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Review Article

Epidemiology Section

# H3N2 Influenza Virus Pathogenesis, Transmission and Complications: A Narrative Review

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## ABSTRACT

The recent outbreak of the influenza virus has grown to be a significant issue and a matter of great concern in terms of controlling the impending influenza pandemic. The influenza virus poses a serious threat as it directly infects and impairs the immune system reaction and the respiratory tract. The virus effectively produces infectious viral particles when haemagglutinin molecules are properly cleaved at the respiratory epithelium. The mode of transmission is via droplets from an affected case. The lungs, responsible for the vital exchange of gases, can fail due to various mechanisms, including the destruction of epithelial cells, significant degradation of the extracellular matrix, and airway obstruction. Influenza is a primary cause of severe pneumonia, but it can be accompanied by further bacterial infections, commonly involving bacteria such as *Streptococcus pneumoniae* and *S. aureus*. Influenza infection increases the susceptibility to developing Acute Respiratory Distress Syndrome (ARDS) and bacterial sepsis. Both adults and children have a 30-50% chance of experiencing viral infections along with bacterial pneumonia. Notably, Influenza A virus (H3N2) influenza has been associated with a significant increase in admissions to intensive care units. Among the factors contributing to the development of ARDS, individuals between the ages of 36 and 55 years, pregnant women, and obese individuals are at a higher risk. However, infection with influenza viruses A (H3N2) or B, female sex, and influenza vaccination have been identified as protective factors against ARDS. Influenza infection increases the susceptibility to developing ARDS and bacterial sepsis. Disease progression can be limited by spreading awareness among the people about the factors responsible for transmission, clinical manifestations, and preventive methodologies.


**Keywords:** Haemagglutinin, Influenza A virus, Neuraminidase

## INTRODUCTION

Globally, annual Influenza A Viruses (IAVs) are responsible for approximately 3-6 lakh deaths, posing a significant global problem [1]. Haemagglutinin and Neuraminidase (NA) are two major antigens found on the surface of the influenza A virus. These glycoproteins evolve rapidly to evade herd immunity, with haemagglutinin being the primary focus of vaccine development and influenza virus evolution studies [2]. Current research suggests that NA also plays a role in combating influenza infection [3-6], making it a potential target for vaccines [7]. However, the evolutionary biology of NA is not yet fully understood. The function of NA involves cleaving sialic acids from cellular receptors to promote viral release and prevent haemagglutinin aggregation [8]. Since the introduction of H3N2 in the human population, NA has undergone approximately 75 amino acid mutations, accounting for 15.8% of the entire protein [9]. Recently, there has been influenza A and B viruses co-circulation in human populations. Among them, H3N2 subtype viruses have been associated with severe influenza seasons. H3N2 influenza viruses have undergone rapid genetic and antigenic changes to evade host immunity since their first detection in humans in 1968. These changes include adding numerous N-linked glycans, increasing the overall net charge of the viral haemagglutinin molecule, altering receptor binding preferences for $\alpha$2,3 to $\alpha$2,6-linked SA receptors, and modifying the agglutination capacity of NA on red blood cells prior to infection. As a result, characterising these viruses has become increasingly challenging over time. This article explores these modifications in H3N2 influenza viruses and discusses the methodologies currently being developed by researchers to study these viruses [10].

### Pathogenesis of Influenza

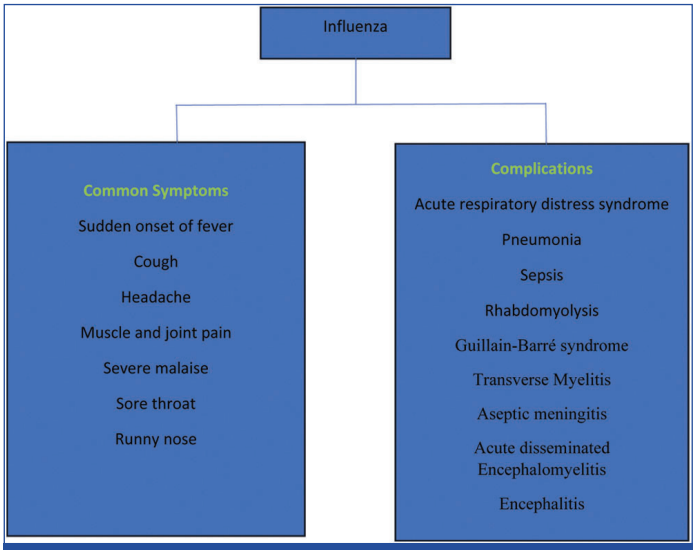
The influenza virus is a member of the Orthomyxoviridae family and is characterised by having a negative-sense single-stranded Ribonucleic Acid (ssRNA) genome. This genetic material is enclosed within a proteinaceous nucleocapsid and surrounded by a lipid membrane derived from the host. Recently, a fourth type of influenza virus, known as type D, has been identified in addition to the major types A, B, and C. Influenza A affects a wide range of animals, including humans, swine, and dogs. In humans, influenza B primarily infects the natural host, but it can also affect seals. Influenza C mainly affects pigs and humans; however, infections are typically not severe and infrequent. Influenza D, which has been primarily found in cattle reservoirs, has not been associated with human infection thus far [11]. The genetic material of the influenza virus is segmented, and the number and composition of these segments vary among different types. Influenza type A possesses ten proteins encoded by eight segments, while influenza B and C have 8 and 7 gene segments, respectively. This review primarily focuses on Influenza A because of its significance as a possibility of the zoonotic pathogen for causing pandemics in animals and humans. The ability of most zoonotic IAV to replicate in humans is limited [12]. Furthermore, there are numerous genetic elements that influence their potential to cause a pandemic, their ability to infect different hosts, their transmissibility, and their virulence. The RNA polymerase expressed by IAV is prone to errors and lacks postreplication repair mechanisms and proofreading activity. This characteristic allows mutations to accumulate quickly, which are exposed to positive and negative selection dependent on the host. This procedure, known as genetic drift, leads to the generation of distinct viral offspring within populations and individual hosts.

The replication of the human influenza virus primarily takes place in the respiratory epithelium. Once infected, immune cells and other cell types initiate the production of viral proteins. However, effective cleavage of the haemagglutinin molecule at the respiratory epithelium is crucial for the generation of infectious viral particles. The speed at which the virus replicates varies from cell to cell. The virus spreads

by exposure to droplets or respiratory spores from an affected case [1]. The main mechanism underlying influenza pathology is both inflammation and injury due to infection of the epithelium of the respiratory tract by the virus, also the inflammatory response triggered by the immune system to control the virus's transmission. Inflammation of the lungs and subsequent systemic inflammation can lead to the failure of multiple organs, although these outcomes typically occur as a result of severe respiratory distress and lung damage [13]. There have been observed associations between infection of the influenza virus and cardiac issues, including raised susceptibility to cardiac disease within days following influenza infection [14]. The general inflammatory profile associated with these cardiac sequelae is known, but the specific underlying mechanisms remain unresolved [15,16].

## Transmission and Complications

Transmission of influenza rapidly occurs in overcrowded areas. Infection spreads via droplets from an affected case to a person in close contact. Hand contamination can lead to infection. Prevention can be done by simple measures like washing hands properly and covering the nose and mouth while coughing. It takes one to four days to manifest the symptoms after infection [Table/Fig-1] [17].




**[Table/Fig-1]:** Common symptoms and late manifestations of influenza.

### Impact of influenza Acute Respiratory Distress Syndrome (ARDS)

The influenza virus impacts the cells of the respiratory tract lining. The extent of infection in the respiratory tract is the primary factor in determining the severity of the related disease [16]. The virus invasion in alveolar epithelium cells drives the progression of the disease to a severe stage, causing damage to crucial mediators responsible for gas exchange and exposing the virus to the endothelial cells. The advancement of alveolar disease relies on influenza virus and alveolar macrophage interactions, and the epithelium lining [18]. The nature and intensity of innate and adaptive immune responses are subsequently influenced by proinflammatory cytokines stored in endothelial cells. This inflammatory response becomes amplified when there is a breach in the fragile layer, resulting in cytokine release and exposure of viral antigens to the endothelial layer [19]. Ultimately, physiological failure can be attributed either directly to viral infection or to harm caused by the immune system's response, as specific areas of the airways react to the infection. Lung failure, leading to unable to perform its primary function of gaseous exchange, can occur through various non exclusive mechanisms, such as obstructive airways, structural loss of alveoli, damage to the lung epithelium through direct cell death, and breakdown of the extracellular matrix that supports lung structure [20].

### Clinical progression of influenza to pneumonia and Acute respiratory distress syndrome

Acute pneumonia is diagnosed in patients admitted with influenza. Individuals at a higher risk of developing pneumonia include young children (under five years old), the elderly, Caucasians, and residents of nursing homes. Additionally, those with a history of chronic respiratory or cardiovascular disease, immunocompromised individuals, and smokers are more susceptible. Pregnant women and individuals who are extremely obese are also prone to serious complications related to influenza [21-24].

Among adults, the Influenza A virus primarily causes ARDS, while only a small portion of affected individuals are children, as suggested by observational studies [25,26]. Pneumonia and ARDS are the complications of influenza, and bacterial coinfections are also possible. The most common bacterial coinfections are due to Staphylococcus aureus and Streptococcus pneumoniae, or they can arise as a result of hospital-acquired pneumonia [27]. Clinicians may fail to clinically diagnose around one-third of confirmed cases of influenza virus infection [28]. Differentiating between symptoms of influenza and other bacterial or viral infections in patients with pneumonia and ARDS can be challenging. Respiratory symptoms worsen subsequently and/or persistently in primary influenza pneumonia, whereas the occurrence of secondary bacterial pneumonia typically happens one to three weeks later as a "relapse" once the influenza's initial manifestations have faded. But bacterial coinfection can happen a few days after influenza disease starts [29].

### Influenza as sepsis

The body generates an influenza immune response that activates several common pathways also involved in a reaction to bacteria. Consequently, patients with influenza can experience clinical symptoms similar to those seen in bacterial sepsis [19,30,31]. Multiple studies have elucidated the role of toll-like receptors two and four, which are crucial receptors for both gram-positive and gram-negative bacteria, in the pathogenicity of influenza [32-34]. Similar to bacterial sepsis, influenza virus infection can lead to endothelial damage, changes in microvasculature permeability, tissue oedema, and organ failure [35,36]. The influenza virus also significantly increases the likelihood of developing secondary bacterial sepsis, in addition to vulnerability to subsequent bacterial pneumonia [37]. Individuals with severe organ failure resulting from influenza, especially children with severe renal failure and high Paediatric Index of Mortality (PIM) scores, have a higher risk of death [38-40].

### Influence of coinfections between virus and bacteria along with their impact on outcomes

Ghoneim HE et al., have focused on investigating the mechanisms underlying raised vulnerability to coinfection with bacteria following infection of the influenza virus. One notable change observed in the immune environment of the lungs after viral infection is a reduction in the number of alveolar macrophages [41]. This decrease in macrophages in the alveoli can contribute to heightened vulnerability, as these cells perform a crucial function in responding to various bacterial infections.

In addition to the inflammatory response that triggers normal regulatory mechanisms, viral infections also activate these mechanisms. One such example is the upregulation of key negative regulators like CD200 on airway surfaces and macrophages in the lungs' immune cells. This type of suppression is necessary to facilitate tissue repair and prevent the detrimental effects of an overly active immune response. However, it can create an opportune window for bacterial growth [42].

In a similar way, influenza virus infection stimulates the synthesis of systemic glucocorticoids that suppress the inflammatory reaction to maintain tissue integrity. However, this also creates an environment conducive to bacterial expansion, as shown in a mouse model

of coinfection with influenza virus and listeria. Failure of the glucocorticoid reaction due to the inflammatory reaction induced by influenza virus infection resulted in death. This highlights the balance between pathogen resistance and tolerance in co-infected hosts, a challenge in determining the optimal response [43].

### Other serious complications

A rare complication associated with influenza is acute myositis accompanied by rhabdomyolysis, which is more commonly observed in children. These individuals typically present with severe tenderness in the lower extremities, and laboratory investigations reveal increased levels of Creatine phophokinase and myoglobinuria [44]. Although pericarditis and myocarditis have been explained in autopsy studies, these complications are rarely observed in clinical cases [45,46].

Influenza is also linked with various Central Nervous System (CNS) complications, such as Guillain-Barré syndrome, transverse myelitis, aseptic meningitis, acute disseminated encephalomyelitis, and encephalitis [47-49].

## CONCLUSION(S)

Influenza can be transmitted through various modes of transmission. The most common mode is via droplets from an affected case. Recovery is seen in many cases in a week without any treatment, although it can be severe or fatal in the high-risk population, particularly in people suffering from chronic diseases. Disease progression can be limited by spreading awareness among people about the factors responsible for transmission. However, infection with influenza viruses A (H3N2) or B, female sex, and influenza vaccination have been identified as protective factors against ARDS.

## REFERENCES


[1] Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: A modelling study. Lancet. 2018;391(10127):1285-300. Doi: 10.1016/S0140-6736(17)33293-2.

[2] Wu NC, Wilson IA. A perspective on the structural and functional constraints for immune evasion: Insights from influenza virus. J Mol Biol. 2017;429(17):2694-2709. Doi: 10.1016/j.jmb.2017.06.015.

[3] Couch RB, Atmar RL, Franco LM, Quarles JM, Wells J, Arden N, et al. Antibody correlates and predictors of immunity to naturally occurring influenza in humans and the importance of antibody to the neuraminidase. J Infect Dis. 2013;207(6):974-81. Doi: 10.1093/infdis/jis935.

[4] Memoli MJ, Shaw PA, Han A, Czajkowski L, Reed S, Athota R, et al. Evaluation of antihemagglutinin and antineuraminidase antibodies as correlates of protection in an influenza A/H1N1 virus healthy human challenge model. mBio. 2016;7(2):e00417-16. Doi: 10.1128/mBio.00417-16.

[5] Monto AS, Petrie JG, Cross RT, Johnson E, Liu M, Zhong W, et al. Antibody to influenza virus Neuraminidase: An independent correlate of protection. J Infect Dis. 2015;212(8):1191-99. Doi: 10.1093/infdis/jiv195.

[6] Weiss CD, Wang W, Lu Y, Billings M, Eick-Cost A, Couzens L, et al. Neutralizing and neuraminidase antibodies correlate with protection against influenza during a late season A/H3N2 outbreak among unvaccinated military recruits. Clin Infect Dis. 2020;71(12):3096-102. Doi: 10.1093/cid/ciz1198.

[7] Krammer F, Fouchier RAM, Eichelberger MC, Webby RJ, Shaw-Saliba K, Wan H, et al. NAction! how can neuraminidase-based immunity contribute to better influenza virus vaccines? mBio. 2018;9(2):e02332-17. Doi: 10.1128/mBio.02332-17.

[8] McAuley JL, Gilbertson BP, Trifkovic S, Brown LE, McKimm-Breschkin JL. Influenza virus neuraminidase structure and functions. Front Microbiol. 2019;10:39. Doi: 10.3389/fmicb.2019.00039.

[9] Wang Y, Lei R, Nourmohammad A, Wu NC. Antigenic evolution of human influenza H3N2 neuraminidase is constrained by charge balancing. Elife. 2021;10:e72516. Doi: 10.7554/eLife.72516.

[10] Allen JD, Ross TM. H3N2 influenza viruses in humans: Viral mechanisms, evolution, and evaluation. Hum VaccinImmunother. 2018;14:1840-47. Doi: 10.1080/21645515.2018.1462639.

[11] Ducatez MF, Pelletier C, Meyer G. Influenza D virus in cattle, France, 2011-2014. Emerg Infect Dis. 2015;21:368-71. Doi: 10.3201/eid2102.141449.

[12] Beare AS, Webster RG. Replication of avian influenza viruses in humans. Arch Virol. 1991;119:37-42. Doi: 10.1007/BF01314321.

[13] Zangrillo A, Biondi-Zoccai G, Landoni G, Frati G, Patroniti N, Pesenti A, et al. Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: A systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO. Crit Care. 2013;17(1):R30. Doi: 10.1186/cc12512.

[14] Kadoglou NPE, Bracke F, Simmers T, Tsiodras S, Parissis J. Influenza infection and heart failure-vaccination may change heart failure prognosis? Heart Fail Rev. 2017;22(3):329-36. Doi: 10.1007/s10741-017-9614-7.

[15] Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T. et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med. 2018;378(4):345-53. Doi: 10.1056/NEJMc1805679.

[16] Sanders CJ, Vogel P, McClaren JL, Bajracharya R, Doherty PC, Thomas PG. Compromised respiratory function in lethal influenza infection is characterized by the depletion of type I alveolar epithelial cells beyond threshold levels. Am J Physiol Lung Cell Mol Physiol. 2013;304(7):L481-88. Doi: 10.1152/ajplung.00343.2012.

[17] "Influenza (Seasonal)." Accessed 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).

[18] Cardani A, Boulton A, Kim TS, Braciale TJ. Alveolar macrophages prevent lethal influenza pneumonia by inhibiting infection of type-1 alveolar epithelial cells. PLoSPathog. 2017;13(1):e1006140. Doi: 10.1371/journal.ppat.1006140.

[19] Teijaro JR, Walsh KB, Cahalan S, Fremgen DM, Roberts E, Scott F, et al. Endothelial cells are central orchestrators of cytokine amplification during influenza virus infection. Cell. 2011;146:980-91. Doi: 10.1016/j.cell.2011.08.015.

[20] Boyd DF, Thomas PG. Towards integrating extracellular matrix and immunological pathways. Cytokine. 2017;98:79-86. Doi: 10.1016/j.cyto.2017.03.004.

[21] Casalino E, Antoniol S, Fidouh N, Choquet C, Lucet JC, Duval X, et al. Influenza virus infections among patients attending emergency department according to main reason to presenting to ED: A 3-year prospective observational study during seasonal epidemic periods. Plos One. 2017;12(8):e0182191. Doi: 10.1371/journal.pone.0182191.

[22] Maruyama T, Fujisawa T, Suga S, Nakamura H, Nagao M, Taniguchi K, et al. Outcomes and prognostic features of patients with influenza requiring hospitalization and receiving early antiviral therapy: A prospective multicenter cohort study. Chest. 2016;149(2):526-34. Doi: 10.1378/chest.14-2768.

[23] Garg S, Jain S, Dawood FS, Jhung M, Pérez A, D'Mello T, et al. Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection-United States, 2005-2008. BMC Infect Dis. 2015;15:369. Doi: 10.1186/s12879-015-1004-y.

[24] Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al. Clinical practice guidelines by the infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenzaa. Clin Infect Dis. 2019;68(6):895-902. Doi: 10.1093/cid/ciy866.

[25] Kalil AC, Thomas PG. Influenza virus-related critical illness: Pathophysiology and epidemiology. Critical Care. 2019;23(1):258. Doi: 10.1186/s13054-019-2539-x.

[26] Li H, Weng H, Lan C, Zhang H, Wang X, Pan J, et al. Comparison of patients with avian influenza A (H7N9) and influenza A (H1N1) complicated by acute respiratory distress syndrome. Medicine (Baltimore). 2018;97(12):e0194. Doi: 10.1097/MD.0000000000010194.

[27] Zhou F, Li H, Gu L, Liu M, Xue CX, Cao B, et al. Risk factors for nosocomial infection among hospitalised severe influenza A(H1N1)pdm09 patients. Respir Med. 2018;134:86-91. Doi: 10.1016/j.rmed.2017.11.017.

[28] Dugas AF, Valsamakis A, Atreya MR, Thind K, Manchego PA, Faisal A. et al. Clinical diagnosis of influenza in the ED. Am J Emerg Med. 2015;33(6):770-75. Doi: 10.1016/j.ajem.2015.03.008.

[29] van Asten L, Luna Pinzon A, de Lange DW, de Jonge E, Dijkstra F, Marbus S, et al. Estimating severity of influenza epidemics from severe acute respiratory infections (SARI) in intensive care units. Crit Care. 2018;22(1):351. Doi: 10.1186/s13054-018-2274-8.

[30] Steinberg KK, Gwinn M, Khoury MJ. The role of genomics in public health and disease prevention. msJAMA. 2001;286(13):1635.

[31] Florescu DF, Kalil AC. The complex link between influenza and severe sepsis. Virulence. 2014;5(1):137-42. Doi: 10.4161/viru.27103.

[32] Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, et al. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. Cell. 2008;133(2):235-49. Doi: 10.1016/j.cell.2008.02.043.

[33] Nhu QM, Shirey K, Teijaro JR, Farber DL, Netzel-Arnett S, Antalis TM, et al. Novel signaling interactions between proteinase-activated receptor 2 and Toll-like receptors in vitro and in vivo. Mucosal Immunol. 2010;3(1):29-39. Doi: 10.1038/mi.2009.120.

[34] Shirey KA, Lai W, Scott AJ, Lipsky M, Mistry P, Pletneva LM, et al. The TLR4 antagonist Eritoran protects mice from lethal influenza infection. Nature. 2013;497:498-502. Doi: 10.1038/nature12118.

[35] Wang S, Le TQ, Kurihara N, Chida J, Cisse Y, Yano M, et al. Influenza virus-cytokine-protease cycle in the pathogenesis of vascular hyperpermeability in severe influenza. J Infect Dis. 2010;202(7):991-1001. Doi: 10.1086/656044.

[36] Armstrong SM, Mubareka S, Lee WL. The lung microvascular endothelium as a therapeutic target in severe influenza. Antiviral Res. 2013;99(2):113-18. Doi: 10.1016/j.antiviral.2013.05.003.

[37] Jain S, Benoit SR, Skarbinski J, Bramley AM, Finelli L. 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team: Influenza-associated pneumonia among hospitalized patients with 2009 pandemic influenza A (H1N1) virus--United States, 2009. Clin Infect Dis. 2012;54(9):1221-29. Doi: 10.1093/cid/cis197.

[38] Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA. 2009;302(17):1872-79. Doi: 10.1001/jama.2009.1496.

[39] Domínguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, et al. Critically Ill patients with 2009 influenza A(H1N1) in Mexico. JAMA. 2009;302(17):1880-87. Doi: 10.1001/jama.2009.1536.

[40] Farias JA, Fernández A, Monteverde E, Vidal N, Arias P, Montes MJ, et al. Critically ill infants and children with influenza A (H1N1) in pediatric intensive care units in Argentina. Intensive Care Med. 2010;36:1015-22. Doi: 10.1007/s00134-010-1853-1.

[41] Ghoneim HE, Thomas PG, McCullers JA. Depletion of alveolar macrophages during influenza infection facilitates bacterial super infections. J Immunol. 2013;191(3): 1250-59. Doi: 10.4049/jimmunol.1300014.

[42] Goulding J, Godlee A, Vekaria S, Hilty M, Snelgrove R, Hussell T. Lowering the threshold of lung innate immune cell activation alters susceptibility to secondary bacterial super infection. J Infect Dis. 2011;204(7):1086-94. Doi: 10.1093/infdis/jir467.
[43] Jamieson AM, Yu S, Annicelli CH, Medzhitov R. Influenza virus-induced glucocorticoids compromise innate host defense against a secondary bacterial infection. Cell Host Microbe. 2010;7(2):103-14. Doi: 10.1016/j.chom.2010.01.010.
[44] Dell KM, Schulman SL. Rhabdomyolysis and acute renal failure in a child with influenza A infection. Pediatr Nephrol. 1997;11:363-65. Doi: 10.1007/s004670050299.
[45] Mamas MA, Fraser D, Neyses L. Cardiovascular manifestations associated with influenza virus infection. Int J Cardiol. 2008;130(3):304-09. Doi: 10.1016/j.ijcard.2008.04.044.
[46] Paddock CD, Liu L, Denison AM, Bartlett JH, Holman RC, Deleon-Carnes M, et al. Myocardial injury and bacterial pneumonia contribute to the pathogenesis of fatal influenza B virus infection. J Infect Dis. 2012;205(6):895-905. Doi: 10.1093/infdis/jir861.
[47] Goenka A, Michael BD, Ledger E, Hart IJ, Absoud M, Chow G, et al. Neurological manifestations of influenza infection in children and adults: Results of a National British Surveillance Study. Clin Infect Dis. 2014;58(6):775-84. Doi: 10.1093/cid/cit922.
[48] Okuno H, Yahata Y, Tanaka-Taya K, Arai S, Satoh H, Morino S, et al. Characteristics and outcomes of influenza-associated encephalopathy cases among children and adults in Japan, 2010-2015. Clin Infect Dis. 2018;66(15):1831-37. Doi: 10.1093/cid/cix1126.
[49] Sellers SA, Hagan RS, Hayden FG, Fischer WA. The hidden burden of influenza: A review of the extra-pulmonary complications of influenza infection. Influenza Other Respir Viruses. 2017;11(5):372-93. Doi: 10.1111/irv.12470.

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