

Perspectives

A Public Health Perspective on Influenza Status in the Context of COVID-19 Pandemic, 2019–2020

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The possible dual epidemic of coronavirus disease 2019 (COVID-19) and influenza in the coming winter raises serious concerns for the northern hemisphere as it will likely result in an expanded disease burden and overloading of public health institutions and clinical capacities as a result of continued increasing mental stress for the public and depletion of public resources. Several questions remain regarding how the flu season might affect the COVID-19 pandemic and vice versa.

DECREASED INFLUENZA ACTIVITY AND POTENTIAL CONTRIBUTORS

Some signs of the interaction between the flu and COVID-19 were shown in the past flu season in the southern hemisphere. Australia, Chile, and South Africa recorded not only much lower influenza activity compared with usual seasons, but fewer positive test results of influenza viruses — 51 influenza positive specimens out of 83,307 samples, or 0.06% [95% confidence interval (95% CI): 0.04–0.08] (1). In the northern hemisphere, the United States, Republic of Korea, and Singapore reported an interruption to the then ongoing influenza circulation of the 2019–2020 season and a historically low interseasonal level of influenza incidence (1–3). Reduced activity was also observed for other common respiratory viral agents (4).

Non-pharmaceutical interventions (NPI) aimed against COVID-19 were supposed to be responsible for reducing transmission of influenza. A range of mitigation measures focusing on social distancing, including bans on mass gatherings, school closures, teleworking, and national or regional lockdowns, have been widely implemented for COVID-19 and whose effectiveness has been demonstrated by the corresponding incidence curves of many countries across the world, such as China, Germany, Australia, and South Africa (5). These community measures, in addition to recommended or mandatory individual measures against COVID-19 such as mask wearing and hand hygiene, can also curb the transmission of

the seasonal influenza virus that shares same transmission routes with COVID-19 (6) but is less contagious ($R_0=1.28$ for the flu compared to $R_0=2-3.5$ for COVID-19) (7). Among these mitigation measures, school closures may have played an additional role in reducing transmission in children, who are important drivers of influenza virus transmission in the community (6).

Viral interference could also be at play (8–9) as infection with a virus can prevent or partially inhibit infection with another virus within the same host (9). The interference is variable between virus-pairs and could be modified by the time interval from primary to secondary viral exposure (8,10). In COVID-19 patients, the infection rate with non-COVID-19 respiratory viral pathogens was much lower than that in non-COVID-19 patients during the same time period (2.99% *vs.* 13.1%), which suggested a competitive advantage of COVID-19 in the interaction with other respiratory viruses including influenza (11).

COINFECTION AND PRIOR INFECTION WITH INFLUENZA

The coinfection rate of COVID-19 with other respiratory viral pathogens was reported vary widely between 0% to 25%, with a pooled estimate of 3% (12). The variety of virus targeted, the detection method used, and the seasonality of other respiratory viral pathogens during the research period (13) may contribute to heterogeneity among studies. Among the identified coinfecting viral pathogens, influenza virus was among the most common (12).

Coinfection with influenza virus has been reported in Middle East respiratory syndrome (MERS) cases (14). The coinfection rate with influenza virus was generally low in confirmed COVID-19 patients with a combination of different clinical severities (0.1%–2.7%), according to studies using PCR-based testing methods across the world, from Switzerland (4), Brazil

(15), the United States (16–17), Spain (18), and China (19–20). Although the clinical impact of coinfection has not been conclusive, some evidence has suggested that coinfection with influenza virus may worsen the clinical outcome of COVID-19 patients. In coinfecting patients, substantially higher neutrophils and inflammatory markers and higher incidence of acute cardiac injury were observed (21), and the risk of ventilator use and death was elevated (22), in which the provoked hyperinflammatory state and the up-regulated pulmonary angiotensin-converting enzyme 2 (ACE2) receptors induced by influenza virus infection might play a role (23–24). In a study conducted in Iran, 22.3% of the dead COVID-19 patients were coinfecting with influenza virus (25).

In contrast, the rate of recent influenza infection was high in COVID-19 patients (26). Over a half of the confirmed COVID-19 patients in a hospital in Wuhan, China tested positive for the influenza immunoglobulin M (IgM) antibody test (26). A study in Italy observed that 63.6% of COVID-19 patients reported a recent (1–3 weeks) influenza-like-illness prior to the appearance of COVID-19-related symptoms (27). Thus, the upper airway mucosal damage and local immune impairment triggered by prior infection may predispose individuals for subsequent COVID-19 infection (27).

THE ROLE OF INFLUENZA VACCINATION

To reduce the public health, economic, and societal hardship associated with long-term stringent lockdown measures, many countries have been relieving public health and social measures against COVID-19, but a resurgence of COVID-19 cases has been observed to follow in many countries and areas (28). The transmission activity of other respiratory viruses, particularly influenza, could also spike along with the relief of NPI against COVID-19 in the coming winter of the northern hemisphere, challenging the already stressed public health and healthcare capacities. This spike may be more obvious in countries or territories where society has returned to a certain level of normalcy.

To reduce the epidemiological noise of influenza in the context of COVID-19, mass influenza vaccinations are strongly recommended. However, this would be tricky given the tampered routine immunization services as manufacturing capacity is diverted to

COVID-19 and other vaccines. In that case, the elderly, healthcare workers, etc., could be targeted as priority groups for influenza vaccination due to risks of elevated mortality and exposure and the importance of maintaining healthcare services.

In addition to the potential of avoiding complicated coinfections, the influenza vaccination was found to be associated with lower risk of infection, severe clinical manifestation, and death with COVID-19 at the individual level (29–31). At the population level, an ecological study also showed that the coverage rate of the influenza vaccination in people aged 65 or over was associated with a reduced spread and a less severe clinical presentation of COVID-19 (32). It is possible that influenza vaccination could act as a non-specific immune stimulator leading to earlier activation of the immune system to combat COVID-19 (33).

Nevertheless, the effectiveness of influenza vaccine is generally modest and even lower in individuals aged 65 years or older, who are at higher risk of severe infection for both the influenza virus and COVID-19. Mismatch between the circulating influenza strains and the vaccine influenza strains would further jeopardize the vaccine's effectiveness. This is more likely to happen in the next influenza season of southern hemisphere, as very few isolates of influenza virus were able to be collected in the past flu season making it especially difficult to predict the upcoming circulating strains. Thus, faster and more widely available testing is needed to distinguish between the influenza virus and COVID-19, which cause similar symptoms but requires different treatments and emergency response strategies. In addition, some NPI including wearing mask and social distance should be preserved as the new standard until a valid COVID-19 vaccine is available.

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