

Letter to Editor

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The seesaw oscillations of influenza and COVID-19 in China: 2022-2023

Yan Yang, Lina Geng, Lirong Huang, Chenli Ding, Linlin Yu, Zheng Xue✉

Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Corona virus disease 2019 (COVID-19) is one of the worst infectious disease pandemics in the world since the 20th century. On 11 March 2020, the World Health Organization declared that the COVID-19 outbreak constituted a "global pandemic." Finally, it was not until May 2023 that the global emergency was declared over. Initially, non-drug interventions by countries, such as restricting inter-regional movement, reducing gatherings, and wearing masks, were effective in slowing the spread of COVID-19, while also decreasing influenza activity. In the winter of 2020 and spring of 2021, influenza activity was almost silent in many parts of the world and China, noting that before the spread of COVID-19, there were about 1 billion influenza cases and 290000 to 650000 deaths due to influenza globally every year[1] and there were about 3 million influenza cases annually and an average of 88000 deaths from influenza in China[2]. However, after the downgrade of epidemic prevention and control measures in the second half of 2022 in China, influenza and COVID-19 showed an alternating epidemic trend as shown in Figure 1, which we call the "seesaw effect".

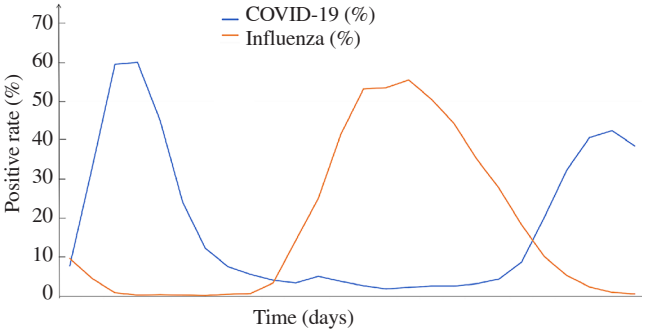

Figure 1. Comparison of COVID-19 and influenza positive rates between December 5, 2022 and June 4, 2023. (The data were from Chinese Center for Disease Control and Prevention. Epidemic situation of COVID infection in China. (https://www.chinacdc.cn/)

1. Vaccination and herd immunity are the most effective interventions for controlling infectious diseases

Cohen *et al.*[3] put forward the concept of "immune debt". Immunization debt during COVID-19 increases susceptibility to influenza and reduces immunity levels. When non-drug interventions are reduced or eliminated, the number of COVID-19 infections peaks at the end of December and the population temporarily gains memory immunity, but then the memory immunity of naturally infected people to the pathogen gradually weakens and antibody levels decline, leading to a decline in herd immunity levels. As of the end of December 2022, the coverage rate of the COVID-19 vaccine in China has exceeded 90 percent, but its effectiveness is being challenged as SARS-CoV-2 variants continue to emerge. The study found that after two doses of vaccine, the effectiveness of the vaccine against SARS-CoV-2 infection in all age groups decreased[4]. In the context of COVID-19, more and more Chinese residents are willing to get flu vaccine, but its coverage is still much lower than that of high-income countries[5]. Vaccine effectiveness can be greatly compromised by production cycles and mutants caused by antigenic drift, with effective protective antibodies typically maintained in the body for 6-12 months, depending on how well the seed strain matches the current circulating strain[6]. After entering the influenza

✉To whom correspondence may be addressed. E-mail: xuezheng@shutcm.edu.cn

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epidemic season, the time, target, location, and medical resources of the influenza vaccine and COVID-19 vaccine overlap, requiring overall coordination. Researchers are currently working on a "two-in-one" vaccine to address this challenge.

2. Virus interference may be the potential cause of the seesaw effect

The concept of "viral interference" was proposed as early as 1804, in which one viral infection can inhibit the replication of another virus. This phenomenon is likely to be the same between COVID-19 and influenza[7]. SARS-CoV-2 and influenza A viruses (IAV) enter cells through different receptors but have similar modes of transmission, susceptible populations, and clinical manifestations. The two may compete for biological resources and biological processes to inhibit replication of each other, such as competing for the same receptor cells-alveolar epithelial Type Ⅱ cells (AT2), stimulating the same antibody response-such as the NGVEGF/NGVKGF antibody response, the same signaling pathway-Raf/MEK/ERK signaling pathway, the same pathogen-associated molecular pattern recognition-Retinoid inductor gene Ⅰ (RIG-Ⅰ), Toll-like receptor 3 (TLR3) and NLR family pyrin domain 3 (NLRP3)[8].

The interferon response is the most widespread and direct innate immune response during viral infection and plays an important role in COVID-19 and influenza. In the cytokine storm of COVID-19 and pandemic influenza, several cytokines were upregulated, such as those with antiviral properties (IFN-α, IFN-β), inflammation (TNF-α, IL-12, IL-22), regulation (IL-10), chemical attractants (CXCL8, CCL4, CCL5, CXCL9, CXCL10), and angiogenic growth factors (FGF, PDGF, PDGF)

There may also be metabolite competition between the two viruses. The presence of a "lung-gut axis" allows the microbiota to interact between the respiratory tract and the intestine tract[9]. Metabolites associated with microorganisms also play an important role in immunity. It was found that the functional diversity of the microbial community was reduced in COVID-19/influenza patients[10].

3. Practical significance of virus interference

Both SARS-CoV-2 and IAV belong to the RNA virus family, which has a high mutation rate and severe drug resistance, and traditional vaccines and drug treatments are easily challenged. Although the current epidemic wave has ended currently, it is of great practical significance to study the causes, sum up experience, and develop broad-spectrum antiviral drugs and vaccines using viral interference mechanisms to deal with future infectious disease threats. In the future, we can: 1) Study further to explore the interaction mechanism between the homology of COVID-19 and influenza in immunopathology. 2) Promote the development of broad-spectrum antiviral drugs for better prevention and control of the disease. 3) Select appropriate adjuvants according to receptors, factors, enzymes, *etc*., and develop effective universal vaccines to enhance the breadth and amplitude of antibody response caused by vaccination. 4) Strengthen disease surveillance and early warning system by appropriate allocation of resources to better prevent and respond to infectious disease threats.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

YY drafted the manuscript and analyzed the data; LNG, LRH CLD, LLY preliminarily searched and organized literature; ZX designed and supervised the project.

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