White Paper:
SARS-CoV-2 Co-Infections - Influenza and Other Pathogens

Background & Overview
On March 11th, 2020 the World Health Organization (WHO) characterized COVID-19 as a global pandemic. COVID-19 is the disease caused by an infection of the SARS-CoV-2 virus. The fundamental steps recommended by public health agencies around the globe to mitigate the spread of COVID-19 have included social distancing, properly wearing masks, and good hygiene practices. These measures are also known to be beneficial in reducing the spread of other acute respiratory pathogens, and are believed to have contributed to the significantly reduced rates of seasonal influenza throughout the pandemic, as reported around the world. As communities begin to return to everyday activities and the measures taken to mitigate the spread of COVID-19 are relaxed, it is likely that SARS-CoV-2 will co-circulate with other acute respiratory pathogens, such as influenza.

This raises concerns about the incidence of concurrent infections, or co-infections, of the SARS-CoV-2 virus and other seasonal respiratory pathogens. Here, the term co-infection refers to the simultaneous infection of an individual by at least two pathogens which creates a complex biological phenomenon impacted by numerous compounding factors. At this time, there are limited studies describing COVID-19 co-infections and without clear characterization it is premature for public health agencies to provide recommendations for clinical diagnosis and management. The overlapping circulation of seasonal respiratory pathogens with the SARS-CoV-2 virus make it likely that the incidence and evidence of co-infections will increase.

SARS-CoV-2 Co-infections with Influenza Viruses
Both the U.S. National Institutes for Health (NIH) and Centers for Disease Control and Prevention (CDC) have released guidelines stressing that diagnostic testing is the only reliable method to distinguish viral infections caused by SARS-CoV-2, influenza, or a co-infection of both viruses. To date, the general consensus is that while co-infections of SARS-CoV-2 and influenza viruses have been uncommon, when it does occur overall clinical prognosis for those individuals is much worse. Yue et al. found that COVID-19 and influenza co-infections had significantly different rates of incidence in Wuhan, China during two distinct time periods of the COVID-19 pandemic and that co-infection with influenza B virus was more likely to result in a poor prognosis. In another study, experimental cell culture and mouse models found that an influenza A infection led to the promotion of increased SARS-CoV-2 infectivity and viral load resulting in increased lung damage. In agreement, a literature review also concluded that severe pulmonary damage resulted from SARS-CoV-2 co-infection with influenza A. A recent article published by the International Journal of Epidemiology found that while it was rare, patients that did develop co-infection with SARS-CoV-2 and influenza A had much higher risks of morbidity and mortality. These findings reiterate the complex pathophysiology that arise from dual infections of SARS-CoV-2 and influenza viruses in addition to the importance of vigilant detection and diagnosis. In a retrospective study of deceased SARS-CoV-2 positive patients in Northeastern Iran, a high rate of co-infection with influenza A in addition to co-infections from respiratory syncytial virus (RSV), bocavirus, adenovirus, and human metapneumovirus (HMPV) were identified.
SARS-CoV-2 Co-infections with Other Pathogens

In agreement with the previous study, evidence is accumulating that COVID-19 co-infections will occur with viral, bacterial, and fungal pathogens and recommendations for diagnostic testing as a means to provide appropriate treatment decisions are increasing.\textsuperscript{11,12,19-26} Pathogens may influence one another with both positive and negative effects, adding complexity to clinical diagnosis, treatment, and comprehensive patient management.\textsuperscript{11,18,26}

In Korea and Northern California, independent studies found high rates of SARS-CoV-2 co-infections with rhinovirus/enterovirus, RSV, and other non-SARS-CoV-2 coronaviruses to be the most common.\textsuperscript{24,27} A study of patients hospitalized in China found RSV and \textit{Mycoplasma pneumonia} to be the most frequent pathogens associated with SARS-CoV-2 co-infection.\textsuperscript{25} The CDC has shared a website describing the increasing frequency of fungal co-infections with COVID-19, particularly due to \textit{Aspergillus} or \textit{Candida auris}.\textsuperscript{28} Additional studies are raising awareness on the extent of COVID-19 co-infections with an even broader range of diseases such as dengue, human immunodeficiency virus (HIV), hepatitis B virus (HBV), and malaria.\textsuperscript{11,12}

Conclusions

Over a year into the global COVID-19 pandemic, a great deal about the SARS-CoV-2 virus remains unknown. As COVID-19 vaccination rates increase and some communities begin to see decreased prevalence, individuals will begin returning to everyday activities. The rise of SARS-CoV-2 variants have led to reoccurring “waves” of transmission. As COVID-19 continues to circulate, with fluctuations across geographical regions, the need for further investigation into co-infections is critical. In July 2021, WHO and UNICEF confirmed that globally, throughout the pandemic, childhood vaccinations have significantly decreased.\textsuperscript{29}

Taken all together, it is clear that SARS-CoV-2 virus will co-circulate with other acute respiratory pathogens, including influenza.\textsuperscript{6,11} The U.S. NIH and CDC endorse diagnostic testing, particularly for discrimination of SARS-CoV-2 and influenza.\textsuperscript{13-15} As reports of COVID-19 coinfections increase, effective patient management and treatment will rely on further detection and investigation.
References


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