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Influenza in the COVID-19 Era

Daniel A. Solomon, MD; Amy C. Sherman, MD; Sanjat Kanjilal, MD, MPH

The annual influenza epidemic substantially affects health care systems worldwide and has resulted in an estimated 12 000 to 61 000 deaths annually since 2010 just in the US.[1] The extent of the morbidity and mortality in any given year reflects the degree of genetic drift or shift in the dominant strain of the influenza virus and the efficacy and coverage of vaccination. With the coronavirus disease 2019 (COVID-19) pandemic, clinicians face a second respiratory virus associated with morbidity and mortality several-fold higher than that of influenza, in part due to its spread in an immunologically naive population. A looming threat of concurrent influenza and COVID-19 epidemics is a major concern for public health officials and clinicians.

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A Population Perspective

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, and influenza are vastly different pathogens, but there are important areas of overlap (**Table**).[2-4] Both viruses are primarily transmitted by respiratory droplets. Thus, the adoption of nonpharmacologic interventions (NPIs), such as mandated face coverings in public, closure of schools and retail spaces, and restrictions on movement, would be expected to influence the incidence of both infections to varying degrees. Studies have consistently shown a pattern of decreased influenza incidence in 2020 (January through May) after adoption of NPIs as compared with prior seasons.[5,6] A similar trend has occurred in the US, with the number of influenzalike illnesses for the 2019-2020 season decreasing earlier than expected. Caution should be taken when interpreting these data because the rates of testing for non–SARS-CoV-2 respiratory viruses were greatly curtailed during the initial pandemic wave.

The expectation that the pattern of decreased influenza transmission will endure through the next influenza season presumes ongoing adherence to NPIs. Continued use of face coverings and reinstating local lockdowns during periods of increased transmission could substantially reduce the rates of infection for both diseases, but as restrictions on movement relax, the transmission of both influenza and SARS-CoV-2 can be expected to increase.

In addition to NPIs, there is a heightened importance for seasonal influenza vaccination to minimize the viral reservoir in the population. Despite widespread availability of multiple influenza vaccines, national vaccination coverage is consistently lower than 50% in adults. National education campaigns paired with community-based vaccination programs that focus on populations with lower access to health services and groups with historically low vaccine uptake, such as young adults, will be critical to increasing coverage above levels in previous years.

Table. Comparison Between Seasonal Influenza and SARS-CoV-2

Characteristics	Seasonal influenza viruses	SARS-CoV-2
Primary route of transmission	Droplet	Droplet (airborne, fomite, and fecal-oral transmission possible but less important)
Overall infectivity	Less contagious	More contagious
	The basic reproduction number (R_0) of both viruses is highly dependent on NPIs effective in decreasing transmission	
Dynamics of infectivity	Patients are most infectious after symptom onset	Patients are most infectious starting 48 h prior to symptom onset[2]
	Both viruses capable of asymptomatic transmission, but less than during presymptomatic and symptomatic phases	
Incubation period	1-4 d (median, 2 d)	2-14 d (median, 5 d)
Risk factors for severe disease	• Age >65 y and <2 y • Immunosuppression • Pregnancy (through 2 weeks postpartum) • Morbid obesity • Chronic lung disease, cardiac disease, advanced liver disease, chronic kidney disease • Residence in nursing home or long-term care facilities • American Indian/Alaska Native heritage	• Advanced age (risk increases with age) • Male sex • Obesity • Hypertension • Chronic lung disease, cardiac disease, type 2 diabetes, cancer,chronic kidney disease, advanced liver disease • Surgery during incubation period • Residence in nursing home • Structural racism, poverty[3]
Most common clinical manifestations	Fever, chills, headache, myalgias, cough, nasal congestion, sore throat, fatigue	Fever, chills, headache, myalgias, cough, shortness of breath, fatigue, anosmia
	For both viruses, the majority of infections are either subclinical or mild	
Pediatric disease	• Common, especially high risk in children <2 y • Children play a leading role in propagating outbreaks	• Uncommon, with typically mild disease • Multisystem inflammatory syndrome has been observed in children, but is rare • Limited evidence on children as a source of infection
Case-fatality rate	≈0.1%	≈0.25%-3.0%[4]
Dynamics of symptoms	Symptoms typically peak during first 3-7 d of illness	Symptoms can peak during week 2 or 3 of illness
Vaccine	Multiple approved	No vaccine currently licensed
Clinical diagnostics	Nucleic acid amplification and antigen-based assays from respiratory samples	• Nucleic acid amplification and antigen-based assays from respiratory samples • Serologies
Available antiviral agents	• Neuraminidase inhibitors • Cap-dependent endonuclease inhibitors • M2 channel blockers	Nucleoside analogue (remdesivir)

Abbreviations: NPI, nonpharmacologic intervention; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Effects on Clinical Practice

Although no specific clinical manifestations reliably distinguish between early influenza disease and COVID-19, it will be important to identify the viral etiology in clinical practice.

First, the approach to management of the 2 viruses is different. Influenza can be treated with a neuraminidase inhibitor or a cap-dependent endonuclease inhibitor, neither of which have antiviral activity against SARS-CoV-2. Remdesivir is available for treatment of COVID-19 under an Emergency Use Authorization, but because it is administered parenterally, it is reserved for hospitalized patients. It is also essential to confirm a diagnosis of COVID-19 to encourage early participation in clinical trials, especially for patients who may have contraindications to remdesivir. Many other treatments for COVID-19 are under investigation, including oral antivirals that could have important implications for outpatient management.

Second, the syndrome caused by each virus follows a different course. Patients with influenza typically experience most severe symptoms during the first week of illness, whereas patients with COVID-19 may experience a longer duration of symptoms with a peak during the second or third week of illness. Distinguishing between the viruses could allow clinicians to provide patients with anticipatory guidance about how symptoms are expected to evolve and can help identify complications later in the disease course.

Third, correctly identifying the virus has important infection control implications, including appropriate guidance regarding isolation and quarantine, return to school and work recommendations, and COVID-19 case identification and contact tracing.

As the 2020 respiratory virus season begins, any patient presenting with the nonspecific features of a respiratory viral infection should receive testing for SARS-CoV-2 at a minimum, a break from prior practice in which such patients were often managed based solely on clinical criteria. An additional layer of complexity is that coinfection with influenza and SARS-CoV-2 has been observed, so a positive result for one virus does not exclude infection with the other.[7] It is not yet clear whether initial testing should include both viruses or whether influenza testing can be added after SARS-CoV-2 results return. The preferred diagnostic algorithm will depend on which diagnostic tests are locally available with careful consideration of test characteristics, cost, turnaround time, and supply chain issues.

Managing the pediatric population may differ because there are several unique characteristics of the viruses in children. Influenza is a source of significant morbidity and mortality in children, and individuals between the ages of 5 and 17 years are considered to play a critical role in propagating seasonal influenza outbreaks.[8] In contrast, the disease trajectory of COVID-19 in children is typically mild, and children may be less likely to be infected or infect others.[9] Therefore, while surveillance for pediatric spread of COVID-19 remains important to guide plans for school and daycare reopening, the health effects of COVID-19 in children is expected to be much lower than in older individuals.

An Evolving Diagnostic Landscape

The cornerstone of efforts to control the COVID-19 pandemic has been mass surveillance for SARS-CoV-2. Scaling up diagnostic testing can be accomplished by validation of alternative specimen types (such as anterior nasal swabs and saliva) that increase the ease of collection and dissemination of rapid point-of-care diagnostics. Both of these would facilitate serial testing, which could improve case detection, thereby reducing asymptomatic and presymptomatic spread, use of personal protective equipment, and duration of isolation. Importantly, a number of manufacturers are modifying existing assays to allow for multiplex testing of influenza, SARS-CoV-2, and respiratory syncytial virus using a single cartridge. These tests could help fill an important need for clinicians seeking to diagnose infection efficiently while minimizing risk and inconvenience to patients and staff. Further work remains to validate these assays for use with saliva and for use at the point of care.

Conclusions

Despite the rapid pace of progress in the areas of SARS-CoV-2 diagnostics, treatment, and vaccine development, the population remains vulnerable to concurrent influenza and COVID-19 epidemics. The scale of morbidity and mortality will be directly related to the strength of the public health response, which must stress the importance of the 2 most effective infection prevention tools currently available: widespread implementation of seasonal influenza vaccination and preservation of NPIs until community immunity is achieved through an effective SARS-CoV-2 vaccine and/or natural infection. As clinicians and members of local communities, physicians and other health care professionals should promote these important interventions and remain flexible in the approach to diagnosis during these times of unprecedented challenges.

ARTICLE INFORMATION

Author Affiliations: Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts (Solomon, Sherman, Kanjilal); Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Healthcare Institute, Boston, Massachusetts (Kanjilal).

Corresponding Author: Daniel A. Solomon, MD, Division of Infectious Diseases, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (dasolomon@bwh.harvard.edu).

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REFERENCES

1. Burden of influenza. CDC. Published April 17, 2020. Accessed July 13, 2020. https://www.cdc.gov/flu/about/burden/index.html

2. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020;26(5):672-675.

3. Yancy CW. COVID-19 and African Americans. *JAMA*. Published online May 19, 2020. doi:10.1001/jama.2020.6548

4. Wilson N, Kvalsvig A, Barnard LT, Baker MG. Case-fatality risk estimates for COVID-19 calculated by using a lag time for fatality. *Emerg Infect Dis*. 2020;26(6):1339-1441. doi:10.3201/eid2606.200320

5. Cowling BJ, Ali ST, Ng TWY, et al. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong. *Lancet Public Health*. 2020;5(5):e279-e288. doi:10.1016/S2468-2667(20)30090-6

6. Sakamoto H, Ishikane M, Ueda P. Seasonal influenza activity during the SARS-CoV-2 outbreak in Japan. *JAMA*. 2020;323(19):1969-1971.

7. Kim D, Quinn J, Pinsky B, et al. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. *JAMA*. 2020;323(20):2085-2086.

8. Worby CJ, Chaves SS, Wallinga J, et al. On the relative role of different age groups in influenza epidemics. *Epidemics*. 2015;13:10-16.

9. Li X, Xu W, Dozier M, et al. The role of children in transmission of SARS-CoV-2. *J Glob Health*. 2020;10(1):011101. doi:10.7189/jogh.10.011101

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