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# COVID-19 and flu: Dual threat, dual opportunity

**T**HIS FALL, THE NORTHERN HEMISPHERE faces the dual threat of the annual influenza epidemic and the pandemic of coronavirus disease 2019 (COVID-19), which arrived here in March 2020 and never went away. But all is not bleak. Although the COVID-19 pandemic continues and has had a negative impact on preventive, routine, and acute medical care, the silver lining is that measures to combat the COVID-19 pandemic can help minimize the impact of seasonal influenza, and vice versa.

COVID-19 has justifiably occupied most of our attention in the last 10 months, but we need to keep our eyes on the ball of the upcoming flu season.

## ■ COVID-19: THE ONGOING THREAT

At the time of this writing, 1 million of the 33 million people with COVID-19 have died.<sup>1</sup>

The situation was similar in the 1918 influenza pandemic. Then, like now, no effective vaccine or medication was available to prevent or treat the pandemic disease. And despite significant advances in hygiene and supportive medical care achieved in the 100 years between these pandemics, the mortality rate during the early phase of the COVID-19 pandemic in New York City was comparable to that in the 1918 influenza pandemic.<sup>2</sup>

### Youth at risk

During the early months of the COVID-19 pandemic, the incidence, disease severity, and mortality rates were highest among older adults. However, during June, July, and Au-

gust 2020, the pattern shifted so that the incidence was highest in persons ages 20 to 29,<sup>3</sup> and increases in incidence in this age group preceded increases in incidence in those age 60 and older by 4 to 15 days.

In the years 1999 to 2014, global surveillance data from 29 countries showed that young adults ages 18 to 39 accounted for 30% of influenza cases.<sup>4</sup> Influenza vaccination coverage in the United States in adults ages 18 to 49 for the 2018–19 influenza season was 35%, the lowest among all age groups.<sup>5</sup> Even though disease severity of both COVID-19 and influenza may be less in healthy young adults than other age groups, it is becoming clear that the fight against both diseases may not be won without decreasing the incidence of both infections in that age group.

### Concurrent infection is common

From March 3 to March 25 of this year, 20% of specimens testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were positive for 1 or more additional pathogens, including influenza.<sup>6</sup> Numerous reports have since documented simultaneous SARS-CoV-2 and influenza co-infection.<sup>7</sup>

## ■ COMPARING THE COVID-19 AND THE 2009 INFLUENZA PANDEMICS

The COVID-19 pandemic, the 2009 influenza A (H1N1) pandemic (the most recent flu pandemic), and seasonal influenza have several things in common that we need to recognize.

**Table 1** summarizes similarities and differences between COVID-19 and 2009 influenza A (H1N1).<sup>8</sup> Both have similar modes of transmission, but COVID-19 is much more contagious. Patients with COVID-19 are

**Measures to combat COVID-19 can help minimize the impact of seasonal influenza, and vice versa**

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TABLE 1

**The coronavirus disease 2019 and influenza 2009 pandemics compared**

	<b>Coronavirus disease 2019 pandemic</b>	<b>Influenza 2009 pandemic</b>
<b>Causative virus</b>	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Influenza A (H1N1)
<b>Mode of transmission</b>	Respiratory droplets most common, but contact with surfaces contaminated with viral particles and airborne routes are possible	
<b>Prevalence</b>	0.11%	25%
<b>Number of secondary transmissions from 1 infected person</b>	2.5	1.7
<b>Incubation period (days)</b>	2–14	2
<b>Interval from symptom onset to maximum infectivity (days)</b>	0	2
<b>Duration of infectivity after onset of illness (days)</b>	8–10	5–7
<b>Typical course of illness</b>	Gradual onset, then sudden escalation in severity, then recovery within 2 weeks in those with mild or moderate illness, and 3–6 weeks in those with severe illness	Sudden onset of acute illness, which lasts 2–5 days, followed by milder symptoms that can last for several weeks
<b>Typical clinical presentation</b>	Fever, headache, myalgia, malaise, and dry cough; less commonly, vomiting and diarrhea	
<b>Unique manifestations</b>	Sudden loss of smell or taste	None
<b>Asymptomatic or presymptomatic</b>	30%–40%	20%
<b>Illness requiring hospitalization</b>	20%	5%–10%
<b>Illness requiring intensive care</b>	1/16,000	1/104,000
<b>Complications</b>	Respiratory failure, myocarditis, encephalitis, myositis, multi-organ failure, and secondary bacterial pneumonia	
<b>Case fatality rate</b>	0.5%–1%	0.02%–0.05%
<b>Antiviral therapy</b>	Intravenous remdesivir (investigational)	Oral oseltamivir, inhaled zanamivir, intravenous peramivir, and oral baloxavir
<b>Dexamethasone therapy</b>	Only if hypoxic	Not recommended
<b>Convalescent plasma therapy</b>	Investigational, only for severe cases	
<b>Preventive measures other than vaccine</b>	Social distancing, hand hygiene, face masks, isolation and contact tracing of confirmed cases, and quarantine of those exposed	
<b>Preventive vaccine</b>	In development; now 6 months into the pandemic	Was developed and approved within 5 months
<b>Pandemic duration</b>	Ongoing; 8 months so far	15 months

most contagious on the day of onset of symptoms, while those with 2009 pandemic influenza were most contagious during the first 2 days after the onset of illness. Asymptomatic or presymptomatic infections are up to twice as common with COVID-19 compared with influenza. Onset of illness with COVID-19 is

usually gradual, while that of influenza is typically acute. Loss of sense of smell and taste are features of COVID-19, not influenza. Although the prevalence of influenza A (H1N1) during the 2009 pandemic was much higher than that of COVID-19 in the current pandemic, the latter is associated with up to 4

times higher rates of hospitalization, 5 times higher rates of need for admission to an intensive care unit, and up to 10 times higher case-fatality, all possibly due to readily available, effective antiviral therapy for influenza.

### ■ THE PANDEMIC'S NEGATIVE IMPACT ON OTHER MEDICAL CARE

A major negative impact of social distancing measures to curb the COVID-19 pandemic is their indirect effect on preventive health care. Shortly after the pandemic was declared, rates of routine childhood immunizations in Michigan fell by about 20%.<sup>9</sup> Yet Abbas et al<sup>10</sup> estimated that 84 deaths in African children would be prevented by sustaining routine childhood immunizations for every 1 excess COVID-19 death attributed to SARS-CoV-2 infections acquired during these routine vaccination clinic visits. The risk-benefit ratio extended to children's siblings, parents or adult caretakers, and older adults. This and other studies have led to a "call to action" to avoid the catastrophic negative impact the COVID-19 pandemic would have on vaccine-preventable diseases, including influenza.<sup>11</sup>

People are also avoiding routine and even urgent care. An estimated 40.9% of adults in the United States delayed or avoided routine medical care due to the COVID-19 pandemic.<sup>12</sup> In the 10 weeks after declaration of a national emergency in the United States in response to the COVID-19 pandemic, emergency department visits for heart attack decreased by 23% and visits for stroke decreased by 20%.<sup>13</sup> Primary percutaneous coronary interventions for ST-segment elevation myocardial infarction decreased by 38% after March 1, 2020.<sup>14</sup>

### ■ MEASURES TO CONTAIN COVID-19 HELP CONTROL SEASONAL INFLUENZA

Several teams around the world are at work on COVID-19 vaccines. Unfortunately, 31.6% of adults surveyed indicated they were not sure they would accept such a vaccine, and 10.8% said they did not intend to be vaccinated.<sup>15</sup> Not surprisingly, not having received the influenza vaccine the year before was one of the factors associated with vaccine hesitancy.

When a COVID-19 vaccine is approved,

transparency and scientific integrity will be necessary to gain public trust and, hopefully, convince the hesitators and refusers.<sup>16</sup> We may need to choose our battles wisely by focusing on the slim majority (57.6%<sup>15</sup>) who intend to be vaccinated, and by implementing measures well-established in annual influenza vaccination to close the intention-to-behavior gap,<sup>17</sup> such as providing the vaccine free of charge at the workplace or school.

As an unexpected upside of the COVID-19 pandemic, the public health, nonpharmaceutical interventions for it such as social distancing, hand hygiene, face masks, isolation and contact tracing of confirmed cases, and quarantine of those exposed have resulted in collateral benefit on influenza activity. In the United States, within 2 weeks of the COVID-19 pandemic being declared on March 11, 2020, the percent of samples testing positive for influenza decreased sharply, from more than 20% before to 2.3%.<sup>18</sup> In addition, interseasonal influenza circulation has remained at a historically low level of 0.2%, compared with 1% to 2% in recent interseasonal periods. Moreover, data from several countries in the southern hemisphere<sup>18,19</sup> and others such as Taiwan,<sup>20</sup> Korea,<sup>21</sup> Hong Kong,<sup>22</sup> and Singapore<sup>23</sup> indicate influenza activity in 2020 is at historically low levels.

Despite the negative psychological impact social distancing measures may have, recent surveys suggested that more Americans have embraced healthy lifestyles amid the COVID-19 pandemic.<sup>24,25</sup>

### ■ MEASURES TO CONTROL SEASONAL INFLUENZA HELP FIGHT COVID-19

Cross-reactivity of immune responses to influenza virus and coronavirus infections<sup>26</sup> offers some insight into the potential beneficial effect of influenza vaccination on the COVID-19 pandemic. Similarity in structures and evolution of these viruses<sup>27</sup> may explain this cross-reactivity of immunity. Another explanation is a "bystander immunity" induced by influenza vaccine against other viral infections.<sup>28,29</sup>

Preliminary data from more than 90,000 COVID-19 cases in Brazil showed that those who received influenza vaccine during the

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2020 influenza vaccination campaign, even after the onset of symptoms of COVID-19, were 8% less likely to require treatment in an intensive care unit, 18% less likely to require invasive respiratory support, and 17% less likely to die.<sup>30</sup> The authors of this publication, which has not been peer-reviewed, cite adaptation in innate immunity as the most plausible mechanism for these beneficial effects.

Other intuitive beneficial effects of influenza vaccination during the COVID-19 pandemic include conserving resources, such as personal protective equipment, and more importantly healthcare providers. Healthcare systems were strained during the first several weeks of the pandemic,<sup>31</sup> and all efforts to maintain this capacity should be implemented.

Variability in influenza vaccine efficacy<sup>32</sup> has fueled continued suboptimal confidence in vaccination and therefore suboptimal vac-

cination rates.<sup>33</sup> Bartsch et al<sup>32</sup> estimate that if we could produce a vaccine that was reliably 70% effective, it could avert up to 54 million influenza cases, saving up to \$6.5 billion in direct medical costs and up to \$64.7 billion in productivity losses.<sup>32</sup>

In an earlier article,<sup>34</sup> I addressed how to respond to influenza vaccine doubters. In addition, for those who believe there is an association between maternal vaccination during pregnancy and autism spectrum disorder in offspring, a recent article has refuted any such association.<sup>35</sup>

While patients with suspected or confirmed COVID-19 should postpone influenza immunization until they recover,<sup>36</sup> everyone else 6 months of age and older who has no history of severe allergic reaction to any component if the vaccine, or to a previous dose of any influenza vaccine, should be immunized, preferably early in the flu season.<sup>37</sup>

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