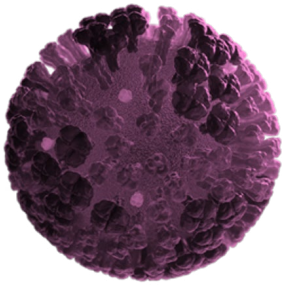
Global Influenza Initiative

InFluNews



The monthly newsletter from the Global Influenza Initiative (GII)

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Welcome to the latest issue of InFluNews, guest edited by Mine Durusu Tanriover, Hacettepe University, Ankara, Turkey.

The previous issue of InFluNews explored advances in influenza vaccine technology, with a focus on novel vaccine platforms and vaccine delivery systems in development.

*If you have missed any of the past issues of InFluNews or would like to find out more about the GII, please visit the **GII LinkedIn page**.*

Comparison of the disease severity and clinical outcomes of influenza and SARS-CoV-2

In this issue, InFluNews looks at comparisons between influenza and COVID-19 and summarises the latest supporting information.

Influenza virus image from CDC/Douglas Jordan.

FOCUS THIS MONTH:

Similarities and differences between influenza and SARS-CoV-2
What are the key differences in disease severity and clinical outcomes?

Emergence of the omicron variant
How has this changed the clinical picture?

Protection against influenza and SARS-CoV-2
Vaccination remains key to prevention

Should influenza and COVID-19 infections be compared?

Since the start of the COVID-19 pandemic, mainstream and medical media have compared and contrasted its characteristics and potential outcomes with influenza infection.[1] In some cases, media reports have suggested that COVID-19 is 'just another flu' in terms of its severity.[2] Although there are some similarities between two disease presentations, attempting to compare the population impact of the two infections may not be the best approach, as COVID-19 is a pandemic (in March 2022), whereas influenza usually occurs as a seasonal epidemic.[3]

Influenza viruses have affected the human population for centuries,[4] initially entering the population as pandemics then settling into seasonal epidemics, whereas SARS-CoV-2 entered a naïve human population in 2020, leading to a worldwide pandemic. Pandemics are expected to impose a higher burden than seasonal epidemics, because the population is naïve and the proportion of susceptible individuals may be higher. While influenza has also been associated with pandemic outbreaks (in 1918, 1957, 1968, 2009),[4] most of the comparisons made have been between seasonal influenza and COVID-19.

Key similarities and differences between influenza and SARS-CoV-2 clinical presentations

The data summarised here were gathered from selected studies and reviews that have compared the clinical characteristics of influenza and COVID-19. The focus of this section is on studies of COVID-19 patients including data gathered in 2020 and data from seasonal influenza patients gathered between 2017 and 2019, representing diverse patient populations, geographical regions and timeframes. As wide-scale COVID-19 vaccine distribution commenced in December 2020,[5] these studies evaluate the characteristics of COVID-19 in the absence of vaccination.

A description of the characteristics of the included studies is provided in the table. Although the study populations are not directly comparable, they provide some insight into some key differences between seasonal influenza and SARS-CoV-2.

Study characteristics of selected comparisons of seasonal influenza and SARS-CoV-2

Bai and Tao, 2021[6]	Literature search that included Chinese, US and WHO sources to 3 Oct 2020
Brehm et al., 2021[7]	German hospital-based study of 255 influenza patients from the 2017/18 season and 166 COVID-19 patients during Feb–June 2020
Fröhlich et al., 2022[8]	Patients admitted to Swiss hospitals with community-acquired infections: 1381 patients with influenza from 2018/20 seasons; 2843 COVID-19 patients during Feb–July 2020
Lee et al., 2022[9]	Retrospective cohort study of ≈2.4 million influenza patients from the 2017/18 seasons and 21,615 COVID-19 patients followed for 1 year from diagnosis or until Dec 2020 from a South Korean health claims database
Ludwig et al., 2021[1]	Anonymised German healthcare claims data: 6762 hospitalised influenza patients from the 2017 to 2019 seasons and 2343 hospitalised patients with COVID-19 during Feb–July 2020
Oliva et al., 2021[10]	74 patients admitted to ICU in a single hospital in Rome: influenza during Jan–Dec 2019; COVID-19 during March–Sept 2020
Piroth et al., 2021[11]	Hospitalised patients from a French national database: 45,819 patients with influenza during Dec 2018–Feb 2019; 89,530 patients with COVID-19 during March–April 2020

Viral transmission

Most studies that compared transmission rates during 2020 indicated that R_0 (the average number of additional individuals infected during the course of an infection [index] case) was higher for SARS-CoV-2 than for influenza. In a review by Bai and Tao (2021),[6] the range for R_0 was 1.40–6.49 for SARS-CoV-2 and 1.30–1.71 for influenza. However, it is important to note that viral, host and environmental factors can affect transmission. Viral factors include, for example, how well the SARS-CoV-2 spike protein binds to its receptor (ACE2) and its ability to replicate.[12] The susceptibility of the host is also a key factor; the higher the number of susceptible people in the population, the higher the R_0 value. Additionally, R_0 has evolved over time with the emergence of new SARS-CoV-2 variants, where the omicron variant was found to have a higher R_0 than the delta variant,[13] which in turn was found to have a higher R_0 than the ancestral SARS-CoV-2 virus.[14]

Patient demographics

Based on the selected studies, which included COVID-19 patients from 2020, one study found patients with influenza to be younger than those with COVID-19,[9] while two studies found those with influenza to be older.[7,8] However, it should be noted that an increasing proportion of children and young adults were affected by COVID-19 as the pandemic progressed during 2020.[15,16] Some studies found more male patients to be affected by COVID-19 than influenza,[8,10] whereas others found the proportion of male patients affected by either virus to be similar.[1,6] One study found that males were more likely to have severe SARS-CoV-2 infections[1] and another that more patients under the age of 5 required intensive care for COVID-19 than influenza.[11]

Symptoms

COVID-19 and influenza share several symptoms, including fever, cough, shortness of breath, fatigue, sore throat, runny nose, muscle pain, headache, vomiting and diarrhoea.[17] Due to the similarity in symptoms, it is not possible to make a diagnosis of influenza or COVID-19 based on symptoms alone, which is why testing is needed.[17] In their comparison of the characteristics of influenza and COVID-19, Bai and Tao (2021)[6] highlighted symptoms that were more characteristic of one disease than another, these included chemical sensory disturbance, damage to the reproductive system, constitutional symptoms and rash with COVID-19, and eye symptoms with influenza.

Hospitalisation

Overall, the data indicate that patients hospitalised with COVID-19 during 2020 had more severe disease than those hospitalised for influenza in seasons prior to the COVID-19 pandemic, had a longer hospital stay and were more likely to be admitted to the ICU or require ventilation.[1,7,10]

Mortality

All studies reporting mortality data – except one, which reported on a small number of patients from a single hospital – reported significantly increased mortality rates for hospitalised patients with COVID-19 versus those hospitalised with influenza.[1,7,8,10,11]

Risk factors and comorbidities

Piroth *et al.* (2021)[11] found that heart failure, chronic respiratory disease and deficiency anaemia were more common in patients with influenza than COVID-19, whereas more patients with COVID-19 than influenza had diabetes, hypertension, dyslipidaemia and were overweight/obese. Another study found that chronic kidney disease and chronic obstructive pulmonary disease were more common in influenza patients.[10] By contrast, Ludwig *et al.* (2021)[1] found that hypertension, diabetes, chronic kidney disease and chronic obstructive pulmonary disease were common comorbidities in both diseases.

Bai and Tao (2021)[6] found that pregnancy and young age were associated with more severe influenza disease, while obesity, comorbidities and old age were associated with increased mortality in COVID-19 patients.

Complications

Complications following COVID-19 can include long-term damage to the lungs, heart, kidneys, brain and other organs and a variety of long-lasting symptoms known as 'long-COVID'.[18] Influenza complications can include inflammation of the heart (myocarditis), brain (encephalitis) or muscles (myositis, rhabdomyolysis), multi-organ failure and secondary bacterial infections, particularly pneumonia.[18] Bai and Tao (2021)[6] noted that COVID-19 patients are most often transferred to the ICU because of acute respiratory distress syndrome, arrhythmia and shock, whereas influenza patients are most commonly transferred to the ICU due to acute respiratory distress syndrome, septicaemia and secondary severe bacterial infection. One study that

included ≈2.4 million influenza patients and more than 21,000 COVID-19 patients found that the risk of one or more new complications was higher in influenza patients than COVID-19 patients.[9]

Comparison of influenza type A and B with COVID-19: A global systematic review

Pormohammad *et al.* (2020)[19] conducted a global systematic review that included a clinical comparison of influenza type A and B with COVID-19. The review included 540 studies published between 2000 and 2020 for influenza and during 2020 for COVID-19 and includes data on both seasonal and pandemic influenza. Key differences between COVID-19 and influenza type A and B are summarised in the table.

In line with the previously described data, fever and cough were very common in COVID-19, influenza A and influenza B. Other symptoms, including runny nose, dyspnoea, sore throat and rhinorrhoea were found less frequently with COVID-19 (14%, 15%, 11.5%, 9.3%) than with influenza type A (70%, 45.5%, 49%, 44.5%) and type B (74%, 33%, 38%, 49%). Acute respiratory distress syndrome and hypertension were the most common comorbidities with COVID-19 and influenza A, whereas viral and fungal coinfections were most common with influenza B, followed by diabetes. Abnormal chest radiology was significantly more common with COVID-19 than with influenza A or B ($p<0.001$ for both). The incubation period for COVID-19 was almost double that for influenza A. In line with other findings the length of hospital stay for COVID-19 was longer than either influenza A or B; however, the mortality rate for patients hospitalised with COVID-19 was similar to that of influenza A, and higher than that of influenza B.[19]

Key differences between COVID-19, influenza type A and influenza type B (Pormohammad 2020)[19]

	COVID-19	Influenza A	Influenza B
Mean age, years	49.7	36.5	38.5
Most common symptoms	Fever Cough Fatigue	Fever Cough Runny nose	Fever Cough Runny nose
Most common comorbidities	ARDS Hypertension	ARDS Hypertension Smoking	Viral coinfection Fungal coinfection Diabetes
Abnormal chest radiology	84%	57%	33%
Incubation period	6.4 days	3.4 days	N/A
Length of hospital stay	14 days	6.5 days	6.7 days
Hospital mortality rate	6.5%	6%	3%

ARDS, acute respiratory distress syndrome.

What has changed with the emergence of the omicron variant of SARS-CoV-2?

Although the above findings did not distinguish between different variants of SARS-CoV-2, we sought to describe how the clinical picture changed with the emergence of the omicron variant by summarising the findings of recent relevant studies. Importantly, a significant portion of the COVID-19 patients included in these studies were fully vaccinated, and it is therefore likely that vaccination has contributed to an overall reduction in the severity of disease observed with the omicron variant.

Study characteristics of selected studies of the SARS-CoV-2 omicron variant

Meo et al., 2021[20]	Worldwide COVID-19 case report review – 2152 confirmed omicron cases: Nov–Dec 2021
Kim et al., 2022[21]	40 patients treated in a single South Korean medical centre during 4–17 Dec 2021
Modes et al., 2022[22]	1076 patients admitted to a single California hospital – delta variant period: July–Sept 2021; omicron variant period: Dec 2021–Jan 2022
Wolter et al., 2022[23]	South African national, laboratory testing, genome testing and hospital admission data: 1 Oct–6 Dec 2021; 161,328 COVID-19 cases

In summary, infections with the omicron variant appear to be more contagious and induce milder symptoms than other variants of SARS-CoV-2.[20,21,23] Disease severity is reduced as well as the risk of hospitalisation.[22,23] Younger and middle-aged patients seem to be the primary population affected.[20,23] Although the effects of COVID-19 vaccination on the omicron variant are not well documented, Modes *et al.* (2022)[22] showed that full vaccination (particularly with a booster dose) was associated with a lower risk of ICU admission and a lower risk of hospital mortality in patients ≥65 years.

Prevention of influenza and SARS-CoV-2

Vaccination remains the mainstay of pharmaceutical protection against both viruses. Non-pharmaceutical interventions (NPIs) introduced as an emergency measure to curb SARS-CoV-2 transmission have had a significant impact in reducing transmission of both SARS-CoV-2 and influenza (for more information see InFluNews Issue 1 2021 available **here**), but the sustainability of stringent NPIs over the long-term is likely to be challenging.[24,25] Nevertheless, some behaviours, such as improved hand hygiene, may be sustained post-pandemic and therefore continue to have an impact on respiratory virus prevention.

The rapid development of effective COVID-19 vaccines has been a success story requiring commitment, collaboration and hard work from many different stakeholders. Rapid advances in the COVID-19 vaccine field may help to accelerate next-generation influenza vaccine development, while the rollout of COVID-19 vaccines continues to inform our understanding of effective vaccine delivery.

Guest editor Mine Durusu Tanriover comments:

The northern hemisphere has witnessed the resurgence of influenza in the 2021–22 season, which brought about new challenges of managing seasonal influenza against a background of the upheaval wrought by the new SARS-CoV-2 omicron variant. First of all, both influenza and COVID-19 can present with severe disease in the same high-risk patient population who are elderly, frail, immunosuppressed and/or have a high burden of accompanying chronic diseases. We have started to see influenza patients who have already been infected by SARS-CoV-2 and are left with systemic and respiratory complications that make them more prone to severe influenza disease. Secondly, some hospitals have had to prioritise the admission of COVID-19 patients over those with influenza resulting in long waiting times for influenza patients. Hence, it's clear that while we are comparing the two infections in terms of clinical presentations and severity at this time, as more people are affected by COVID-19, we will see complicated cases of influenza in patients already harmed and disabled due to COVID-19 and vice versa. The COVID-19 pandemic has taught us that we need to build resilient health systems that are capable of managing patients with severe influenza in addition to those with COVID-19. Vaccination against influenza and COVID-19 is and will remain our most valuable tool for prevention of severe disease, complications and hospitalisation.

GII Summary Statement

This issue of InFluNews provides a snapshot of the clinical characteristics of pandemic COVID-19 during 2020 and compares them to those of influenza, predominantly from data gathered prior to the start of the COVID-19 pandemic. Although both diseases have potentially serious consequences, in general, COVID-19 in 2020 was a disease with more serious consequences than seasonal influenza. Since 2020, however, several new variants of SARS-CoV-2 have emerged which have changed the clinical picture, the latest being the omicron variant, which although it is more contagious, causes milder symptoms than other variants and is less likely to cause severe disease and hospitalisation. While the threat from SARS-CoV-2 appears to be reducing, influenza cases are rising rapidly in many countries and reaching epidemic status in some. The cocirculation of both viruses is adding to the strain on healthcare systems in some countries and can lead to more complex clinical outcomes. Vaccination against both influenza and SARS-CoV-2 remains a critical tool to reduce the impact of both diseases at this time.

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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