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A Review on the Seasonal and Pandemic Potential of Influenza a(H3N2) virus

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***Abstract*:-**Influenza is considered an infectious respiratory disease; in humans, and the symptoms vary from a mild respiratory disease confined to the upper respiratory tract and characterized by fever, sore throat, runny nose, cough, headache, muscle pain, and fatigue. Severe cases often end in lethal pneumonia. Although these infections are characterized by annual seasonal epidemics and sporadic and unpredictable cases, global pandemic outbreaks also occur involving influenza A virus strains of zoonotic origin. The H3N2 subtype is affiliated with severe influenza seasons. H3N2 influenza viruses pre-dominated during 3 of the last 5 quite severe influenza seasons.Pandemic influenza has been reported to occur every 10–50 years and is characterized by the introduction of a new influenza A virus strain that is antigenically different from previously circulating strains. Both serological and molecular detection techniques are available for the diagnosis including PCR, ICT, Virus isolation in cell culture, etc. Despite the presence of standard techniques, optimal prevention and treatment of Influenza are deemed a herculean task owing to the rate of mutation in these viruses which is high. Improvement in the vaccine efficiency and pandemic risk assessment for the currently-dominant H3N2 influenza viruses is possible only upon the proper study of these viruses. This review provides a detailed into the various aspects of the H3N2 strains and on their potential in causingseasonal and pandemic outbreaks.

Keywords: *H3N2,Influenza Virus, Pandemic, Vaccine.*

1. Introduction

Infections with the human influenza virus can occur everywhere in the world. Wintertime seasonal influenza outbreaks are common in both the Northern and Southern hemispheres and are thought to result in 500,000 fatalities annually.[1] An emerging infectious disease (EID) is an infectious disease whose prevalence has risen in the last 20 years and is expected to rise further in the near future. [2]The influenza virus is made up of three parts: the envelope, the matrix, and the core protein. Hemagglutinin (HA) and neuraminidase (NA) are glycoproteins embedded in the envelope that play key roles in virus invasion and release. As a result, NA and HA have become important targets in the development of influenza vaccines and therapeutic drugs.[3]It is a contagious viral infection caused primarily by influenza A or B viruses. It primarily affects the upper respiratory organs (nose, throat, bronchi, and, in rare cases, lungs), but it can also affect the heart, brain, and muscles.[2]Throughout history, influenza outbreaks have caused widespread illness in humans. In 1968, an avian reassortant virus of the H3N2 subtype was introduced into the human population, resulting in a global pandemic that killed over one million people worldwide.[4]In 2009, an influenza pandemic caused by a novel H1N1 strain resulted in millions of infections in over 214 countries.[5]During 1982-1990, there was a significant seroprevalence of H1N1, H2N2, and H3N2 viruses in human and swine sera in Calcutta, India[6]. The first active IAV infection in Indian swine was reported in 2009, when A(H1N1)pdm09 virus isolates were discovered at a swine farm in Uttar Pradesh.Interestingly, the obtained A(H1N1)pdm09 virus sequences were comparable to those found in North America and Korea, which could be due to trade or long-distance transmission[7]. On March 4,2023 the Indian

Council of Medical Research (ICMR) determined that the disease was caused by Influenza Subtype H3N2. According to ICMR data, H3N2 infections increased in the first nine weeks of 2023. Since December 15, this virus has been the most prevalent (92 %hospitalised SARI, 86%cough,27% breathlessness,16%wheezing symptoms, 16% pneumonia and 6%seizures)[8].H3N2 influenza viruses have undergone extensive genetic and antigenic evolution since their introduction in 1968, resulting in numerous seasonal epidemics, as evidenced by the WHO recommending 28 vaccine strain changes during that time. H3N2 influenza viruses' receptor binding properties have also changed over the last half-century, and they now have a lower affinity for oligosaccharide.[9]Recent research has shown that most modern H3N2 strains have acquired the ability to agglutinate red blood cells via neuraminidase-sialic acid interactions.[10] Therefore, many researchers have modified existing assays and created new methods for characterising modern H3N2 influenza viruses.Several methods for diagnosing influenza infections in humans are currently available, including viral isolation in cell culture, immunofluorescence assays, nucleic acid amplification tests, immunochromatography-based rapid diagnostic tests, and so on. Newer diagnostic approaches are being developed to overcome the limitations of some traditional detection methods.[11]In the seasonal pandemic, descendants of the pandemic strain established a new viral lineage in humans, replacing or co-circulating with previously circulating strains.The pandemic 2009 H1N1 (H1N1pdm09) influenza A virus is currently circulating alongside H3N2 and influenza B viruses.The study's goal is to examine these recent changes in modern H3N2 Seasonal influenza infection significant mortality, and burden.

Influenza Virus Types:

Currently, there are three types of influenza viruses: A, B, and C.Influenza and other members of the Orthomyxoviridae family are enveloped viruses with eight segmented, negative-sense RNA genomes.[12] Influenza A viruses (IAV) viruses can infect humans, birds, pigs, horses, and other animals, whereas influenza B and C viruses can only infect humans.[13] IAV are classified based on the surface HA and neuraminidase NA.[14-15] There are currently 18 known HA subtypes (H1-18) and 11 known NA subtypes (N1-11), but only a few of these, namely H1N1, H3N2, H3N3 and H5N1, are currently circulating in humans.[13]HA is a trimeric glycoprotein that is typically divided into two groups: H1, H2, H5, H6, H8, H9, H11, H12, H13, and H16, and H3, H4, H7, H10, H14, and H15. In bats, two new HA subtypes, H17 and H18, have been discovered. NA is a tetrameric glycoprotein classified into three groups: group 1 (N1, N4, N5, and N8), group 2 (N2, N3, N6, N7, and N9), and group 3 (NA from B influenza viruses). N10 and N11 were discovered relatively recently and are primarily found in bats.[16]

H3N2

One of the three major influenza pandemics that occurred in the last century was caused by H3N2. In 1968, a novel strain of H3N2 influenza virus (A/Hong Kong/1/1968 [HK/68]) emerged in Hong Kong, sparking a global epidemic that resulted in over one million deaths worldwide.[17]There was no evidence of H3N2 viruses circulating in humans prior to this outbreak. Most likely, circulating human H2N2 viruses recombined with avian H3N2 influenza viruses, resulting in a novel H3N2 viral strain capable of infecting and transmitting between humans.[18]Further examination of this virus revealed that the avian H3N2 HA and PB1 fragments, as well as the NA from the 1957 H2N2 pandemic strain, combined to form a new H3N2 viral strain.[16]H2N2 and H2N3 viruses continued to circulate in humans until 1971, when H2N2 viruses began to decline. However, H3N2 IAVs have circulated seasonally in the human population since 1968, resulting in numerous epidemics, significant morbidity, and significant mortality.[18]The hemagglutinin proteins on the surface of pandemic influenza viruses typically differ from their avian counterparts by at least one or two mutations in the receptor binding site (RBS), which change viral receptor specificity from preferentially binding to α2,3 linked SAs to preferentially binding to α 2,6 SAs.A combination of five amino acid substitutions in the HA of Hong Kong 1968 H3N2 isolates were linked to the viruses bird-to-human adaptation and pandemic emergence.A novel H3 hemagglutinin and two genes from an avian influenza A virus, as well as the N2 neuraminidase from the 1957 H2N2 virus, were present in the influenza A (H3N2) virus that produced the 1968 pandemic. In September 1968, it was first noticed in the US. Around 100,000 people in the United States and 1 million people globally were thought to have died. The majority of extra deaths occurred in aged 65 and older. The H3N2 virus is a

seasonal influenza A virus that is still spreading around the world (Fig.1).[19] Some of the ways for the virus to increase diversity in viral protein sequences, escape antibody pressure, and evade the host's immune system are reassortment between influenza viruses, mutations, and genomic evolution. IAVs typically evade the host immune response by changing the antigenicity of HA and NA, both gradually through antigenic drift and abruptly through what is known as antigenic shift.[20]In the 1980s, groundbreaking research identified 131 amino acid positions in five antigenic sites (A-E) in the globular head of H3 near the RBS as the main targets for specific antibodies, implying that antigenic shift is likely caused by substitutions in these sites.[21] The virus can also evade immune attack by incorporating N-linked glycosylation sites on the globular heads of its glycoproteins. These sites allow sugar molecules to attach to the side chain amide nitrogen of Asn (N) found in the sequence Asn-X-Ser/Thr, where X can be any amino acid except Pro N-glycosylations of HA and NA serve to mask antigenic epitopes, limit binding to host antibodies, and protect NA's enzymatic sites.[22]To date, no O-linked glycosylation (attachment of a sugar molecule to the hydroxyl group of Ser or Thr on the polypeptide chain) of IAVs has been reported. At residues 81 and 165, the globular head of HK/68 contained two N-glycosylation sites. H3N2 viruses have evolved and gained up to 7 additional N-glycosylation sites on the HA globular head and 5 on the HA stem region since their introduction into the human population.The most recent H3N2 vaccine strain, A/Hong Kong/4801/2014, has 11 N-glycosylation sites in the HA and 8 in the NA. 14 N-glycans are beneficial to the virus because they physically interfere with antibody binding to antigenic sites, but they may also be harmful to viral fitness because they mask the RBS and reduce receptor binding activity.[23]

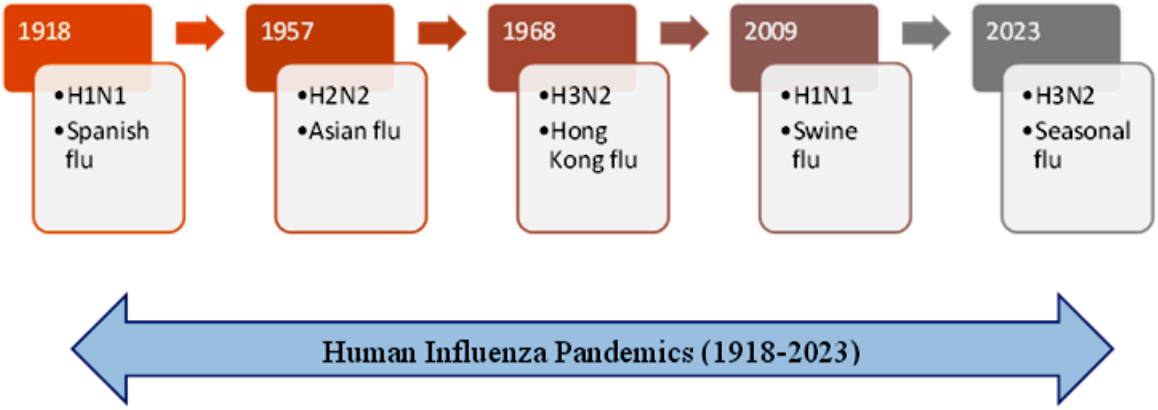

Fig:1 Timeline showing the occurrence of human influenza pandemics from 1918 to 2023

During the 2014/2015 influenza season, H3N2 IAVs from clade 3c.2a first appeared.[24] These viruses differed by »10-12 amino acids from the previous vaccine strain, A/Texas/50/2012 ((Tx/12)(Clade 3c.1)). F159Y and K160T substitutions at antigenic site B, along with an existing N at site 158, represented the potential gain of a glycosylation site, which is likely to mask viral epitopes and reduce antibody access to the antigenic site.[25]These antigenic site B mutations reduce the binding of ferret, sheep, and human antibodies elicited by the Tx/12 vaccine strain significantly. Another A (H3N2) clade, 3c.3a, co-circulated in humans during the same influenza season. Because both clade 3c.2a and 3c.3a viruses were found to be antigenically distinct from Tx/12, the WHO recommended that the northern hemisphere influenza vaccine be updated with an A/Switzerland/9715293/2013-like (Sz/13) (clade 3c.3a) virus in 2015/2016.However, antigenic site B of clade 3c.2a and 3c.3a viruses differ due to glycosylation at site 159 on 3c.2a viruses, and 3c.3a viruses began to fade from human circulation by early 2015.[24] The additional glycosylation site may have conferred a selective evolutionary advantage, allowing 3c.2a viruses to be more efficient at human-to-human transmission than 3c.3a viruses. As a result, the WHO once again recommended a vaccine strain change for the northern hemisphere for the 2016/2017 season, this time to include a clade 3c.2a representative, A/Hong Kong/4801/2014 (HK/14). Clade 3c.2a viruses are currently divided into two sub-clades, 3c.2a1 and 3c.3a2, both of which carry the N121K mutation that distinguishes them from clade 3c.2a. Viruses from 3c.2a1 have a signature amino acid substitution N171K at antigenic site D. These viruses are distinguished further by antigenic site A substitutions D122N and T135K, which result in the loss of N-linked glycosylation sites.Clade 3c.2a2 viruses are part of a

newly emerging group that the WHO has yet to recognise as an official clade. The S144K substitution, which is located in an antigenic site flanking the RBS, distinguishes viruses from this clade. 3c.2a2 viruses are further classified into two groups. Cluster I contains the substitutions I58V and S219Y, while Cluster II contains the substitutions N122D and S262N, with N122D resulting in the loss of a potential N-linked glycosylation site. During the 2016/2017 influenza season, influenza surveillance and vaccine efficacy studies in Greece, London, Canada, and Japan all linked recent A (H3N2) epidemics to newly emerged clade 3c.2a viruses.The World Health Organization's recommendation to include the same H3N2 vaccine virus, HK/14, in the 2017/ 2018 vaccines suggests that the viruses of the newly emerged sub-clades are antigenically similar to HK/14. Nonetheless, an increased level of genetic diversification has been observed among circulating 3c.2a1 viruses, prompting the WHO to recommend another vaccine strain change to a clade 3c.2a1 virus, A/Singapore/INFIMH-16-0019/2016 (Sing/16), for the upcoming 2018/2019 season. Because antigenic drift variants emerge and escape vaccine-induced protection, the genetic composition of new H3N2 strains must be closely monitored as they emerge and spread.[26]

Detection techniques of Infuenza A(H3N2) virus

Techniques for finding the influenza virus have been divided into four groups: conventional approaches, serological methods, rapid and advanced methods, and biosensing methods. Viral culture falls within the category of conventional techniques (Fig.2). Virus neutralisation, hemagglutination, immunodifusion testing, complement fixation, immunofluorescence assays, and fast antigen testing are a few of the serological procedures. Nasopharyngeal swabs, as opposed to nasal and throat swabs, have been found to produce higher yields for fast influenza detection (CDC 2018). Besides serological techniques, rapid and efficient techniques based on the molecular biology of elements are explored.It consists of the rapid influenza technique, Real-Time PCR, multiplex PCR, NonPCR-based RNA-specific detection methods, nucleic acid sequence-based amplifcation (NASBA), and conventional PCR. Optical biosensors, giant magneto-resistance biosensors, aptamer-based biosensors, and electrochemical biosensors are examples of biosensors. We present a comprehensive discussion of all available methods for detecting H3N2, with a focus on bio-sensing methods. Previously, we discussed various H1N1 detection methods.[27-28]

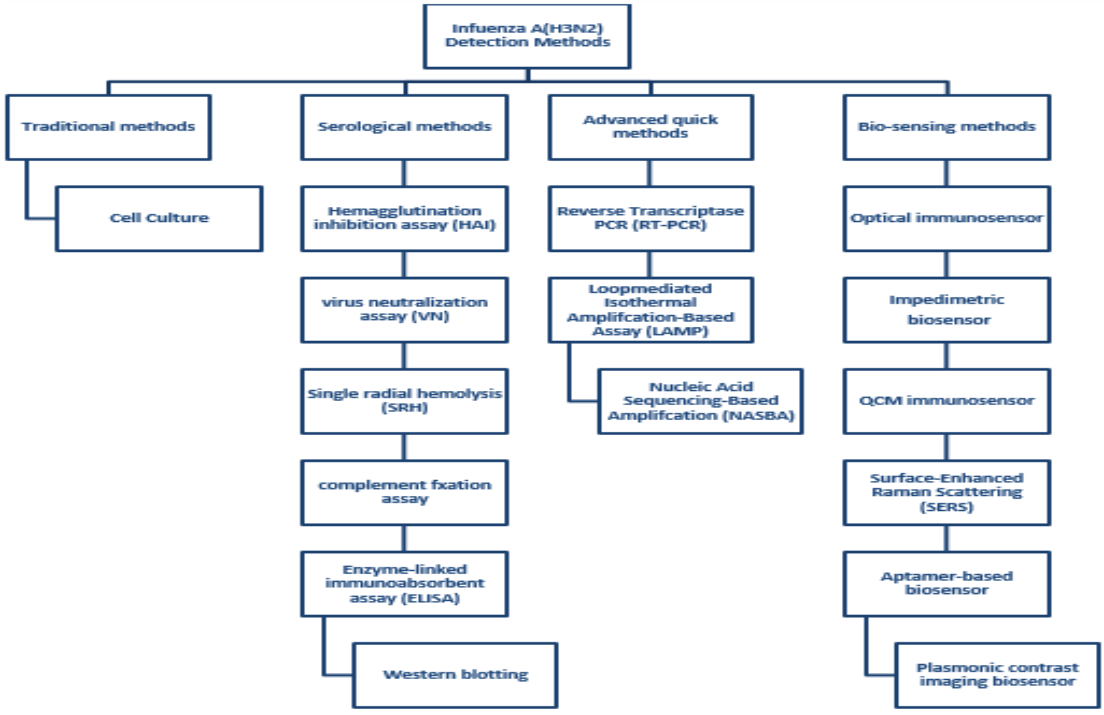

Fig. 2 A flow diagram depicts methods for detecting the influenza A (H3N2) virus.

H3N2 treatment

A simple case of seasonal flu, whether H3N2 or another strain, is treated by symptom management while the patient recovers. Among the options are:

- ✓ getting enough rest
- ✓ consuming adequate fluids
- ✓ taking over-the-counter pain relievers to treat symptoms such as fever, headache, and aches and pains

Doctors may prescribe an antiviral medication, such as oseltamivir, in some cases (Tamiflu). Evidence suggests that some antiviral drugs, particularly neuraminidase inhibitors (oseltamivir and zanamivir), can shorten the duration of viral replication and improve chances of survival; however, further clinical research is required. Resistance to oseltamivir has been reported. Antiviral medication, if started within 48 hours of developing flu symptoms, can help to shorten the duration of illness and prevent complications from developing.[29]

Some people are more likely than others to develop serious flu complications. These complications may include pneumonia or a worsening of an existing medical condition, such as asthma.

Consult a doctor if you suspect you have the flu and fall into one of the following categories:

- ✓ adults aged 65 and up
- ✓ children under the age of five
- ✓ pregnant women
- ✓ individuals suffering from long-term medical conditions such as asthma, diabetes, or heart disease
- ✓ people whose immune systems have been weakened by medication (steroids, chemotherapy) or a medical condition (HIV, leukemia).[30]

H3N2 prevention and control:

To avoid becoming ill from seasonal flu viruses, take the following precautions:

- Every year, get the flu vaccine. If possible, try to get it by the end of October.
- Hands should be washed frequently, especially after using the lavatory, before eating, and before touching your face, nose, or mouth.
- Avoid crowded places where the flu can easily spread. Schools, public transportation, and office buildings are some examples.
- Avoid coming into contact with sick people.

If you have the flu, you can avoid spreading it to others by staying at home until your fever has subsided and covering your mouth when you cough or sneeze.[31-32]

Influenza vaccines

The magnificent work done by Edward Jenner (1796) against small pox was the real ice breaker in the discovery of the vaccine. It took nearly two centuries to develop an effective vaccine, global campaigns to administer small pox vaccine, and the subsequent eradication of the virus from the world on May 8, 1980, thanks to the World Health Organization's highly coordinated work (WHO). Smallpox, Diphtheria, Tetanus, Yellow Fever, Pertussis, HaemophilusInfluenza Type B Disease, Poliomyelitis, Measles, Mumps, Rubella, Typhoid, and rabies are among the 12 successful vaccines against infectious diseases. Vaccines against influenza viruses have been developed since 1931, when E.W. Good pasture of Vanderbilt University grown influenza virus in embryonated Hen's egg.[33]This work was followed by Macfarlane Burnet, Wilson Smith, Thomas Francis, and Jonas Salk, who developed an early influenza vaccine. Later, the United States Army developed a fully approved Influenza vaccine to protect its soldiers during World War II.[34]Embryonated hen eggs were used to continue the production of viruses used in influenza vaccines. Several others, however, have improved its purity by lowering the egg proteins that cause hypersensitivity reactions. The problems with influenza vaccines for that wild type virus continue to mutate, and the vaccine strain became obsolete at some point (Fig.3). In recent years, influenza infections have been caused by both influenza A and influenza B. As a result, current vaccines against influenza

epidemics contain two influenza A subtypes, H1N1 and H3N2, as well as one or two influenza B virus variants.The trivalent vaccine contains two influenza A subtypes, H1N1 and H3N2, as well as one influenza B strain isolated during the recent flu season. In general, influenza a subtype vaccine strains are adapted to grow in embryonated hen's eggs or developed through a genetic reassortment method in which the vaccine strain and the current season's wild type clinical strain are allowed to recombine.[35]

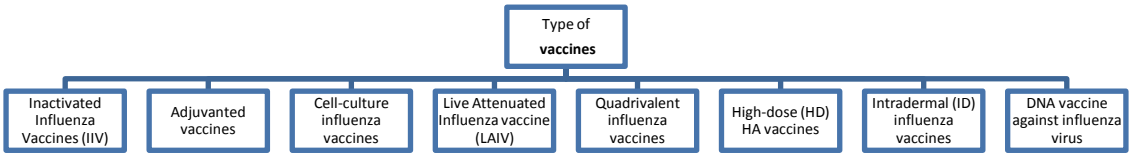

Fig.3: Types of Influenza vaccines

2. Conclusion

In the current scenarios, the occurrences of seasonal and pandemic outbreaks have become a significant threat to the welfare of human society. Viral evolution has occurred on par with human evolution and in a more detailed aspect, they are reported to have several folds higher rates of mutation. The need to study the structural and functional aspect of these viral agents are the need of the hour for designing better and more effective vaccines and for the purpose of curating treatment regimens. Several types of viral vaccines against influenza are currently available in the market but the preventive efficiency of vaccines can be further improved only by the research focused on this group of viruses our study aims in providing several insights into the potential of the Influenza virus thereby promoting the need for an effective measure to be developed to fight in the combat against infectious viruses.

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Conflicts of interest

There are no conflicts of interest.

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