

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

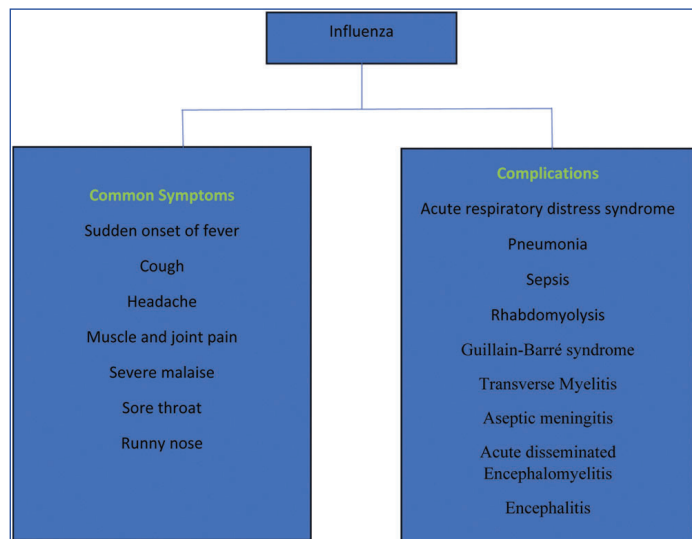
Ribonucleic Acid (ssRNA) genome. This genetic material is enclosed within a proteinaceous nucleocapsid and surrounded by a lipid membrane derived from the host. Recently, a fourth type of influenza virus, known as type D, has been identified in addition to the major types A, B, and C. Influenza A affects 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 phosphokinase 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.

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