstract At the peak of the 2021 wave of the SARS-CoV-2 alpha variant in North America, there was concern for a superimposed wave of viral respiratory infections. There was, however, an apparent shift in the usual epidemiology of these pathogens, especially during the traditional influenza season from approximately October 2020 to March 2021. This article seeks to briefly describe the epidemiology of notable respiratory pathogens during the first wave of the COVID-19 pandemic and to focus on one possible factor for the trends observed. There are many contributory elements to the observed viral trends, but in particular, we present a synopsis of the data supporting the phenomenon of viral interference in relation to the clinically relevant early variants of SARS-CoV-2 (ancestral lineage, alpha, delta, omicron). Viral interference has been implicated in previous pandemics and is currently not well characterized in the setting of the COVID-19 pandemic. It is important to understand this dynamic and its effect on the predominant variants of COVID-19 thus far so that we may appropriately consider its possible influence in patient pathology going forward. (*J Patient Cent Res Rev.* 2023;10:91-97.)

Keywords influenza; coronavirus; COVID-19; viral interference; rhinovirus; respiratory pathogens; pandemic

The influenza virus is a common respiratory pathogen that causes significant morbidity and mortality in the general population on a traditionally seasonal basis. As the SARS-CoV-2 virus emerged on the international scene, there were concerns for a superimposed wave of illness caused by coinfection.[1] In the United States, it appears these fears were not realized on the large scale that was initially expected, due in part to the historically low rates of viral respiratory pathogens, such as influenza and respiratory syncytial virus (RSV).[2,3] Although the occurrence of viral interference has been well characterized between several of the common respiratory viruses, the COVID-19 pandemic presents an opportunity to review the data supporting this effect with some of the predominant variants of SARS-CoV-2 virus (alpha, delta, omicron). These effects may suggest its potential contributory role in the epidemiologic trends noted during the North American pandemic from 2020 to 2022.

In this topic synopsis, we briefly outline the currently understood mechanisms of viral interference and previously established examples of viral interference. These principles are then applied contemporarily by reviewing respiratory virus infection trends during the COVID-19 pandemic and the current pool of data relating to viral interference with SARS-CoV-2.

Corresponding author: Spencer Deleveaux, Advocate Christ Medical Center, 4440 W. 95th St., Oak Lawn, IL, USA 60453 (spencer.deleveaux@aah.org)

Currently Acknowledged Mechanisms of Viral Interference

The current pool of literature supports three main mechanisms for interference. The resource competition theory is examined by the use of a mathematical model[4] showing that coinfection of a virus with a fast replication rate can mitigate the replication of a virus with a slow growth rate, while coinfection of a virus with a slow rate of replication does not appreciably impact the virus with a faster replication rate. The model also demonstrated that if the replication rates of both viruses are approximately equal, the replication of both are negatively impacted.[4]

The host immune response theory is further elucidated by the classification of viral interference into the categories of either homologous and heterologous.[5] Homologous interference occurs when there is a specific immune reaction to two viral infections of similar types. Heterologous interference occurs due to the innate immune response that is nonspecific that mitigates a secondary infection.

Finally, the third mechanism involves superinfection exclusion, in which the entry of virions to an uninfected cell is favored. This protects a primary infecting virus from a competing virus.[6]

Previously Established Examples of Interference in Respiratory Viral Pathogen Seasonal Epidemics

The concept of viral interaction is not new and has been demonstrated in several studies prior to the arrival of SARS-CoV-2. Common respiratory pathogens can have both negative and positive interactions with other microbes, both viral and bacterial, on the host and ecosystem level. One of the earliest indications of viral interference was the observation of decreased occurrence of respiratory virus in children who had an attenuated enterovirus administered as a vaccine. Despite the difference in pathogenicity of these two viral classes, there seemed to be an association between the presence of one virus and a reduced potential of infection with another.[7,8] This observation was one of the starting points for investigations surrounding this theory.

Specifically investigating respiratory viruses, a multivariate Bayesian disease-mapping framework analysis was applied demonstrating a negative interaction between the influenza A virus and rhinovirus.[9] Furthermore, it appears that there are few, if any, studies indicating a cooperative or synergistic effect with influenza and rhinovirus. Most of the current literature appears to support a competitive effect of rhinovirus on influenza.[10] While no consensus has been reached explaining the mechanism of interaction between rhinovirus and influenza, it is likely a combination of the rhinovirus consuming substrates as it rapidly replicates, as well as a host immune-mediated interference likely mediated by interferon activity.[4,9] These theories may be applied to respiratory virus interactions as whole.

Role of Viral Interference in Pandemics Prior to COVID-19

It is likely that the effect of viral interference goes beyond the normal seasonal cycles of respiratory pathogens and extends to occurrence of abnormal viral activity. One example of this is the 2009 influenza H1N1 pandemic, for which it was suggested that rhinovirus may have played a role in altering the spread of the influenza virus during that time.[11] In Sweden and other European countries, there was an acute decline in the activity of influenza H1N1 despite a relatively unchanged climate and unchanged social behaviors. This was attributed to the start of a rhinovirus epidemic in the region.[12] While there is no proof that identifies a single mechanism as the cause for mitigation of the spread of influenza H1N1 during this time, it was hypothesized that the host immune response theory outlined above may have played a role.[12] The upregulation of interferon in a population infected by rhinovirus may have partially reduced the susceptibility for influenza H1N1 infection and buffered the high rate of spread.

Further in support of this mechanism, it has been suggested that rhinovirus presence is responsible for a reduced risk of infection by the H1N1 virus.[13] This activity was exhibited when human airway epithelial cells were infected with rhinovirus followed by human influenza H1N1 virus. The interferon-stimulated genes expressed as a result of rhinovirus infection had a protective effect against influenza H1N1, shown by a significant reduction in influenza H1N1 RNA.[14] When interferon signaling was blocked, influenza H1N1 viral load rebounded. While studies have shown that influenza A induces similar patterns of interferon as rhinovirus,[15] we have not been able to find any studies demonstrating a reduced risk of rhinovirus infection in the setting of prior influenza infection.

Trends of Viral Respiratory Infection During the COVID-19 Pandemic

Data from the Centers for Disease Control and Prevention (CDC) show suppression of normal cyclical trends of influenza, RSV, parainfluenza, and other human coronaviruses from the spring of 2020 to the spring of 2021. Unlike these other viral pathogens, the pattern of rhinovirus activity deviated from this with an initial decrease in the spring of 2020 but a rebound to normal activity levels by later spring 2020.[3] There is little variance in the rate of infection of influenza in the recent prior seasons before the COVID-19 pandemic. With much fewer cases of influenza being detected in 2020–2021, this represents a notable shift away from the data collected over prior influenza seasons.

Data utilized from the U.S. World Health Organization Collaborating Laboratories System and the CDC's National Respiratory and Enteric Virus Surveillance System highlight unprecedented low rates of influenza activity in the United States during the period coinciding with the traditionally recognized "flu season" from late 2020 to early 2021.[3] Similar trends were noted in countries outside of the United States, including Canada, Brazil, South Africa, and Japan.[16–19] In the Brazilian study, approximately 19.7% of samples from patients with acute respiratory distress syndrome (ARDS) were positive for influenza A in 2019. In comparison, in 2020, only 1.62% of ARDS samples were positive for influenza A.[17] Similarly, there was a reduction in the detection of influenza virus during the time period of the usual influenza season in the South African study in 2020, but

of note, there was no rebound increase in influenza virus detection after COVID-19 social restrictions were eased.[18] Perhaps most striking, in the national observational study of a Canadian pediatric population, there were no hospitalizations or deaths linked to influenza during the 2020-2021 influenza season.[16]

Since the initial wave of COVID-19, the rates of influenza have rebounded. According to CDC data, there have been two peaks of influenza-positive tests in late 2021 and early 2022. The first peak occurred around epidemiologic weeks 50 to 52 of 2021. This appears to coincide with the period immediately prior to a peak of delta strain of SARS-CoV-2 cases in the United States. During a peak of COVID-19, between epidemiologic weeks 2 and 3 of 2022, there was a strong progression to a trough of influenza activity, with the nadir noted at epidemiologic week 5. There was a second influenza peak around epidemiologic week 14 of 2022, which occurred during a trough of COVID-19 cases. As the number of cases of COVID-19 began to rise due to the SARS-CoV-2 omicron variant (weeks 14 to 18) and reached the highest rate since January 2021, there was a notable downturn in influenza activity, although this time period also corresponds to the ending of the traditional influenza season.

It is essential to note that there are likely several contributory factors to these trends. In the period preceding the availability of COVID-19 vaccines, many countries instituted nonpharmacological measures to mitigate the burden of this deadly virus, such as masks, hand washing/sanitizing, and social distancing. These measures appeared to be efficacious.[20]

Widespread use of surgical masks was one of the interventions implemented to reduce the spread of COVID-19. Previously, this practice has been efficacious in prior outbreaks of respiratory illness and has been shown to reduce the aerosol transmission of influenza A.[21] Again, in this context, it seems that masking and social restrictions had a significant effect on the normal spread of other common respiratory viruses, including influenza.[2,22] Interestingly, a study comparing the relative efficacy of surgical masks in reducing the exhaled viral load of common respiratory viruses found a relatively decreased effectiveness in the filtering of human rhinovirus compared to influenza virus and coronavirus.[23] This finding is thought to be a cause for the aforementioned persistence of human rhinovirus in several countries despite the efficacy of social distancing, masking, and school shutdowns. Although rhinovirus infections increased in the pediatric population despite the implementation of social precautions, the frequency of infection with influenza and other respiratory diseases decreased.[24] Another study demonstrated that the pathogens detected in SARS-CoV-2 coinfection were found to reflect the respiratory viruses in circulation in the community at that time,[25] rather than demonstrating a predilection to a particular type of coinfecting virus.

It is important to recognize the impact of these public health initiatives during the onset of the pandemic and frame the dynamics of viral interference during this time with this in mind. Nevertheless, there may be an additional, less recognized contributor to the epidemiologic dynamics observed during the first wave of the pandemic. Given the occurrence of a newcomer to the respiratory pathogen ecosystem, SARS-CoV-2, the evidence for a novel viral interaction is worth exploring.

Evidence Supporting Other Viral Interference During COVID-19 Pandemic

The prior sections have demonstrated that observational data suggest suppression of normal influenza trends during the COVID-19 pandemic,[3,26,27] while the rate of rhinovirus infection in the community remained relatively high.[24] We found the literature describing the possible link between observed trends in SARS-CoV-2 and other common respiratory virus interactions to be relatively sparse, still, this section outlines the most relevant reports.

Mathematical Modeling. One study examined the circulation of SARS-CoV-2 and other common respiratory viruses through a mathematical model. Co-circulation of RSV and SARS-CoV-2 caused suppression of SARS-CoV-2, while co-circulation of influenza, rhinovirus, and SARS-CoV-2 had no effect on SARS-CoV-2 but rather displaced the timing of the expected seasonal influenza and rhinovirus epidemic.[28] The latter effect is similar to the phenomenon seen with the influenza H1N1 viral pandemic in Europe in 2009. It is important to note that the data used in the creation of this model was derived from previous years of seasonal trends and did not account for the exact data in real time of influenza, rhinovirus, and RSV trends during the COVID-19 pandemic.

Another modeling study suggested that given the relatively low growth rate of SARS-CoV-2, early coinfection with another respiratory pathogen like rhinovirus or influenza A could lead to suppression of SARS-CoV-2 growth.[29] This model also demonstrated that timing of coinfection may influence patterns of infection. It was shown that there was a shortened course of coinfection of rhinovirus and influenza A when introduced on day 10 after initial SARS-CoV-2 infection, with a minimal effect on SARS-CoV-2 replication. Earlier coinfections (day 1 and day 5) were able to suppress SARS-CoV-2 replication. This suggests that a virus with a faster replication cycle may

overwhelm one with slower replication unless a sufficient "head start" is given. One caveat of this study was that its mathematical model was based on the resource competition theory and did not take into account other mechanisms like the immune response theory.

Animal Modeling. There are animal studies regarding the interaction of SARS-CoV-2 and the influenza virus. A hamster model demonstrated a lower SARS-CoV-2 viral load when infected with influenza A 1 day prior[30] (few good animal models for influenza B were found). These findings also were reproduced in a ferret model exhibiting a decreased level of SARS-CoV-2 viral replication as well as a decreased time of viral shedding.[31] Interestingly, a mouse model also demonstrated antibody-dependent protection against severe COVID-19 disease with prior influenza A infection. Like the previous two studies referenced, severe clinical disease was associated with influenza A and SARS-CoV-2 coinfection.[32]

Human Studies. The pool of studies regarding infection in human cells is growing. In cultured human airway epithelium cells, rhinovirus appears to have a negative impact on SARS-CoV-2 via an innate immune response.[33] This negative interaction with COVID-19 appears to be interferon-mediated. Conversely, initial infection with SARS-CoV-2 did not impair replication of rhinovirus.[5]

Another study utilizing the human epithelial cell model investigated differences in replication in simultaneous and sequential viral infections.[34] When SARS-CoV-2 and influenza H1N1 were inoculated simultaneously, there was minimal effect on the growth rate of either virus, with a slight decrease in replication at 72 hours after infection in both viruses. In the case of sequential SARS-CoV-2 and influenza H1N1 infection, 24 hours after the cells were infected with the primary virus, the growth rate of the secondary infecting virus (whether it was SARS-CoV-2 or influenza H1N1) was reduced by the presence of the first virus. In this same study, it was found that RSV growth was reduced in the presence of SARS-CoV-2 infection in the case of a simultaneous infection. When SARS-CoV-2 infection followed RSV infection by 24 hours, there was a reduction in SARS-CoV-2 replication at 24 hours post-coinfection, but not at 48 and 72 hours postinfection. When RSV coinfected a cell infected by SARS-CoV-2 24 hours earlier, there was an increase in SARS-CoV-2 replication in the 24 hours following coinfection but a significant reduction in the replication rate of RSV at 48 and 72 hours following coinfection. The pathway of these results was postulated to be effected by the interferon pathway due to recovery of replication rates when an agent blocking interferon response was introduced. These findings underscore those from the aforementioned mathematical models[29] and animal models[30,31] demonstrating that timing of coinfection may have an impact on the dynamics observed. They also agree with prior results from a study by Essaidi-Laziozi et al utilizing the alpha strain of SARS-CoV-2.[35]

It is worth noting that one study contradicted these findings and suggested that influenza A coinfection may induce increased infectivity of SARS-CoV-2 via upregulation of the angiotensin-converting enzyme 2 receptor.[36]

Finally, a more recent study[37] replicated some of the findings reviewed above. Using the human airway epithelial cell model, simultaneous infection of influenza H1N1 and SARS-CoV-2 was performed. A reduction in both SARS-CoV-2 and influenza H1N1 viral genome was noted. In sequential infection where primary SARS-CoV-2 was followed by influenza H1N1 infection, a minimal reduction in SARS-CoV-2 replication was demonstrated. In this study, replication of primary influenza H1N1 infection was not affected by a sequential SARS-CoV-2 infection, which mirrors the findings of Fage et al.[34] The study by Pizzorno et al went further by examining the effect of sequential SARS-CoV-2 infection 7 days after a primary respiratory virus infection.[37] Assessing viral genome copies 48 hours following the introduction of SARS-CoV-2, they found there was no significant impact on the replication of primary influenza H1N1, rhinovirus, or human metapneumovirus infection, but a minor reduction in RSV replication. However, SARS-CoV-2 replication was significantly lower in the case in all 4 of these superinfections, with rhinovirus superinfection having the least pronounced effect. This study explored patterns of immune response and again highlights the importance of the interferon response in this mechanism.[37]

Limitations

While the models we report represent the best means to understanding the real-world trends that have played out over the last few years at the time of writing, it is important to recognize their limitations. The mathematical model may be unable to effectively account for asymptomatic viral spread.[28] The in vitro models referenced cannot account for the host-host and host-environment interactions that take place and are limited in their ability to model complex intrahost dynamics. In vitro animal models are limited in their ability to model the range of respiratory pathogens affecting humans. Most of the in vitro human cell models also used different SARS-CoV-2 strains (Quebec/CHUL/21697 in Fage et al,[34] BetaCoV/France/IDF0571/2020 in Pizzorno et al[37]). Both strains are earlier variants in the course of the pandemic and may not replicate the dynamics of more recent strains.

Of course, the magnitude of the role played by viral interference in the trends of respiratory infection have yet to be understood among the myriad other factors that could be implicated (pharmacological and nonpharmacological interventions like masking, differences in SARS-CoV-2 variants, epidemiology of other respiratory viruses, etc).

Summary

Overall, the current pool of data seems to support the idea that both SARS-CoV-2 and rhinovirus interfere with the infectivity of the influenza A virus. Rhinovirus also appears to attenuate the replication of SARS-CoV-2, but SARS-CoV-2 does not seem to have a significant effect on rhinovirus.[33,38] Respiratory syncytial virus has a minimal effect on SARS-CoV-2, but SARS-CoV-2 can suppress replication of RSV, while influenza A can reduce SARS-CoV-2 replication if influenza is the primary infecting pathogen.

Based on these observations, the question of viral interference between SARS-CoV-2 and other respiratory viral pathogens should be recognized as relevant to the understanding of the initial trends of infection during the first wave of the COVID-19 pandemic. Viral interference between influenza A and rhinovirus has been well demonstrated, with rhinovirus driving both protective mechanisms against influenza A at the host level and asynchronous circulation of influenza A on the environmental level. However, the link between SARS-CoV-2 and these other respiratory pathogens is not as well understood. It is possible that SARS-CoV-2 negatively interacts with the influenza virus, and with this relative dearth of influenza virus circulating in the population, the opportunity for a comparatively high level of rhinovirus infections may have arisen.

The current body of knowledge appears to be incomplete, and the known occurrence of interferon-mediated host protection would seem not to completely explain the trends observed as of 2022. The known occurrence of rhinovirus outcompeting other pathogens, potentially by rapid replication and consumption of necessary substrates and interferon response, does not seem to have meaningfully impacted epidemiological trends of COVID-19 pneumonia as observed since the onset of the pandemic. It is important to note that numerous nonpharmacological interventions were put into place with the surge of COVID-19. Wearing masks, social distancing, and remote occupations all likely contributed to the reduction of viral infections, both respiratory and otherwise.[39,40]

Further work is necessary to better equip the health care community in allocating resources and anticipating the needs of the communities they serve. By improving our understanding of the mechanism(s) of viral interference, especially as it applies to SARS-CoV-2 and the ecosystem of common respiratory pathogens, it may possible to decrease patient morbidity and mortality from these pathogens by exploiting these mechanisms to decrease viral replication.

Patient-Friendly Recap

- When a novel virus such as SARS-CoV-2 emerges, it can impact the spread of existing viral diseases through a process called viral interference.
- Authors reviewed the literature to identify data patterns that indicate how the early variants of SARS-CoV-2 may be interacting with influenza A and other respiratory pathogens.
- At the time of this writing, authors concluded that SARS-CoV-2 interferes with the infectivity of influenza A, whereas it does not appear to have a significant effect on rhinovirus infections.
- It is important to view these findings within the context that atypical changes in human behavior (eg, masking and social distancing), likely contributed to reduced viral infections in general.

Author Contributions

Study design: Deleveaux, Mekhaiel. Data acquisition or analysis: all authors. Manuscript drafting: all authors. Critical revision: all authors.

Conflicts of Interest

None.

References

1. Burlacu A, Crisan-Dabija R, Popa IV, Covic A. The second wave of COVID-19 pandemic strikes during the flu season: an awareness perspective. *Medicina (Kaunas).* 2020;56(12):707. CrossRef
2. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic – United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69:1305-9. CrossRef
3. Olsen SJ, Winn AK, Budd AP, et al. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic – United States, 2020-2021. *MMWR Morb Mortal Wkly Rep.* 2021;70:1013-9. CrossRef
4. Pinky L, Dobrovolny HM. Coinfections of the respiratory tract: viral competition for resources. *PLoS One.* 2016;11(5):e0155589. CrossRef
5. Piret J, Boivin G. Viral interference between respiratory viruses. *Emerg Infect Dis.* 2022;28:273-81. CrossRef
6. Bellecave P, Gouttenoire J, Gajer M, et al. Hepatitis B and C virus coinfection: a novel model system reveals the absence of direct viral interference. *Hepatology.* 2009;50:46-55. CrossRef

7. Chumakov MP, Voroshilova MK, Antsupova AS, et al. [Live enteroviral vaccines for the emergency nonspecific prevention of mass respiratory diseases during fall-winter epidemics of influenza and acute respiratory diseases]. *Zh Mikrobiol Epidemiol Immunobiol.* 1992;(11-12):37-40.
8. Voroshilova MK. Potential use of nonpathogenic enteroviruses for control of human disease. *Prog Med Virol.* 1989;36:191-202.
9. Nickbakhsh S, Mair C, Matthews L, et al. Virus-virus interactions impact the population dynamics of influenza and the common cold. *Proc Natl Acad Sci U S A.* 2019;116(52):27142-50. CrossRef
10. Opatowski L, Baguelin M, Eggo RM. Influenza interaction with cocirculating pathogens and its impact on surveillance, pathogenesis, and epidemic profile: a key role for mathematical modelling. *PLoS Pathog.* 2018;14(2):e1006770. CrossRef
11. Ånestad G, Nordbø SA. Virus interference. Did rhinoviruses activity hamper the progress of the 2009 influenza A (H1N1) pandemic in Norway? *Med Hypotheses.* 2011;77:1132-4. CrossRef
12. Linde A, Rotzén-Östlund M, Zweygberg-Wirgart B, Rubinova S, Brytting M. Does viral interference affect spread of influenza. *Euro Surveill.* 2009;14(40):19354.
13. Casalegno JS, Ottmann M, Bouscambert Duchamp M, et al. Rhinoviruses delayed the circulation of the pandemic influenza A (H1N1) 2009 virus in France. *Clin Microbiol Infect.* 2010;16:326-9. CrossRef
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;1:e254-62. CrossRef
15. Khaitov MR, Laza-Stanca V, Edwards MR, et al. Respiratory virus induction of alpha-, beta- and lambda-interferons in bronchial epithelial cells and peripheral blood mononuclear cells. *Allergy.* 2009;64:375-86. CrossRef
16. Groves HE, Papenburg J, Mehta K, et al. The effect of the COVID-19 pandemic on influenza-related hospitalization, intensive care admission and mortality in children in Canada: a population-based study. *Lancet Reg Health Am.* 2022;7:100132. CrossRef
17. Eisen AKA, Gularte JS, Demoliner M, et al. Low circulation of influenza A and coinfection with SARS-CoV-2 among other respiratory viruses during the COVID-19 pandemic in a region of southern Brazil. *J Med Virol.* 2021;93:4392-8. CrossRef
18. Tempia S, Walaza S, Bhiman JN, et al. Decline of influenza and respiratory syncytial virus detection in facility-based surveillance during the COVID-19 pandemic, South Africa, January to October 2020. *Euro Surveill.* 2021;26(29):2001600. CrossRef
19. Sakamoto H, Ishikane M, Ueda P. Seasonal influenza activity during the SARS-CoV-2 outbreak in Japan. *JAMA.* 2020;323:1969-71. CrossRef
20. Redlberger-Fritz M, Kundi M, Aberle SW, Puchhammer-Stöckl E. Significant impact of nationwide SARS-CoV-2 lockdown measures on the circulation of other respiratory virus infections in Austria. *J Clin Virol.* 2021;137:104795. CrossRef
21. Milton DK, Fabian MP, Cowling BJ, Grantham ML, McDevitt JJ. Influenza virus aerosols in human exhaled breath: particle size, culturability, and effect of surgical masks. *PLoS Pathog.* 2013;9(3):e1003205. CrossRef
22. Zhang K, Misra A, Kim PJ, Moghadas SM, Langley JM, Smieja M. Rapid disappearance of influenza following the implementation of COVID-19 mitigation measures in Hamilton, Ontario. *Can Commun Dis Rep.* 2021;47:202-9. CrossRef
23. Leung NHL, Chu DKW, Shiu EYC, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. *Nat Med.* 2020;26:676-80. CrossRef
24. Takashita E, Kawakami C, Momoki T, et al. Increased risk of rhinovirus infection in children during the coronavirus disease-19 pandemic. *Influenza Other Respir Viruses.* 2021;15:488-94. CrossRef
25. Temte JL, Barlow S, Temte E, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) codetection with influenza A and other respiratory viruses among school-aged children and their household members – March 12, 2020, to February 22, 2022, Dane County, Wisconsin. *Clin Infect Dis.* 2022;75(Suppl 2):S205-15. CrossRef
26. Spantideas N, Bougea AM, Drosou EG, Khanderia N, Rai S. COVID-19 and seasonal influenza: no room for two. *Cureus.* 2021;13(9):e18007. CrossRef
27. Uyeki TM, Wentworth DE, Jernigan DB. Influenza activity in the US during the 2020-2021 season. *JAMA.* 2021;325:2247-8. CrossRef
28. Pinky L, Dobrovolny HM. Epidemiological consequences of viral interference: a mathematical modeling study of two interacting viruses. *Front Microbiol.* 2022;13:830423. CrossRef
29. Pinky L, Dobrovolny HM. SARS-CoV-2 coinfections: Could influenza and the common cold be beneficial? *J Med Virol.* 2020;92:2623-30. CrossRef
30. Zhang AJ, Lee AC, Chan JF, et al. Coinfection by severe acute respiratory syndrome coronavirus 2 and influenza A(H1N1) pdm09 virus enhances the severity of pneumonia in golden Syrian hamsters. *Clin Infect Dis.* 2021;72:e978-92. CrossRef
31. Bao L, Deng W, Qi F, et al. Sequential infection with H1N1 and SARS-CoV-2 aggravated COVID-19 pathogenesis in a mammalian model, and co-vaccination as an effective method of prevention of COVID-19 and influenza. *Signal Transduct Target Ther.* 2021;6(1):200. CrossRef
32. Achdout H, Vitner EB, Politi B, et al. Increased lethality in influenza and SARS-CoV-2 coinfection is prevented by influenza immunity but not SARS-CoV-2 immunity. *Nat Commun.* 2021;12(1):5819. CrossRef
33. Dee K, Goldfarb DM, Haney J, 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;224:31-8. CrossRef
34. Fage C, Hénaut M, Carbonneau J, Piret J, Boivin G. Influenza A(H1N1)pdm09 virus but not respiratory syncytial virus interferes with SARS-CoV-2 replication during sequential infections in human nasal epithelial cells. *Viruses.* 2022;14(2):395. CrossRef
35. Essaidi-Laziosi M, Alvarez C, Puhach O, et al. Sequential infections with rhinovirus and influenza modulate the replicative capacity of SARS-CoV-2 in the upper respiratory tract. *Emerg Microbes Infect.* 2022;11:412-23. CrossRef
36. Bai L, Zhao Y, Dong J, et al. Coinfection with influenza A virus enhances SARS-CoV-2 infectivity. *Cell Res.* 2021;31:395-403. CrossRef

37. Pizzorno A, Padey B, Dulière V, et al. Interactions between severe acute respiratory syndrome coronavirus 2 replication and major respiratory viruses in human nasal epithelium. *J Infect Dis.* 2022;226:2095-104. CrossRef
38. Kiseleva I, Ksenafontov A. COVID-19 shuts doors to flu but keeps them open to rhinoviruses. *Biology (Basel).* 2021;10(8):733. CrossRef
39. Park JY, Kim HI, Kim JH, et al. Changes in respiratory virus infection trends during the COVID-19 pandemic in South Korea: the effectiveness of public health measures. *Korean J Intern Med.* 2021;36:1157-68. CrossRef
40. Belingheri M, Paladino ME, Piacenti S, Riva MA. Effects of COVID-19 lockdown on epidemic diseases of childhood. *J Med Virol.* 2021;93:153-4. CrossRef