Current Trends in Pharmaceutical Research, 2023 Vol 10 Issue 2
© Dibrugarh University www.dibru.ac.in/ctpr ISSN: 2319-4820 (Print)
2582-4783 (Online)

Review article

GLOBAL PERSPECTIVE ON EMERGING STRAIN OF INFLUENZA VIRUSES

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Abstract

Background: *In recent years, H3N2 has been associated with more server flu seasons, with higher rates of hospitalization and deaths, especially among older adults and young children. According to the World Health Organization, during the 2020-2021 flu season, H3N2 was reported to be the dominant strain in many parts of the world, including the United States, Europe, and Asia.*

Objective: *Extensive epidemiological studies and genomic analysis have revealed a wide range of risk factors linked to complications in various health conditions. Currently, three major influenza A virus lineages are circulating in humans, including the seasonal H1N1, H3N2, and pandemic H1N1 viruses. It is uncertain which lineage (s) will become predominant or replaced in the future. The current review aims to assess ongoing surveillance and research which is essential for understanding and predicting the evolution of these viruses and developing effective strategies for controlling their spread.*

Methods: *An extensive search for our review was conducted using a variety of platforms such as Google Scholar, PubMed, Research Gate, Science Direct, CDC website.*

Conclusion: *An extensive epidemiological studies and genomic analysis are recommended for a better understanding of H3N2 infection which may cause an impact on global health.*

Keywords: H3N2; Influenza A virus; Flu symptoms; Epidemiology.

Introduction

The Influenza A virus (IAV) is a highly contagious virus that has caused pandemics and significant damage to the respiratory tract [1]. IAV has the ability to infect different types of cells found in the respiratory tract. These include ciliated cells, club cells, type I and II alveolar cells, as well as immune cells. Influenza viruses are regularly identified in various animal hosts, including birds, humans, horses, minks, pigs, and whales. These viruses are classified into four types: A, B, C, and D. The two most common subtypes of influenza A viruses circulating in humans are influenza A (H1N1) and A(H3N2). The H1N1 and H3N2 Viruses can be differentiated based on their origin and the specific subtypes of their surface proteins, hemagglutinin (H) and neuraminidase (N)[2]. The H1N1 virus caused the 1918 Spanish flu pandemic and has been found in both humans and animals such as pigs, birds, and horses. It is believed to have originated from birds and underwent reassortment in pigs before spreading to humans. On the other hand, the H3N2 virus caused the 1918 Hong Kong flu pandemic and has been found in humans and animals such as birds and pigs. It is believed to have originated from birds and undergone reassortment in humans or pigs before causing the pandemic. The H3N2 virus has continued to evolve since its emergence and is responsible for seasonal influenza outbreaks in humans therefore, the differentiation between the H1N1 and H3N2 viruses is based on their origins, evolutionary history, and including the type of genetic changes that have occurred in their surface proteins [3].

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Type of influenza viruses

Globally, seasonal outbreaks of influenza A and B viruses typically occur during the winter months. However, it's important to note that only influenza A viruses have the potential to cause a pandemic, which refers to global epidemics of flu diseases [4]. A pandemic arises when a new strain of influenza virus emerges, capable of infecting and efficiently spreading among individuals, with little to no pre-existing immunity against it [5]. Influenza C virus infections generally result in mild illness and are not considered to contribute significantly to human epidemics [6]. Influenza D viruses predominantly infect cattle and are not known to afflict humans. Hemagglutinin (H) and neuraminidase (N) are surface proteins on influenza viruses that are used to classify them into different subtypes [7].

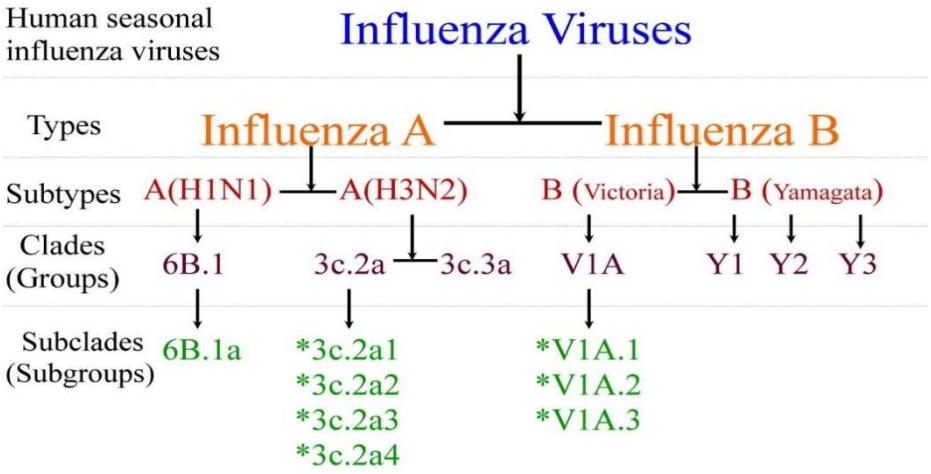

Fig. 1: Phylogenetic tree of influenza virus A & B

Influenza A viruses are further classified into different genetic groups and subgroups, also known as clades and subclades, respectively, based on the similarity of their HA gene sequences (Fig. 1) [8]. In phylogenetic trees, clades and subclades are represented as collections of viruses that often have similar genetic changes and are represented as nodes with a shared ancestor. However, clades and subclades that differ genetically do not necessarily differ antigenically [9]. Antigens are molecular elements on the surface of viruses that are identified by the immune system and can cause an immunological response [10]. Antigenic differences between two influenza viruses indicate that immunity generated against one virus may not protect against the other virus. Influenza A (H3N2) viruses undergo genetic and antigenic changes and have created distinct clades in recent years. In contrast, influenza B viruses are categorized into two lineages: B/yamagata and B/Victoria, and are further classified into particular clades and subclades [11]. Influenza B viruses often undergo slower genetic and antigenic changes than influenza A viruses, especially influenza A(H3N2) viruses [12]. The severity of the H3N2 flu strains can vary from season to season, and different regions of the world can be affected differently [13]. The WHO reported that the H3N2 viruses circulating during the 2020-2021 season were similar to the strains included in the seasonal flu. However, the effectiveness of the vaccine against H3N2 can vary from year to year depending on how well the vaccine matches the circulating strains. The 2021-2022 influenza (flu) season was different in timing and severity compared to most seasons before the COVID-19 pandemic [14]. Despite its relatively mild nature, the 2021-2022 influenza season exhibited heightened levels of activity compared to the preceding 2020-2021 season. Notably, this elevated activity persisted into late spring, surpassing historical records for flu season intensity.

Global perspective

Flu prevalence in the 2021-2022 season surged starting in November and persisted at elevated levels until mid-June, marked by two distinct periods of influenza A(H3N2) virus activity.[15]. The peak of the wave occurred in April 2022. In seasons prior to the pandemic, the typical pattern involved a gradual rise in flu activity starting around October or November, reaching its highest point in February. In the 2021-2022 season, flu activity exhibited a noteworthy extension into the later spring, presenting a distinctive deviation from pre-pandemic patterns. Notably, there was a second national peak in April, marking an unusually late occurrence.[16]. It's typical to observe two waves of flu activity in a given season, with the predominant flu virus differing between each wave. There were two distinct waves of A (H3N2) viruses. The first wave peaked in mid-December nationwide, and the second wave varied by region, with the timing of peak activity ranging from mid-March through May. It is worth noting that the second wave, which peaked nationally in April, occurred much later than what has been observed in the previous flu season. Two systems were used to monitor influenza-associated hospitalizations during the 2021-2022 flu season: the Influenza hospitalization surveillance network (FluSurv-NET) and HHS Protect Hospitalization Surveillance.

History

Throughout the 20th century, five significant influenza viruses triggered global pandemics in the human population. These include the H1N1 virus responsible for the 1918 Spanish flu [17], the H2N2 virus responsible for the 1957 Asian flu, the H3N2 virus responsible for the 1977 Russian flu, and the H1N1 virus responsible for the 2009 swine flu pandemic [18]. Each of these pandemics resulted from the introduction and successful adaptation of a new influenza virus subtype to humans from an animal origin. This process, known as antigenic shift, resulted in significant changes in the viral surface proteins, particularly the hemagglutinin protein, which allowed the virus to evade pre-existing immunity in the human population and cause widespread disease. A notable characteristic of the pandemics induced by H1N1, H2N2, and H3N2 influenza viruses in the 20th century was a change in mortality patterns, with an increased proportion of deaths observed in individuals under the age of 60 [19]. This was in contrast to seasonal influenza, where the majority of deaths occur in the elderly. Furthermore, the diverse range of hosts targeted by the virus, including humans, swine, and domestic poultry, increases the likelihood of the emergence of novel influenza strains with the potential to trigger a new pandemic similar to the 2009 avian influenza outbreak [20].

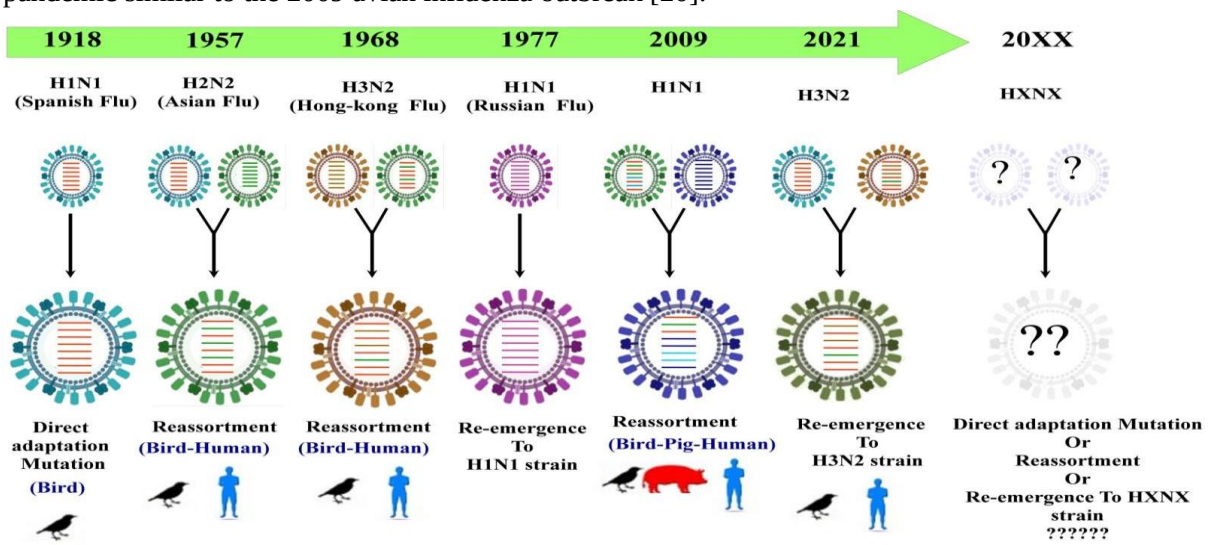

Fig. 2: Emergence of Influenza strains

These viruses underwent further antigenic drift, leading to the emergence of new strains and the need for updated vaccines. The virus caused significant illness and death in many countries, promoting a coordinated international response to try to control its spread and mitigate its Impact. Influenza viruses from different lineages will undergo further reassortment and generate new variants. Reassortment is a common mechanism for influenza virus evolution, and it can result in the emergence of novel viruses with pandemic potential (Fig 2).

Host immune response and virology IAV is a highly recognized respiratory pathogen that requires significant attention for a multitude of reasons. The airway epithelial cells have different types of mechanisms to safeguard the respiratory tract against IAV infections. For instance, club cells can produce antimicrobial compounds that help in protecting the respiratory tract. The ability of these club cells to survive in the long- term is attributed to their ability to produce a stronger antiviral response during a secondary infection and produce type I interferon, which helps to fight against viral infections [21]. The H3N2 influenza virus has been persistently circulating among humans for over fifty years. Recent studies have utilized deep mutational scanning to investigate the evolution and antibody escape of SARS-CoV-2 receptor-binding domains, providing critical insights into COVID-19 vaccine design [22].

Distinguishing between Influenza A, B, and C viruses can be differentiated based on the antigenic distinctions in their nucleocapsid (NP) and matrix (M) proteins. Subtypes within Influenza A are categorized based on the antigenic characteristics of their HA (hemagglutinin antigen) and NA (neuraminidase antigen) glycoproteins. Other important characteristics that distinguish these virus types are: (a) influenza A viruses can infect a wide range of avian and mammalian species, including humans, swine, and horses. In contrast, influenza B virus mainly infects humans, and Influenza C viruses have been isolated mainly from humans, as well as swine in China. (b) Influenza A viruses exhibit more diversity in amino acid sequence within the HA and NA glycoproteins compared to influenza B viruses. In contrast, influenza C viruses possess a single multifunctional glycoprotein known as the HA-esterase-fusion protein (HEF). (c) While these viruses share certain proteins, each virus type employs a unique mechanism for encoding these proteins. (d) Influenza A and B viruses possess eight RNA segments each, whereas influenza C viruses have a total of seven RNA segments. [23].

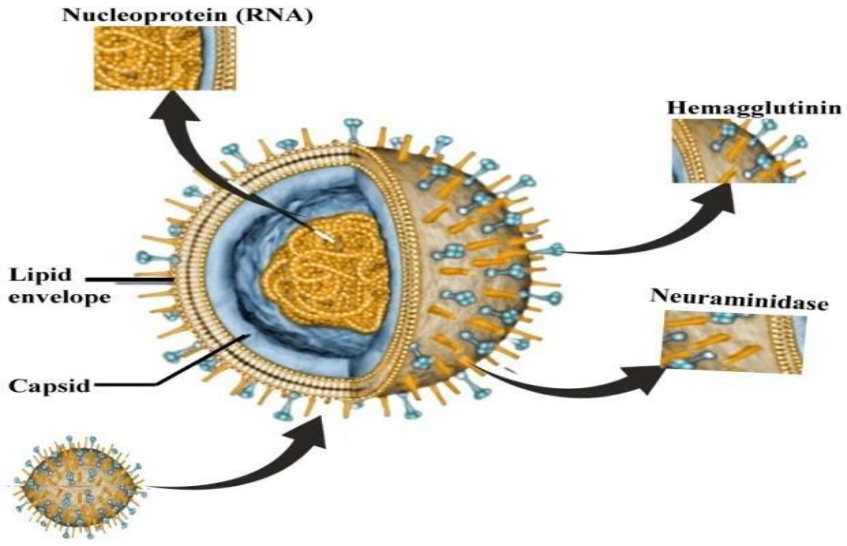

Fig. 3a: Structure of influenza virions

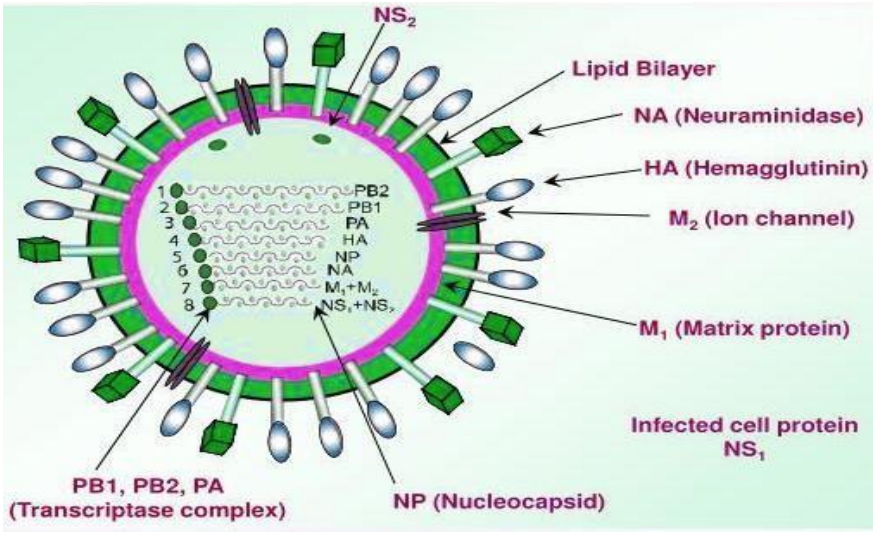

Fig. 3b: Characteristic features of influenza virus

The influenza A virion is surrounded by a lipid envelope, featuring approximately 500 spikes extending outward, measuring between 10-14 nm in length. (Fig 3A). As seen in fig.3a&b, spikes come in two types: rod-shaped spikes composed of HA and mushroom-shaped spikes mode of NA. The ratio between HA and NA can fluctuate but generally hovers around 4 to 5 to 1. Additionally, the Influenza A, B, and C viruses encode other integral membrane proteins: M2 in the influenza A virus, NB and BM2 in the influenza B virus, and CM2 in the influenza C virus. The viral matrix proteins (M1) are believed to underlie the lipid bilayer and engage with the cytoplasmic tails of glycoproteins and the ribonucleoprotein (RNP) core within the virus. [24]. The interior of the Influenza virus contains RNP structures, which can be observed through thin sectioning of the virus or by breaking apart the particles. These RNPs can be divided into different size classes and are made up of eight segments of single-stranded RNA [25]. They appear as flexible rods with loops on one end and periodicity of major and minor grooves, suggesting that a strand has folded back on itself and then coiled to form a twin-stranded helix. The RNPs consist of four protein species and RNA, with NP being the primary protein submit of the nucleocapsid that coats the RNA at a rate of around 20 nucleotides per NP subunit [26]. The RNA-dependent RNA polymerase complex made up of the three P (polymerase) proteins -PB1, PB2, and PA -is associated with the RNPs and is present at only 30 to 60 copies per virion. The NS2/NEP proteins are also present in the virions, with a quantity of 130 to 200 molecules. Influenza A and B viruses possess eight single-stranded RNA segments, varying in chain lengths from 2341 nucleotides to 890 nucleotides. Conversely, influenza C viruses feature seven single-stranded RNA segments and do not include an NA gene. Regarding the influenza A virus, gene assignments are as follows: RNA segment 1 encodes PB2, segment 2 for PB1, and in certain strains, PB1-F2; segment 3 for PA; segment 4 for HA; segment 5 for NP; segment 6 for NA; segment 7 for M1 and M2; and segment 8 for NS2 and NS2/NEP [27]. The RNA-dependent RNA polymerase is constituted by PB1, PB2, and PA, and when combined with the NP protein, they collectively shape the ribonucleoprotein complexes (RNPs). M1 is situated beneath the lipid bilayer, forming connections with the cytoplasmic tails of glycoproteins and the ribonucleoprotein (RNP) core within the virus [28]. PB1-F2 is thought to promote apoptosis of host cells. The M2 protein in influenza A virus and the BM2 protein in influenza B virus serve as proton-selective ion channels, inducing acidification within the interior of the virus particle during the uncoating process within endosomes. [29]. The Influenza B virus NB protein confers a growth advantage in infections of mice, but its function is not fully understood [30]. The Influenza C virus CM2 protein may have ion channel activity, similar to M2 and BM2, but this has not been definitively

shown. Finally, it is worth noting that the different proteins and RNA segments in influenza viruses work in a coordinated manner to facilitate efficient viral replication and infection.

Clinical manifestations

It is important to note that symptoms of influenza are not specific to the H3N2 virus but can occur with other strains of influenza and respiratory viruses [31].

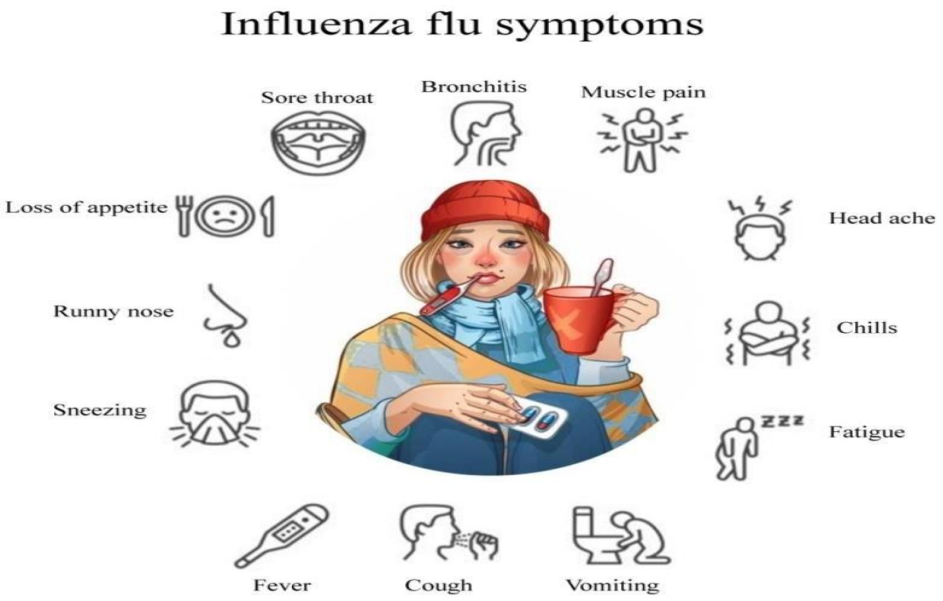

Fig. 4: Clinical picture of influenza virus

In severe cases, influenza infection can lead to complications such as pneumonia, bronchitis, and worsening of underlying medical conditions [32].

Risk factors

These risk factors encompass diverse aspects such as age, gender, lifestyle choices (such as smoking or alcohol consumption), pre-existing medical conditions, genetic predispositions, and environmental influences.

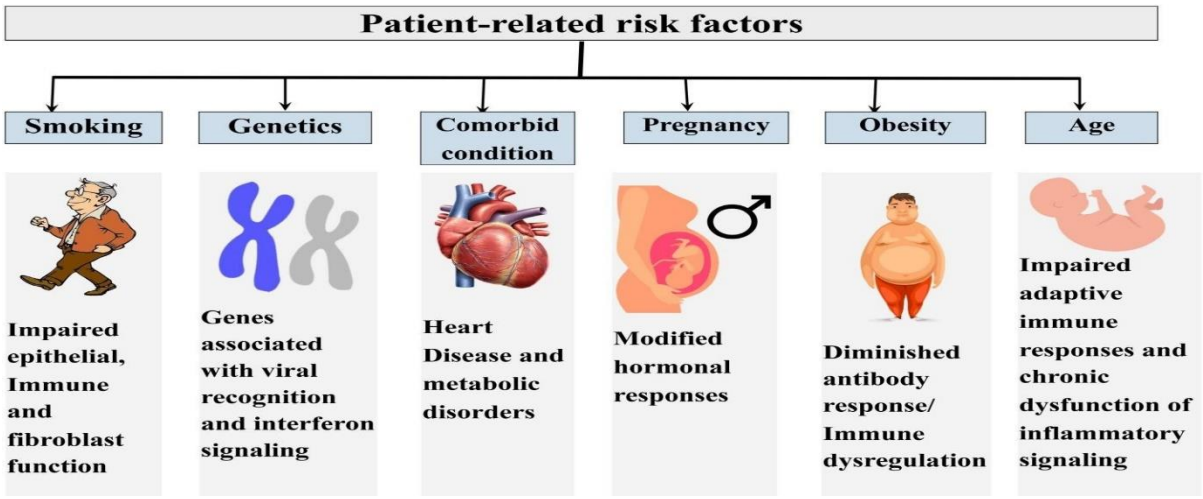

Fig. 5: Predisposing risk factors for influenza viral infection [33, 34]

Recognizing these risk factors empowers healthcare professionals to evaluate a patient's susceptibility to complications and implement appropriate measures for management and prevention [35].

Diagnosis

The diagnosis of the H3N2 virus is usually determined by a combination of the patient's clinical symptoms and laboratory tests. The primary laboratory test used to diagnose influenza viruses is the rapid influenza diagnostic test (RIDT), which can identify influenza antigens, or surface proteins, in respiratory samples such as nasal or throat swabs. RIDTs are a type of immunoassay used to detect the presence of influenza A and B viral nucleoprotein antigens in respiratory specimens [36]. However, it should be noted that RIDTs are not always accurate and may produce false-negative results, particularly early in the course of infection. To confirm influenza virus infection in respiratory specimens, laboratory tests such as reverse transcription- polymerase chain reaction (RT-PCR) or viral culture are considered reference standards [37]. However, these tests can take several hours or even days to produce results. Therefore, the use of RIDTs should be balanced with the need for accurate and reliable results. However, RIDTs may have limited sensitivity and specificity, leading to false-negative or false-positive results, and cannot distinguish between different strains of influenza viruses [38].

There are various methods used for influenza surveillance, including laboratory-based surveillance, sentinel surveillance, and syndromic surveillance. Laboratory-based surveillance involves the collection and testing of respiratory specimens from patients with influenza-like illnesses (ILI) to identify circulating influenza viruses and detect any changes in virus activity or characteristics using RT-PCR or viral culture. Sentinel surveillance involves the monitoring of a specific group of healthcare providers or facilities, such as hospitals or clinics, for ILI cases and laboratory-confirmed influenza cases. This provides a more targeted and localized view of influenza activity in a particular area or population. Syndromic surveillance involves the monitoring of non-specific indicators of ILI, such as absenteeism from school or work, over-the-counter medication sales, or emergency room visits. This can provide early warning of increased influenza activity in a population and can help inform public health decision-making. Influenza surveillance data is used to inform public health decision-making at the local, national, and global levels leading to decisions related to vaccine development and distribution, antiviral treatment, and the implementation of public health measures for prevention of the spread of influenza viruses, such as social distancing measures and school closures [39].

Further, genetic sequencing can be used to determine its exact genetic makeup and track its evolution over time. This can be particularly important in the case of influenza viruses like H3N2, which are known to mutate rapidly and can quickly develop resistance to antiviral drugs or other treatments.

Management

Conventional anti-influenza therapies that target viral proteins are often associated with the development of drug-resistant strains. Therefore, alternative therapeutic strategies with different mechanisms of action are required.

Neuraminidase inhibitors (NAIs), such as Oseltamivir, zanamivir, peramivir, and laninamivir, are antiviral drugs that specifically target influenza viruses. By inhibiting neuraminidase, these medications effectively reduce the number of cells that can be subsequently infected, thus impeding the spread of the virus throughout the body [40]. Baloxavir is a newer antiviral medication used specifically for influenza viruses. It functions by targeting the cap-snatching endonuclease activity of the viral RNA-

dependent RNA polymerase (RdRP) complex, which is associated with the polymerase acidic (PA) subunit. By doing so, it interrupts viral replication and halts the spread of the virus. Clinical studies have shown that baloxavir can significantly reduce the duration of influenza symptoms by approximately 26 hours after infection. Furthermore, baloxavir has demonstrated the ability to reduce viral load more rapidly compared to Oseltamivir [41].

Conclusion

It is concluded from the present review that influenza infection spreads fast in human beings. An extensive epidemiological studies and genomic analysis is recommended for better understanding of H3N2infection. An extensive literature is available for understanding influenza virus infection at molecular level but still lots of research needed for development of vaccine and drugs to combat influenza viral infection.

Acknowledgment

NA

Conflict of Interest

The authors have no conflict of interest.

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How to cite this article:

Panchal A, Goswami S. Global perspective on emerging strain of Influenza viruses, *Curr Trends Pharm Res*, 2023; 10 (2): 1-10.