Co-circulation, Co-infection of SARS-CoV-2 and Influenza Virus, Where Will it Go?

Shuai-xing Wang¹ and Da-yan Wang¹,*

Abstract
COVID-19 has led to unprecedented public health challenges and may become a long-term problem for humans. Influenza, an important infectious disease that causes seasonal influenza, and can potentially reach pandemic status, has led to concerns regarding co-circulation with COVID-19. On the basis of surveillance data for COVID-19 and influenza reported to the WHO in the past 3 years, both infections did not peak together. The co-infection rate (0.7%) for COVID-19 and influenza was relatively low. However, the co-infection rate was significantly higher among people with relatively low immunity and severe symptoms, and co-infection might increase the proportion of severe illness and mortality. Awareness of co-infection is important, and timely evaluation of the risk of co-circulation and co-infection of SARS-CoV-2 and influenza virus will be critical in upcoming influenza seasons. Measures should be taken to prevent co-infection with SARS-CoV-2 and influenza virus, including maximizing uptake of the influenza vaccination and early use of anti-influenza drugs, particularly in groups at high risk of both diseases. Furthermore, prevention and control strategies should include not only SARS-CoV-2 and influenza virus, but also other respiratory diseases, to better prevent the co-occurrence of multiple diseases.

Key words: COVID-19, Influenza, Co-infection, Circulation, Surveillance

COVID-19 has led to unprecedented challenges in public health and devastating economic losses. As of January 6, 2023, the World Health Organization (WHO) reported 657.18 million confirmed cases of COVID-19, including approximately 6.68 million deaths in more than 200 countries and regions [1]. Moreover, the emerging novel variant, Omicron, has caused a rapid resurgence of cases worldwide since late 2021 [2]. Therefore, COVID-19 might become a long-term problem for humans, similarly to seasonal influenza.

Recently, co-infection with SARS-CoV-2 and influenza virus has been reported in some countries, and has been found to potentially worsen COVID-19 clinical outcomes and severity, and increase mortality [3,4]. China optimized the COVID-19 prevention and control policy in early December 2022, which influences the epidemic characteristics of COVID-19 and other respiratory infectious diseases including influenza. Because winter and spring have been the main influenza seasons in China, assessing the risk of co-circulation and co-infection with SARS-CoV-2 and influenza virus is crucial.
EFFECTS OF COVID-19 INTERVENTIONS ON THE INCIDENCE RATE OF INFLUENZA

The outbreak of COVID-19 greatly altered the epidemiology of respiratory tract infections in several ways. Influenza data from China have shown that the positivity rate of specimens collected from cases of influenza-like illness decreased since the onset of the COVID-19 pandemic in early 2020 and was subsequently maintained at a very low level in the following months of 2020 [5]. Global surveillance data have indicated similar trends. Influenza and COVID-19 have similar clinical symptoms and transmission routes [6,7]. The implementation of non-pharmaceutical interventions including social distancing decreased both the number of reported cases of COVID-19 and the incidence of influenza [8]. Since the second half of 2020, some countries have decreased the use of NPIs, thus diminishing the effects of COVID-19 control measures on influenza virus transmission.

Global influenza activity increased in 2021 but remained below pre-pandemic levels overall [9]. In China, despite the absence of a clear epidemic peak of influenza in the winter of 2020–2021, an influenza epidemic peak was observed in the winter of 2021–2022 [10]. With the arrival of the 2023 influenza season, both COVID-19 and seasonal respiratory pathogens, particularly influenza, are likely to co-circulate at different levels.

Fortunately, no evidence indicates that influenza and COVID-19 can be highly prevalent simultaneously. Global surveillance data released by the WHO [11] have indicated that COVID-19 and influenza were not highly prevalent simultaneously in the past 3 years (Fig 1). Detailed analysis of data from 22 representative countries globally from week 1 of 2019 through week 45 of 2022 have demonstrated alternating prevalence of SARS-CoV-2 and influenza virus [12]. These findings may be explained by the ability of influenza A virus and SARS-CoV-2 to block each other in cell studies [13]. However, robust epidemiological data remain lacking. Learning how SARS-CoV-2 and other viruses interfere with each other outside laboratory settings will require prospective studies that closely monitor the same populations for several seasons.

CO-INFECTION WITH COVID-19 AND INFLUENZA

SARS-CoV-2 and influenza viruses spread through similar mechanisms. Moreover, both COVID-19 and influenza diseases present with overlapping clinical features ranging from mild influenza-like symptoms to pneumonia [14,15], including cough, sore throat, headache, muscle aches, breathlessness, fever, acute respiratory distress syndrome, and death. Therefore, co-infection with SARS-CoV-2 and influenza virus increases patient risk and complicates patient condition.

Co-infection rate of SARS-CoV-2 and influenza virus

The rates of co-infection with influenza viruses in COVID-19 have varied among studies, according to the period of study and region. A cohort study of 307 SARS-CoV-2 infected patients with severe acute respiratory syndrome in Wuhan has indicated that co-infection with SARS-CoV-2 and influenza viruses was highly prevalent (influenza A: 49.8% and influenza B: 7.5%) soon after the COVID-19 outbreak (January 12 to February 21 2020) [16]. However, influenza diagnosis was based on a single IgM antibody test, which is generally not recommended for influenza diagnosis. The SARS-CoV-2 co-infection rates with influenza significantly differed in March 3–25, 2020, in northern California (0.9% and 0% for influenza A and influenza B, respectively) [17] and in March 10 to
May 10, 2020, in Turkey (0.5% for influenza infection) [18]. This difference might potentially have been caused by several factors. On the one hand, the spread of respiratory viruses is affected by geographical factors such as the temperature, humidity, and population density. On the other hand, influenza incidence is low as expected when exiting the influenza season.

Therefore, to decrease the effects of regional differences and influenza seasons, Dao et al. have conducted a meta-analysis to determine the proportion of co-infection with influenza viruses in SARS-CoV-2 positive patients (including 54 research articles; most recent search conducted on July 15, 2021) [19]. The data indicated that the overall proportion of co-infection was 0.7%, and a very low co-infection rate between COVID-19 and influenza was observed.

**Risk of co-infection between SARS-CoV-2 and influenza virus**

Co-infection with SARS-CoV-2 and influenza virus is relatively more likely to occur in high-risk groups, such as older people and children. In data from the UK Department of Public Health England of cases from January to April 2020 has found that people infected with both viruses are more at risk of severe illness [3]. People infected with both influenza and COVID-19 are more than twice as likely to die as those with SARS-CoV-2 alone. The mortality rate of co-infected individuals is 2.53 times that (95% confidence interval 1.07–5.12) in people with SARS-CoV-2 alone [21]. These results suggest possible synergistic effects on the severity of infections in co-infected people. Similarly, in Wuhan, people co-infected with SARS-CoV-2 and influenza B virus have been found to be more likely to have fatigue (13%), abnormalities on chest computed tomography (100%), or decreased lymphocytes (0.84, 0.68–1.27) and eosinophils (0.00, 0.00–0.01), thereby indicating more severe disease. Remarkably, although all patients received similar treatment during hospitalization, patients co-infected with influenza B virus had a higher rate of poor prognosis (30.4%) than SARS-CoV-2 single positive patients (7.6%) or influenza A virus co-infected patients (5.9%) [16]. Furthermore, influenza pre-infection has been found to interfere with SARS-CoV-2 replication but to increase disease severity [22]. Furthermore, other research has indicated that patients with SARS-CoV-2 and influenza co-infection are more likely to need mechanical ventilation (OR 2.01, 95% CI 1.19–3.39) [23,24]. In general, co-infection with SARS-CoV-2 and influenza virus causes more severe disease in vivo than single infection with either virus.

Further experimental studies have confirmed that co-infection can cause more serious inflammation in the nasal cavity and lungs. In a mammalian model involving co-infection with influenza virus and SARS-CoV-2 in ferrets, on the basis of detection of respiratory and lung tissue related pathological indicators, co-infection has been found to induce significantly more severe inflammation than either influenza or SARS-CoV-2 infection alone [25]. Bao et al. have found that co-infection prolongs the duration of clinical manifestations of COVID-19 and aggravates lung injury [26]. Furthermore, another study has found that influenza virus has a ability to aggravate SARS-CoV-2 infection. Increased SARS-CoV-2 viral load and more severe lung injury have been observed in mice co-infected with influenza virus. However, enhanced infectivity of SARS-CoV-2 has not been observed in other respiratory viruses, possibly because influenza virus enhances the expression of ACE2 [27]. The compounding effects of SARS-CoV-2 and influenza viral infection may be partly explained by both viruses primarily affecting alveolar type II cells (AT2 pneumocytes). Therefore, co-infection with these viruses may exacerbate respiratory epithelial damage.

Co-infection is usually accompanied by viral interference. This phenomenon, in which one virus competitively inhibits the replication of another co-infecting virus, is generally believed to decrease viral virulence, cell death, disease severity and transmissibility [28]. In hamsters, although influenza appears to interfere with SARS-CoV-2 replication, it actually increases disease severity [22]. Viral interference can be mediated by the innate immune interferon response, defective interfering particles, viral proteases and proteins, competition for cellular factors, and RNA interference. However, the induction of the interferon response in simultaneous or sequential influenza infection may also increase the inflammatory cytokine storm associated with SARS-CoV-2 infection [22]. Moreover, the defense against SARS-CoV-2, including decreased production of interferons [29], makes the existence of interference with other viruses uncertain.

In summary, co-infection with SARS-CoV-2 and influenza virus is more likely to occur in people with relatively lower immunity, such as older people and children. Co-infection aggravates injury and increases the severity rate and mortality.

**Mitigating the effects of co-infection**

With the ongoing COVID-19 pandemic and the arrival of seasonal influenza epidemics, early prophylactic measures, including vaccination against SARS-CoV-2 and influenza virus, may help decrease disease burden and improve clinical outcomes. Vaccination may have effects beyond preventing single viral infections: some studies have shown that influenza vaccination is associated with a decrease in the risk of SARS-CoV-2 infection [30]. Preimmunization...
against influenza rather than SARS-CoV-2 can prevent severe disease and mortality [31]. Among people with SARS-CoV-2 during the first wave of the pandemic in England, influenza vaccination was associated with a 15%–24% lower odds of hospitalization or all-cause mortality [32]. A negative correlation ($r = -0.5874, n = 21, P = 0.0051$) has been found between the influenza vaccination rate and deaths caused by COVID-19. A high influenza vaccination rate led to lower mortality due to COVID-19. The percentage of COVID-19 deaths in each region was found to decrease by 0.3450 for each percentage unit of adults older than 65 years old and vaccinated against influenza [33]. In addition, specific antiviral drugs and various vaccines have been developed for the treatment and prevention of influenza, and should help prevent the adverse effects of co-infection.

Studies have indicated that influenza vaccination may offer an additional means of alleviating severe adverse complications of SARS-CoV-2. Treatment and prevention of influenza can mitigate the damage caused by co-infection. Further research should aim to verify these findings in larger more diverse cohorts. The duration from vaccination administration to SARS-CoV-2 acquisition is additionally important.

FUTURE CONSIDERATIONS
Co-infection with viruses may significantly affect morbidity, mortality, and health-service demand. The effects and severity of co-infection with SARS-CoV-2 and influenza virus should be further considered in the upcoming influenza seasons. Although current research and surveillance data show that the co-infection rate is low, populations with immunocompromise and severe symptoms will face higher risk and are a matter of concern. Prevention and control strategies should include influenza and SARS-CoV-2 as well as other respiratory viruses, and measures against influenza can mitigate co-infection, including maximizing uptake of influenza vaccination, timely recognition of influenza virus, and timely use of anti-influenza drugs, particularly in groups at elevated risk of both diseases. Further research and investigation are needed to understand the potential mechanisms underlying any synergistic interactions. Strengthening of surveillance must always be emphasized globally.

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CONFLICTS OF INTEREST
The authors declare no competing interests.

REFERENCES