

Received: 2021.09.27

Accepted: 2021.09.28

Available online: 2021.09.29

Published: 2021.10.04

# Editorial: A Decline in Influenza During the COVID-19 Pandemic and the Emergence of Potential Epidemic and Pandemic Influenza Viruses

**Dinah V. Parums, MD PhD**

Science Editor, Medical Science Monitor, International Scientific Information, Inc., Melville, NY, USA

e-mail: [dinah.v.parums@isi-science.com](mailto:dinah.v.parums@isi-science.com)

**Conflict of interest:** None declared

**Abstract** There have been five viral pandemics in the past century, four were due to influenza, and the ongoing COVID-19 pandemic is due to SARS-CoV-2 infection. During the COVID-19 pandemic, there has been a 99% global reduction in the diagnosis of influenza. Also, from 2020, global mortality rates from influenza fell to record levels during the influenza seasons in the southern and northern hemispheres. However, as social restrictions become lifted and the winter season begins in the northern hemisphere, it is expected that influenza will re-emerge. The World Health Organization (WHO) FluNet surveillance platform provides global surveillance data on influenza, and the US Centers for Disease Control and Prevention (CDC) records national weekly infection rates. Both surveillance programs have identified zoonotic avian and swine influenza variants in humans. The WHO Pandemic Influenza Preparedness (PIP) Framework requires WHO Member States to share data on cases of emerging influenza viruses with pandemic potential in a regular and timely way. The WHO PIP Framework organizes the Global Influenza Surveillance and Response System (GISRS), a global network of public health laboratories developing candidate virus vaccines. This Editorial aims to present the reasons for concern regarding the emergence of pandemic influenza viruses driven by the social and public health responses to the COVID-19 pandemic and highlights the importance of global influenza surveillance at this time.

**Keywords:** Editorial • Influenza, Human • Epidemiology • Pandemics • COVID-19 • SARS-CoV-2

Influenza A and B viruses express membrane proteins, hemagglutinin (H) and neuraminidase (N), resulting in human antibody responses [1]. Strains of influenza virus are classified by the core proteins (A, B, or C), the species of origin (mainly avian or swine), and the country or region of initial isolation [1]. Influenza A is classified by the subtypes of hemagglutinin (H) and neuraminidase (N) [1]. Worldwide, influenza A causes annual outbreaks and epidemics during the ‘flu season,’ or occasional pandemics [1]. Outbreaks of influenza B occur every two to four years [1]. There are 16 H virus subtypes in the natural bird reservoir and nine N virus subtypes, but only three hemagglutinin subtypes cause human respiratory infection, H1, H2, and H3 [1]. In the past century, there have been four influenza pandemics [1]. In 1918, the H1N1 pandemic virus originated from an avian strain adapted to infect humans and transmit between humans [1]. Two other pandemics were human–avian strains, H2N2 in 1957 and H3N2 in 1968 [1]. A further pandemic was caused by a quadruple re-assortment of two swine influenza strains, one human strain, and one avian strain, H1N1, in 2009 and 2010 [1]. There are concerns that avian H5N1 influenza could repeat the adaptation in 1918 and cause another influenza pandemic [1,2]. Pigs have a role

in generating pandemic influenza virus strains because their tracheal epithelial cells express receptors for both the avian and human influenza viruses [1,3]. Pigs may promote avian and human viral genetic re-assortment to produce a novel pandemic strain of the influenza virus. [3]. New strains arising from antigenic shift often emerge from Southeast Asia, where the proximity of humans, birds, and pigs may encourage viral re-assortment [1,3]. However, in 2009, pandemic H1N1 influenza was identified in North America, highlighting the importance of global influenza virus surveillance programs [3].

During the COVID-19 pandemic, there has been a 99% reduction in the diagnosis of influenza virus infection [4,5]. From early 2020, during the influenza seasons in the southern and northern hemispheres, global mortality rates from influenza fell to record levels [4,5]. The World Health Organization (WHO) FluNet surveillance platform provides global surveillance data on influenza infections [6]. The US Centers for Disease Control and Prevention (CDC) records national weekly infection rates, including influenza [7,8]. In the US, between October 2020, and July 2021, the CDC reported that out of 1.3 million laboratory tests, there were 2,136 positive test results for the influenza

virus, and 748 reported deaths due to influenza [7,8]. Of the identified cases, 60% were positive for influenza A, and 40% were positive for influenza B [8]. These findings were in dramatic contrast to surveillance data from the 2019-2020 influenza season that reported 38 million cases of influenza and 22,000 deaths due to influenza [7,8].

There is now concern that more than a year of such low reported cases of influenza makes predictions for the coming year uncertain [4,5]. Some epidemiologists predict that the low rates will continue, and others expect a global pandemic of variants of influenza A [4,5]. Social distancing behaviors that began during the COVID-19 pandemic may maintain the low levels of influenza and other respiratory viruses. Social distancing, wearing face masks, hand washing, travel restrictions, and closing schools effectively reduced viral transmission during the COVID-19 pandemic [9]. Despite these public health prevention strategies, SARS-CoV-2 is still spreading, highlighting how more infectious it is than the influenza virus. However, because epidemiological research, health funding, and viral genotyping resources have been redirected to the pandemic caused by SARS-CoV-2 and away from other infectious diseases, emerging variants of influenza may result in a second viral pandemic [10].

Several clinical and epidemiological observations support the possibility of a pandemic of a new influenza variant [4,10]. There is uncertainty regarding how well current influenza vaccines are matched to new circulating influenza virus variants [10]. Where there have been successful vaccination programs for COVID-19, social restrictions and travel restrictions have eased, and children and young adults are returning to schools and universities at a time when the influenza season usually commences [9]. Reduced exposure to more commonly circulating respiratory viruses reduces the levels of population immunity [9,11,12]. As an example, studies from the US, Europe, and Japan have shown that the social restrictions during the COVID-19 pandemic in mid-2020 reduced the levels of respiratory syncytial virus (RSV) infections in children [8,9]. However, RSV infection rates in children rose, and infection duration was prolonged when children returned to school in September 2020 [12].

The efficacy of seasonal influenza vaccines depends on availability, uptake, and immunity to the circulating influenza virus variants [10]. The US CDC Advisory Committee on Immunization Practices (ACIP) recommends combining vaccination for both COVID-19 and influenza, and this approach has been supported in the UK and Europe [13]. The result of these recommendations is an anticipated increase in the manufacture and distribution of influenza vaccines during the 2021-22 influenza season [13].

The development of influenza vaccines requires annual updates because the virus regularly mutates. In February of each year,

the World Health Organization (WHO) recommends vaccines against four main influenza virus variants for the northern hemisphere, based on surveillance data [6]. There are then at least six months required for vaccine development, based on the recommendations of the WHO [6]. If there are low levels of circulating influenza virus, as seen this year, it will be more difficult to predict which strains or variants the 2021-22 influenza vaccines should target. The CDC has estimated that even when infection surveillance has been highly predictive, influenza vaccines only reduce infection in 60% of vaccinated individuals [7]. During 2020 and part of 2021, national and global surveillance of influenza viruses was disrupted by the COVID-19 pandemic. The WHO global influenza surveillance platform, Flu-Net, was initiated in September 2020 and included data from 139 countries, territories, and areas [6]. Despite increased testing, there were few cases identified [6]. Therefore, the WHO recommendations for the 2021-22 northern hemisphere influenza season were based on limited surveillance data [6]. The new influenza virus subtype A(H3N2) was identified to update the vaccines [6].

There have been five viral pandemics in the past century, four were due to influenza, and one ongoing pandemic is caused by SARS-CoV-2 [10]. A pandemic strain of influenza usually replaces the previously identified seasonal variant. As social restrictions become lifted and the winter season begins in the northern hemisphere, it is expected that influenza will re-emerge. Several potential new candidate variants of the influenza virus could result in future pandemic influenza [10]. Influenza A viruses circulate between avian populations (bird 'flu) and mammals (swine 'flu) and are reservoirs for zoonotic transmission to humans [14,15]. In 2020, influenza viruses A(H1N1), A(H3N2), and B/Victoria were identified in France, India, and China [6,15]. These findings are of particular interest because the 1968 influenza pandemic was caused by the influenza A/Hong Kong/1968 (H3N2) virus [10].

In 2021, the WHO global and ongoing assessment of zoonotic influenza virus variants has identified avian influenza A(H5) variants, swine influenza A(H1) variants, and other zoonotic influenza variants [15]. Since May 2021, there have been isolated influenza A(H5N6) virus infections [15]. On February 18, 2021, the Russian Federation notified the WHO of the avian influenza A(H5N8) virus in seven patients [15]. Most reported human cases of avian influenza A(H5) have been associated with contact with poultry [15]. For example, two cases of human infection with influenza A(H9N2) were reported from China on June 9, 2021 [15]. However, on May 27, 2021, the US reported a human case of infection with swine influenza A(H1N2) variant virus [16]. In June, 2021, a case from Taiwan and a case from Canada of influenza A(H1N2) variant virus were also reported [15]. These recent influenza virus variants were all confirmed by using validated genome sequencing methods and reverse transcription-polymerase

chain reaction (RT-PCR) [15]. The WHO Pandemic Influenza Preparedness (PIP) Framework requires WHO Member States to share data on cases of emerging influenza viruses with pandemic potential in a regular and timely way [16]. The WHO PIP also organizes a global network of public health laboratories, the Global Influenza Surveillance and Response System (GISRS), to develop candidate virus vaccines [17].

Although it has not been possible to predict or model the possible scenarios for influenza 2021-22, several scenarios have been proposed [10]. Firstly, seasonal influenza could return with the same variants as in late 2019 [10]. This scenario would be optimal as current vaccines would offer immunological antiviral protection [10]. This scenario cannot be confirmed and may be less likely, because the influenza viruses isolated since April 2020 have been limited [10]. Second, seasonal influenza may return, but some variants disappear, particularly if they do not have large zoonotic reservoirs [10]. The third possible

scenario is that there are only intermittent outbreaks of seasonal influenza [10]. However, this scenario is unlikely because of the return of international travel and because even the best influenza vaccines have limited efficacy [10]. The fourth and most concerning scenario is that this influenza season is associated with the emergence of a new zoonotic influenza strain that could result in another viral pandemic [10].

## Conclusions

During the COVID-19 pandemic of 2020 and 2021, reports of influenza virus infections have dramatically fallen worldwide. As public health and social restrictions are lifted, there are concerns about the emergence of pandemic influenza. The importance of the CDC and WHO global influenza surveillance programs at this time is highlighted by the identification of new influenza viruses ahead of the 2021-22 influenza season.

## References:

1. Stephenson I, Zambon M. The epidemiology of influenza. *Occup Med (Lond)* 2002;52: 241.
2. Hvistendahl M. Avian influenza. Enigmatic bird flu strain races across the U.S. Midwest. *Science* 2015;348:741
3. Guan Y, Poon LL, Cheung CY, et al. H5N1 influenza: A protean pandemic threat. *Proc Natl Acad Sci USA*. 2004;101:8156
4. Olsen SJ, Winn AK, Budd AP, et al. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic – United States, 2020-2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1013
5. Rubin R. Influenza's unprecedented low profile during COVID-19 pandemic leaves experts wondering what this flu season has in store. *JAMA* 2021;326(10):899-900
6. World Health Organization (WHO). FluNet. September 2021. Available at: <https://www.who.int/tools/flunet>
7. Centers for Disease Control and Prevention (CDC). Influenza (Flu). September 2021. Available at: <https://www.cdc.gov/flu/swineflu/index.htm>
8. Centers for Disease Control and Prevention (CDC). Weekly U.S. Influenza Surveillance Report. (FluView). September 2021. Available at: <https://www.cdc.gov/flu/weekly/>
9. Chu DK, Akl EA, Duda S, Solo K, et al.; COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: A systematic review and meta-analysis. *Lancet*. 2020;395(10242):1973-87
10. Laurie KL, Rockman S. Which influenza viruses will emerge following the SARS-CoV-2 pandemic? *Influenza Other Respir Viruses*. 2021;15(5):573-76
11. Di Mattia G, Nenna R, Mancino E, et al. During the COVID-19 pandemic where has respiratory syncytial virus gone? *Pediatr Pulmonol*. 2021;56(10):3106-9
12. Wagatsuma K, Koolhof IS, Shobugawa Y, Saito R. Decreased human respiratory syncytial virus activity during the COVID-19 pandemic in Japan: An ecological time-series analysis. *BMC Infect Dis*. 2021;21(1):734
13. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). 2020-21 Seasonal Influenza Recommendations. September 2021. Available at: <https://www.cdc.gov/vaccines/acip/index.html>
14. Petrova V, Russell C. The evolution of seasonal influenza viruses. *Nat Rev Microbiol*. 2017;16:47-60
15. World Health Organization (WHO). Influenza at the human-animal interface, Summary and assessment, from 24 October to 9 December 2020. Available at: <https://www.who.int/teams/global-influenza-programme/avian-influenza>
16. Gostin LO, Phelan A, Stoto MA, et al. Virus sharing, genetic sequencing, and global health security. *Science*. 2014;345(6202):1295-96
17. Hay AJ, McCauley JW. The WHO global influenza surveillance and response system (GISRS) – a future perspective. *Influenza Other Respir Viruses*. 2018;12(5):551-57