ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Review Article

Influenza Infection Post-COVID-19 Pandemic

Amira R Albannai[1]*, Mohammed Saleh Alonazi[2], Abdulmajeed Mohammed Alsalem[3], Abdullah Mohammed Baajaj[4], Mohammed Ahmed Alabyad[5], Badriah Ibrahim Yahya Haqawi[6], Rana Mohammed Rahimaldeen[5], Atif Abdullah Althobaiti[7], Shatha Mohammed Althobaiti[8], Mohammad R M R H Alajmi[9], Khaled Ibrahim Alrefai[10], Maram Hussain S Saleh[11], Abdulmajeed Suwaylh Al Rabie[8] and Yousef Mohammad Alharbi[8]

[1]General Medical Committee, Dammam, Saudi Arabia
[2]Prince Sultan Military Medical City (Psmmc), Riyadh, Saudi Arabia
[3]Security Forces Polyclinic, Ministry of Interior, Riyadh, Saudi Arabia
[4]Alnoor Specialist Hospital, Makkah, Saudi Arabia
[5]King Fahad General Hospital, Jeddah, Saudi Arabia
[6]King Khaled Hospital, Najran, Saudi Arabia
[7]King Abdulaziz Specialist Hospital, Taif, Saudi Arabia
[8]King Faisal Complex Hospital, Taif, Saudi Arabia
[9]Adan Hospital, Kuwait, Saudi Arabia
[10]King Salman Bin Abdulaziz Medical City, Medina, Saudi Arabia
[11]King Abdulaziz Hospital, Jeddah, Saudi Arabia

***Corresponding Author:** Amira R Albannai, General Medical Committee, Dammam, Saudi Arabia.

Received: December 27, 2022; **Published:** December 30, 2022

Abstract

Introduction: The COVID-19 pandemic has caused unprecedented-scale global disruptions in our daily lives. With more than 6 million deaths worldwide, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused coronavirus disease 2019 (COVID-19) has had a devastating impact on the world's demography and is now the most significant global health disaster since the 1918 influenza pandemic. Since the beginning of 2020, adjustments to contact and transportation patterns have impacted the seasonal patterns of several infectious diseases around the world, including influenza. The impact of these perturbations can help clarify important epidemiological mechanisms that, after decades of study, remain obscure. The potency and mechanisms that underlie seasonality in transmission, immunity to natural infection's persistence, evolutionary bottlenecks operating during low transmission seasons, and the effect of non-pharmaceutical interventions (NPI) that might be used in influenza pandemics in the future are some of these.

Aim of the Study: The aim of the present study is to understand the severity, morbidity, and variation associated with viral infection influenza post-COVID-19 pandemic.

Methodology: The review is a comprehensive research of PUBMED since the year 2011 to 2022.

Conclusion: Influenza is thought to cause more serious outcomes and complications more frequently. Although it was first believed that our newest foe, COVID-19, would have more severe effects than previous respiratory tract viruses, recent research has once again shown that influenza is not such a benign virus, particularly in youngsters. Despite the fact that social isolation and mask use have reduced the spread of other respiratory viruses, including influenza, influenza vaccination, especially for the elderly, is highly advised following COVID-19 due to the significance of the issue and the potential for serious complications in a population of high-risk or hospitalized patients.

Keywords: *Influenza Virus; COVID-19; SARS-Cov Virus; Pandemic*

Introduction

More than 6 million people have died as a result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the cause of the coronavirus disease 2019 (COVID-19), the most serious global health crisis since the 1918 influenza pandemic. This has had a devastating impact on the world's demographics. SARS-CoV-2 spread quickly throughout the world when the first instances of this primarily respiratory viral illness were initially recorded in Wuhan, Hubei Province, China, in late December 2019. As a result, the World Health Organization (WHO) was forced to declare it a worldwide pandemic on March 11, 2020 [1].

Since being declared a global pandemic, COVID-19 has devastated numerous nations and negatively impacted numerous healthcare systems. Due to protracted closures brought on by the pandemic, many people have lost their jobs, which has had a negative ripple impact on the world economy. Many countries are experiencing a second or third wave of outbreaks of this viral illness that are primarily attributed to the emergence of mutant variants of the virus. Despite significant advancements in clinical research that have improved understanding of SARS-CoV-2 and the management of COVID-19, limiting the ongoing spread of this virus and its variants has become a matter of increasing concern [1].

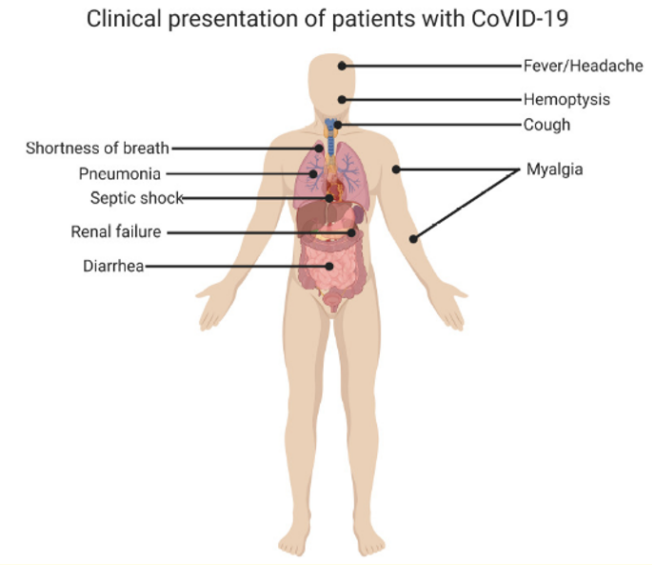

Figure 1: *Clinical presentation of COVID-19 [1].*

Pathophysiology

To understand the pathophysiology of SARS-CoV-2, a general description of viral structure and its genome is necessary. The genomic structure of CoVs, which are positive-stranded RNA viruses with an envelope and a nucleocapsid, is arranged in a +ssRNA of about 30 kb in length, with a 5′-cap structure and a 3′-poly-A tail, making it the largest among RNA viruses. Polyprotein 1a/1ab (pp1a/pp1ab) is created when the viral RNA enters the host, starting the process of replication. Subgenomic RNA (sgRNA) sequences are produced during transcription through the replication-transcription complex (RCT), which is arranged in double-membrane vesicles [2].

On the other hand, transcription is terminated at transcription regulatory sequences, which are positioned in between the so-called open reading frames (ORFs) that serve as templates for the synthesis of subgenomic mRNAs. There can be at least six ORFs in an

abnormal CoV genome. Among these, a frameshift between ORF1a and ORF1b directs the production of both pp1a and pp1ab polypeptides, which are processed by virally encoded chymotrypsin-like protease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases, for producing 16 non-structural proteins with known or predicted RNA synthesis and modification functions (NSPs 1-16). Other ORFs, in addition to ORF1a and ORF1b, encode structural proteins such as spike, membrane, envelope, and nucleocapsid proteins, as well as auxiliary protein chains. Different CoVs have distinctive structural and auxiliary proteins that are translated by specific sgRNAs [3].

The NSPs' and structural proteins' roles in CoV and SARS-CoV-2 pathogenesis are connected. For instance, researchers have described how NSPs work to suppress the host's innate immune response. The envelope, one of the functions of structural proteins, is essential to the pathogenicity of viruses because it facilitates viral assembly and release. The spike glycoproteins, which have two subunits, are one of the components of CoVs (S1 and S2). The spikes on the viral surface, which direct the connection to host receptors, are made up of homotrimers of S proteins [2,4].

SARS-CoV-2 is made up of four main structural proteins: spike (S), envelope (E) glycoprotein, nucleocapsid (N), and membrane (M), as well as 16 non-structural proteins and 5-8 auxiliary proteins. It is structurally and phylogenetically identical to SARS-CoV and MERS-CoV. The surface spike (S) glycoprotein, which has a crown-like shape and is found on the exterior of the virion, is cleaved into two subunits: the amino (N)-terminal S1 subunit helps the virus enter the host cell, and the carboxyl (C)-terminal S2 subunit, which contains a fusion peptide, a transmembrane domain, and a cytoplasmic domain, is in charge of fusing the membrane. The N-terminal domain (NTD), which enables viral entrance into the host cell and serves as a possible target for neutralization in response to antisera or vaccinations, and the receptor-binding domain (RBD) are further split into the S1 subunit. Because it serves as a binding site for the human ACE2 receptors, the RBD is a crucial peptide domain in the pathogenesis of infection. As was previously believed, inhibiting the renin-angiotensin-aldosterone system (RAAS) does not raise the risk of COVID-19 and severe disease-related hospitalization [5].

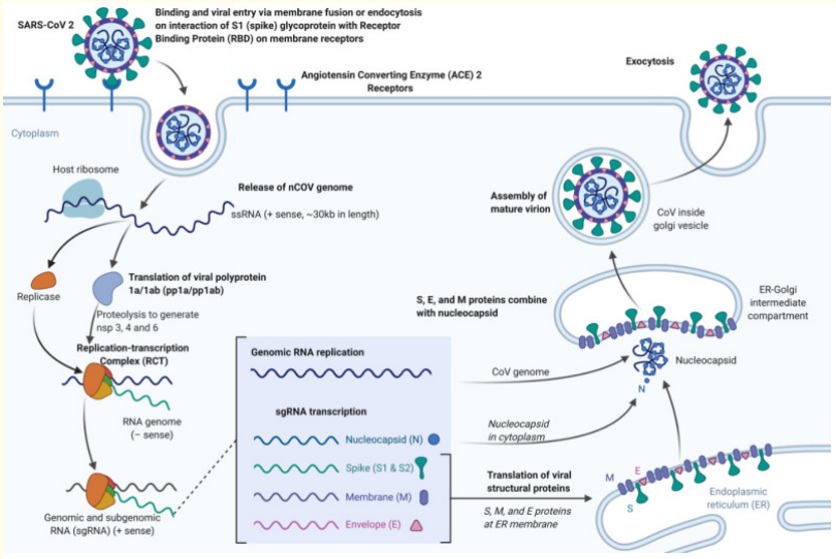

Figure 2: *Replication process of SARS-Cov Virus [1].*

Twenty-two investigations have so far reported co-infection in COVID-19, and 16 of these studies include viral co-infection evidence. Up to 35% of serious cases have been documented to have viral co-infections. Early research suggested that concurrent bacterial infections were present in 50% of patients who died. This figure exceeds what was previously observed during the 2009 influenza pandemic when 25% of patients with influenza illness also had secondary bacterial co-infection. SARS-CoV-2 is a single-stranded RNA betacoronavirus that is a member of the Coronaviridae coronavirus family. According to a phylogenetic study, SARSCoV-2 is genetically distinct from Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and closely linked to SARS-CoV-1 [6,7].

Angiotensin-converting enzyme 2 (ACE-2) receptors, which are also cellular receptors for other viruses in this group, including SARS-CoV and MERS-CoV, are used by SARS-CoV-2 in the lower airways. Despite equivalent ACE-2 receptor expression in many human organs, lung tissue is the most affected area. Lung damage is also brought on by influenza strains through ACE-2 receptor-mediated effects. On the other hand, it was proposed that type I and III interferons produced during bacterial infection may facilitate SARS-CoV2 attachment because the ACE-2 receptor utilized by SARS-CoV-2 is an interferon-stimulated gene [8].

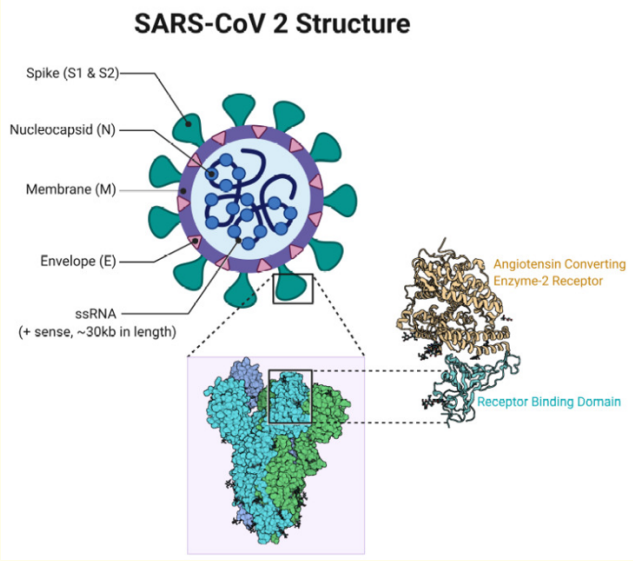

Figure 3: *Structure of SARS-Cov virus [1].*

Influenza is an Orthomyxoviridae virus called IAV, which is a respiratory pathogen. Eight segmented negative-sense RNAs make up the genome. The viral ribonucleoproteins (vRNPs) are made up of the replicase complex (PA, PB1, and PB2) and several viral nucleoproteins (NPs) (vRNPs). Nuclear export protein (NEP) and matrix 1 (M1) may also be present in newly constructed vRNPs (NEP). The influenza virus's lipid bilayers Hemagglutinin (HA), neuraminidase (NA), and matrix 2 (M2) are three viral integral membrane proteins found in virus particles. The proteins HA, NA, M1, and M2, are crucial for influenza, a virus developing and assembling. It is well known that deadly mutations can be added to the M2 component in the cytoplasmic tail by amino acid alterations in the M1 protein of influenza viruses [9].

The discovery of the novel virus during pandemics may result in the underreporting of other infections that may be the etiological agent enhancing the severity of the disease. In fact, 44.3% of individuals during the influenza A (H1N1) pdm09 pandemic had undetected respiratory viruses. Adenovirus, RSV, and influenza viruses are among the prevalent viral co-infections found in COVID-19 patients, according to other investigations. More frequently than viral co-infections, bacterial co-infections can cause mild, moderate, or severe dis-

ease. *Mycoplasma pneumoniae, Pseudomonas aeruginosa, Haemophilus influenza*, and *Chlamydia pneumoniae* are the most well-known COVID-19 co-infecting microorganisms. These findings unequivocally highlight the value of screening for other clinically significant co-circulating respiratory infections that may be causing the disease [10].

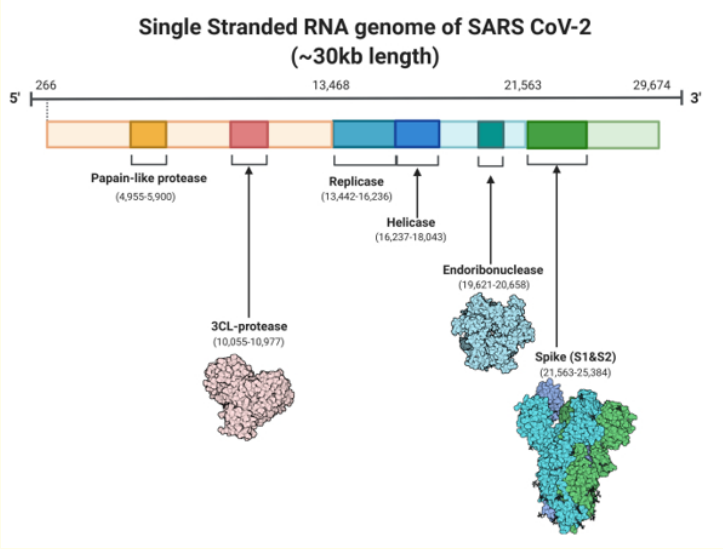

Figure 4: *The single-stranded RNA genome of SARS-CoV2 [1].*

The incidence of COVID-19 pneumonia and influenza co-infection has been partially documented in a number of studies. Data on the clinical significance of COVID-19 and influenza A H1N1 co-infections, however, are scarce. It is difficult to distinguish between respiratory viruses in circulation like influenza A H1N1 and SARS-CoV-2 due to their comparable clinical symptoms. Viral co-infections have been linked in numerous studies to the severity of the disease, acute respiratory distress syndrome (ARDS), and even death. According to these studies, patients who report co-infections have higher admission rates to intensive care units. Co-infected cases of influenza A H1N1 COVID-19 were more serious and required ICU admission. Influenza A H1N1, which is known to cause a significant inflammatory cytokine/chemokine response, may be responsible for the severity and increased case fatality among COVID-19 viral co-infected patients (cytokine storm). However, the co-infection with H1N1 and COVID-19 may hasten and significantly contribute to the development of ARDS [11].

The impact of these perturbations can help clarify important epidemiological mechanisms that, after decades of study, remain obscure. The potency and mechanisms underlying seasonality in transmission, immunity to natural infection's persistence, evolutionary bottlenecks operating during low transmission seasons, and the effect of non-pharmaceutical interventions (NPI) that might be used in influenza pandemics in the future are some of these. Flu activity decreased significantly globally in 2020 as a result of lockdowns and travel-related quarantines implemented in many nations [12].

In the Southern Hemisphere, influenza activity spiked out of season in late 2021, signaling the beginning of a resurgence. Seasonal trends had not reverted to normal in the first half of 2022, with early season activity in the Southern Hemisphere and extremely late and prolonged influenza seasons in the Northern Hemisphere. The A/H3N2 subtype dominated the peak in weekly influenza cases reported in Australia in June 2022, greatly above the country's 5-year average and occurring earlier than usual (Department of Health and Aged

Care. Australian Government, 2022). After the Omicron (B.1.1.529) wave peaked in January 2022, there was an increase in influenza cases, and SARS-CoV2 and influenza A have since been co-circulated, according to reports [12].

In the interpandemic era, seasonality is a defining feature of influenza epidemiology, a complicated phenomenon affected by the interaction of population contact patterns, virus survival, and host immunity [13]. Although it has been demonstrated that environmental and climatic factors influence influenza seasonality, they do not entirely account for the spatiotemporal heterogeneity in the incidence of seasonal outbreaks. In temperate climate zones of the Northern and Southern Hemispheres, influenza seasons are well-synchronized during the interpandemic period and are planned around their respective winters. However, depending on the season, peak timing can vary by up to 3 - 4 months [13].

Large deviations from normal seasonal cycles can take place during influenza pandemic seasons, which signify the development and spread of antigenically new strains. During the 1918 and 2009 influenza pandemics, out-of-season waves were documented. Usually, these disturbances only occur during the first year when the pandemic virus is in circulation. It should be noted that the emergence of new pandemic strains is unpredictable and involves cross-species transmission (for example, from swine to humans), a process that may theoretically happen at any time of year [14].

Compared to previous influenza pandemics, COVID-19 has caused more disruption in influenza activity. Little to no influenza activity was noted in the Northern and Southern Hemispheres in 2020, the year COVID-19 first appeared. The lack of or rapid decline in influenza circulation is probably due to a decrease in human mobility and contact as a result of COVID-19. The influenza situation was largely quiet in 2020, but it has been more challenging to interpret in 2021 - 2022. The variety of COVID-19 control tactics can be partially responsible for the variation in the scope and timing of influenza activity across the globe. Although the global impact on influenza coverage has not yet been completely assessed, the roll-out of COVID-19 vaccinations in 2021, with variable coverage between countries, age groups, and time periods, resulted in decreased uptake for other vaccines. For instance, the COVID-19 vaccine in the US has widened state-by-state differences in influenza vaccine coverage [15].

According to experimental evidence, co-infected mice develop severe sickness, making the co-infection of the influenza virus and the SARS-CoV-2 virus a condition to be concerned about. The persistent recurrence of COVID-19 outbreaks driven by novel variations, combined with a comeback of influenza, may raise the risk of infection with influenza/SARS-CoV-2. Although co-infection, when it happened, increased the risk of serious illness and mortality, epidemiological studies conducted in England and the USA have shown that influenza infection was associated with a decreased risk of SARS-CoV-2 infection. The likelihood of co-infection may be reduced by antagonistic competition between these two viruses, which may be influenced by the innate immune response. Similar trends have been observed for COVID-19 and rhinoviruses, also known as the common cold and influenza viruses. Even though co-infections are still uncommon, the combined effects of a COVID-19 and influenza outbreak could have a devastating effect on a nation's healthcare infrastructure. In this situation, NPIs and vaccinations may be crucial instruments for the prevention of influenza [16].

Numerous studies have documented evidence of a decline in seasonal influenza activity during the 2019–20 season, taking into consideration both the direct and indirect effects of COVID-19 PHSMs, which also internationally reduced influenza activity to low levels in succeeding seasons. Although the uptake of the seasonal influenza routine vaccine increased during the COVID-19 pandemic in several countries, population immunity to influenza would have fallen significantly with low influenza circulation in the community for around two years. By the middle of 2022, the governments of many places and nations have partially or totally eased the COVID-19 PHSMs at varying levels. The impact of upcoming influenza seasons could be significantly greater than that of the pre-COVID-19 pandemic seasons across the globe in terms of infections and related healthcare utilization rates, given the increases in susceptibility to influenza viruses and the relaxation of COVID-19 PHSMs [18].

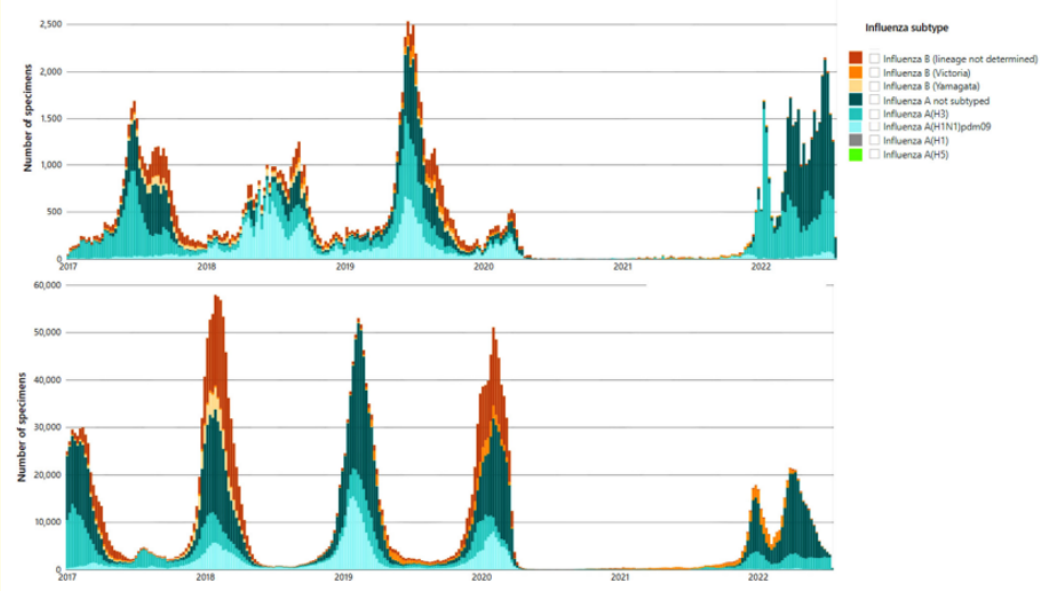

Figure 5: *Patterns of weekly influenza virus circulation in the Northern (top) and Southern (bottom) hemispheres [17].*

Conclusion

Influenza is thought to cause more serious outcomes and complications more frequently. Although it was first believed that our newest foe, COVID-19, would have more severe effects than previous respiratory tract viruses, recent research has once again shown that influenza is not such a benign virus, particularly in youngsters. Despite the fact that social isolation and mask use have reduced the spread of other respiratory viruses, including influenza, influenza vaccination, especially for the elderly, is highly advised following COVID-19 due to the significance of the issue and the potential for serious complications in a population of high-risk or hospitalized patients.

Bibliography

1. Cascella M., *et al*. "Features, evaluation, and treatment of coronavirus (COVID-19)". Statpearls (2022).

2. Chan JFW., *et al*. "Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan". *Emerging Microbes and Infections* 9.1 (2020): 221-236.

3. Biryukov J., *et al*. "Increasing temperature and relative humidity accelerates inactivation of SARS-CoV-2 on surfaces". *MSphere* 5.4 (2020): e00441-20.

4. Song W., *et al*. "Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2". *PLoS Pathogens* 14.8 (2018): e1007236.

5. Jiang S., *et al*. "Neutralizing antibodies against SARS-CoV-2 and other human coronaviruses". *Trends in Immunology* 41.5 (2020): 355-359.

6. Liu Y., *et al*. "Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury". *Science China Life Sciences* 63.3 (2020): 364-374.

7. Gorbalenya AE., *et al*. "Severe acute respiratory syndrome-related coronavirus: The species and its viruses–a statement of the Coronavirus Study Group". *Bio Rxiv* (2020).

8. Bengoechea JA and Bamford CG. "SARS-CoV-2, bacterial co-infections, and AMR: the deadly trio in COVID-19?" *EMBO Molecular Medicine* 12.7 (2020): e12560.

9. Liu H., *et al*. "Mutations in the influenza A virus M1 protein enhance virus budding to complement lethal mutations in the M2 cytoplasmic tail". *Journal of Virology* 92.1 (2018): e00858-17.

10. Lai CC., *et al*. "Co-infections among patients with COVID-19: The need for combination therapy with non-anti-SARS-CoV-2 agents?" *Journal of Microbiology, Immunology and Infection* 53.4 (2020): 505-512.

11. Konala VM., *et al*. "Co-infection with Influenza A and COVID-19". *European Journal of Case Reports in Internal Medicine* 7.5 (2020).

12. Faico-Filho KS., *et al*. "Peculiar H3N2 outbreak in São Paulo during summer and emergence of the Omicron variant". *Journal of Infection* (2022).

13. Tamerius J., *et al*. "Global influenza seasonality: reconciling patterns across temperate and tropical regions". *Environmental Health Perspectives* 119.4 (2011): 439-445.

14. Andreasen V., *et al*. "Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies". *The Journal of Infectious Diseases* 197.2 (2008): 270-278.

15. Kim J., *et al*. "Changing influenza activity in the Southern hemisphere countries during the COVID-19 pandemic". *International Journal of Infectious Diseases* 108 (2021): 109-111.

16. Nickbakhsh S., *et al*. "Virus–virus interactions impact the population dynamics of influenza and the common cold". *Proceedings of the National Academy of Sciences* 116.52 (2019): 27142-27150.

17. Lee SS., *et al*. "Understanding the rebound of influenza in the post COVID-19 pandemic period holds important clues for epidemiology and control". *International Journal of Infectious Diseases* 122 (2022): 1002-1004.

18. Ali S T., *et al*. "Prediction of upcoming global infection burden of influenza seasons after relaxation of public health and social measures during the COVID-19 pandemic: a modelling study". *The Lancet Global Health* 10.11 (2022): e1612-e1622.

Volume 19 Issue 1 January 2023