Global variability of influenza activity and virus subtype circulation from 2011 to 2023

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ABSTRACT

Background Although decreased influenza activity has been reported in many countries during the COVID-19 pandemic, it remains unknown how global influenza activity has changed. We described the global variability of influenza activity and virus subtype circulation from 2011 to 2023 to prepare for the potential influenza outbreak with the control of the COVID-19 pandemic.

Methods Influenza virological surveillance data between 2011 and 2023 were obtained from the WHO-FluNet database. We first calculated and compared the influenza activity before and during the COVID-19 pandemic. For countries whose influenza activity has recovered, we also described changes in the duration of influenza epidemics. We then determined the proportion of influenza cases caused by the different influenza virus types.

Results In total, 73 countries with 2.17 million influenza cases were included. In the early stage of the COVID-19 pandemic, decreased influenza activity was observed in all WHO regions. In 2022 and 2023, rebound in influenza activity was observed in all WHO regions, especially in Western Pacific Region. At the same time, a change in the duration of the influenza epidemic was observed in several Southern Hemispheres countries. Moreover, in all WHO regions, few B/Yamagata viruses were detected during the COVID-19 pandemic.

Conclusions Lack of exposure to influenza will diminish population immunity and increase the severity of large epidemics in the future global resurgence. Ongoing monitoring of the changes in the duration of the influenza epidemic and circulation subtypes should be the focus of future work.

INTRODUCTION

Seasonal influenza is a common respiratory infectious disease that circulates in all regions of the world and affects millions of people every year. As reported by the WHO in 2018, influenza respiratory infections are responsible for 654,832 fatalities worldwide. In addition, an influenza pandemic occurs every 10–50 years, nearly all of which have resulted in millions of illnesses and deaths globally. In the latest influenza pandemic (H1N1 pandemic in 2009), deaths associated with influenza were as high as 575,000 worldwide.

Updated knowledge on influenza virus circulation including its types and subtypes is essential in the management of public health and the development of proper prevention and control strategies (such as immunisation programme). Many factors can impact the mode of influenza virus transmission, including the epidemic of other respiratory viruses, air temperature and humidity, and influenza vaccination coverage. It has been shown that COVID-19 and its related non-pharmaceutical interventions (NPIs) could impede the spread of influenza virus. Moreover, changes in virus subtype circulation have also been reported. However, previous studies have been mostly conducted in the early stage of the COVID-19 pandemic for a single country, and it remains unknown how global influenza activity changed after the COVID-19 pandemic occurred for 3 years.

The need for a global perspective on the transmission of influenza viruses has been growing since it contributes to understanding the variability of influenza after many countries have lifted NPIs for COVID-19, and social activities have started to return to prepandemic levels. In addition, latest information of influenza subtype circulation is crucial to optimise the strategy for preventing influenza, preparing for potential influenza
METHODS

Data source

Influenza data were obtained from the FluNet surveillance platform developed and maintained by the WHO, which is a publicly available tool for influenza virological surveillance first launched in 1997. There are three types of surveillance systems, including sentinel surveillance systems, non-sentinel surveillance systems and undefined systems. Influenza data at the country level were updated weekly and reported by six WHO regions. The WHO regions include the African Region (AFR), Region of the Americas (AMR), Eastern Mediterranean Region (EMR), European Region (EUR), South-East Asia Region (SEAR) and Western Pacific Region (WPR).

The Influenza Weekly Report mainly included the number of samples submitted for influenza testing and positive samples for multiple influenza subtypes (A[H1], A[H1N1pdm09], A[H3N2], A[H5], A[H7N9]), A/unsubtyped, B/Victoria, B/Yamagata and B/uncharacterised. Furthermore, the COVID-19 data were obtained from the WHO COVID-19 Dashboard, which presented official daily counts of COVID-19 cases (the number of daily new cases and the cumulative number of cases) and deaths reported by countries, territories and areas.

To explore the changes in influenza activity during the COVID-19 pandemic, the number of newly reported COVID-19 cases was further extracted. Since the surveillance systems are run differently in different countries and could change over time, the number of countries with available data varied among years. Online supplemental table 1 shows the number of countries from different type of surveillance systems included in the FluNet database and from 1997 to March 2023. To exclude the influence of the 2009 H1N1pdm09 pandemic, data from January 2011 to March 2023 were extracted and analysed for this study. In 2022, influenza data from 163 countries were reported, whereas only 124 countries reported their influenza data to the WHO in 2011. For countries with sentinel surveillance data and other surveillance data in the same week, influenza data from sentinel surveillance systems were used. However, for countries without sentinel surveillance data, influenza data from non-sentinel or undefined surveillance systems were extracted to maximise use of all available data. Influenza data from 178 countries with 81,841 surveillance weeks were primary included. Next, to ensure the robustness of the results, only countries with data available for at least 60% of surveillance weeks for each year between 2011 and 2022 were included. Finally, influenza data from 73 countries with 45,620 surveillance weeks were extracted for the analysis, 34% of which were reported from sentinel surveillance systems and 66% from other surveillance systems. Moreover, A[H1], A[H5] and A[H7N9] subtype were very rarely reported, which accounted for around 2 out of 10,000 of total cases in the study database and have been excluded in the final analysis.

Definitions

Influenza activity was defined as the per cent of samples submitted for influenza testing that yielded positive results, which was widely used in previous studies. In addition, from the website: https://www.latlong.net/, we extracted the geographical coordinates of each country (latitude and longitude). All countries were divided into Northern Hemisphere countries (centroid lying north of the Tropic of Cancer, latitude 23°27′N), Southern Hemisphere countries (centroid lying south of the Tropic of Capricorn, latitude 23°27′S) and tropical regions (centroid lying between the two tropics) according to latitude. For Northern Hemisphere countries, influenza season was defined as the calendar year (from week 1 to week 52 or 53). However, for countries situated in the Southern Hemisphere and tropical regions, influenza season was grouped from week 27 of the year through week 26 of its next year according to the previous literature.

The average annual percentage (AAP) technique, which was derived using a three-step procedure as reported in prior research, was used to determine the length of each influenza epidemic. Initially, we calculated the AAP for each month using the following formula:

$$AAP_i = \frac{n_i}{\sum_{i=1}^{n} n_i} \times 100\%$$

where i stands for the month and n for the quantity of cases. Second, the monthly AAP rankings were performed in reverse. Finally, the duration of epidemics was determined by using the first n months, which accounted for 75% of the AAP.

Statistical analysis

We conducted a descriptive analysis of influenza surveillance data by subtype for six WHO regions between 2011 and 2023. The changes in influenza activity and the number of newly reported COVID-19 cases across the globe were first plotted by six WHO regions. To demonstrate the changes in influenza activity worldwide, we then generated a heatmap of the median influenza activity by influenza season and country. According to the previous literature, countries with fewer than 50 influenza cases in a given season were excluded from this analysis of that season to enhance robustness to the study results. We also plotted monthly AAP between the 2011–2012 and 2021–2022 influenza seasons by latitude. Moreover, we calculated the percentage of each influenza subtype between 2011 and 2022 for six WHO regions to visualise its change over time. Furthermore, in addition to the mixed surveillance data, we conducted the sensitivity analysis using sentinel data (from sentinel surveillance systems) and non-sentinel data (from non-sentinel and undefined surveillance systems).
systems), respectively. All statistical analyses and graph generation were conducted in Python software, V.3.9 (Python Software Foundation) and Rstudio V.4.1.0 (RStudio Team).

Patient and public involvement
Our study was conducted using deidentified data. There was no direct interaction with any individual participant, and therefore, members of the public were not involved in study design, recruitment or conduct of the study.

RESULTS
Changes in influenza activity from 2011 to 2023
In total, 73 countries (24 in EUR, 21 in AMR, 10 in AFR, 9 in WPR, 5 in SEAR and 4 in EMR) with 2.17 million influenza cases were available for this analysis. Online supplemental figure 1 shows the influenza activity from 2011 and 2019 by six WHO regions. Distinct seasonal variation in influenza activity was observed in WPR, EUR and AMR. Much more variability emerged among SEAR, EMR and AFR. Figure 1 shows the influenza activity and number of new-onset cases of COVID-19 between 2020 and 2023 by six WHO regions. In 2020, decreased influenza activity was observed in all WHO regions. Among these, a decrease in influenza activity was first observed in WPR, where COVID-19 cases were first reported. In 2021, influenza activity remained continuously low (<10%) in EUR and AMR, where the weekly new-onset cases of COVID-19 were relatively high during this period. However, increased influenza activity (>10%) has been observed in WPR, EMR and AFR, where the weekly new-onset cases of COVID-19 were relatively low. In 2022, there was an increase in influenza activity in six WHO regions, but still lower than that levels before the COVID-19 pandemic. Of note, in WPR, the number of new-onset cases of COVID-19 rose rapidly by the end of 2022 and dropped to extremely low levels in January 2023. Then, a significant increase in influenza activity (>45%) in WPR was observed in March 2023, which was higher than that from 2011 to 2019.

Figure 1  Influenza activity from January 2020 to March 2023 by six WHO regions. The red line represents the influenza activity, and the bar graphs indicate the number of new cases of COVID-19. The new confirmed COVID-19 cases for China in December 2022 were also reported from WHO COVID-19 Dashboard.
Changes in median influenza activity from 2011 to 2023

Figure 2 shows the median influenza activity from 2011 to 2023 by influenza season, country and WHO region. Between 2011–2012 and 2018–2019 influenza seasons, influenza activity varied across countries. Influenza activity>30% was mainly observed in EUR and AMR, whereas in SEAR and WPR, influenza activity<20% was mainly observed. However, in 2020–2021 influenza season, there was large variability in influenza activity compared with earlier influenza seasons for many countries. But in 2021–2022 and 2022–2023 influenza seasons, influenza activity in many countries has returned to levels that observed between 2011–2012 and 2018–2019 influenza seasons, including Canada, the USA and China.

Duration of influenza epidemics from 2011 to 2023

Online supplemental figure 2 shows the duration of the influenza epidemic for 73 countries before and during the COVID-19 pandemic by latitude. Before the COVID-19 pandemic, the duration of the influenza epidemic in Northern Hemisphere countries was focused from January through March, whereas in Southern Hemisphere countries, it was focused from May through August. During the COVID-19 pandemic, however, variability in the duration of the influenza epidemic became larger for Southern Hemisphere countries. Figure 3 shows the duration of the influenza epidemic for countries in the Southern Hemisphere countries.
Hemisphere by influenza season. We found an advanced in time of the influenza epidemic in the 2020–2021 influenza season in Argentina, Australia, South Africa and Uruguay. However, in the 2021–2022 influenza season, it has been observed that the time of the influenza epidemic in South Africa was delayed. In the latest influenza season, the duration of the influenza epidemic in South Africa was from May through September, which was consistent with that before the COVID-19 pandemic.

**Global distribution of influenza virus subtypes from 2011 to 2023**

Figure 4 shows the percentage of each influenza subtype from 2011 through 2023. Between 2011 and 2019, influenza A were dominant in all WHO regions and often alternated between A(H1N1)pdm09 and A(H3N2). The proportion of B/Yamagata and B/Victoria viruses remained low from 2011 to 2019. In all WHO regions except for WPR, influenza A were also dominant during the COVID-19 pandemic, but the majority of samples detected were positive for A(H3N2). In AMR, about 98% and 90% of the samples detected in 2021 and 2022 were positive for A(H3N2), respectively. In WPR, B/Victoria viruses dominated in 2021, accounting for 90% of the total positive samples. However, in 2022 and 2023, influenza A were dominant again in WPR. Furthermore, few B/Yamagata viruses were detected during the COVID-19 pandemic. Online supplemental table 2 shows the distribution of influenza B/Yamagata virus between 2011 and 2023 by six WHO regions. From 2011 to 2019, the majority of B/Yamagata influenza cases were collected in WPR and AMR. Since 2020, there has been a marked decline in the number of B/Yamagata viruses. In 2020, 295 cases were reported to be positive for B/Yamagata viruses across the globe and 74.9% (221/295) of specimens were collected in AMR. Only 39 cases were reported to be positive for B/Yamagata viruses across the globe and 82.1% (32/39) of specimens were collected in WPR in 2021. In 2022, no specimens were reported for influenza B/Yamagata viruses across the globe. However, there have been four specimens reported for B/Yamagata viruses in AMR as of March 2023.

**Sensitivity analysis**

Based on sentinel surveillance systems, influenza data in 20 countries were available from 2013 to 2023, all of which were located in EUR. Online supplemental figure 3 shows the influenza activity and number of new-onset cases of COVID-19 between 2013 and 2023 for 20 countries. Distinct seasonal variation in influenza activity was observed before the COVID-19 pandemic. A first decline and then rising trend in influenza activity was observed during the COVID-19 pandemic. Online supplemental figure 4 shows the median influenza activity from 2013 to 2023 by influenza season for 20 countries. In addition to the 2020–2021 influenza season, influenza activity was maintained above 30% in many countries between 2013 and 2023. Online supplemental figure 5 shows the percentage of each influenza subtype for 20 countries. Between 2013 and 2023, influenza A were always dominant. Furthermore, online supplemental figure 6 shows the results of non-sentinel surveillance data, which were available in 40 countries. There was not an appreciably difference in

the results of mixed surveillance data (derived from sentinel, non-sentinel and undefined surveillance systems), sentinel surveillance data and non-sentinel surveillance data.

**DISCUSSION**

In this study, we describe the pattern of changes in influenza activity and virus subtype circulation from 2011 to 2023 across the globe. Between 2011 and 2019, high influenza activity was mainly observed in some European countries, and influenza A virus (IAV) was dominant in all WHO regions. During the COVID-19 pandemic, however, influenza activity showed a trend of first decline and then rise in all WHO regions, and few B/Yamagata viruses were detected during the COVID-19 pandemic. In addition, several Southern Hemisphere countries showed a different duration of the influenza epidemic than that of 2011–2019. Given the impact of subtype circulation and duration of the epidemic on influenza vaccination programmes, as well as the fact that lack of exposure to influenza will lower population immunity, urgent action is needed to prepare for the potential influenza outbreak with the control of the COVID-19 pandemic.

Although previous studies have reported a decrease in influenza activity during the COVID-19 pandemic, evidence from our study improves the understanding of the negative association of COVID-19 with the transmission of the influenza virus. First, a decrease in influenza activity was first observed in the region where COVID-19 cases were first reported. Second, in 2021, rebound of influenza activity was observed in AFR and EMR, whereas influenza activity remained low in EUR and AMR, which have suffered more severe COVID-19 pandemics. Third, in WPR, a significant increase in influenza activity was observed after COVID-19-related NPIs became less stringent. There were several possible reasons for the negative association between the transmission of influenza and COVID-19. First, both SARS-CoV-2 and influenza viruses are mainly transmitted through droplets and aerosols. Many public health measures implemented for controlling the spread of COVID-19 are also useful to prevent the transmission of influenza viruses, such as...
wearing masks and hand hygiene. A previous meta-analysis indicated that hand hygiene provided a significant protective effect against influenza infection, with an OR of 0.62. Second, the COVID-19 pandemic led to significant changes in social behaviour, such as remote work and limited social interactions. These changes also resulted in reduced opportunities for the transmission of respiratory viruses, including influenza. Third, higher influenza vaccination rates during the COVID-19 pandemic may have also made a significant contribution. Recent data from the USA indicated that influenza vaccination rates increased by 9% during the last quarter of 2020 compared with the same time period in 2018 and 2019.

Important repercussions for public health campaigns regarding influenza vaccination stem from our findings as well. Vaccination timing was one of the most important factors of the assurance of influenza vaccine effectiveness. After receiving the influenza vaccine, it typically takes 2–4 weeks for particular antibodies to manifest, and the protection produced by the vaccine usually lasts for 3–4 months. Before the COVID-19 pandemic, the epidemic peak typically focused on July or August in Southern Hemisphere countries, so the recommended timing of vaccination was usually March and April of each year. Given the changes in the duration of the influenza epidemic in Southern Hemisphere countries during the COVID-19 pandemic and its impact on vaccine effectiveness, temporal dynamics of the influenza epidemic should be the focus of future monitoring. If the changes in the duration of the influenza epidemic persisted for the following influenza seasons, consideration should be given to adjusting the timing of immunisation campaigns for Southern Hemisphere countries.

In addition, vaccine components were also another important factor in the assurance of influenza vaccine effectiveness. Antigenic drift is anticipated to occur, so monitoring the current influenza strains is necessary to determine the ideal vaccine formulation for the upcoming season. This study suggested that large changes occur in the distribution of influenza subtypes during the COVID-19 pandemic, including the stark reduction in global prevalence of B/Yamagata viruses and a temporal increased prevalence of B/Victoria viruses in WPR. Although there were 39 cases reported to be positive for B/Yamagata viruses across the globe in 2021, none of them were verified by any of the WHO Collaborating Centres. The changes in subtype could be interpretable in the following factors. First, from the pathogen’s perspective, influenza B/Victoria viruses tend to undergo faster lineage turnover and antigenic drift than B/Yamagata viruses. This indicated that the suspension of transmission was more likely to be seen in B/Yamagata viruses because they may have an innate vulnerability during evolution. Second, from the route of transmission, B/Yamagata viruses (R0=1.1) have a lower reproductive number than B/Victoria viruses (R0=1.25–1.3). Moreover, from the standpoint of the vulnerable population, children were approximately four times more susceptible to B/Victoria virus infections than adults, whereas adults were more susceptible to the spread of SARS-CoV-2 and more affected by NPIs implemented during the COVID-19 pandemic. This may make B/Yamagata more vulnerable to breakdowns than B/Victoria and SARS-CoV-2 throughout viral dissemination and population expansion. The recommended vaccination strain faces difficulty due to the likely extinction of B/Yamagata viruses. If the extinction of B/Yamagata viruses could be observed over long periods, a trivalent vaccine including two IAV strains and a B/Victoria strain might emerge as the most practical and cost-effective option. This would result in an increase in the number of available doses that could be distributed globally from 500 to 700 million doses. However, due to the potential for B/Yamagata strains to escape global circulation for at least 1–2 seasons and subsequently resurface, the WHO recommended the use of both quadrivalent vaccines (comprising two IAV strains and two influenza B virus strains) and trivalent vaccines for the 2022–2023 influenza season. Consequently, ongoing monitoring of changes in B/Yamagata strains is imperative.

Strengths and limitations
This study included more than 2.17 million influenza cases that reported from 73 countries from 2011 to 2023. To our knowledge, this is the longest time span study exploring the patterns of changes in seasonal influenza activity and virus type/subtype before and after the COVID-19 pandemic. Although the sheer volume of data supports the substantial robustness of our conclusions, there are a few limitations that should be mentioned as well. First, the number of countries with completed data was constrained, since the data collected in this analysis came from surveillance systems, which have operated differently across countries and can also alter over time in the same country. Second, only aggregated data are available in the FluNet database, which restricts the analysis of influenza circulation within different disease states and age groups. Third, a large proportion of countries without completed data are located in Africa, which may lead to the neglect of its changes in influenza activity during the COVID-19 pandemic.

Conclusion
In summary, our data suggest that ongoing monitoring of the changes in the duration of the influenza epidemic and circulation subtypes is urgently needed in order to be prepared for future outbreak. The components and inoculation time of influenza vaccines may need adjustments to the pattern of changes in influenza circulation during the COVID-19 pandemic. Only then can we plan for seasonal influenza circulation and avoid the potential peak of influenza infection followed by the COVID-19 pandemic.

Contributors LZ and YL contributed to the study equally. MZ and JW conceived and designed the study. LZ, YL and JY acquired the data and performed analyses assisted by JW and MZ. LZ and YL drafted the manuscript and all authors critically assisted by JW and MZ. L.
revised. MZ is the guarantor. All authors were responsible for interpretation of data and for approving the final manuscript.

Funding This study was funded by Zhejiang University K. P. Chao’s High Technology Development Foundation (2022R017), Mega-Project of National Science and Technology for the 13th Five-Year Plan of China (2018ZX1071012-003-006, 2018ZX1071013-003-003), the Fundamental Research Funds for the Central Universities (2022SFJHK03, K20210205), Technological Innovation Leading Talents of ‘Ten Thousand Talents Plan’ of Zhejiang Province (2020RS2010), and the National Natural Science Foundation of China (71904170).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data are available at the following URL: https://www.who.int/tools/fluNet.

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