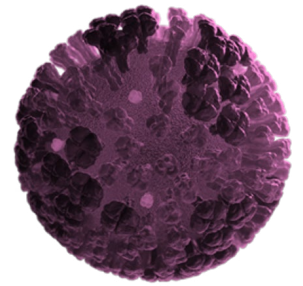




InFluNews



The monthly newsletter from the Global Influenza Initiative (GII)

APRIL 2022 | ISSUE 3

Welcome to the April issue of InFluNews!

The previous issue of InFluNews explored the similarities and differences between influenza and SARS-CoV-2, and described how the emergence of the omicron variant has changed this clinical picture.

If you have missed any of the past issues of InFluNews or would like to find out more about the GI, please visit the [GII LinkedIn page](#).

Human seasonal influenza under COVID-19 and the potential consequences of influenza lineage elimination

This issue of InFluNews summarises key findings from the recent Nature Communications publication by Dhanasekaran *et al.* which considers the short- and long-term implications of COVID-19 control measures on the epidemiology and evolution of seasonal influenza viruses: [Human seasonal influenza under COVID-19 and the potential consequences of influenza lineage elimination](#).¹

Prof. Ben Cowling (University of Hong Kong), one of the paper's authors, is our guest editor this month and provides additional insight into the paper's findings.

Influenza virus image from CDC/Douglas Jordan.

FOCUS THIS MONTH:

Seasonal influenza virus circulation and diversity

What are the effects of the COVID-19 pandemic?

Consequences for the future

How might COVID-19 impact the circulation of influenza virus in the future?

Influenza virus strain circulation before COVID-19

Influenza virus circulation differs in temperate and tropical zones; in temperate zones, influenza viruses have strong seasonal cycles whereas, in tropical zones, influenza circulation is increased in the rainy season, as well as in the cooler, drier months.^{2,3} Seasonal cycles in temperate zones are maintained through continuous reintroduction of influenza viruses from tropical zones and from opposing hemispheres.^{4,5}

Seasonal influenza viruses also evolve on a global scale in order to evade host immunity,⁶ hence the need for surveillance to monitor circulating influenza virus strains, and the requirement to update the seasonal influenza vaccine annually with the aim of providing protection against those strains. The WHO Global Influenza Surveillance and Response System coordinates influenza surveillance, and the results inform seasonal influenza vaccine formulation in the northern and southern hemispheres every year.⁷

Global drop in seasonal influenza cases

The COVID-19 pandemic led to an unprecedented drop in seasonal influenza cases across the world, which was largely attributed to non-pharmaceutical interventions such as travel restrictions, quarantine and social distancing.¹ Although routine influenza testing was disrupted during the early stage of the pandemic, testing and reporting was subsequently restored,⁸⁻¹⁰ therefore, the drop in cases was not simply due to the disruption of testing.

The northern hemisphere recorded a 99.8% drop in influenza cases in May 2020 relative to February 2020 (from a peak of ~50,000 cases per week in February to <100 cases per week in May, remaining below 100 weekly cases until September).¹

In the southern hemisphere, <12 influenza-positive cases per week were reported from May 2020 to July 2021 (from a peak of 1500 and 3500 positive specimens per week in the 2017–2019 seasons).¹

(InFluNews Issue 1, 2021 provides further information on how the COVID-19 pandemic affected influenza circulation).

Reduction in influenza virus diversity

Not only has the COVID-19 pandemic led to a dramatic reduction in seasonal influenza cases, but this in turn has led to a reduction in influenza virus diversity.¹ A comparison of the influenza clades circulating prior to the start of the COVID-19 pandemic in 2019/early 2020 with those that continued to circulate during the pandemic (to mid-2021) showed that certain clades/subclades of virus were no longer being detected. A summary of these findings is shown in the table.¹

The major changes in virus diversity that have occurred since the start of the pandemic (to mid-2021) include:

- No detections of three of eight A(H3N2) subclades since April 2020 (A3, A1b/135K, and A1b/197R)
- No detections of two B/Victoria clades (V1A.1 and V1A.2)
- No confirmed detections of the B/Yamagata lineage between March 2020 to February 2022, as reported by WHO,¹¹ suggesting that B/Yamagata may have been eliminated¹

Comparison of seasonal influenza HA clades circulating before and during the COVID-19 pandemic (from Dhanasekaran *et al.*, 2022)¹

Clades circulating in 2019/early 2020	Clades circulating since COVID-19 emergence to mid-2021
A(H3N2)	
A1b/94N	A1b/94N
A1b/131K	A1b/131K
A1b/197R	–
A1b/186D	A1b/186D
A1b/137F	A1b/137F
A1b/135K	–
A3	–
3c3.A	3c3.A
A(H1N1)	
6b1.A/187A	6b1.A/187A
6b1.A/156K	6b1.A/156K
6b1.A/183P-5a	6b1.A/183P-5a
6b1.A/183P-5b	6b1.A/183P-5b
6b1.A/183P-5	–
6b1.A/183P-6	–
6b1.A/183P-2	–
6b1.A/183P-7	6b1.A/183P-7
6b1.A/183P-1	–
6b1.A	–
6b1	6b1
B/Victoria	
V1A.3/150K	V1A.3/150K
V1A.3/133R	V1A.3/133R
V1A.3	V1A.3
V1A.2	–
V1A.1	–
V1A/165N	V1A/165N
V1A	V1A
B/Yamagata	
172Q	–

Patterns of influenza virus circulation and transmission

In an analysis of virus lineages that originated from viruses circulating during March 2020, most were found to be derived from viruses circulating within the same country, province, or geographical region.¹ These results highlighted the lack of global dissemination of seasonal influenza viruses during the pandemic and revealed smaller regions with high population densities that could independently sustain influenza virus transmission lineages for extended periods.¹ This was evident in West and Central Africa where A(H1N1), A(H3N2), and B/Victoria viruses detected during late 2020 to early 2021 largely circulated.¹

Implications and consequences for influenza virus circulation in the future

The authors speculate that heterogeneity in COVID-19 vaccination rates and control policies will initially slow the global resurgence of influenza and enable spatially separated influenza lineages to become more divergent. Once influenza begins to circulate more widely, the combination of divergent influenza lineages and waning natural immunity could lead to more severe influenza seasons in the future.¹

Garza *et al.* (2022)¹² provide an alternative viewpoint in a recent pre-print. Based on data from 165 adults in the Netherlands, this group estimated that waning of seasonal influenza-specific antibody titres during the first 2 years of the pandemic has been negligible, that limited circulation of influenza viruses has restricted the opportunity for major evolutionary changes, and argued that the sizes of upcoming influenza epidemics could be similar to those observed before the pandemic, because natural immunity to influenza has not been substantially impaired during the pandemic.

The long-term impact of potential B/Yamagata elimination on the evolution of influenza B viruses is uncertain, but Dhanasekaran *et al.* suggest that the extinction of B/Yamagata would leave a higher proportion of individuals susceptible to influenza B viruses, enabling faster B/Victoria antigenic evolution.¹

The authors also warn that apparently extinct influenza virus lineages can still re-emerge in the future to pose a major risk to the population, further highlighting the importance of ongoing influenza surveillance.¹

Importance of vaccination and surveillance

This article highlights the uncertainties and concerns regarding future seasonal influenza circulation and the need for rapid development of vaccines that are able to confer broad protection against influenza viruses, such as universal vaccines.¹

The authors emphasise that, in the immediate future, surveillance remains the key to better understanding and control of influenza virus infections.¹

Indeed, FluNet surveillance data from the WHO show that global influenza activity increased at the end of 2021 and a steep upward trend was again observed in February and March of 2022.¹³ Countries reporting a steep rise in cases throughout March include France, Italy and the Netherlands, and several countries have reported numbers of influenza cases per week (in winter or in March 2022) that are comparable to, or higher than, pre-pandemic levels.¹⁴ The recent rise in influenza activity could alter the course of influenza activity described by Dhanasekaran *et al.* and lead to an increase in genetic diversity.¹⁴ These recent observations further reinforce the need to maintain effective surveillance for both influenza and SARS-CoV-2 to better understand viral circulation and diversity, and inform vaccine strain selection.

Guest editor Ben Cowling comments:

Influenza has returned to many parts of the northern hemisphere in the recent winter, with varying intensities in different parts of the world. While community-wide public health and social measures are gradually being relaxed, personal behavioural changes such as mask-wearing and social distancing are likely to persist to some extent and these behaviours could also reduce influenza transmission in the medium term. Many eyes will now turn to the temperate southern hemisphere as their autumn turns to winter and their influenza seasons begin, and we learn more about the renewed threat posed by influenza in the post-COVID-pandemic era.

GII Summary Statement

Restrictions implemented to prevent the transmission of SARS-CoV-2 have also impacted the global circulation of influenza virus. Dhanasekaran *et al.* have described how this reduced circulation has led to a reduction in influenza diversity and the potential elimination of the B/Yamagata lineage. The authors speculate that the combination of divergent influenza lineages and waning natural immunity could lead to more severe influenza seasons in the future, with the possibility that apparently extinct viral lineages could also re-emerge.

While there are still uncertainties regarding future seasonal influenza circulation, a steep increase in global influenza cases has been observed in February and March of 2022. This further highlights the need for ongoing vigilance around influenza, as well as SARS-CoV-2, and the importance of effective surveillance and prevention through vaccination.

About the GII

The GII is a global expert scientific forum that includes international scientists, researchers and clinicians with expertise in epidemiology, virology, infectious diseases, immunology, health economics, public health, primary care and geriatrics.

The GII receives financial support from Sanofi which covers the involvement of Ogilvy Health, a medical communications agency which acts as the secretariat for the GII as well as coordinating logistics for the annual meeting, managing other GII projects and offering strategic counsel.

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