Comment

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The role of influenza in the era of COVID-19: Can we forget it?

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SUMMARY COVID-19 has been a topic of interest since a pandemic struck in 2019. The morbidity of influenza tended to decrease due to the measures to prevent COVID-19. Indeed, influenza seems to be "ignored" in this era of COVID-19. However, influenza has not disappeared from the scene. Presented here are two examples of recent influenza epidemics in China and Australia. Possible interactions between COVID-19 and influenza are discussed. Measures against COVID-19 may reduce contact with influenza, subsequently reducing adaptive immunity against influenza in the general population. Influenza might not be center stage right now, but insufficient adaptive immunity in the population may potentially trigger a future influenza pandemic. Coinfection with COVID-19 and influenza might potentially be a thorny problem. Hence, influenza cannot be ignored. Governments around the world should take measures to prepare for a possible influenza pandemic in the future.

Keywords COVID-19, influenza, coinfection, pandemic

Influenza has been the greatest public health challenge. The terms "Spanish flu" or "the Great Influenza epidemic" were used to describe the 1918 influenza pandemic, a deadly global pandemic of the H1N1 influenza A virus that infected approximately 500 million people and caused 24.7-39.3 million deaths (*1*). The subsequent Asian flu in 1957, Hong Kong flu in 1968, and swine flu in 2009 were major public health incidents with appreciable morbidity and mortality. The World Health Organization (WHO) estimated that global there are approximately 1 billion new influenza cases per year, including 3-5 million severe cases and 290,000-650,000 deaths (*2*). However, since the COVID-19 pandemic struck in 2019, the higher morbidity and mortality of COVID-19 seem to have garnered more public attention, and influenza seems to have been forgotten. Unfortunately, influenza has never actually disappeared from the scene, even in this era of COVID-19. Data from the WHO Global Influenza Surveillance and Response System (GISRS) indicated a resurgence of influenza in 2021-2022 (Figure 1A). GISRS laboratories tested 161,959 samples reported by 107 countries from May 30 to June 12, 2022 and found influenza A in 97.5% and influenza B in 2.5% (*3*). A point worth noting is that despite the lower global total morbidity during the second wave of 2022, data from two countries, namely China (Figure 1B) and Australia (Figure 1C), revealed markedly higher numbers of influenza cases, indicating a resurgence of influenza. Clustered cases were reported in several provinces in the south of China and mainly involved primary and secondary schools. The rate of infection is known to be significantly higher in children than in adults during this wave. Data from the Chinese National Influenza Center (CNIC) revealed that cases of influenza-like-illness (ILI) reported in the past two weeks were markedly higher than during the same period in previous years and that the predominant subtype of the influenza A virus is H3N2 (*4*). CNIC also reported that Guangdong Province has the highest morbidity (*vs.* other provinces). There were 126,857 new ILI cases reported in Guangdong, which is 10.38 times the normal figure from the previous year (*5*). However, actual data on influenza morbidity might be underestimated due to the strict prophylactic measures against COVID-19 in China, which have prompted patients to refrain from seeking medical advice. The situation in Australia is also daunting. Australia is now suffering its worst epidemic of influenza. Australia's National Notifiable Communicable Disease Surveillance System (NNDSS) has reported 147,155 cases during this wave, and 55,101 of those cases were reported from June 6 to 19, 2022. Six-point-one percent of patients with severe influenza had to be admitted to the ICU. Influenza's morbidity is approximately 300 times the normal rate (Figure 1C)

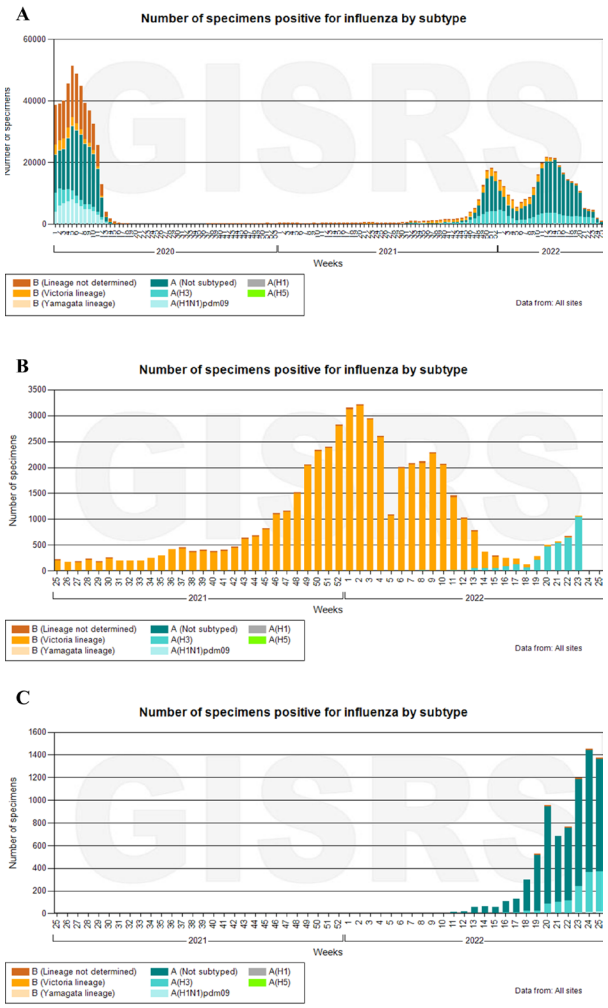

Figure 1. Status of current influenza infections from 2020 to 2022. **(A)**, Global data on influenza infections from 2020 to 2022. **(B)**, Data on influenza infections in China from 2021 to 2022. **(C)**, Data on influenza infections in Australia from 2021 to 2022. All of the data are publicly available from the WHO Global Influenza Surveillance and Response System. *http://www.who.int/flunet*.

(*6*). A "twindemic" of COVID-19 and influenza is a knotty problem now facing the Australian Government. The examples of China and Australia indicate that the influenza problem is far from being resolved despite this being an era of COVID-19.

One crucial problem, namely coinfection with COVID-19 and influenza, should be seriously considered during this "twindemic" scenario. Several recent studies reported coinfection with COVID-19 and influenza in Japan (*7*), the US, Australia, Chile, South Africa (*8*), Turkey (*9*), and the UK (*10*). Kawai *et al*. conducted a retrospective study of 193 patients with COVID-19 using a rapid diagnostic approach, and they found that no patients with COVID-19 were coinfected with influenza (*7*). They therefore concluded that coinfection with COVID-19 and influenza was rare during the winter of 2020 in Japan, but they urged that attention be paid to the coinfection problem during the next influenza season. Ozaras *et al*. reported six patients coinfected with COVID-19 and influenza among 1,103 patients with COVID-19 (0.54%) in Turkey. All of these patients with a coinfection had a mild to moderate infection (*9*). Swets *et al*. examined 6,965 patients with COVID-19 in the UK and found that 227 were coinfected with influenza (3.26%) (*10*). All of these studies reported that cases of coinfection with COVID-19 and influenza are rare at the present time but that attention needs to be paid to this situation because the clinical outcomes of coinfection with COVID-19 and influenza remain unknown. Swets *et al*. found that coinfection with COVID and influenza was significantly associated with an increased probability of death. Moreover, coinfection with COVID-19 and other respiratory viruses significantly increased the likelihood being placed on invasive mechanical ventilation (*10*). That study predicted a worse outcome due to coinfection, but the actual situation requires further investigation.

The interactions between COVID-19 and influenza are complicated and not fully understood. Several issues need to be kept in mind: 1) As respiratory viruses, both viruses have analogous transmission characteristics and common clinical manifestations. Hence, measures to prevent COVID-19 are also effective in preventing influenza (*11*). This suggests that the morbidity of influenza decreased since many measures had been taken against COVID-19 (such as mask wear, city lockdowns, and social distancing) (*12,13*). 2) Prioritizing COVID-19 while neglecting influenza might lead to diminished adaptive immunity against influenza in the general population, increased the risk of infecting with influenza particularly among specific populations of the elderly and individuals with certain underlying medical conditions. 3) A previous study indicated that infection with COVID-19 tends to involve coinfection with other respiratory viruses (*10*). However, distinguishing between COVID-19 and influenza in the early stages based solely on symptoms is extremely difficult. More effective differential diagnosis tools are needed. Other than the PCR assays, thoracic radiology findings might be useful in screening for patients coinfected with COVID-19 and influenza (*9*).

The morbidity of influenza has recently tended to decline, possibly due to the measures against COVID-19 (*13*). That said, influenza has definitely not disappeared. Measures against COVID-19 may conversely reduce contact with influenza, subsequently reducing adaptive immunity against influenza in the general population. Hence, these measures against COVID-19 are a double-edged sword with regard to influenza. Influenza might not be center stage right now, but insufficient adaptive immunity in the population may potentially trigger a future influenza pandemic. Coinfection with COVID-19 and influenza might potentially be a thorny problem in the near future. Public health authorities around the world should be aware of this situation and make preparations ahead of time, particularly with regard to the coming influenza season. More effective vaccines and antivirals should be developed. In addition, correct knowledge

regarding the prevention of COVID-19 and influenza needs to be updated and conveyed to the public. Put simply, this may be an era of COVID-19, but it may act as a Trojan horse for influenza. In any event, influenza should never be forgotten.

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