Human Influenza Virus - A Systematic Review

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Influenza is an acute respiratory disease caused by the influenza A or B virus. It often occurs in outbreaks and epidemics worldwide, mainly during the winter season. WHO, 2023 estimates the worldwide annual epidemics of influenza to be 3 to 5 million severe cases. Influenza virus replicates inside nucleus of the host cell and access the nuclear machinery during replication. The severity depends on multiple factors entailing pandemic virus strain and level of immunity in an individual. Although, the epidemiology of the influenza virus has been studies intensively for several years but the various facts regarding its transmission still need thorough understanding. Thus, this review article focuses on significant aspects of virological, epidemiological, and clinical features related to influenza virus to comprehend better the disease transmission and its pathogenesis.
INTRODUCTION:
Lower respiratory tract infections are the most common type of infection encountered by people in their routine life. Parts involved in respiratory infections are- the sinuses, throat, airways, and lungs. Influenza viruses are commonly known for causing respiratory infections. They belong to Family Orthomyxoviridae and have various types of viruses including A, B, C, and D-type viruses whereas Influenza types A and B are known to cause seasonal epidemics of the disease. According to WHO, 2023, the worldwide annual epidemics of influenza have resulted in about 3 to 5 million cases of severe illness and about 290,000 to 650,000 respiratory deaths. Structurally these viruses consist of negative sense-segmented RNA covered within an envelope. They are responsible for causing a condition as mild as the flu and as severe as respiratory failure, acute respiratory distress syndrome (ARDS). These viral infections also exacerbate underlying conditions such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, heart failure, coronary artery disease, and diabetes. As a matter of concern these viral diseases are known to have a deep impact on the global economy as they cause seasonal as well as annual epidemics however, the novel subtypes of the Influenza A virus (IAV) also have the potential of causing global pandemics. Beginning in 1918, the Spanish flu (Swine H1N1) was followed by the Asian flu in 1957 (H2N2), the 1968 Hongkong flu (H3N2), and finally, in 2009 Swine flu (H1N1), Influenza caused various pandemics in history. Seasonal epidemics refer to the regional spread of infection due to an existing agent, in a particular climate. In the case of influenza, seasonal epidemics occur mainly during winters in temperate regions, due to better stability of the influenza virus at cold temperatures, whereas in tropical regions, epidemics of influenza are generally observed in the monsoon season. The environmental factors responsible for the transmission of influenza viruses resulting in seasonal epidemics are- Temperature and Humidity. On the other hand, Pandemics like swine flu, and avian flu refer to the spread of a novel subtype in wider regions across various countries. Epidemics can result in high levels of worker/school absenteeism and productivity losses. Clinics and hospitals can be overwhelmed during peak illness periods. Research estimates 99% of deaths in children under 5 years of age in developing countries with influenza-related lower respiratory tract infections. The treatment of influenza depends on the correct diagnosis. Nowadays there has been great advancement in diagnostics, antiviral drugs, and vaccinations, but the world still faces a huge risk of influenza pandemics due to continuous reassortment (antigenic shift) and antigenic drift of the viral genomic segments.

TYPES OF INFLUENZA VIRUSES
Four types of influenza viruses have been reported namely: A, B, C, and D. Influenza A and B viruses cause seasonal epidemics of disease in people (known as flu season). Influenza A viruses are the only viruses known to cause flu pandemics (i.e., global epidemics of flu disease). A pandemic can occur when a new and different influenza A virus emerges that infects people, has the ability to spread efficiently among people, and against which people have little or no immunity. Influenza C virus infections generally cause mild illness and are not thought to cause human epidemics. Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people. Influenza A viruses are divided into subtypes based on the proteins present on the surface of the virus: hemagglutinin (H) and neuraminidase (N). There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes (H1 through H18 and N1 through N11, respectively). There are many more influenza A subtype combinations given the propensity for virus “reassortment.” Reassortment is a process by which influenza viruses swap gene segments and it occurs when two influenza viruses infect a host at the same time and swap genetic information. Current subtypes of influenza A viruses that routinely circulate in people include A(H1N1) and A(H3N2). Influenza A subtypes can be further broken down into different genetic “clades” and “sub-clades.” These are also called “groups” and “sub-groups,” respectively. An influenza clade or group is a further
subdivided based on the similarity of their HA gene sequences. Clades and subclades are shown on phylogenetic trees as groups of viruses that usually have similar genetic changes (i.e., nucleotide or amino acid changes) and have a single common ancestor represented as a node in the tree. Dividing viruses into clades and subclades helps flu experts track the proportion of viruses from different clades in circulation. Clades and sub-clades that are genetically different from others are not necessarily different in there antigens. Flu viruses have hemagglutinin (H) and neuraminidase (N) surface proteins which acts as antigens. Antigens are molecular structures on the surface of viruses that are recognized by the immune system and can trigger an immune response (such as antibody production). The antigenic properties are a reflection of the antibody or immune response triggered by the antigens on a particular virus. When two flu viruses are antigenically different, this means that a host’s immune response (antibodies) elicited by infection or vaccination with one of the viruses will not as easily recognize and neutralize the other virus. Therefore, for antigenically different viruses, immunity developed against one of the viruses will not necessarily protect against the other virus as well. On the other hand, when two flu viruses are antigenically similar, a host’s immune response (antibodies) elicited by infection or vaccination with one of the viruses will recognize and neutralize the other virus, thereby protecting against the other virus.

Influenza B viruses are not divided into subtypes, but instead are further classified into two lineages: B/Yamagata and B/Victoria. Similar to influenza A viruses, influenza B viruses can then be further classified into specific clades and sub-clades. Influenza B viruses generally change more slowly in terms of their genetic and antigenic properties than influenza A viruses, especially influenza A(H3N2) viruses. Influenza surveillance data from recent years shows co-circulation of influenza B viruses from both lineages in the United States and around the world. However, the proportion of influenza B viruses from each lineage that circulate can vary by geographic location and by season. In recent years, flu B/Yamagata viruses have circulated much less frequently in comparison to flu B/Victoria viruses globally.

**Human Seasonal Influenza Viruses**

This graphic shows the two types of influenza viruses (A and B) that cause most human illness and that are responsible for flu seasons each year. Influenza A viruses are further classified into subtypes, while influenza B viruses are further classified into two lineages: B/Yamagata and B/Victoria. Both influenza A and B viruses can be further classified into clades and sub-clades (which are sometimes called groups and sub-groups.) Note that this graphic is an example, and currently circulating influenza clades and subclades may differ from those presented here.

**SYMPTOMS:**
Onset of influenza symptoms is sudden. Respiratory symptoms include cough, sore throat, and runny or
stuffy nose. Systemic symptoms generally include fever, chills, headache, malaise, and myalgia. Vomiting and diarrhoea may also occur, especially in children. Recovery is rapid; fever usually resolves within 3 to 4 days and other symptoms within approximately 7 days. Some patients may have lingering asthenia (lack of strength or energy) for several weeks.

**STRUCTURE OF INFLUENZA VIRUS**

The influenza virus comprises 8 segmented Negative-sense RNA genomes in its core which code for about 20 proteins. Each of these viral RNA segments consists of viral RNA (vRNA) molecule associated with viral polymerase proteins – Polymerase basic 1 (PB1) and 2 (PB2), Polymerase acidic (PA), and nucleoprotein (NP) which is referred to as Viral Ribonucleoprotein (vRNP).

Out of eight, two of the gene segments of viral RNA are responsible for the production of Nonstructural protein (NS1)/ nuclear export protein (NEP) and matrix M1/proton channel M2 proteins. However, the other six segments of these viral RNA encode mRNAs which in turn are translated into nucleoprotein (NP), polymerase subunit (PA, PB1 PB2), hemagglutinin (HA), and NA (Neuraminidase). These NP and polymerases are responsible for the formation of the eight vRNP. These eight vRNPs thus formed are covered by the lipid membrane and M1 which are in turn derived from the Host cell. HA, NA and M2 proteins are embedded in the outer layer of the lipid membrane of the virus.

The other proteins present in the infected cells but not on virions include NS1, NEP, PB1-F2, PA-X, and N40.

**Figure 1: Structure of Influenza Virus (Adapted from Lamb RA and Krug RM (2001))**

IAVs are divided into various subtypes based on virus glycoproteins HA and NA structure. Currently, there are 18 known subtypes of HA (1-18) and 11 of NA (1-11). Influenza strains that cause infection in humans are H1N1 and H3N2.

**REPLICATION CYCLE OF INFLUENZA VIRUS:**

The replication cycle of the Influenza virus occurs when HA binds to sialic acid receptors on the surface of the target epithelial cells of the respiratory tract, dendritic cells, type 2 pneumocytes, alveolar macrophages, or retinal epithelial cells. This interaction of HA (Hemagglutinin) with sialic acid receptors facilitates the virion entry inside the epithelial cells mediated through the process of endocytosis. The virion then gets transported to late endosomes. The elements essential for the virus dynamin-dependent endocytic uptake are Cellular Clathrin, epsin-1 Ras-related GTPase, and COPI.
The virion experiences pH changes when passing from early to late endosomes. This reduced pH in the endosomes results in the production of conformational changes in the HA (through activation of serine proteases) which results in the fusion of the viral-endosomal membrane followed by the degradation of the M1(matrix) protein24,25 resulting in the release of the segmented viral genome into the host cell cytoplasm26.

The vRNPs then enter inside the nucleus from the host cell cytoplasm which is mediated by cytoplasmic importins through nuclear pore complex (NPC), where the negative sense vRNA is first transcribed into positively sense mRNA using a viral polymerase27,28. The regulatory factors for the transcription of vRNA—Cellular hCLE, cyclin T1, CDK9, ANP32A, and pol II favor the transcription of vRNA after which the post-transcriptional changes are induced by PTBP1, NHP2L1, SNRP70, SF3B1, SF3A1, CLK1, UAP56, p14, and PRPF8. Cellular NXF1, E1B-AP5, Rae1, and p15, transport viral mRNAs into the cytoplasm. Stimulated by GRSF1, the viral pre-mRNA is further translated from mRNA in the cytoplasm in a cap-dependent manner by ribosomes. Some of these are transported into the nucleus to replicate vRNA.

After the completion of the whole process of transcription and translation of viral RNA, the quality check of the produced molecules is mediated by chaperones and chaperonins. Certain processes are also responsible for the modification of novel protein molecules which are ISGylation, SUMOylation, and phosphorylation.

Importins and HSP90 are known to assist in the translocation of viral polymerase, NP, and NEP via NPC back to the nucleus where they form NEP-vRNP complexes4. Certain transporters like Crm1, HRB, hNup98, and Raf–MEK–ERK is required for the transport of NEP-vRNPs into the cytoplasm through NPC.

In the cytoplasm, microtubules and Rab11 bring the complexes to the plasma membrane which is necessary for the budding process of new virions. Newly synthesized M1, M2, HA, and NA are also...
transported to the plasma membrane through the trans-Golgi network with the help of COPI and Rab8. Beta-actin, CK2, and Rab11 are cellular proteins required for the budding and release of new virions. Influenza virus also actively exploits cell metabolism to produce viral RNA, proteins, and Lipids. In addition, IAV utilizes amino acids to synthesize viral proteins by hijacking the PI3K–mTor–Akt-mediated autophagy. Virus assembly and budding depend on lipid metabolism (including fatty acid biosynthesis, phospholipid metabolism, and de novo synthesis of cholesterol). Finally, virus replication is sensitive to the cellular redox state, which is essential for the maturation of HA and for the quality of released viral particles.

The overall replication of the viral RNA can be explained in two steps:

1. Synthesis of positive sense complementary RNA strand (cRNA)
2. Conversion of cRNA into new negative sense vRNAs

The newly produced viral RNA and vRNPs are assembled and transported to the atypical cell plasma membranes atypical side, where NA assembles and releases virions.

**CELLULAR FACTORS RESPONSIBLE FOR LIMITING VIRAL REPLICATION AND TRANSLATION:**

The antiviral responses of the target cells begin on entry of IAV inside the cells. The very first response generated by the cells is the activation of antiviral responses along with the production of interferons. Pattern recognition receptors (PRRs), such as TLR3, TLR7, IRF7, MDA5, and RIGI sense incoming viruses and activate transcription of interferon (IFN) genes, such as IFNB1, IL28A, IL29, IL28B, IFNW1, IFNA7, IFNA14, IFNA10, IFNA13, IFNA16, IFNA8, IFNA1, IFNG, IFNA2, and IFNA21. These IFNs stimulate the expression of ISGs (IFN-stimulated genes) in infected and non-infected cells, protecting them from the potential invasion of virions.

**Table 1:** These ISGs result in the production of various antiviral proteins with different modes of action.

<table>
<thead>
<tr>
<th>S no.</th>
<th>Anti-viral protein</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>IFITM1, SAMD9</td>
<td>Prevent the fusion of viral and endosomal membranes</td>
</tr>
<tr>
<td>2.</td>
<td>HERC5, HERC6, USP18, ISG15, TRIM22, ISG20</td>
<td>Mark the viral proteins for degradation</td>
</tr>
<tr>
<td>3.</td>
<td>IFIT1, IFIT2, OASL, IRF7, DDX60, DDX58/RIG-1, IFIH1/MDA5, EIF2AK2/PKR,</td>
<td>Recognizes vRNA</td>
</tr>
<tr>
<td>4.</td>
<td>OAS1, OAS2, OAS3</td>
<td>Degrades vRNA</td>
</tr>
<tr>
<td>5.</td>
<td>ZBP1, PARP1, PARP9, PARP14, PRIC285</td>
<td>Inhibits transcription and translation of vRNA and activates expression of cellular antiviral genes</td>
</tr>
<tr>
<td>6.</td>
<td>RSAD2</td>
<td>Prevents coating of vRNPs with host membrane</td>
</tr>
<tr>
<td>7.</td>
<td>IFITM3</td>
<td>Inactivates budding viruses</td>
</tr>
<tr>
<td>8.</td>
<td>IFI27, XAF1</td>
<td>Regulates apoptosis</td>
</tr>
</tbody>
</table>
Therefore, ISG-expressed proteins inhibit Influenza virus replication in the infected cells and alert non-infected cells to potential infections. They are also responsible for attracting immune cells, triggering an alarm in the central nervous system about the infection.

**RESPONSE OF INFLUENZA VIRUS TO ISG GENE PRODUCTS:**

To counter the effect of ISG gene proteins, IAV produces NS1 (Non-structural proteins) within a few hours of infection. NS1 binds directly to the cellular DNA and blocks anti-viral DNA transcription. NS1 also interacts with vRNA and its replication intermediates to prevent its recognition by cellular PRRs and RNases. It can also bind TRIM25, ISG15, GBP1, and other ISG products to inhibit their functions at transcriptional, post-transcriptional, translational, and post-translational stages. IAV, therefore, influences the innate immune response of the infected individuals to ensure their replication, transcription, and translation.

**HOST RESPONSE’S CONTRIBUTION TO EXAGGERATED INFLUENZA INFECTION:**

Various studies have suggested that the influenza patient mortality rate is due to exaggerated immune responses and not because of influenza.

The prime target of influenza viruses is respiratory epithelial cells which marks the beginning of the anti-viral response. These epithelial cells recognize the Pathogen- or/danger-associated molecular patterns using its diverse pattern recognition receptors. Recognition of such patterns gives rise to an array of signals, ultimately producing Interferon Type 1 and Interferon type 3. The interferon type 1 induces TRAIL i.e., TNF- related apoptosis-inducing ligand, resulting in the induction and sustainment of collateral lung damage by induction of alveolar epithelial cell apoptosis via its receptor DR5 (death receptor 5). Other anti-viral responses include recognition of viral patterns by PKR which activates NF-KB translocation to the nucleus and transcriptional activation of proinflammatory, pro-apoptotic, and antiviral-gene clusters. Other receptors sensing Influenza infection include- NLRP3 inflammasome (NOD-like receptor family, pyrin domain containing 3), and TLR3 and TLR7 (Endosomal toll-like receptors).

**INFLUENZA-RELATED COMPlications:**

The clinical importance of influenza infection is associated not only due to respiratory infections but various other complications as well. Influenza infection is also known to exacerbate the underlying chronic condition of the patient. These underlying conditions are summarized in the table below:

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>9</td>
<td>IDO, COX2, CH25H</td>
</tr>
<tr>
<td>10</td>
<td>Chemokines and Cytokines</td>
</tr>
<tr>
<td>11</td>
<td>MX1, MX2, GBP1, GBP2, GBP3, GBP5, IFI44, GMPR, NT5C3</td>
</tr>
<tr>
<td>11</td>
<td>STAT1</td>
</tr>
</tbody>
</table>

9. IDO, COX2, CH25H Produce neuro- and immuno-modulators

10. Chemokines and Cytokines Activates and recruits immune cells to the site of infection

11. MX1, MX2, GBP1, GBP2, GBP3, GBP5, IFI44, GMPR, NT5C3 GTP catabolism and cytokine processing

11. STAT1 Amplifies autocrine ISG expression and many other antiviral factors
<table>
<thead>
<tr>
<th>Complications</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper-respiratory complications</td>
<td>Otitis media, parotitis, sinusitis, and laryngotracheobronchitis are more common in children than adults</td>
</tr>
<tr>
<td>Lower-respiratory complications</td>
<td>Bronchiolitis is more common in young children than in adults</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>Influenza might precipitate myocardial infarction or heart failure in people with coronary artery disease; cardiac complications can result in critical illness with fatal outcomes</td>
</tr>
<tr>
<td>Gastrointestinal complications</td>
<td>Hepatic failure is rare</td>
</tr>
<tr>
<td>Musculoskeletal complications</td>
<td>Severe myositis (soleus and gastrocnemius) can occur in school-age children; myoglobinuria can cause acute kidney injury</td>
</tr>
<tr>
<td>Renal complications</td>
<td>Can occur with severe pneumonia</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>Encephalopathy and encephalitis are more common in young children, and can be acute or postinfectious with full neurological recovery, sequelae, or fatal outcomes; Reye syndrome is rare in children without salicylate exposure, and Guillain Barre syndrome is uncommon</td>
</tr>
<tr>
<td>Co-infections</td>
<td>Invasive bacterial, viral, and fungal coinfections can cause critical illness and fatal outcomes</td>
</tr>
<tr>
<td>Other complications</td>
<td>People of all ages with chronic disease can experience</td>
</tr>
</tbody>
</table>
toxic shock syndrome, sepsis-like syndrome or sudden death in young infants, premature labour, and fetal loss in pregnant people

worsening of underlying conditions (e.g., chronic obstructive pulmonary disease exacerbation in adults, acute chest syndrome with sickle cell disease, worsening of asthma, and heart failure)

DIAGNOSTIC TESTS FOR INFLUENZA INFECTION:
Clinical diagnosis of influenza is often inaccurate because of overlapping symptoms from infections with other co-circulating respiratory pathogens, including SARS-CoV-2. Diagnostic Testing helps in making of clinical decisions; however, it is very common to obtain false negative results in the case of influenza, which should be properly interpreted in the context of predictive values considering the prevalence of influenza viruses in the tested population, test sensitivity, and specificity. Early diagnosis of the infection aids in the recovery of the patient without much complication and health deterioration. Nasopharyngeal swabs are highly favored for the detection of viruses due to the high yield of viruses obtained. However, based on the test, mid-turbinate nasal swabs or combined nasal and throat swabs are also accepted. Various diagnostic tests available for Influenza testing are:

<table>
<thead>
<tr>
<th>Method</th>
<th>Accuracy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid antigen test</td>
<td>Influenza viral antigen detection by antibodies using a lateral flow immunoassay or rapid immunofluorescent assay, often with a digital analyzer device</td>
<td>Low-to-moderate sensitivity (40–80%) and high specificity</td>
</tr>
<tr>
<td>(10–15 min to results)</td>
<td></td>
<td>Can detect and distinguish influenza A and B virus infection; sensitivity is higher for tests that use an analyzer device; available for point-of-care use; and multiplex tests can detect and distinguish among SARS-CoV-2 and influenza A and B virus infections</td>
</tr>
<tr>
<td>Rapid molecular assay</td>
<td>Influenza viral RNA detection using nucleic acid amplification; requires a small-footprint machine with an embedded analyzer device</td>
<td>High sensitivity (&gt;95%) and high specificity (&gt;99%)</td>
</tr>
<tr>
<td>(15–40 min to results)</td>
<td></td>
<td>Can detect and distinguish influenza A and B virus infection; some assays are available for point-of-care use; multiplex tests can detect and distinguish among SARS-CoV-2 and influenza A and B virus infections; and some assays can also detect RSV</td>
</tr>
</tbody>
</table>
**Molecular assay (45–80 min to results; up to 4–6 h for some assays) done in clinical laboratories**

- Influenza viral RNA detection using nucleic acid amplification; some assays require complex machinery, preanalytical nucleic-acid extraction, and downstream analysis
- High sensitivity (>95%) and high specificity (>99%)
- Can detect and distinguish influenza A and B virus infection; must be done in a certified clinical laboratory or public health laboratory; requires qualified laboratory personnel; multiplex assays can detect and distinguish among SARS-CoV-2 and influenza A and B virus infections; some multiplex assays can also identify influenza A virus subtypes and other respiratory virus and bacterial pathogens

**Immunofluorescence assay (1–4 h to results)**

- Influenza viral antigen detection by antibodies using immunofluorescent staining; requires the collection of upper-respiratory-tract cells and a fluorescent microscope
- Moderate sensitivity and high specificity
- Can detect and distinguish influenza A and B virus infection; must be done in a certified clinical laboratory or public health laboratory; requires qualified laboratory personnel; requires skilled staff; sensitivity depends upon sample preparation; and less commonly used

**Virus culture (1–10 days to results); requires qualified personnel, usually done at public health laboratories**

- Isolation of viable influenza virus using tissue cell culture
- High sensitivity and high specificity
- Can detect and distinguish influenza A and B virus infection; requires complex laboratory space suitable for virus propagation; shell-vial cell culture can yield results in 1–3 days; and standard tissue cell culture might require 3–10 days

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**TREATMENT:**

The effectiveness of anti-viral treatment is based on how early the treatment has started. Nowadays various FDFDA-approved drugs are available for the treatment of influenza A as well as B virus. The medications have different modes of action.

1. Oral oseltamivir, inhaled zanamivir, and intravenous peramivir is Neuraminidase inhibitors (i.e., NAIs)
2. Baloxavir marboxil area cap-dependent endonuclease inhibitor
3. Amantadine and rimantadine are adamantanes.
Note: NAIs and Baloxavir have activity against both influenza A and B viruses. Adamantanes are effective against infection caused by the influenza virus and are therefore not recommended for treatment due to widespread resistance in circulating strains of the influenza A virus. These FDA-approved treatment is only for uncomplicated influenza. 

Table 4: FDA-approved Influenza treatment:

<table>
<thead>
<tr>
<th>Antiviral treatment and age group</th>
<th>Treatment dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir</td>
<td></td>
</tr>
<tr>
<td>Adults (including pregnancy)</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Children (1 year or older) ≤15 kg</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>Children &gt; 15–23 kg</td>
<td>45 mg twice daily</td>
</tr>
<tr>
<td>Children &gt; 23–40 kg</td>
<td>60 mg twice daily</td>
</tr>
<tr>
<td>Children &gt; 40 kg</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Term Infants 0–11 months*</td>
<td>See details in footnote</td>
</tr>
<tr>
<td>Preterm infants**</td>
<td>See details in footnote</td>
</tr>
<tr>
<td>Zanamivir</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>10 mg (two 5-mg inhalations), twice daily</td>
</tr>
<tr>
<td>Children (≥ 7 years)</td>
<td>10 mg (two 5-mg inhalations), twice daily</td>
</tr>
<tr>
<td>Peramivir</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>600 mg intravenous infusion once, given over 15–30 min</td>
</tr>
<tr>
<td>Children (2–12 years)</td>
<td>One 12 mg/kg dose, up to 600 mg maximum, intravenous, given over 15–30 min</td>
</tr>
<tr>
<td>Children (13–17 years)</td>
<td>600 mg intravenous infusion once, given over 15–30 min</td>
</tr>
<tr>
<td>Baloxavir marboxil***</td>
<td></td>
</tr>
<tr>
<td>Adults and children (12 years or older) ≥40–80 kg</td>
<td>Single dose of 40 mg</td>
</tr>
<tr>
<td>Adults and children (12 years or older) ≥80 kg</td>
<td>Single dose of 80 mg</td>
</tr>
</tbody>
</table>

*FDA-approved oral oseltamivir treatment dose for infants 14 days and older and less than 1 year old is 3 mg/kg per dose twice daily. The American Academy of Pediatrics has recommended an oseltamivir treatment dose of 3.5 mg/kg orally twice daily for infants 9–11 months of age.

**Current weight-based dosing recommendations are not appropriate for premature infants. Please refer to American Academy of Pediatrics recommendations (https://pediatrics.aappublications.org/content/142/4/e20182367) for further information.

***Safety and efficacy of Baloxavir marboxil in patients less than 12 years old or weighing less than 40 kg have not been established. There are no data on Baloxavir treatment of hospitalized patients with influenza, and appropriate dosing frequency is unknown. A phase III clinical trial of Baloxavir treatment of hospitalized influenza patients is ongoing: https://clinicaltrials.gov/ct2/show/NCT03684044. The use of influenza-treating anti-viral drugs is associated with certain long-term adverse effects which include.
**VACCINATION:**

Vaccination is the most effective way of preventing influenza infection-associated mortality and morbidity. Annual vaccination against influenza remains the primary mode of prevention against infection. Because previous seasonal vaccinations do not appear to confer protection against 2009 H1N1, new vaccines have been licensed and are available for use.73

**Table 5: Seasonal influenza vaccinations**50

<table>
<thead>
<tr>
<th>Haemagglutinin concentration per virus antigen</th>
<th>Administration</th>
<th>Manufacturing process</th>
<th>Approved age group recommendations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated, split or subunit, at standard dose</td>
<td>7.5 μg or 15 μg (varies by manufacturer and country)</td>
<td>Intramuscular</td>
<td>Egg-grown viruses; inactivated</td>
</tr>
<tr>
<td>Inactivated, split or subunit, at standard dose</td>
<td>15 μg</td>
<td>Intramuscular</td>
<td>Egg-grown viruses; inactivated (aluminum phosphate adjuvant might be used in some countries)</td>
</tr>
<tr>
<td>Inactivated, split or subunit, at standard dose</td>
<td>15 μg</td>
<td>Intramuscular</td>
<td>Tissue cell-culture grown; inactivated</td>
</tr>
<tr>
<td>Live attenuated, at standard dose</td>
<td>15 μg</td>
<td>Intranasal</td>
<td>Egg-grown viruses that replicate in nasal passages, but do not replicate at internal body temperature (cold adapted), and express virus antigens</td>
</tr>
<tr>
<td>Recombinant</td>
<td>45 μg</td>
<td>Intramuscular</td>
<td>Recombinant haemagglutinin DNA expressed in insect-cell culture and purified</td>
</tr>
<tr>
<td>Inactivated, split or subunit, at standard dose, and adjuvanted</td>
<td>15 μg</td>
<td>Intramuscular</td>
<td>Egg-grown viruses; inactivated; administered with MF59 adjuvant</td>
</tr>
</tbody>
</table>
Adapted from Groskopf and colleagues. Vaccines might be available in trivalent or more commonly quadrivalent formulations depending on country and manufacturer. Trivalent vaccines contain antigens for three virus strains; one influenza A(H1N1) pdm 09 strain, one influenza A(H3N2) strain, and either one influenza B or Yamagata lineage or one B/Victoria lineage. Quadrivalent vaccines contain antigens for one representative of both type B lineages in addition to the A(H1N1) pdm 09 and A(H3N2) virus strains.

*Check national guidance for differences in recommended age groups.

CONCLUSION:
Influenza virus infection is a zoonotic disease that spreads rapidly and greatly affects human population across the large geographical regions within a short period of time. High mutational rate in surface glycoproteins such as HA and NA increases the capacity of virus to adapt efficiently in human population and is accountable for varying degree of pathology from mild to severe. A lot of research has been reported in the field of vaccine formulation, however, excess use of drugs in treatment of seasonal and pandemic influenza in post-prophylaxis cases are also challenged by emergence of drug-resistant mutants. Thus, a better comprehension of the ecology, viral and host determinants that allows inter-species transmission and adaptation of influenza viruses to new hosts may facilitate earlier recognition and the risk assessment may help at preventing emergence at the source. Also, diving deep into molecular mechanism unrevealed various metabolic pathways triggered by virus during pathogenesis which will further help in designing new drugs and vaccines.

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CONFLICT OF INTEREST: None

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