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INFLUENZA ISSUE

Editorial

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Cover Image: This is a traditional Chinese door decoration. The important purpose is to fight off influenza and COVID-19 with new technologies.

Editorial

China CDC Weekly's Second Meeting of the Editorial Board, Advisory Committee, and Editorial Office to Celebrate the Second Anniversary of the Inaugural Issue

China CDC Weekly Editorial Office[1]

November 29, 2021 marked the second anniversary of the founding of *China CDC Weekly*. Editor-in-Chief George F. Gao, also Director-General of China CDC, organized a meeting with the *Weekly*'s Editorial Board and Advisory Committee in the multifunction hall of the first floor of the main building in the North Campus of China CDC. In-person and online attendance reached almost 100 participants, including members of the Editorial Board, Advisory Committee, special representatives, CDC department heads, members of the *Weekly*'s Editorial Office.

At the meeting, the Editorial Office first introduced the progress of the *Weekly* up to its second anniversary. Overall, 105 issues were published as scheduled, including 56 public health special issues and 533 total articles. The *Weekly*'s academic quality has been recognized internationally as its full-text has been included in two authoritative databases: the Web of Science's Emerging Sources Citation Index (ESCI) and PubMed Central (PMC). The ESCI's data have also shown that the *Weekly* has a total citation frequency of 2,776. The *Weekly* has also become the second national public health bulletin weekly journal to be included in PMC after the US CDC's *Morbidity and Mortality Weekly Report* (MMWR). All articles and text can be searched via Google Scholar and Google Search, and 237 countries/territories/regions worldwide have recorded visits to the *Weekly*'s website; users from the US have always ranked first in number of page views. Once an article is published, it is widely reprinted and reported by both domestic and foreign media, and the *Weekly* has become highlight influential and an authoritative source of public health information. The *Weekly*'s inaugural issue immediately preceded the emergence of the coronavirus disease 2019 (COVID-19) pandemic. Based on the principles of openness, transparency, and responsible release of information, the *Weekly* has edited and published more than 100 new COVID-19 articles and consolidated them into 20 special issues, promptly conveying the latest findings and practices of China's pandemic response to the international community.

Professor Liming Li, Professor Gabriel Leung, and Professor Zijian Feng, the Deputy Editors-in-Chief of the Editorial Board, as well as Dr. Fujie Xu, the special representative of the Gates Foundation's Beijing Representative Office, also a member of the Editorial Board, gave speeches to fully reaffirm the *Weekly*'s practice of editing, calling for submissions, and continuous publication to reach first-class international journal benchmarks. They further provided opinions and suggestions on the development of the *Weekly*'s continued influence in the post-pandemic era. Members in attendance in person or online spoke highly of the *Weekly*'s academic achievements in the past two years, actively made suggestions for future calls for submissions, and had great expectations and confidence in the *Weekly*'s growth into a world-class journal.

Finally, Deputy Director-General of China CDC Jianjun Liu, the Vice-Director of the Advisory Committee, gave a speech expressing that the Advisory Committee will perform its duties in continuing to watch for and pay attention to the development of the *Weekly*. Editor-in-Chief Gao made closing remarks and put forward specific requirements for the next steps for the *Weekly*. The first is to closely follow the standards and rules of running a scientific journal and for the relevant members of the Editorial Board to continue to fulfill their responsibilities. The second is to remain problem-solution oriented, publish research articles, and contribute knowledge to China and the global community. The third is to report every domestic public health incident in a timely manner to become a world-connected scientific platform. Finally, Editor-in-Chief Gao thanked the members of the Advisory Committee and Editorial Board for their in-depth participation and thanked the various departments of

China CDC, the *Weekly*'s Editorial Office, all authors, and all peer review experts for their continued support.

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Methods and Applications

The Incoming Influenza Season — China, the United Kingdom, and the United States, 2021–2022

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ABSTRACT

Introduction: Seasonal influenza activity has declined globally since the widespread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission. There has been scarce information to understand the future dynamics of influenza — and under different hypothesis on relaxation of non-pharmaceutical interventions (NPIs) in particular — after the disruptions to seasonal patterns.

Methods: We collected data from public sources in China, the United Kingdom, and the United States, and forecasted the influenza dynamics in the incoming 2021–2022 season under different NPIs. We considered Northern China and Southern China separately, due to the sharp difference in the patterns of seasonal influenza. For the United Kingdom, data were collected for England only.

Results: Compared to the epidemics in 2017–2019, longer and blunter influenza outbreaks could occur should NPIs be fully lifted, with percent positivity varying from 10.5 to 18.6 in the studying regions. The rebounds would be smaller if the mask-wearing intervention continued or the international mobility stayed low, but sharper if the mask-wearing intervention was lifted in the middle of influenza season. Further, influenza activity could stay low under a much less stringent mask-wearing intervention coordinated with influenza vaccination.

Conclusions: The results added to our understandings of future influenza dynamics after the global decline during the coronavirus disease 2019 (COVID-19) pandemic. In light of the uncertainty on the incoming circulation strains and the relatively low negative impacts of mask wearing on society, our findings suggested that wearing mask could be considered as an accompanying mitigation measure in influenza prevention and control, especially for seasons after long periods of low-exposure to influenza viruses.

Seasonal influenza activity declines globally during the coronavirus disease 2019 (COVID-19) pandemic (*1–4*). For instance, in China, influenza activity, as measured by percentage of submitted specimens testing positive, dropped from 11.8% to 2.0% in 2020–2021 influenza season, compared to the past 5 years (*5*). The long-period of low-exposure to influenza viruses adds great uncertainty on preparedness for the incoming 2021–2022 influenza season. Influenza vaccination is one of the most effective measures in seasonal influenza prevention and control, but with only a few influenza viruses circulating, it could be difficult to determine the targeted strains for vaccination.

In this context, it is of primary importance to identify alternative mitigation measures for the incoming 2021–2022 influenza season, the first season after long periods of virtually no influenza outbreaks worldwide. Using data from China, the United Kingdom, and the United States, we forecasted the influenza activity in the incoming 2021–2022 influenza season under hypothetical scenarios without non-pharmaceutical interventions (NPIs) and with different assumptions on mask-wearing and mobility levels.

METHODS

Our approach relied on the long-term surveillance of influenza activity, measured as weekly percent positivity, long-term mobility changes, the widespread implementation of mobility mitigations and mask-wearing interventions during the COVID-19 period. We noted that the change of international mobility during the COVID-19 period could capture international travel mitigation; the change of domestic mobility patterns during the COVID-19 period closely coincided with mobility related to NPIs and may have reflected several highly correlated mobility related NPIs including domestic movement restriction and physical distancing.

The virological surveillance data in 2011–2021 were obtained from the corresponding government surveillance systems: National Influenza Surveillance Network in China, Respiratory DataMart System in Public Health England, and the United States (US) CDC.The National Influenza Surveillance Network system monitors influenza viruses circulating in China and consists of 554 sentinel hospitals and 407 network laboratories located in over 300 cities in mainland China. The Respiratory DataMart System serves for systematically monitoring influenza and other respiratory viruses circulating in England, with weekly viral test results reported from 14 laboratories representing all nine regions of England. Surveillance of influenza virus in the U.S. is monitored through the U.S. influenza surveillance system and collated by CDC and over 400 public health and clinical laboratories located throughout all 50 states, Puerto Rico, Guam, and the District of Columbia.We considered Northern China and Southern China separately, due to the sharp difference in the patterns of seasonal influenza. For the United Kingdom, since only virological data in England were collected, we considered England only.

International mobility was measured by inbound travel. Inbound travel in 2011–2021 in Northern China and Southern China was represented by the monthly inbound travel in Shanghai released by the Shanghai Bureau of Statistics. Inbound travel data in England and the US were collected from the Department for Transport and US Department of Transportation, respectively. We estimated the weekly international mobility using the moving average within the past 2–4 weeks to account for the delay between mobility changes and laboratory testing and reporting. The domestic mobility was estimated by relying on human mobility data and public transportation statistics. Weekly domestic mobility in Northern China and Southern China in 2019–2021 was estimated by aggregating the daily relative inflow data collected from Gaode Map API; the inflow data in 2019–2020 were further projected into the year 2011–2018. Weekly domestic mobility in England was estimated from monthly released domestic transportation data from Office for National Statistics in the United Kingdom using the same moving average method as above; in the US, it was estimated using the monthly domestic transportation data from US Department of Transportation.

The mask-wearing intervention in China was imposed starting from Week 4 of 2020 until Week 28 of 2021; in England, the mask regulation was in place from Week 30 of 2020 until Week 28 of 2021, according to the Health Protection Regulations 2020. For these countries, we denoted the mask-wearing index with 1 during the implementation period and 0 otherwise. Since the US state governments did not simultaneously comply with the order imposed by US CDC, we estimate the degree of mask-wearing indexes in the US as a proportion of the number of states that imposed the mask-wearing order during the period of US CDC mask-wearing recommendation (i.e., Week 14 of 2020 until the last week of the study, which was Week 28 of 2021). Theses indexes were further adjusted with COVID-19 vaccination coverage, the percentage of daily administered doses in the total population, to estimate the weekly mask-wearing interventions.

To forecast influenza activity under different NPIs, we explored a self-correcting regularized multiple regression. The approach used time series data to predict future points in the series and has been widely used to forecast influenza activity (*6–7*). Unlike the conventional autoregressive integrated moving average method, it allowed for self-selection of multiple lags of past observations as model inputs. As such, it was capable of automatically incorporating the seasonality and stationarity in influenza epidemics as well as changes in other time-serial inputs (e.g., mobility levels and mask-wearing interventions).

Two self-correcting regularized multiple regression models were dynamically trained and regularized with the least absolute shrinkage and selection operator (LASSO) method. First, a linear combination of multiple lags of influenza activity, the current weekly domestic mobility, and the current weekly international mobility was used to fit the weekly percent positivity under the mobility change only. Second, we fitted the observed influenza percent positivity under combined NPIs using the current weekly mask-wearing intervention as well as the predicted influenza activity under the mobility mitigation alone. A separate model was fitted for each of the four regions. The fitted models were then projected into the 2021–2022 season to forecast the influenza activity under different NPIs.

In the analysis, we assumed that there was no substantial difference in climate conditions, sociodemographic features, influenza transmissibility as well as influenza vaccination coverages in 2020–2021 compared with the previous years. We also assumed that the impacts of these external factors in influenza were consistent and could be captured by past influenza activity. We further considered alternative assumptions on the NPIs, including differential assumptions on timing of mask-wearing, magnitude of mobility mitigation, intensity of mask-wearing, and coordination of mask-wearing with vaccination. The model was implemented in scikit-learn 0.24.2 with Python (version 3.6.13, Python Software Foundation, Fredericksburg, VA, US).

RESULTS

Under the scenario without COVID-19 mitigation measures, we predicted that influenza percent positivity would be 18.6 [95% confidence interval (CI): 13.1, 24.2] and 16.9 (95% CI: 12.7, 21.6) for Northern China and Southern China, and 10.5 (95% CI: 6.4, 14.1) and 13.4 (95% CI: 9.3, 17.4) for England and the US, respectively. In Southern China, the rebound could continue until the summer with a secondary peak, a pattern more similar to that in the years before 2018 than in recent years (Figure 1B).

Influenza activity was projected to stay at a low level with percent positivity below 10.0 if the mask-wearing could continue throughout the 2021–2022 season. Late-season rebounds were observed in Southern China if the mask intervention were relaxed. For all regions, if the intervention were relaxed in the mid of influenza season, a sharper rebound could occur

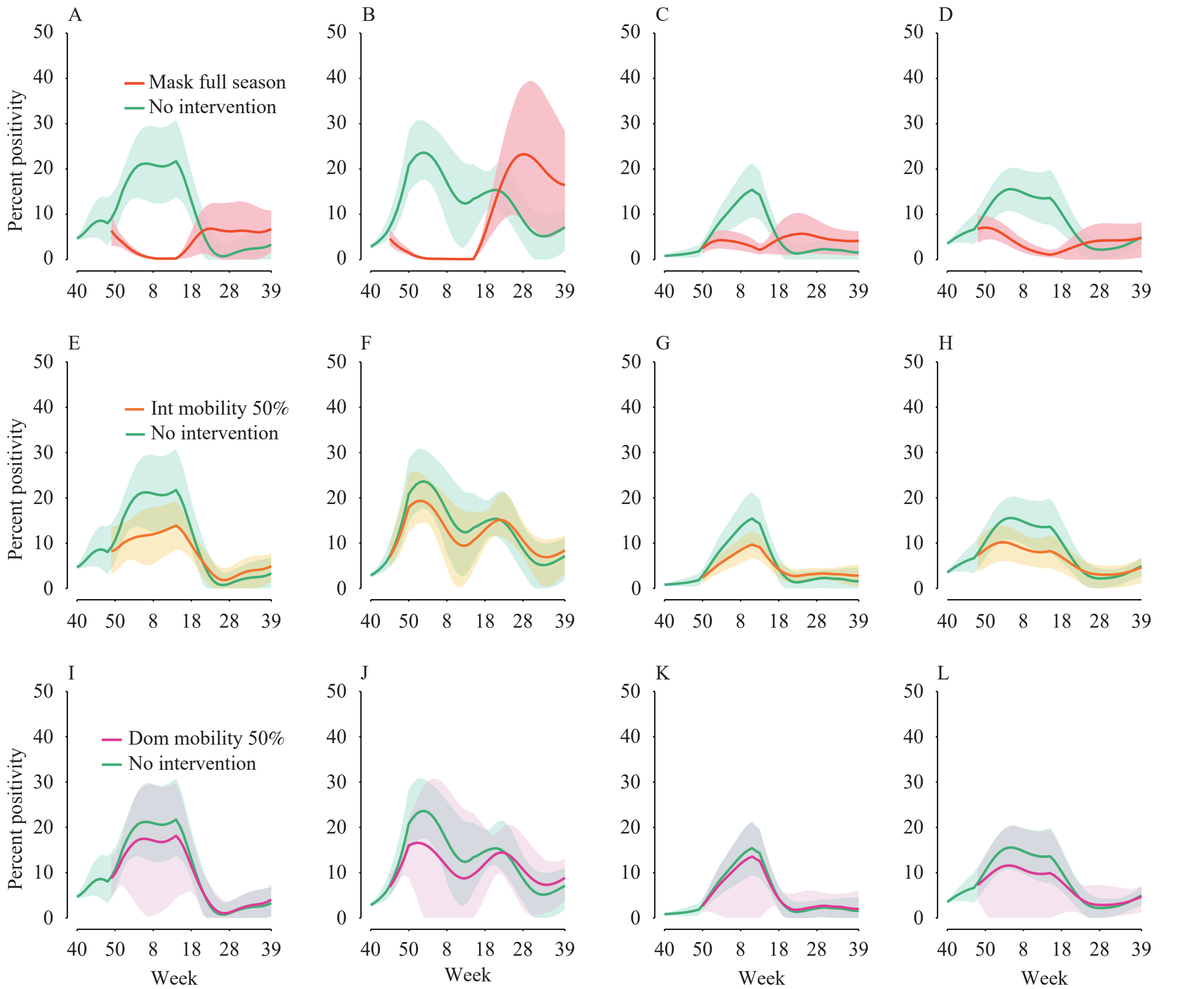

FIGURE 1. Predicted influenza activities in 2021–2022 season under no NPI and varying NPIs. Weekly percent positivity under mask-wearing intervention for (A) Northern China, (B) Southern China, (C) England and (D) the US. Weekly percent positivity under international mobility mitigation being reduced by 50% for (E) Northern China, (F) Southern China, (G) England and (H) the US. Weekly percent positivity under domestic mobility mitigation being reduced by 50% for (I) Northern China, (J) Southern China, (K) England and (L) the US. Shaded area refer to 95% CI.
Abbreviations: NPIs=non pharmaceutical interventions; CI=confidence intervals.

(Figure 2). When implemented in the full 2021–2022 season, mask-wearing alone could reduce 7.0–16.8 influenza activity in the four regions (Table 1).

Our projected estimates for the mask-wearing intervention relied on the actual acceptance of mask-wearing measures during the COVID-19 period. Should a mask-wearing measure with a magnitude 70% less than that during the COVID-19 period be implemented, the incoming winter could still have a modestly large influenza outbreak (Figure 3E–H). Nevertheless, when coordinated with an appropriate vaccination program, a much less stringent mask-wearing measure was capable of keeping the influenza activity at low levels. For example, if an extra of 20% population were vaccinated with influenza vaccines [considering 60% efficacy at all age groups (*8*)] before the influenza season starts, a winter mask-wearing intervention with only 30% magnitude of that in the COVID-19 period for about two months, was able to reduce influenza activity to low levels (Figure 3I–L).

Finally, the rebound would also be smaller if international mobility mitigation measures continued only, but the decline depended on the magnitude of the mitigation as well as the past seasonal patterns.

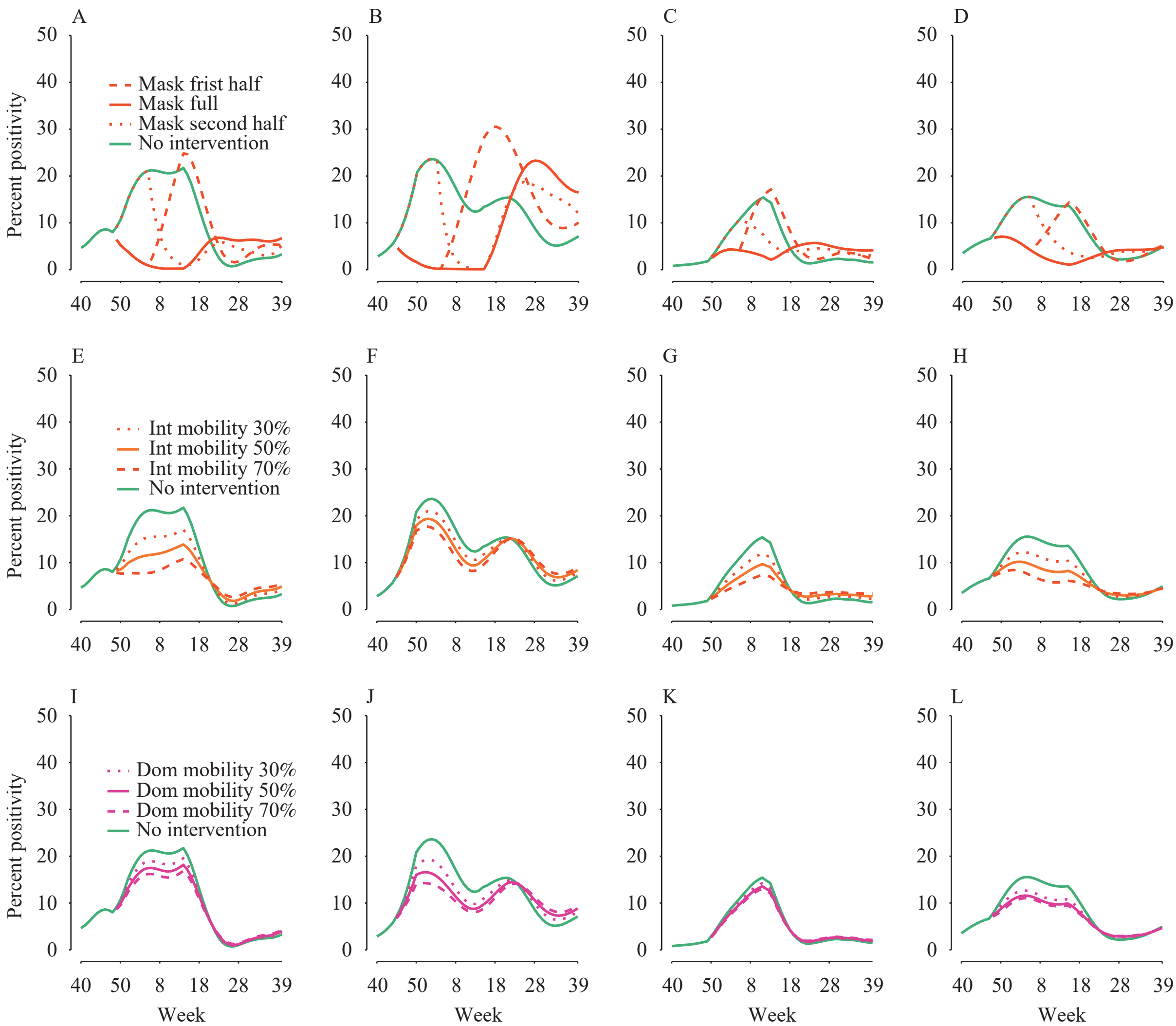

FIGURE 2. Predicted influenza activities in 2021–2022 season under NPIs with alternative assumptions. Weekly percent positivity under no interventions and three timings of mask-wearing intervention, implemented during the full influenza season, the first half of the season the second half of the season, for (A) Northern China, (B) Southern China, (C) England and (D) the US. Weekly percent positivity under international mobility mitigation measures, assuming the international mobility reduced by 30%, 50% or 70%, for (E) Northern China, (F) Southern China, (G) England and (H) the US.
Note: Weekly percent positivity under domestic mobility mitigation measures, assuming domestic mobility reduced by 30%, 50% or 70%, for (A) Northern China, (B) Southern China, (C) England and (D) the US.
Abbreviation: NPIs=non pharmaceutical interventions.

TABLE 1. Predicted reductions on percent positivity under alternative NPIs (relative to no NPIs) in 2021–2022 season.

NPIs	Northern China		Southern China		England		United States	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Mask-wearing alone	16.8	(11.5, 22.2)	15.9	(11.8, 20.6)	7.0	(4.2, 9.5)	9.3	(6.2, 12.4)
International mobility alone (Reduced by 50%)	7.2	(3.8, 10.7)	3.2	(1.0, 5.4)	3.7	(1.5, 5.7)	4.6	(1.9, 7.3)
Domestic mobility alone (Reduced by 50%)	3.0	(−2.6, 11.9)	4.7	(−4.2, 12.9)	1.2	(0, 8.9)	3.3	(0, 14.1)

Abbreviation: NPIs=non pharmaceutical interventions.

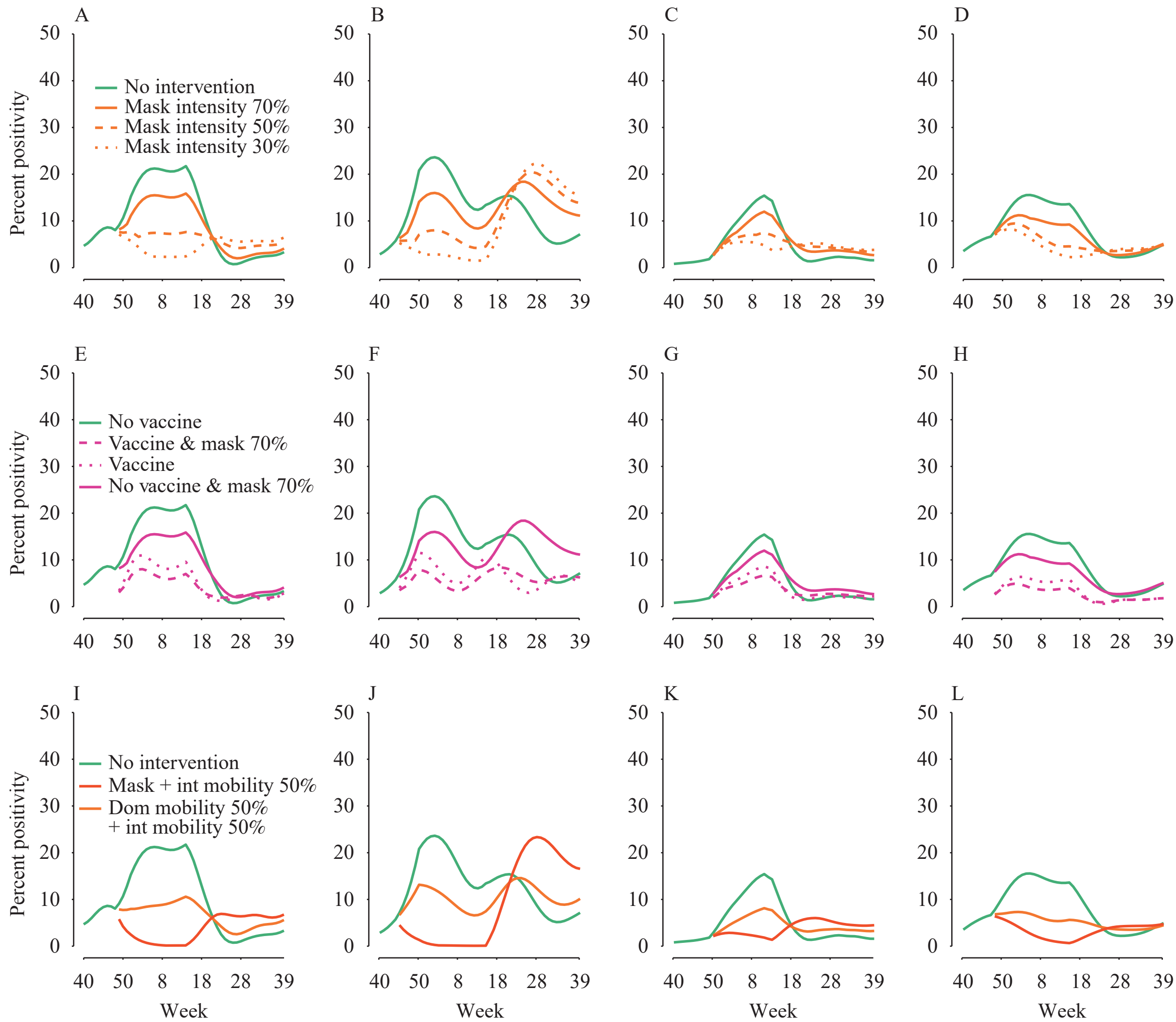

FIGURE 3. Predicted influenza activities in 2021–2022 season under alternative mask-wearing interventions and combined NPIs. Weekly percent positivity under no intervention and the differential magnitude of mask-wearing intervention, for (A) Northern China, (B) Southern China, (C) England and (D) the US. Weekly percent positivity under alternative scenarios considering a mask-wearing intervention with intensity 70% less than (i.e., 30% of) that during the COVID-19 period coordinated with a vaccination program where an extra 20% population vaccinated at 60% vaccine efficacy, for (E) Northern China, (F) Southern China, (G) England and (H) the US. Weekly percent positivity under combined NPIs, mask-wearing and 50% reduction on international mobility as well as 50% reduction on both domestic and international mobility for (I) Northern China, (J) Southern China, (K) England and (L) the US.
Abbreviations: NPIs=non pharmaceutical interventions; COVID-19=coronavirus disease 2019.

Only in regions with the influenza profile exhibiting a single winter-peak outbreak, e.g., Northern China, England, and the US, and with mobility reduced by 50% or higher from normal levels, influenza activity could be deflected substantially (Figures 1 and 2). As expected, simultaneously mitigating both international mobility and domestic mobility could flatten the influenza activity (Figure 3I–L). We estimated that reducing 50% of the international mobility, relative to normal mobility prior to the COVID-19 pandemic, could reduce 3.2–7.2 positivity in the 4 study regions. Domestic mobility mitigation was likely to have a smaller impact than international mobility except in Southern China, where reducing domestic mobility during the influenza season by half could maintain influenza activity at markedly lower levels (Figure 1J and Figure 2). We estimated that reducing 50% of the domestic mobility could reduce 4.7 (95% CI: –4.2, 12.9) influenza activity in Southern China and 1.2–3.3 in the other three regions (Table 1).

DISCUSSION

Influenza activity in the 4 regions was projected to rebound in the incoming 2021–2022 season and the season could be longer and blunter compared to the recent influenza epidemics in 2017–2019, if all the current community mitigation measures are eased. Similar rebounds have been found in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) circulation when the NPIs were lifted (*9*). Notably, the pattern of influenza activity in Southern China would be more similar to that before the year 2018 than that in the recent years, i.e., having a secondary summer peak. Given these new findings, it is important to plan for a longer influenza circulation season this winter and spring.

This study identified sharp rebounds after lifting the mask-wearing intervention in the middle of influenza season. Our findings support the relevance of immunity debt where low viral exposure may spur a growing proportions of susceptible people due to a lack of immune stimulation (*10*). However, we also found that the long period of low exposure to influenza virus — i.e., the plummeting of influenza throughout the year 2020, instead could induce a blunter 2021–2022 season as compared to recent epidemics in 2017–2019 in all 4 regions. The difference could be due to the short duration of protective immunity against influenza virus (*8*,*11*) or the naturally small susceptible population in interannual seasons, where in either case the size of susceptible population in the long term is only loosely related to the infection history. Further work is needed to better understand how the immunity debt varies at the timing and period of low exposure to influenza virus.

The study was subject to some limitations. First, the change of domestic mobility patterns during the COVID-19 period closely coincided with several domestic mobility related NPIs, our analysis on domestic mobility thus cannot further distinguish the highly correlated mobility-related NPIs such as movement restriction and physical distancing. Second, our estimated effectiveness of the mask-wearing order may depend on the type of mask in use (*12*), and the presence of other personal protection behaviour (e.g., hand hygiene and respiratory etiquette), a detailed knowledge of these NPIs could help to depict a more complete picture of the dynamics of influenza under different NPIs. Finally, the analysis for the United Kingdom was limited to England.

Our results are highly timely in this context where there is a high uncertainty on the upcoming strains, due to the long period of low-exposure to influenza viruses; and with respect to the high interannual variation in circulating strains and subtypes as well as the complication of antigenic immunity changes in response to vaccines (*13*–*14*), our findings could also have a far-reaching impact for preventing influenza pandemics. Vaccination is one of the most effective measures in influenza control. Identifying and developing universal vaccines, as well as increasing the vaccination capacity (*15*) are of primary importance after influenza's long-term disruptions to seasonal patterns. However, as the influenza season is approaching and a large part of a population has not been protected by vaccines, there is an increasing call for coordinated mitigation measures. We found that wearing mask for a short period could be highly beneficial in reducing influenza transmission in these contexts. In light of the relatively low negative impacts on society, in the future, mask-wearing could be implemented during influenza epidemics to reduce transmission, particularly in populations at highest risk for developing severe disease or complications or when targeted vaccines are not available.

Conflicts of interest: The authors declared no competing interests.

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Perspectives

Quo Vadis Influenza?

Gabriele Neumann[1,#]; Yoshihiro Kawaoka[1,2,3,#]

ABSTRACT

The number of influenza virus detections declined tremendously after the emergence and worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); an effect most likely caused by non-pharmaceutical interventions to slow the spread of SARS-CoV-2. Recent data suggest that influenza virus detection has slightly increased in parts of the world, perhaps owing to the relaxation of social distancing measures.

Influenza A viruses of the H1N1 and H3N2 subtypes and influenza B viruses of the Yamagata and Victoria lineages cause annual epidemics in human populations with spikes in circulation during the winter months in the Northern and Southern hemispheres, and year-round circulation in tropical and subtropical climates.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel coronavirus that emerged in December 2019 and spread so rapidly around the world that the World Health Organization (WHO) declared a pandemic on March 11, 2020 (*1*). As of November 23, 2021, more than 258 million cases of SARS-CoV-2 had been reported with more than 5.1 million fatalities (*2*).

With the rapid spread of SARS-CoV-2 around the world, the rate of influenza virus detection declined dramatically (*3–6*). WHO Influenza Update No. 376 (*7*) reported that of 145,068 specimens tested from August 17 to 30, 2020, only 34 were positive for influenza virus (0.02%). During a similar time period in 2019, 4,097 of 57,132 specimens (i.e., 7.2%) were positive for influenza viruses (*8*). Similarly, of 200,863 specimens tested from December 21, 2020 through January 3, 2021, only 409 were positive (0.2%) (*9*) while between December 23, 2019 and January 5, 2020, 44,847 of 174,604 specimens were positive (25.7%) (*10*).

Several hypotheses have been proposed to explain the substantial decline in influenza virus detection rates. First and foremost, non-pharmaceutical intervention strategies including social distancing; travel restrictions; closure of schools, universities, and many public and commercial offices; mask wearing; and improved hand hygiene may have curbed the spread of influenza viruses. In addition, viral interference, whereby innate immune responses to a viral infection can affect infection by a second virus (*11–14*) have been discussed as a potential mechanism that might explain the low rates of influenza virus circulation in human populations during the SARS-CoV-2 pandemic. However, several studies have demonstrated that influenza viruses can replicate in animals or cells co- or sequentially infected with SARS-CoV-2 (*15–17*), suggesting that viral interference may not be the major reason for the low influenza virus detection rate during the SARS-CoV-2 pandemic. Interestingly, the decline in detection rates differs among human respiratory viruses. Human coronaviruses, parainfluenza viruses, human metapneumoviruses, respiratory syncytial virus, and adenoviruses have all been detected at very low rates since the outbreak of the SARS-CoV-2 pandemic, whereas rhinoviruses have been detected more frequently (*4–5,18*), perhaps because of their lower sensitivity to alcohol and detergents compared to other enveloped human respiratory viruses. These findings lead to interesting questions about the similarities and differences among human respiratory viruses regarding their transmission mode and the most effective mitigation strategies.

Many of the influenza viruses isolated in 2020 and 2021 originate from the (sub)tropical regions of the world, where the year-round circulation of influenza viruses (believed to be a consequence of climate and behavioral factors) may have supported low-level influenza virus transmission in communities during the SARS-CoV-2 pandemic. Approaching the influenza virus season in the Northern hemisphere, combined with less restrictive non-pharmaceutical interventions in parts of the world due to increasing SARS-CoV-2 vaccination rates, it will be interesting to see whether influenza viruses make a comeback as major human respiratory pathogens. The latest WHO Influenza Update (*19*) showed that of 307,999 specimens tested worldwide, 2,199 were positive for influenza viruses, resulting in a detection rate of 0.7%. While this worldwide detection rate is still much lower than prior to the SARS-CoV-2 pandemic, it may suggest increasing influenza virus activity compared to 2020. In particular, parts of Asia (including India and Nepal) have recently experienced increased influenza activity with the number of influenza virus-positive specimens reaching about 50% of the numbers reported before the pandemic (Figure 1); moreover, China has experienced low levels of B/Victoria virus circulation in 2021 (Figure 1).

The massive reduction in the number of circulating human influenza viruses likely created a substantial genetic bottleneck. In fact, the influenza A and B viruses isolated in 2020 and 2021 fall into a limited number of (sub)clades, while other (sub)clades have virtually disappeared, although viruses of these (sub)clades may still be circulating at low levels. Most noticeably, influenza B viruses of the Yamagata lineage have been detected at very low levels; for example, of 1,176 influenza B viruses reported in the last WHO Influenza Update (*19*), only one belonged to the

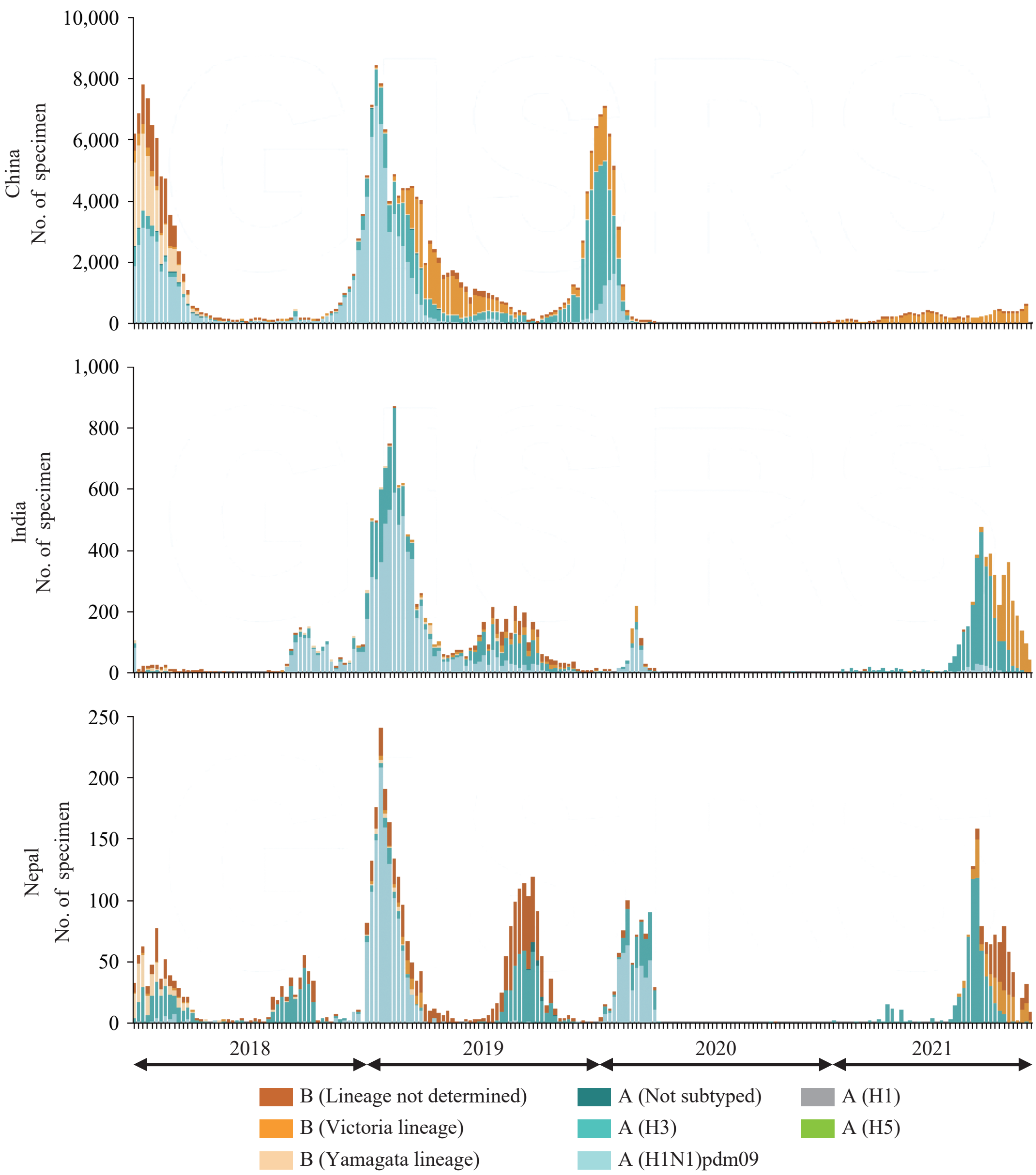

FIGURE 1. Number of influenza virus-positive samples since 2018 in China, India, and Nepal. Figure generated from (*20*).

Yamagata lineage. Currently, it is not clear why certain influenza virus (sub)lineages have declined more than others during the SARS-CoV-2 pandemic. Several factors including population immunity, viral fitness, and the extent of non- pharmaceutical interventions in the areas of virus circulation may have contributed.

In summary, we are currently experiencing an extraordinary event in human influenza virus epidemiology and evolution during which the virus has experienced extreme pressure that may result in major genetic bottlenecks that could shape influenza virus evolution for years to come. With the expected comeback of human influenza virus infections in the ensuing years, which may be fueled by a waning of immune responses in previously exposed people and an increasing number of infants and toddlers who are naïve to influenza viruses, much can be learned about the evolution and spread of influenza viruses in humans.

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Perspectives

GISAID's Role in Pandemic Response

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GISAID is a global data science initiative and the primary source of genomic and associated metadata of all influenza viruses, Respiratory Syncytial Virus (RSV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pandemic coronavirus causing coronavirus disease 2019 (COVID-19). GISAID's publicly accessible data sharing platform enables collaboration of over 42,000 participating researchers from 198 nations and data generators from over 3,500 institutions across the globe. Since the first whole-genome sequences were made available by China CDC through GISAID on January 10, 2020, over 5 million genetic sequences of SARS-CoV-2 from 194 countries and territories have been made publicly available through GISAID's EpiCoV database as of November 9, 2021. This high-quality, curated data enabled the rapid development of diagnostic and prophylactic measures against SARS-CoV-2 including the first diagnostic tests and the first vaccines to combat COVID-19 as well as continuous monitoring of emerging variants in near real-time.

GISAID'S MISSION AND BACKGROUND

GISAID was launched in 2008 with the support of many governments and in partnership with public health and scientific institutions, including the Chinese Academy of Sciences, to respond to an increased reluctance of countries, and scientists around the world, to share their data during disease outbreaks in a timely manner.

Access to the latest genomic data for the highly pathogenic avian influenza (H5N1) was limited, in part due to the hesitancy by WHO Member States to share their virus genomes. In addition, the scientific community's reticence to share data pre-publication (fear of being scooped) delayed sharing. Public-domain archives offer no protection of data providers' interests, nor provide transparency on the use of data as the access and use of data take place anonymously. This limits the incentive to share data voluntarily.

By introducing a new data sharing mechanism, that recognizes the contributions and interests of data providers and users alike, GISAID successfully overcomes the reluctance for data sharing by providing an option to share data with the public. GISAID's sharing mechanism incentivizes and encourages data generators to make their data publicly accessible by guaranteeing that researchers using the data will acknowledge the contributions of, and make efforts to collaborate with, data generators.

The GISAID Initiative is an independent, non-profit, public-private partnership that involves various governments with contributions from Brazil, China, France, Germany, Senegal, Singapore, the United Kingdom, and the United States. Furthermore, GISAID receives grants from the WHO and public donors, including the Rockefeller Foundation in addition to donations from private philanthropy. GISAID is an essential asset for the Global Influenza Surveillance and Response System (GISRS) and for post-regulatory quality control of manufacturer seed viruses relative to candidate vaccine viruses.

SARS-CoV-2 DATA SHARING THROUGH GISAID

Not long after a previously unknown human coronavirus was detected in late 2019 in patients in the City of Wuhan, who suffered from respiratory illnesses including atypical pneumonia (Pneumonia of unknown Etiology, PUE), the human coronavirus disease, later named COVID-19, was identified as a newly emerging viral respiratory disease (*1*). Researchers at China CDC looked to GISAID for its expertise to facilitate the rapid sharing of the first whole genome sequences of the earliest collected samples, thus setting in motion an unparalleled global response. GISAID has gained much experience during previous, significant outbreaks, including the 2009 swine influenza pandemic (H1N1) and the 2013 avian influenza outbreak (H7N9) in China (*2*–*3*). Building over its extensive expertise in influenza data sharing and its extensive collaboration network, GISAID was well positioned to respond to what amounted for GISAID as "Disease X." Thanks to GISAID's longstanding partnership with China CDC, the global scientific community was able to access whole genomes within 48 hours following the identification of the pathogen. Since then, the world continues to witness an unprecedented increase in data submissions to GISAID's EpiCoV database. The World Health Organization's (WHO's) Chief Scientist called GISAID a "game-changer" (*4*). This high-quality, curated initial set of genomes enabled the rapid development of diagnostic and prophylactic measures against SARS-CoV-2 including the first diagnostic tests (*5*) and the first vaccines (*6*) to combat COVID-19.

SALIENT FEATURES OF GISAID

Data contributors rely on sharing their genomic data via GISAID because all submitted data are reviewed and curated in real-time and annotated by a global team of curators (*7*), prior to release. These curated data are enhanced with computed results and delivered downstream for analyses by countless public health and research institutions, via customized data feeds using an Application Programming Interface (API).

GISAID is known for high-quality data standards and being a driver for innovative technology. GISAID facilitates high-throughput submissions by employing Command Line Interface technology (CLI) and API interconnectivity enabling downstream analysis for public health surveillance as well as research and development. GISAID also collaborates with developers and manufacturers of vaccines and therapeutics to facilitate the collection of viral genetic sequence and metadata from clinical trial specimens.

SARS-CoV-2 DATA ANALYSES THROUGH GISAID

GISAID enables real-time monitoring of SARS-CoV-2 genomic data. The submission tracker provides country-wise submission statistics (Figure 1A). Tracking the distribution of emerging variants like the Variant of Concern (VOC) Delta (B.1.617.2 and AY lineages) across the globe along with estimation of country-wise prevalence (Figure 1B) are made possible via GISAID. Other variants that could become relevant are also monitored for signs of increased spread estimated primarily by change in number of locations and other critical factors. A global phylogenetic tree comprising of all high-quality sequences is available to all GISAID users (Figure 1C). The CoVsurver tool performs sequence alignments and annotations highlighting phenotypically or epidemiologically interesting candidate amino acid changes (Figure 1D) along with 3D structural mapping. GISAID's high throughput data sharing provisions enable numerous web applications to facilitate near real-time mutation analysis and genomic epidemiology. GISAID issues analysis updates twice a week that provide comprehensive analyses including time course of variant distribution and receptor binding surveillance to ensure that decision makers are well-informed of the emerging trends in viral spread.

OTHER PRIORITY PATHOGENS

Since its handling of the COVID-19 pandemic, GISAID is considered uniquely positioned to follow the call by WHO Member States and public health authorities to make available its data sharing mechanism to other pathogens. These calls are likely to result in GISAID to host other priority pathogens on its platform, i.e., those with the potential of a significant global outbreak and part of the WHO R&D Blueprint. GISAID may also make its sharing mechanism available to provide access to existing data repositories that are currently not accessible to the public. GISAID's EpiFlu database was launched in May 2008, its EpiCoV database in January 2020 and its EpiRSV database in June 2021.

GISAID continues to adhere to high quality standards and offers a trusted framework for sharing data.

GISAID Core Curation Team: Yi Hong Chew, Meera Makheja, Priscila Born, Gabriela Calegario, Constanza Schiavina, Sofia Romano, Juan Finello, Ya Ni Xu, Suma Tiruvayipati, Shilpa Yadahalli, Lina Wang, Xiaofeng Wei, Mikhail Bakaev, and Motharasan Manogaran.

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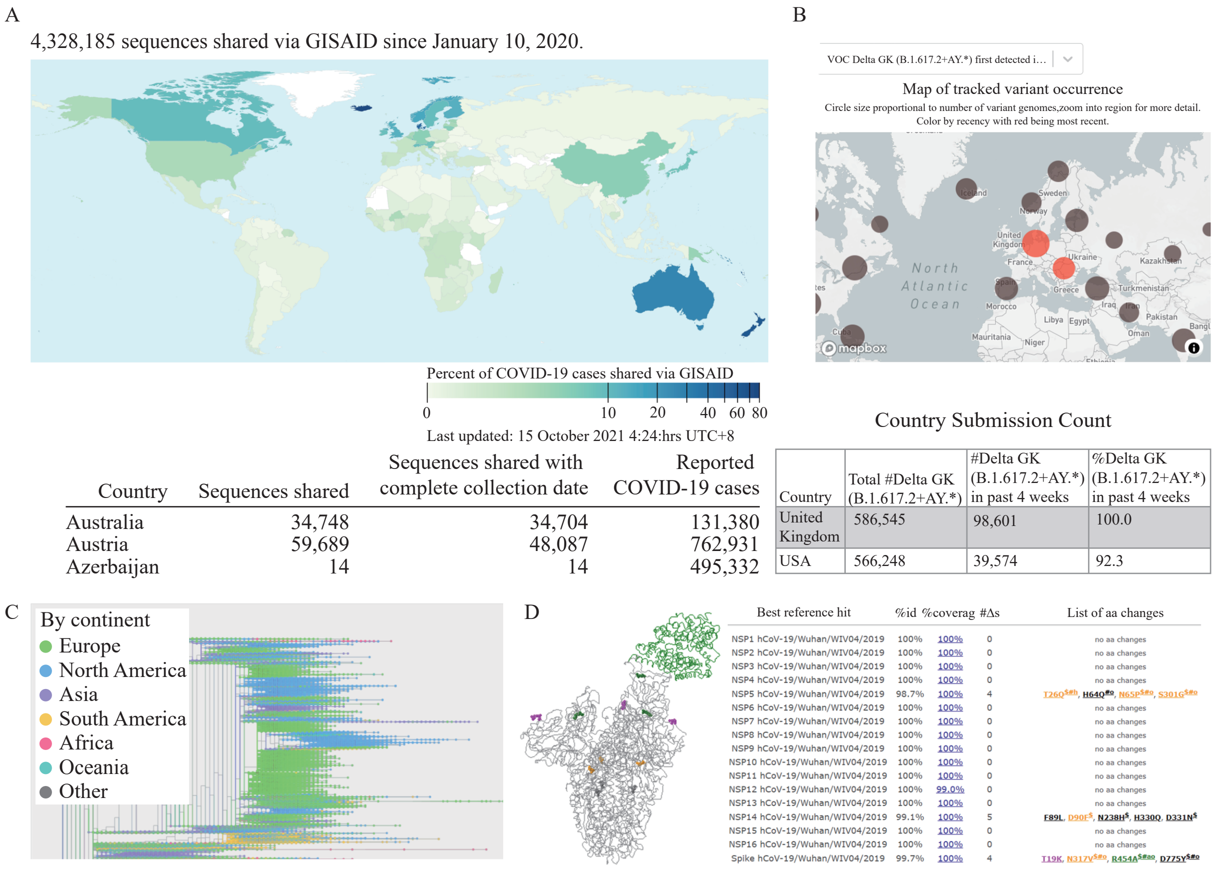

FIGURE 1. Real-time monitoring SARS-CoV-2 genomic data. (A) Submission tracker (source: https://www.gisaid.org/index.php?id=208); (B) Global distribution and country-wise submission statistics of tracked variants, e.g., VOC Delta (source: https://www.gisaid.org/hcov19-variants/); (C) Global phylogenetic tree comprising of all high-quality sequences (source: https://www.epicov.org/epi3/cfrontend#19688e); (D) Monitoring of nucleotide and amino acid variations and 3D structural mapping (source: https://www.gisaid.org/epiflu-applications/covsurver-mutations-app/).
Abbreviations: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; VOC=variant of concern.

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Perspectives

A Tale of Two Cities: From Influenza HxNy to SARS-CoV-z

William J. Liu[1,#]; Shelan Liu[2,3,#]

THE COMMON FEATURES OF VIRUSES WITH PANDEMIC POTENTIAL

In the past hundred years, human population expansion and globalization have changed the pattern of human-nature interactions and accelerated the emergence and spread of novel infectious diseases (*1*). Humans have experienced a long list of microbial threats to health, of which, 70% are believed to be from animal reservoirs (*2*), such as severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and avian influenza A (H7N9) viruses, etc., emerging in 2002–2003, 2012, and 2013, respectively (*3*). Among the microbial threats, pandemic-causing viruses have profound and far-reaching impacts on public health, the economy, and society. Pandemics in the past century were mainly caused by influenza viruses: 1918 H1N1, 1957 H2N2, 1968 H3N2, and 2009 H1N1, defined by World Health Organization (WHO), together with the re-emergence of H1N1 influenza virus in 1977 (*4*–*5*). At the end of 2019, coronavirus disease 2019 (COVID-19) with human coronavirus-19 (hCoV-19, also termed SARS-CoV-2 by International Committee on Taxonomy of Viruses) as the causative agent, emerged and became the largest and most devastating pandemic in the new century (*6*). Currently, the world is still in the midst of this coronavirus pandemic. As two pandemic-risk viruses both transmitting through respiratory tracts, it raises concerns on how SARS-CoV-2 and influenza viruses themselves, and the relevant public health measures and scientific researches influence each other.

SARS-CoV-2 and influenza viruses have many common characteristics which may correlate with the driving force of pandemics. The respiratory tract as the transmission route enables the disease to spread globally in a short time. The considerable number of latent or asymptomatic infections and mild cases brings difficulty to the control of the diseases (*7*). Emerging viral variants present alarming characteristics, including increased transmissibility and infectivity, alternative drug resistance, and immune escape. The wide range of animal hosts for the influenza viruses and the recently-discovered diverse susceptible animals of SARS-CoV-2 provides potentials for reemergence, though the animal reservoir of SARS-CoV-2 has not been confirmed (*8*). Thus, these common features of the two viruses imply that knowledge can be shared in the control of them.

THE PREPARENESS FOR FLU PANDEMIC BENEFITS THE COVID-19 RESPONSES

Looking back on the hundred-year history of humans fighting against influenza, most experience of responding to the pandemic comes from this process. At the very beginning of the COVID-19 pandemics, plenty of experts on influenza took on the mission and applied the experience derived from prevention, control, and research on influenza to COVID-19. The Chinese National Influenza Center undertook most of the hCoV-19 (previous name of SARS-CoV-2) genome sequencing work in the National Institute for Viral Disease Control and Prevention of China CDC (*9*). Since its launch, the Global Initiative on Sharing All Influenza Data (GISAID) played an essential role in the sharing of data from influenza viruses. After initial deposition of the hCoV-19 whole genome sequences by China CDC, authorities and researchers looked to GISAID for its expertise in facilitating rapid sharing of trusted data (*9*). Currently, more than five million hCoV-19 genome sequences have been shared on GISAID since January 2020 and are helping the scientists study the new virus (*10*), together with other SARS-CoV-2 databases, such as RCoV19 from the China National Center for Bioinformation (*11*). Thus, the accumulated experiences, techniques, and human resources from influenza pandemic preparation have played an important role in the responses to COVID-19 pandemic (*12*). Interestingly, the in-depth and extensive researches on COVID-19 by a large number of scientists gathered in a short period of time have also promoted our understanding of influenza viruses and improved the prevention and response capacity. New vaccines and drugs, such as mRNA vaccine and monoclonal antibody drugs, are quickly being developed and used with emergency authorizations (*13*). Nucleic acid testing is becoming widely accepted (*14*), and traceability of the new virus has received unprecedented attention not only from the scientific community (*15*). The evidence of the introduction and spread of SARS-CoV-2 through cold chain also brings into reconsideration of the seasonal features of influenza viruses (*16*).

THE SITUATIONS AND REASONS OF IMPACT OF COVID-19 ON THE FLU EPIDEMIC

Since the emerging of COVID-19, influenza activity in different countries plunged in early 2020 and stayed at lower levels than expected during the 2020–2021 season (*17–18*). In China, influenza-like illness (ILI) activity across the country was significantly lower in 2020 compared to 2015–2019 (Figure 1). Furthermore, the influenza positive rate in 2021 has remained below the national epidemic threshold (15.5%) as of Week 43, although the overall weekly ILI rate and influenza positive rate since Week 13 of 2021 was slightly higher than the rate during the same period in 2020 (Figure 1). Public health interventions against COVID-19 decreased influenza activity directly. With similar routes of transmission, the mitigation methods used to prevent COVID-19 transmission also reduced influenza transmission (*19*). Hygiene habits of the public, including mask wearing, hand washing, and proper ventilation, have been broadly advocated. Other non-pharmaceutical interventions (NPIs) for COVID-19 also restricted the transmission of influenza, e.g., canceling of mass gatherings, closing public entertainment venues and schools, restricting domestic and international travel, issuing stay-at-home orders, and active and passive quarantine of cases with febrile respiratory syndrome. However, the reported SARS-CoV-2 and influenza virus co-infections indicated that SARS-CoV-2 itself does not repel the influenza virus in the host and no cross-immunity between the two viruses exits (*20–21*).

THE CHALLENGES OF CO-CIRCULATION OF FLU AND COVID-19 IN THE SECOND HALF

During the second half of the war against COVID-19, the influenza activities will become complicated and difficult to predict. Key challenges are posed to the prevention and control of the two viruses (*22*). First, some countries no longer consider COVID-19 a social critical disease and have lifted their social restrictions. The NPIs will be relaxed incrementally, which is expected to result in higher influenza infection over the following flu season. Second, the low circulation of the influenza virus in recent seasons challenges the prediction of potential prevalent influenza viruses from the currently limited genetic variants, which increases the likelihood of influenza vaccine mismatch. Third, similar to the emerging of the new variants of SARS-CoV-2 with higher transmission capacity and changed antigenicity, the new genetic variants of influenza viruses may also erupt under a selective pressure of current NPIs against COVID-19. Fourth, global population immunity to influenza will have decreased with very low levels of influenza activity in the recent seasons. Fifth, the shifting of medical personnel and resources in favour of COVID-19 in some countries and regions will continuously impact the capacity of health services to respond to a potential influenza pandemic (*23*). Furthermore, a potential co-circulation of other respiratory viruses, including respiratory syncytial virus, will make the situation more complicated in the future seasons (*24*).

PERSPECTIVES AND SUGGESTIONS

Facing the complicated situation of co-circulation of SARS-CoV-2 and influenza viruses together with other respiratory pathogens, comprehensive prevention and control strategies are needed. First, it is important to enhance the WHO's Global Influenza Surveillance and Response System to monitor the respiratory viruses (*25*). Effective continuous surveillance of any new variants is key for providing early warnings. The epidemic model based on the new circumstances remolded by the diseases will provide new insights into the regularity and give useful references for the strategies. Second, active NPIs are still an economic tool to control the spread and to decrease the impact of an influenza endemic. The relaxation of NPIs with the increasing coverage of SARS-CoV-2 vaccination in some countries should be gradually stepped up and fully assessed for risks. Third, rapid differential diagnosis of COVID-19, influenza, and other respiratory pathogens is needed, especially during the winter. It is a good choice to develop rapid dual or multiplex diagnostic tests to distinguish between these two viruses and other respiratory pathogens,

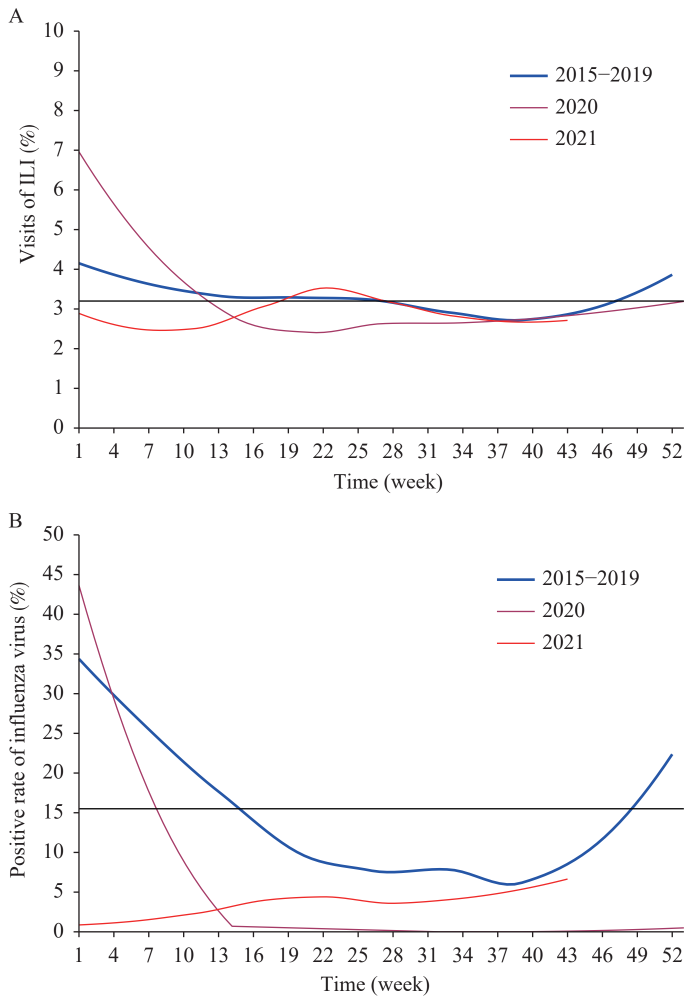

FIGURE 1. Percentage of visits for (A) influenza like illness and (B) influenza virus positivity at sentinel hospitals in overall China, during 2020 and 2021 compared with 2015 to 2019.

Notes: Average weekly percentage of visits for ILI was 3.0% in 2020 compared with the average ILI 3.2% of 2015–2019, with a drop of 6.25% (*P*<0.001); the percentage was further decreased by 10% from the ILI 3.0% in 2020 to ILI 2.7% in 2021 (*P*<0.001). Average weekly positive influenza virus rate decreased by 61.94% (*P*<0.001) from 2015–2019 (15.5%) to 2020 (5.9%), and continuously decreased by 44.07% (*P*<0.001), from 2020 (5.9%) to 2021 (3.3%). 1) All data were collected from Chinese National Influenza Center Weekly Report (http://www.chinaivdc.cn/cnic/zyzx/lgzb/202111/t20211105_252585.htm). 2) R software (R4.0.4 version, R Development Core Team, Auckland, New Zealand) was used to analyze the data and generate the figures. 3) Two proportional tests were used to check the differences in average weekly ILI percentage and influenza virus positivity over the years from 2015 to 2021. 4) Black lines in Panel A and B denoted the national epidemic thresholds during 2015–2019, i.e. 3.26 ILI cases per 100 outpatient visits and the influenza positive rate (15.5%), respectively. 5) The blue line in Panel A indicates the calculated mean values of ILI in each week during 2015–2019. The mean values of ILI= the sum of ILI among 2015–2019/the total visits for ILI at sentinel hospitals among 2015–2019 in overall China by week; 6) The blue line in Figure B indicates the calculated mean influenza virus positivity in each week among 2015–2019. The mean influenza virus positivity = the sum of influenza virus positive samples among 2015–2019/the total samples collected for ILI at sentinel hospitals among 2015–2019 in China overall by week.

Abbreviation: ILI=influenza-like illness.

particularly among front-line healthcare professionals and other populations with high risks for exposure. Early diagnosis will facilitate isolation, management, and treatment of both hospitalized patients and outpatients. Fourth, the average national vaccination coverage for influenza varies greatly across countries. Thus, at the same time as popularizing the COVID-19 vaccines and even its booster, influenza vaccination coverage should also be encouraged. The immunological barrier at the population-level established through vaccination is always a safe and economic pathway to interrupt transmission (*26*). The theme of World Flu Day this year (the 4th) is "Flu and COVID-19: Let's get vaccinated" (*27–28*). Lastly, scientific investigations on these pandemic-risk viruses should also be enhanced. For instance, we should assess the risks of already emergent influenza viruses, such as human-infecting avian influenza A (H5N6) viruses including the transmission, infection, immunogenicity and drug resistance, etc. (*29*). The development of universal vaccines, drugs, and testing reagents will be prepared for future pandemics induced by the viruses from the same family or at least the same genera.

The emergence and re-emergence of diverse subtypes of influenza A viruses, which are known as "HxNy" mediated through the reassortment of viral genomes, together with influenza B viruses will continuously account for future pandemics. Beyond SARS-CoV and current SARS-CoV-2, we are not sure whether there will be a "SARS-CoV-z" in the future. However, with experiences from the responses to influenza and SARS-CoV-2, a series of prevention and mitigation measures, including new diagnosis and surveillance technologies, pharmaceutical measures and NPIs are developed to help preserve and boost the capacity and function of health systems across the world. We can do these better for the next virus!

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