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

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Recommended Citation

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.
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.

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). 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 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
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.  

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. 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. 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. 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. 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. 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. 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. 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. 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. When interferon signaling was blocked, influenza H1N1 viral load rebounded. While studies have shown that influenza A induces similar patterns of interferon as rhinovirus, 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. 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. Similar trends were noted in countries outside of the United States, including Canada, Brazil, South Africa, and Japan. 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. 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
eye 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.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
preference 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,2,6,27 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
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 (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. 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.

Another study utilizing the human epithelial cell model investigated differences in replication in simultaneous and sequential viral infections. 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 and animal models 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.

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.

Finally, a more recent study 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. 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. 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.

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. 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, BetaCoV/ France/IDF0571/2020 in Pizzorno et al). 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. 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.

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

38. Kiseleva I, Ksenafontov A. COVID-19 shuts doors to flu but keeps them open to rhinoviruses. *Biology (Basel)*. 2021;10(8):733. [CrossRef]
