Orthomyxoviridae

Influenza viruses

Objectives

— 1- Describe the important properties of Orthomyxoviruses.
— 2- Differentiate between the two types of antigenic changes in influenza viruses.
— 3- Discuss the clinical findings & laboratory diagnosis.
— 4- Specify the treatment & prevention of infections.
— 5- Explain the differences between avian & swine influenza viruses in humans.

Types of influenza viruses

1. Influenza type A

This type includes influenza A viruses of human and also widespread in animals, particularly aquatic birds, chickens, ducks, pigs, horses, and seals. Influenza type A is
responsible for pandemic and for most cases of epidemic influenza (antigenically highly variable).

2. **Influenza type B**
   This type includes influenza B viruses which are mainly found in humans. Influenza type B may exhibit antigenic changes and sometimes causes epidemics.

3. **Influenza type C**
   This type includes influenza C viruses of human and swine. Influenza type C is antigenically stable.

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**Important properties of Orthomyxoviruses**

**Virion:**
Spherical, pleomorphic, 80-120 nm in diameter (helical nucleocapsid)

**Genome:**
Single-stranded RNA, segmented (eight molecules), negative-sense (polarity).
**Envelope:**
Contains viral hemagglutinin (HA) and neuraminidase (NA) proteins.
The single-stranded, negative-sense RNA genomes of Influenza A and B viruses occur as eight separate segments; influenza C viruses contain seven segments of RNA, lacking a neuraminidase gene.
The nucleocapsid (NP) and matrix (M) proteins, are used to divide influenza viruses into 3 types.
Influenza A virus
## Influenza virus proteins and its function

<table>
<thead>
<tr>
<th>Segment</th>
<th>Designation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PB2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PB1</td>
<td>RNA transcriptase components</td>
</tr>
<tr>
<td>3</td>
<td>PA</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>HA</td>
<td>Hemagglutinin, trimer, mediates virus attachments to cells (cell surface receptor neuraminic acid, sialic acid). Target of neutralizing antibody</td>
</tr>
<tr>
<td>5</td>
<td>NP</td>
<td>Associated with RNA and polymerase proteins, helical structure, nucleocapsid</td>
</tr>
<tr>
<td>6</td>
<td>NA</td>
<td>Neuraminidase; tetramer; cleaves (neuraminic acid, sialic acid) and promotes virus release</td>
</tr>
<tr>
<td>7</td>
<td>M1</td>
<td>Matrix protein, major component of virions; lines inside of envelope, involved in assembly.</td>
</tr>
<tr>
<td></td>
<td>M2</td>
<td>Integral membrane protein; ion channel; essential for virus uncoating</td>
</tr>
<tr>
<td>8</td>
<td>NS1</td>
<td>Non-structural; high abundance; inhibit pre-mRNA splicing.</td>
</tr>
<tr>
<td></td>
<td>NS2</td>
<td>Minor component of virions; Nuclear export of viral RNPS</td>
</tr>
</tbody>
</table>
Viral transmission

Influenza virus spreads from person to person by airborne droplets or by contact with contaminated hands or surfaces. Close contact and close environments favor transmission.

Clinical findings

Influenza attacks mainly the upper respiratory tract. It poses a serious risk for the elderly, the very young, and people with underlying medical conditions such as lung, kidney, or heart problems, diabetes, or cancer.

A. Uncomplicated influenza

After an incubation period of 1-4 days, symptoms of classic influenza usually appear abruptly. The symptoms usually resolve spontaneously in 4-7 days, but in some cases may last up to two weeks.

B. Pneumonia

Serious complications usually occur only in elderly and debilitated, especially those with underlying chronic disease. Pregnancy appears to be a risk factor for lethal pulmonary complications.

Pneumonia complicating influenza infections can be viral, secondary bacterial, or a combination of the two. Combined viral-bacterial pneumonia is approximately three times more common.
Staphylococcus aureus coinfection has been reported to have a fatality rate of up to 42%. Some Staphylococcus aureus strains secrete a protease able to cleave the influenza HA, thereby allowing production of much higher titers of infectious virus in the lungs.

C. Reye’s syndrome:

An Acute encephalopathy of children and adolescents (2-16) years of age. The mortality rate (10-40%). It is recognized rare complication of influenza B, A and Herpes virus infections. There is a possible relationship between salicylate use and subsequent development of Reye’s syndrome.
Genetic variation in influenza viruses

A. Events leading to different subtypes

**Antigenic shift**: Major antigenic changes in one or both surface glycoproteins (HA and/ or NA) in influenza A viruses. This due to:

1- Genetic **reassortment** of surface glycoprotein genes occurs between different strains of a given type (possibly involving animal strains).

2- **Reemergence** of strains which had previously been in circulation.

Every 10-40 years when a new subtype of influenza A appears, a pandemic results. This happened in:

1918 H1N1 (Spanish flu)
1957 H2N2 (Asian flu)
1968 H3N2 (Hong Kong flu)
1977 H1N1 (Russian flu), i.e. H1N1 subtype reemerged in 1977

B. Events leading to variation within subtypes

**Antigenic drift**: Minor antigenic changes due to accumulation of point mutations in the gene, resulting in amino acid changes in the protein. Sequence changes can alter antigenic site.

The period between epidemic waves of influenza A (2-3) years.
The interepidemic period for type B (3-6) years. (no subtypes).
**Nomenclature system for influenza virus isolates:**

Type, host of origin, geographic origin, strain number, and year of isolation. Antigenic descriptions of the HA, NA for type A.

e.g : A / Hong Kong / 03 / 68 (H3N2)

So far 16 subtype of HA (H1-H16) and nine subtypes of NA (N1-N9) have been recovered from birds, animals or humans. Four HA (H1, H2, H3, H5) and two NA (N1, N2) subtypes have been recovered from humans.
**Avian influenza**

In 1997, in Hong Kong, the first documented infection of humans by avian influenza A virus (H5N1) occurred. The source was domestic poultry. 2003-2009 more than 408 human cases were reported worldwide. The mortality rate is high (62%). A few rare cases of human-human spread occurred.

**Swine influenza**

A novel swine-origin H1N1 virus appeared in early 2009 and reached pandemic spread by mid-year. It was quadruple reassortant, containing genes from both North American and Eurasian swine viruses, as well as from avian and human influenza viruses. The virus was readily transmissible among humans.
The HA, NP and NS protein genes are of North American swine origin. The NA & M protein genes are of Eurasian swine origin. The genes that encode two subunits of polymerase are of North American avian origin, the third subunit of the polymerase is of human H3N2 origin.

**Laboratory Diagnosis**

- **Specimens:**
  Nasal washings, gargles, and throat swabs.

- **Isolation:**
  1. Embryonated eggs
  2. Primary monkey kidney cells

  Cell cultures can be tested for the presence of virus by hemadsorption 3-5 days after inoculation.

- **Identification:**
  Viral isolates can be identified by hemagglutination inhibition test (HI)

- **Serology:**
  Routine serodiagnostic tests in use are based on (HI) and ELISA.

- **Polymerase chain reaction (PCR).**
  Rapid tests based on detection of influenza RNA in clinical specimens using reverse-transcription polymerase chain reaction (RT-PCR) are
preferred for diagnosis of influenza. RT-PCR is rapid (<1 day), sensitive, and specific.

**Prevention (vaccines):**
The different types of vaccines in use today for influenza included an annual vaccine available for influenza A and B, typically two A strains and one B strain.

A. **Inactivated-virus vaccines**, are either whole virus, split or subunit (surface Ag preparations purified HA & NA) vaccines. These vaccines are administered intramuscularly.

B. **Live-virus vaccines**

**Treatment**
Amantadine and rimantadine for systemic use in treatment and prophylaxis of influenza A (blocks viral uncoating). Resistant viruses emerge during therapy.

Zanamivir (Relenza) and Oseltamivir (Tamiflu) NA inhibitors. These drugs are effective against both influenza A and B viuses
Summary

—1-Influenza is enveloped virus with segmented, single-stranded RNA of negative polarity. The two major antigens are HA & NA on separate surface spikes.

—2-The two surface antigens undergo antigenic variation independent of each other, minor (antigenic drift), major (antigenic shift).

—3-Pneumonia complicating influenza.

—4-Oseltamivir (Tamiflu) & zanamivir (Relenza) are used for treatment & prevention of influenza.

—5-The main mode of prevention is the vaccine, which consists of influenza A & B viruses, typically two A strains & one B strain currently causing disease.

—6-Swine influenza virus (H1N1) spread readily from human to human in contrast to avian (H5N1) strain that does not (spread rarely).