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Resurgence of Influenza A (H3N2) in India: Clinical Outcomes and Public Health Preparedness in 2023

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Abstract

Influenza is a highly contagious respiratory illness with the potential to cause seasonal epidemics and global pandemics due to its continuous genetic evolution. In 2023, India experienced a significant outbreak of Influenza A(H3N2), leading to increased hospital admissions, particularly among children, the elderly, and individuals with comorbidities. Influenza A(H3N2) is known for its rapid antigenic evolution, reduced vaccine effectiveness, and association with severe seasonal outbreaks. This review provides a comprehensive analysis of the 2023 H3N2 outbreak in India, focusing on viral structure, classification, molecular mechanisms of antigenic drift and shift, clinical manifestations across different age groups, diagnostic strategies, vaccination challenges, antiviral treatment options, and prevention measures. Emphasis is placed on the molecular basis of viral evolution and its implications for vaccine design and public health preparedness. Understanding the mechanisms underlying influenza virus variability is essential for strengthening surveillance systems and mitigating the impact of future outbreaks.

1. Introduction

Influenza, commonly referred to as flu, is a contagious respiratory illness caused by influenza viruses that primarily infect the nose, throat, bronchi, and occasionally the lungs. Transmission occurs through respiratory droplets expelled during coughing or sneezing and through contact with contaminated surfaces. Influenza viruses are characterized by high genetic variability, enabling them to evade host immune responses and cause recurrent outbreaks.

The emergence of novel influenza virus strains poses a major global health threat because the general population often lacks pre-existing immunity (Vemula *et al*., 2016). Historically, influenza pandemics have resulted in widespread morbidity, mortality, and socioeconomic disruption. The most devastating pandemic occurred in 1918–1919 ("Spanish flu"), followed by the Asian flu (1957–1958) and the Hong Kong flu (1968–1969). More recently, the 2009 influenza A(H1N1)pdm09 pandemic highlighted the capacity of influenza viruses to spread rapidly across the globe.

In 2023, India reported a resurgence of Influenza A(H3N2), a subtype associated with more severe seasonal outbreaks and comparatively lower vaccine effectiveness. This review aims to critically analyze the virological, molecular, clinical, diagnostic, and preventive aspects of the H3N2 outbreak in India, emphasizing the role of antigenic evolution and public health implications.

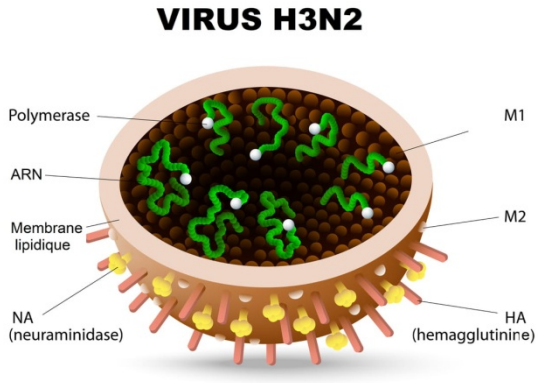
2. Influenza virus: Classification and structure

Influenza viruses belong to the family *Orthomyxoviridae* and are enveloped viruses containing a segmented, negative-sense, single-stranded RNA genome (Shim *et al*., 2017). The viral genome consists of eight RNA segments, each encoding one or more viral proteins essential for replication and assembly.

The virion surface is studded with two major glycoproteins:

- **Hemagglutinin (HA):** Facilitates viral attachment and entry into host cells by binding to sialic acid receptors.
- **Neuraminidase (NA):** Enables release of newly formed virions from infected host cells.

These surface proteins serve as the primary antigens recognized by the host immune system and are central to viral classification, immune escape, and vaccine design (Moss *et al*., 2023).



Courtesy: https://sante.journaldesfemmes.fr/fiches-maladies/2875225-virus-a-h3n2-grippe-symptomes-france-vaccin/

3. Types of influenza viruses

Influenza viruses are classified into four types:

- **Influenza A:** Infects humans and animals; responsible for seasonal epidemics and pandemics.
- **Influenza B:** Causes seasonal epidemics; divided into B/Victoria and B/Yamagata lineages.
- **Influenza C:** Causes mild illness; not associated with epidemics.
- **Influenza D:** Primarily infects cattle; no known human disease.

Influenza A viruses are further subdivided based on HA and NA proteins. To date, 18 HA (H1–H18) and 11 NA (N1–N11) subtypes have been identified. Among these, A(H1N1) and A(H3N2) currently circulate in humans (Alymova, 2016).

4. Molecular evolution of influenza viruses

4.1 Antigenic Drift

Antigenic drift refers to gradual, continuous genetic changes caused by point mutations in the HA and NA genes during viral replication (Yang et al., 2016). These mutations alter antigenic sites, reducing recognition by pre-existing antibodies and allowing immune escape. Antigenic drift is responsible for seasonal influenza epidemics and necessitates annual updates of influenza vaccines.

4.2 Antigenic Shift

Antigenic shift is an abrupt, major genetic change resulting from reassortment of gene segments when two different influenza A viruses infect the same host cell (Wolf *et al*., 2013). This process can generate a novel influenza virus subtype to which the human population has little or no immunity, potentially leading to pandemics. Antigenic shift occurs exclusively in influenza A viruses.

5. Influenza A(H3N2): virology and global significance

Influenza A(H3N2) has been a dominant seasonal influenza strain for several decades and is associated with increased disease severity, higher hospitalization rates, and reduced vaccine effectiveness. The H3N2 subtype undergoes rapid antigenic drift, often resulting in vaccine mismatch (Lin *et al*., 2017). Multiple genetic clades and subclades of H3N2 co-circulate globally, complicating surveillance and control efforts (Fall *et al*., 2023).

6. Clinical manifestations

6.1 Adults

Symptoms include fever, chills, headache, myalgia, fatigue, dry cough, sore throat, and nasal congestion. Severe cases may present with pneumonia, respiratory distress, or exacerbation of chronic illnesses (Longsompurana *et al*., 2023).

6.2 Children

Children may exhibit gastrointestinal symptoms such as nausea, vomiting, and diarrhea in addition to respiratory symptoms (Taubenberger *et al*., 2010). Severe complications include dehydration, pneumonia, and otitis media.

6.3 Infants

Influenza can be life-threatening in infants, presenting with poor feeding, lethargy, respiratory distress, and high fever. Immediate medical attention is required in severe cases.

7. Diagnosis

Diagnostic methods include (Jones *et al*., 2008):

- **Rapid Influenza Diagnostic Tests (RIDTs):** Provide quick results but have lower sensitivity.
- **Molecular Tests (RT-PCR):** High sensitivity and specificity; considered the gold standard.
- **Viral Culture:** Used mainly for surveillance and research purposes.

8. Vaccination and vaccine effectiveness

Seasonal influenza vaccines are formulated annually to include circulating strains of influenza A(H1N1), A(H3N2), and influenza B lineages (Horton., 2010). Vaccine effectiveness against H3N2 is often lower due to rapid antigenic drift. Despite this, vaccination remains the most

effective strategy for reducing disease severity, complications, and transmission.

9. Treatment

Antiviral medications are most effective when administered within 48 hours of symptom onset and include:

- **Neuraminidase inhibitors:** Oseltamivir, zanamivir, peramivir
- **Cap-dependent endonuclease inhibitor:** Baloxavirmarboxil

Supportive care remains essential for symptom management.

10. Prevention and public health measures

Preventive strategies include:

- Annual vaccination
- Hand hygiene and respiratory etiquette
- Isolation of infected individuals
- Surveillance and early outbreak detection

High-risk populations should receive priority vaccination and early antiviral therapy.

11. Timeline of infection

Influenza symptoms typically appear 1–4 days after exposure. Infectivity peaks within the first 3–4 days of illness, (Jain *et al*., 2009) with most individuals recovering within one week, although cough and fatigue may persist longer.

12. Conclusion

The 2023 outbreak of Influenza A(H3N2) in India underscores the persistent threat posed by rapidly evolving influenza viruses. Antigenic drift and reassortment continue to challenge vaccine effectiveness and outbreak control. Strengthened genomic surveillance, timely vaccine updates, public awareness, and early therapeutic interventions are critical for mitigating the impact of seasonal influenza. Continued research into viral evolution and host immune responses will enhance preparedness for future outbreaks.

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