Babol university of Medical Sciences
Current Research in Medical Sciences
ISSN: 2538-6212
Student Research Committee
Current Research in Medical Sciences

Severe Acute Respiratory Syndrome Coronavirus-2 and Influenza Virus Co-infection: Friend or Foe?

Arghavan Zebardast [1], Farzin Sadeghi [2*]

[1.] Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.,

[2.] Cellular & Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

Article Info

Article type:
Review Article

Received:
9 December 2020
Revised:
20 January 2021
Accepted:
5 February 2021

ABSTRACT

Abstract: Currently, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the etiological factor of the coronavirus disease 2019 (COVID-19) pandemic condition. Based on the evidence, the number of infected patients is increasing around the world. SARS-COV2 infection could show both pulmonary and extra-pulmonary manifestations in patients. The Influenza virus is the cause of influenza disease which is a seasonal viral disease with clinical symptoms similar to COVID-19. Influenza could be a major public health problem throughout the world, as each year approximately 10%-20% of the world's population are infected and is the major cause of death, particularly among the elderly. Since influenza has an effective and preventive vaccine, maximizing influenza vaccination has been suggested. Until now (November 20, 2020) COVID-19 doesn't have any approved drug or vaccine, So the universal influenza vaccination will probably decrease the health burden of this co-infection. In this review, we will focus on the importance of COVID-19 and influenza co-infection in the COVID-19 pandemic era.

Keywords: SARS-COV-2, COVID-19, Influenza, Co-infection

Cite this article: Zebardast, et al. Severe Acute Respiratory Syndrome Coronavirus-2 and Influenza Virus Co-infection: Friend or Foe?; *Current Research in Medical Sciences*. 2021; 5(1):16-26.

Publisher: Babol University of Medical Sciences

Introduction

The coronavirus disease 2019 (COVID-19) is a novel disease caused by severe acute respiratory syndrome coronavirus 2 (SARS COV 2) a member of the beta coronavirus genus (1, 2). It emerged in China and promptly widespread around the world. Soon after it was declared as a pandemic disease by the world health organization (WHO) (3, 4). The transmission occurs majorly through person to person in the course of close contact with each other (5-7). The main primary symptoms are fever, cough, and fatigue, or myalgia (8, 9). In some cases, gastrointestinal presentations were reported (10, 11). Prevention and early diagnosis are the key strategies to decrease the burden of this pandemic (12).

*Corresponding Author: Farzin Sadeghi **(PhD)**
Address: Cellular & Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
Tel: +98 9190213969 **. E-mail:** Sadeghifarzin6@gmail.com

[DOI: 10.22088/crms.5.1.16]

Influenza is a seasonal, highly transmissible viral disease and its activity peaked in the Northern hemisphere in the autumn and winter months (13, 14). The clinical manifestations of influenza syndrome is characterized by fever, headache, cough, sore throat, myalgia, chills, nasal congestion, generalized weakness, and loss of appetite remain for 14 days(15, 16). Vaccines are the most cost-effective preventive measure, which reduces the risk of influenza infection (17-19).

At the time of the COVID-19 pandemic, the number of patients who co-infected with SARS-CoV-2 and the influenza virus in some areas may be increased as the flu season arrives, so the COVID-19-influenza co-infection serves as a major concern for public health. In this review we decided to clarify the importance of this co-infection.

SARS-CoV-2 infection

SARS-COV-2 is a new member of human coronavirus, which was initially identified in Wuhan, China in December 2019(20). World health organization declared "COVID-19" as the name of SARS-COV-2 disease on 11 February 2020(21). As COVID-19 promptly infected many people around the world, this outbreak quickly becomes a global health emergency with 50,676,072 confirmed cases and 1,261,075 deaths reported to date (22, 23).

Different members of the coronavirus family show variable clinical manifestations due to structural differences in virus proteins, affecting tropism and replication (24, 25). Coronaviruses surface spike (S) protein is responsible for virus entry to target cells by interacting with cell receptors, angiotensin-converting enzyme-2 (ACE2) (26, 27). Angiotensin-converting enzyme-2 expresses on various cells including, lung (28), liver cholangiocyte, kidney, testis, colon, esophagus keratinocytes, brain, heart, and bladder (29-31). Binding of S-protein to ACE2 contributes directly to viral pathogenesis (32). Upon viral binding to ACE2, the virus may be entering to cell and the positive-sense viral genomic RNA is then translated by the host cell, yielding the viral replication machinery and infection (33).

SARS-COV-2 infection is divided into three stages: stage I, an asymptomatic incubation period with or without detectable virus; stage II, symptomatic period but not severe and the virus is detectable; stage III, the symptomatic stage with high viral load and severe respiratory manifestations (34). After initial coronavirus infection, immune responses provoke to controlling the viral infection. Genetic differences could be accounted for various immune responses among individuals (34)

The main clinical symptoms of patients are fever, cough, and fatigue, or myalgia (9). Some patients show gastrointestinal presentations like vomiting and diarrhea (10, 35, 36). Whereas some of them have neurological symptoms like unstable walking and headache (37, 38). So, SARS-COV2 infection could show both pulmonary and extrapulmonary manifestations in patients (39, 40).

Influenza virus infection

The Influenza virus is a member of the Orthomyxoviridae family, which contains negative-sense single-stranded RNA with eight segment genome tightly enclosed by nucleoprotein (41). The haemagglutinin (HA) and the neuraminidase (NA), are the two main superficial glycoproteins that protruded above the viral envelope (42). Haemagglutinin initiates infection by attaching the virus to sialic acid (SA) or other

[DOI: 10.22088/crms.5.1.16]

receptors on the surface of target cells and has a key role in endocytic membrane fusion (43, 44). While NA plays an essential role in the final stage of infection by its receptor destroying function (45, 46).

Influenza viruses enter the host bodies through the oral or nasal cavities (47). These viruses initially encounter by the mucosa that covers the respiratory tract. If the virus could be reached the mucous layer, it will then attach and invade the respiratory epithelial cells (48-50). Influenza viruses can infect diverse host species, including humans, swine, and poultry (51). Three main types of influenza viruses are (A, B, and C), that are among the most common causes of human respiratory infections(52), whereas based on the US Centers for Disease Control and Prevention (CDC) and WHO publications, mortality and morbidity caused by influenza virus have been estimated 298000 to 646000 seasonal influenza-associated deaths worldwide in 2015(44, 53). The major clinical presentations of influenza infection are, fever, cough, dyspnea in humans, like the symptoms of influenza A (H1N1) disease in the 2009 pandemic (54, 55). The activity and severity of influenza viruses are varied from different seasons and also different regions (56-58). According to the CDC announcement, each year the influenza epidemic substantially affects health care systems worldwide and has resulted in an estimated 12000 to 61000 deaths since 2010 just in the united states (59).

SARS-CoV-2 and Influenza co-infection

In the time of the COVID-19 pandemic, the number of patients who co-infected with SARS-CoV-2 and the influenza virus specifically type A, in some regions may be elevated as the flu season arrives (60). Among the various studies conducted from the onset of the SARS-COV2 pandemic era and investigated the multiple viral co-infections, influenza A virus was one of the most frequent pathogens causing co-infection among patients with COVID-19(61).

Based on a study by Iranian researchers on 105 COVID-19 positive dead patients, they found influenza co-infection 22.3% while the other viruses like Adenovirus, Respiratory syncytial virus (RSV), and parainfluenza possessed the lower percentages (62). In the study conducted by Ding et al, 3 out of 115 confirmed COVID-19 patients had influenza co-infected patients (63). In another research among 128 hospitalized patients with COVID-19 pneumonia, 64 co-infected patients were detected that 54 (84.4%) were co-infected with influenza A, and 10 (15.6%) with influenza B (64). In pediatric patients were found to have a 15% rate of SARS-COV2 co-infection with influenza A and B viruses (65).

Although SARS-COV2 and influenza virus are immensely different pathogens, they can have overlapping clinical courses. Particularly, SARS-COV2 infections may show similar symptoms as that of influenza disease, which is known as “Flu-like symptoms” (66, 67). On the other hand, as COVID-19 shows non-specific upper respiratory tract presentations, the differentiation between SARS-CoV-2 and other respiratory infections like influenza is not just a simple issue (68).

It is still not understood whether COVID-19 co-infection with other viral infections increases the severity of illness or not, but based on several investigations, since COVID-19 and influenza co-infection result in higher levels of pro-inflammatory cytokines which contributes to frequent cytokine storm may result in more severity and mortality rate in patients(60, 62, 64, 69, 70). In a study conducted by Stowe et al, a total of 43.1% of patients with coinfection lose their life compared to 26.9% of those who tested positive only for SARS-CoV-2(71). Another research by Zhang et al concluded that co-infection with other viruses can increase the rate of mortality (72).

[DOI: 10.22088/crms.5.1.16]

Both viruses are primarily transmitted by respiratory droplets and close contact (73). The average duration of viral shedding was longer for patients with influenza coinfection (17 days vs 12 days) (64). While in another study the duration of viral shedding between two groups of influenza co-infected patients and patients without co-infection, were without differences (74).

One study indicated that the clinical presentations of patients with COVID-19 and influenza virus infection were similar to those who only had COVID-19 infection, but the symptoms of nasal tampon and pharyngalgia may be more prone to appear for those coinfection patients (63). Another research also found that the coinfection with influenza was not associated with an elevation in the severity of COVID-19 pneumonia (64).

Inversely, several studies showed that SARS-COV2 co-infection with other respiratory viruses may decrease the severity of the disease. It has been suggested that when SARS-COV2 infections are initiated simultaneously or after infection with another respiratory virus like influenza, it can be easily suppressed due to the activation of the host immune system. In these cases, SARS-COV2 infection is limited even if the patient is infected by a large inoculum of virus (75). Concordant with this study, another investigation found that this co-infection was associated with decreased risk of severity and death rate to 0.52 fold among COVID-19 confirmed patients (76).

Diagnosis and treatment

SARS-CoV-2 coinfection with different pathogens may prevent accurate disease diagnosis (77). It is highly suggested to adding SARS-CoV-2 to the routine diagnostic systems during the COVID-19 pandemic (78). Since both diseases have common symptoms of fever and cough, it will be difficult to distinguish COVID-19 from other respiratory viral infection only by clinical manifestations (63, 79), so they should screen for the common respiratory pathogens with proper diagnostic tests (80). To make the best decision about treatment, It's reasonable to consider testing all patients presenting with Flu-like illness for different respiratory pathogens along with SARS-CoV-2(78, 81).

As the diagnostic kits are not sufficient enough and because of the low sensitivity of tests, coinfection cases like influenza virus can be misdiagnosed, so poses several challenges to the diagnosis and treatment of COVID-19(64, 82). In the study conducted by Yu et al, among 128 hospitalized patients with COVID-19 pneumonia, 64 cases were co-infected with influenza A and B (54(84.4%) and 10(15.6%), respectively). Among influenza coinfected patients, those treated with lopinavir/ritonavir showed faster pneumonia resolution during 2 weeks after symptom initiation (64).

Prevention

In the pandemic of COVID-19 and with the onset of the influenza season, the high incidence of this co-infection is inevitable (63). As COVID-19 doesn't have any successful drug or vaccine until now (November 20, 2020), So maximizing the universal influenza vaccination will probably decrease the hospital stays due to complications especially in the at-risk groups, and therefore facilitate the hospital and health systems from the burden of dealing with both COVID-19 and influenza at the same time(71, 83, 84).

[DOI: 10.22088/crms.5.1.16]

Unfortunately, according to the CDC announcement, Flu vaccination coverage among adults was 37.1%, a decrease of 6.2 percentage points from the previous flu season in the 2017-2018 season (85). People should be encouraged to take vaccines against pathogens causing respiratory infections like influenza, to reduce the risk of co-infection, diagnostic difficulties, and inappropriate managing in the context of antiviral therapy and infection control (86).

Up to now, only a few studies have investigated the relationship between influenza vaccination and COVID-19 outcomes. All of these studies declared the role of influenza vaccination in reducing the risk of COVID-19 mortality rates (87-89). Although the exact mechanism of this relationship is not clear, according to previous studies, vaccination against one microorganism may affect the host's response to other infectious agents (90-97).

Conclusion

We cannot ignore the co-infection of COVID-19 with other respiratory viruses, like the influenza virus, to make a point that we could provide the best and the most efficacious treatment to the patients. However, it is not clear COVID-19 and influenza lead to more severe disease or not, physicians and health care workers in epidemic regions, should pay more attention and consider COVID-19 as a potential diagnosis especially in combination with other viral causes, to provide the most effective treatment for patients. Actually, additional studies are needed in this area.

ORCID iD

Arghavan Zebardast https://orcid.org/0000-0002-8263-241X/

Dr. Farzin Sadeghi https://orcid.org/0000-0001-8599-3643

[DOI: 10.22088/crms.5.1.16]

References

1.Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of autoimmunity. 2020:102433.

2.Kim J-M, Chung Y-S, Jo HJ, Lee N-J, Kim MS, Woo SH, et al. Identification of Coronavirus Isolated from a Patient in Korea with COVID-19. Osong public health and research perspectives. 2020;11(1):3.

3.Spinelli A, Pellino G. COVID-19 pandemic: perspectives on an unfolding crisis. The British journal of surgery. 2020.

4.Lie SA, Wong SW, Wong LT, Wong TGL, Chong SY. Practical considerations for performing regional anesthesia: lessons learned from the COVID-19 pandemic. Canadian Journal of Anesthesia/Journal canadien d'anesthésie. 2020:1-8.

5.Liu X, Zhang S. COVID-19: Face masks and human-to-human transmission. Influenza and Other Respiratory Viruses. 2020.

6.Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research. 2020.

7.Hâncean M-G, Perc M, Lerner J. Early spread of COVID-19 in Romania: imported cases from Italy and human-to-human transmission networks. Royal Society open science. 2020;7(7):200780.

8.Gulen M, Satar S. Uncommon presentation of COVID-19: Gastrointestinal bleeding. Clinics and Research in Hepatology and Gastroenterology. 2020;44(4):e72-e6.

9.Li Lq, Huang T, Wang Yq, Wang Zp, Liang Y, Huang Tb, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. Journal of medical virology. 2020;92(6):577-83.

10.Gu J, Han B, Wang J. COVID-19: gastrointestinal manifestations and potential fecal–oral transmission. Gastroenterology. 2020;158(6):1518-9.

11.Kotfis K, Skonieczna-Żydecka K. COVID-19: gastrointestinal symptoms and potential sources of 2019-nCoV transmission. Anaesthesiology intensive therapy. 2020;52(1).

12.Yang W, Yan F. Patients with RT-PCR-confirmed COVID-19 and normal chest CT. Radiology. 2020;295(2):E3-E.

13.Keilman LJ. Seasonal influenza (flu). Nursing Clinics. 2019;54(2):227-43.

14.Riphagen-Dalhuisen J, Gefenaite G, Hak E. Predictors of seasonal influenza vaccination among healthcare workers in hospitals: a descriptive meta-analysis. Occupational and environmental medicine. 2012;69(4):230-5.

15.Banning M. Influenza: incidence, symptoms and treatment. British journal of nursing. 2005;14(22):1192-7.

16.Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. Archives of internal medicine. 2000;160(21):3243-7.

17.Jackson ML, Chung JR, Jackson LA, Phillips CH, Benoit J, Monto AS, et al. Influenza vaccine effectiveness in the United States during the 2015–2016 season. New England Journal of Medicine. 2017;377(6):534-43.

18.Casado I, Domínguez A, Toledo D, Chamorro J, Force L, Soldevila N, et al. Effect of influenza vaccination on the prognosis of hospitalized influenza patients. Expert Review of Vaccines. 2016;15(3):425-32.

19.Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. Annals of Internal medicine. 1995;123(7):518-27.

20.Zhang J-j, Dong X, Cao Y-y, Yuan Y-d, Yang Y-b, Yan Y-q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020.

21.World Health Organization Nc-nsRhwwiedn-c-t-gn-t-c-d-c--a-. World Health Organization, Novel coronavirus (2019-nCoV). situation Reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.

[DOI: 10.22088/crms.5.1.16]

22.Favalli EG, Ingegnoli F, De Lucia O, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmunity reviews. 2020:102523.

23.World Health Organization Nc-nsRhwwiedn-c-. World Health Organization, Novel coronavirus (2019-nCoV). situation Reports https://www.who.int/emergencies/diseases/novel-coronavirus-2019.

24.Imani-Saber Z, Vaseghi H, Mahdian M, Safari F, Ghadami M. Variable Clinical Manifestations of COVID-19; Viral and Human Genomes Talk. Iranian Journal of Allergy, Asthma and Immunology. 2020:1-15.

25.Chan RW, Chan MC, Agnihothram S, Chan LL, Kuok DI, Fong JH, et al. Tropism of and innate immune responses to the novel human betacoronavirus lineage C virus in human ex vivo respiratory organ cultures. Journal of virology. 2013;87(12):6604-14.

26.Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS pathogens. 2018;14(8):e1007236.

27.Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. Journal of medical virology. 2020;92(6):595-601.

28.Han K, Blair RV, Iwanaga N, Liu F, Russell-Lodrigue KE, Qin Z, et al. Lung Expression of Human ACE2 Sensitizes the Mouse to SARS-CoV-2 Infection. American Journal of Respiratory Cell and Molecular Biology. 2020(ja).

29.Fan C, Li K, Ding Y, Lu WL, Wang J. ACE2 expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection. MedRxiv. 2020.

30.Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochemical and biophysical research communications. 2020.

31.Saeidi M, Kalantari M, Dordizadeh Basirabad E, Entezari M. ACE-2; an Entry Receptor for SARS-CoV-2. Journal of Marine Medicine. 2020;2(1):33-40.

32.Chowdhury R, Maranas CD. Biophysical characterization of the SARS-CoV2 spike protein binding with the ACE2 receptor explains increased COVID-19 pathogenesis. BioRxiv. 2020.

33.Greenland JR, Michelow MD, Wang L, London MJ. COVID-19 infection: implications for perioperative and critical care physicians. Anesthesiology. 2020;132(6):1346-61.

34.Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. Nature Publishing Group; 2020.

35.Kotfis K, Skonieczna-Żydecka K. COVID-19: gastrointestinal symptoms and potential sources of SARS-CoV-2 transmission. Anaesthesiology intensive therapy. 2020;52(2):171.

36.Cheung KS, Hung IF, Chan PP, Lung K, Tso E, Liu R, et al. Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong cohort and systematic review and meta-analysis. Gastroenterology. 2020.

37.Mao L, Wang M, Chen S, He Q, Chang J, Hong C, et al. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series study. 2020.

38.Wang H-Y, Li X-L, Yan Z-R, Sun X-P, Han J, Zhang B-W. Potential neurological symptoms of COVID-19. Therapeutic Advances in Neurological Disorders. 2020;13:1756286420917830.

39.Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nature medicine. 2020;26(7):1017-32.

40.Lang M, Som A, Carey D, Reid N, Mendoza DP, Flores EJ, et al. Pulmonary vascular manifestations of COVID-19 pneumonia. Radiology: Cardiothoracic Imaging. 2020;2(3):e200277.

[DOI: 10.22088/crms.5.1.16]

41.Dawson WK, Lazniewski M, Plewczynski D. RNA structure interactions and ribonucleoprotein processes of the influenza A virus. Briefings in functional genomics. 2018;17(6):402-14.

42.Gaymard A, Le Briand N, Frobert E, Lina B, Escuret V. Functional balance between neuraminidase and haemagglutinin in influenza viruses. Clinical Microbiology and Infection. 2016;22(12):975-83.

43.Sriwilaijaroen N, Suzuki Y. Molecular basis of the structure and function of H1 hemagglutinin of influenza virus. Proceedings of the Japan Academy, Series B. 2012;88(6):226-49.

44.Bächi T, Yewdell JW, Gerhard W. Antigenic alterations of the influenza virus hemagglutinin during the infectious cycle. Segmented Negative Strand Viruses: Elsevier; 1984. p. 247-52.

45.McAuley JL, Gilbertson BP, Trifkovic S, Brown LE, McKimm-Breschkin JL. Influenza virus neuraminidase structure and functions. Frontiers in microbiology. 2019;10:39.

46.Bradley KC, Galloway SE, Lasanajak Y, Song X, Heimburg-Molinaro J, Yu H, et al. Analysis of influenza virus hemagglutinin receptor binding mutants with limited receptor recognition properties and conditional replication characteristics. Journal of virology. 2011;85(23):12387-98.

47.Richard M, van den Brand JM, Bestebroer TM, Lexmond P, de Meulder D, Fouchier RA, et al. Influenza A viruses are transmitted via the air from the nasal respiratory epithelium of ferrets. Nature communications. 2020;11(1):1-11.

48.Ito R, Ozaki YA, Yoshikawa T, Hasegawa H, Sato Y, Suzuki Y, et al. Roles of anti-hemagglutinin IgA and IgG antibodies in different sites of the respiratory tract of vaccinated mice in preventing lethal influenza pneumonia. Vaccine. 2003;21(19-20):2362-71.

49.Manicassamy B, Manicassamy S, Belicha-Villanueva A, Pisanelli G, Pulendran B, García-Sastre A. Analysis of in vivo dynamics of influenza virus infection in mice using a GFP reporter virus. Proceedings of the National Academy of Sciences. 2010;107(25):11531-6.

50.Perrone LA, Plowden JK, García-Sastre A, Katz JM, Tumpey TM. H5N1 and 1918 pandemic influenza virus infection results in early and excessive infiltration of macrophages and neutrophils in the lungs of mice. PLoS Pathog. 2008;4(8):e1000115.

51.Borkenhagen LK, Salman MD, Ma M-J, Gray GC. Animal influenza virus infections in humans: A commentary. International Journal of Infectious Diseases. 2019;88:113-9.

52.Grunberg M, Sno R, Adhin MR. Epidemiology of respiratory viruses in patients with severe acute respiratory infections and influenza-like illness in Suriname. Influenza and Other Respiratory Viruses. 2020.

53.Troeger CE, Blacker BF, Khalil IA, Zimsen SR, Albertson SB, Abate D, et al. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. The Lancet respiratory medicine. 2019;7(1):69-89.

54.Liem NT, Tung CV, Hien ND, Hien TT, Chau NQ, Long HT, et al. Clinical features of human influenza A (H5N1) infection in Vietnam: 2004–2006. Clinical Infectious Diseases. 2009;48(12):1639-46.

55.Calitri C, Gabiano C, Garazzino S, Pinon M, Zoppo M, Cuozzo M, et al. Clinical features of hospitalised children with 2009 H1N1 influenza virus infection. European journal of pediatrics. 2010;169(12):1511-5.

56.Eick AA, Uyeki TM, Klimov A, Hall H, Reid R, Santosham M, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. Archives of pediatrics & adolescent medicine. 2011;165(2):104-11.

57.Tamerius J, Uejio C, Koss J. Seasonal characteristics of influenza vary regionally across US. PloS one. 2019;14(3):e0212511.

58.Rizzo C, Bella A, Viboud C, Simonsen L, Miller MA, Rota MC, et al. Trends for influenza-related deaths during pandemic and epidemic seasons, Italy, 1969–2001. Emerging infectious diseases. 2007;13(5):694.

[DOI: 10.22088/crms.5.1.16]

59.https://www.cdc.gov/flu/about/burden/index.html CfDCaPC. Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/flu/about/burden/index.html

60.Ma S, Lai X, Chen Z, Tu S, Qin K. Clinical Characteristics of Critically Ill Patients Co-infected with SARS-CoV-2 and the Influenza Virus in Wuhan, China. International Journal of Infectious Diseases. 2020.

61.Lai C-C, Wang C-Y, Hsueh P-R. 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. 2020.

62.Hashemi SA, Safamanesh S, Ghafouri M, Taghavi MR, Mohajeri Zadeh Heydari MS, Abad HNA, et al. Co-infection with COVID-19 and Influenza A Virus in two died patients with Acute Respiratory Syndrome, Bojnurd, Iran. Journal of Medical Virology. 2020.

63.Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients coinfected with 2019 novel coronavirus and influenza virus in Wuhan, China. Journal of medical virology. 2020.

64.Yu C, Zhang Z, Guo Y, Shi J, Pei G, Yao Y, et al. Lopinavir/ritonavir is associated with pneumonia resolution in COVID-19 patients with influenza coinfection: A retrospective matched-pair cohort study. Journal of medical virology. 2020.

65.Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatric pulmonology. 2020;55(5):1169-74.

66.Azekawa S, Namkoong H, Mitamura K, Kawaoka Y, Saito F. Co-infection with SARS-CoV-2 and influenza A virus. IDCases. 2020:e00775.

67.Vacchiano V, Riguzzi P, Volpi L, Tappatà M, Avoni P, Rizzo G, et al. Early neurological manifestations of hospitalized COVID-19 patients. Neurological Sciences. 2020;41(8):2029-31.

68.Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region—case series. New England Journal of Medicine. 2020;382(21):2012-22.

69.Iacobucci G. Covid-19: Risk of death more than doubled in people who also had flu, English data show. British Medical Journal Publishing Group; 2020.

70.Yue H, Zhang M, Xing L, Wang K, Rao X, Liu H, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. Journal of Medical Virology. 2020.

71.Stowe J, Tessier E, Zhao H, Guy R, Muller-Pebody B, Zambon M, et al. Interactions between SARS-CoV-2 and Influenza and the impact of coinfection on disease severity: A test negative design. MedRxiv. 2020.

72.Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. Journal of Clinical Virology. 2020:104364.

73.Solomon DA, Sherman AC, Kanjilal S. Influenza in the COVID-19 Era. Jama. 2020;324(13):1342-3.

74.Tong X, Xu X, Lv G, Wang H, Cheng A, Wang D, et al. Clinical characteristics and outcome of influenza virus infection among adults hospitalized with severe COVID-19: A retrospective cohort study from Wuhan, China. 2020.

75.Pinky L, Dobrovolny HM. SARS-CoV-2 coinfections: Could influenza and the common cold be beneficial? Journal of Medical Virology. 2020.

76.Wang G, Xie M, Ma J, Guan J, Song Y, Wen Y, et al. Is Co-Infection with Influenza Virus a Protective Factor of COVID-19? 2020.

77.Zhu X, Ge Y, Wu T, Zhao K, Chen Y, Wu B, et al. Co-infection with respiratory pathogens among COVID-2019 cases. Virus Research. 2020;285:198005.

[DOI: 10.22088/crms.5.1.16]

78.Xing Q, Li G-j, Xing Y-h, Chen T, Li W-j, Ni W, et al. Precautions are needed for COVID-19 patients with coinfection of common respiratory pathogens. 2020.

79.Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395(10223):497-506.

80.Gayam V, Konala VM, Naramala S, Garlapati PR, Merghani MA, Regmi N, et al. Presenting characteristics, comorbidities, and outcomes of patients coinfected with COVID-19 and Mycoplasma pneumoniae in the USA. Journal of Medical Virology. 2020.

81. Khaddour K, Sikora A, Tahir N, Nepomuceno D, Huang T. Case report: the importance of novel coronavirus disease (COVID-19) and coinfection with other respiratory pathogens in the current pandemic. The American Journal of Tropical Medicine and Hygiene. 2020;102(6):1208-9.

82. Wu X, Cai Y, Huang X, Yu X, Zhao L, Wang F, et al. Co-infection with SARS-CoV-2 and influenza A virus in patient with pneumonia, China. Emerging infectious diseases. 2020;26(6):1324.

83. https://www.cdc.gov/vaccines/pandemic-guidance/index.html CfDCaPC.

Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/vaccines/pandemic-guidance/index.html.

84. Amato M, Werba JP, Frigerio B, Coggi D, Sansaro D, Ravani A, et al. Relationship between Influenza Vaccination Coverage Rate and COVID-19 Outbreak: An Italian Ecological Study. Vaccines. 2020;8(3):535.

85. https://www.cdc.gov/flu/fluvaxview/coverage-1718estimates.htm CfDCaPC. Centers for Disease Control and Prevention (CDC): https://www.cdc.gov/flu/fluvaxview/coverage-1718estimates.htm.

86. Konala VM, Adapa S, Gayam V, Naramala S, Daggubati SR, Kammari CB, et al. Co-infection with Influenza A and COVID-19. European Journal of Case Reports in Internal Medicine. 2020;7(5).

87. Fink G, Orlova-Fink N, Schindler T, Grisi S, Ferrer AP, Daubenberger C, et al. Inactivated trivalent influenza vaccine is associated with lower mortality among Covid-19 patients in Brazil. MedRxiv. 2020.

88. Zanettini C, Omar M, Dinalankara W, Imada EL, Colantuoni E, Parmigiani G, et al. Influenza Vaccination and COVID19 Mortality in the USA. MedRxiv. 2020.

89. Marín-Hernández D, Schwartz RE, Nixon DF. Epidemiological Evidence for Association between Higher Influenza Vaccine Uptake in the Elderly and Lower COVID-19 Deaths in Italy. Journal of Medical Virology. 2020.

90. O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? Nat Rev Immunol. 2020;20(6):335-7.

91. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. MedRxiv. 2020.

92. Horns F, Dekker CL, Quake SR. Memory B cell activation, broad anti-influenza antibodies, and bystander activation revealed by single-cell transcriptomics. Cell Reports. 2020;30(3):905-13. e6.

93. Rieckmann A, Villumsen M, Hønge BL, Sørup S, Rodrigues A, Da Silva ZJ, et al. Phase-out of smallpox vaccination and the female/male HIV-1 prevalence ratio: an ecological study from Guinea-Bissau. BMJ open. 2019;9(10).

94. Wolff GG. Influenza vaccination and respiratory virus interference among Department of Defense personnel during the 2017–2018 influenza season. Vaccine. 2020;38(2):350-4.

95. Zeng Q, Khan K, Wu J, Zhu H. The utility of preemptive mass influenza vaccination in controlling a SARS outbreak during flu season. Mathematical Biosciences & Engineering. 2007;4(4):739.

[DOI: 10.22088/crms.5.1.16]

96. Khan K, Muennig P, Gardam M, Zivin JG. Managing febrile respiratory illnesses during a hypothetical SARS outbreak. Emerging infectious diseases. 2005;11(2):191.

97. Li Q, Tang B, Bragazzi NL, Xiao Y, Wu J. Modeling the impact of mass influenza vaccination and public health interventions on COVID-19 epidemics with limited detection capability. Mathematical Biosciences. 2020:108378.

[DOI: 10.22088/crms.5.1.16]