12

Virology

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Orthomyxoviruses (Influenza Viruses)

Orthomyxoviruses are **enveloped**, viruses containing a **segmented negative**-strand **RNA** genome.

- The negative viral RNA strand must be converted to a positive RNA by RNA polymerase before translation.

- The positive viral RNA strand encodes mRNA (messenger RNA) and protein.

Viruses in this family infect **humans (influenza viruses)**, horses, and pigs, as well as nondomestic water fowl (birds), and are the cause of influenza.

Recall that the most common cause of common cold is the **rhinovirus.** However, there are other causes, like influenza C.

Influenza C virus is associated with **common cold**-like symptoms rather than flu symptoms. On the other hand, Influenza A and B viruses are responsible for seasonal **flu** epidemics each year.

Orthomyxoviruses are divided into 3 types: influenza A, B, and **C**.

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.

Influenza virus particles contain **nine** different **structural** proteins. The nucleoprotein (NP) associates with the viral RNA to form ribonucleoprotein (RNP) structure that assumes a helical configuration and forms the viral nucleocapsid.

Three large proteins (PB1, PB2, and PA) are bound to the viral RNP and are responsible for RNA transcription and replication (polymerase basic and acidic proteins).

The matrix (M1) protein, which forms a shell underneath the viral lipid envelope, is important in particle morphogenesis and is a major component of the virion (~40% of viral protein).

Swine flu (disease of pigs that can be passed to humans) is caused by H1N1 influenza virus.

The (M2) ion channel protein is a target for many anti-influenza drugs.

Antigenic differences exhibited by two of the internal structural proteins, **the nucleocapsid (NP) and matrix (M) proteins,** are used to divide influenza viruses into types A, B, and C types.

Two virus-encoded **glycoproteins**, **hemagglutinin** (**HA**) and **neuraminidase** (**NA**) are inserted into the envelope -of influenza A and B viruses- and are exposed as spikes long on the surface of the particle.

Avian flu (disease of birds that can be passed to humans) is caused by H5N1 influenza virus.

These two surface glycoproteins determine **antigenic variation** of influenza viruses and host immunity; antibodies are targeted against these proteins.

Sub-**typing** and nomenclature of Influenza A viruses are based on protein differences in (HA) and (NA) proteins present on their surfaces.

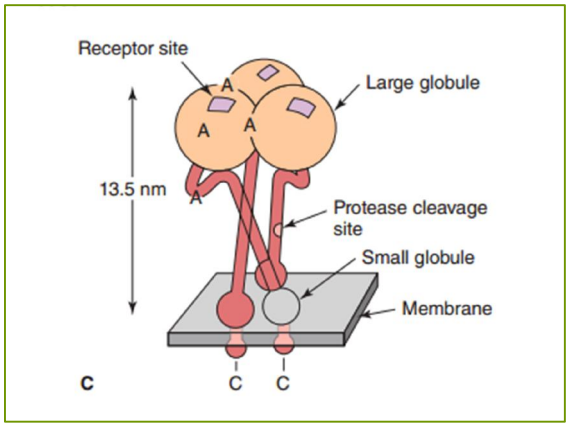
Types A and B's genome is composed of 8 RNA segments coding for the 2 most important proteins, HA and NA

Type C's genome is composed of 7 segments. The missing segment is the segment coding for the NA protein.

(HA) protein structure:

The **(HA)** protein of influenza virus binds virus particles to susceptible cells and is the **major antigen** against which neutralizing **antibodies** are directed.

The (**HA**) protein is cleaved by respiratory proteases into **HA1** and **HA2.**



The HA spike on the virus particle is a **trimer** composed of three intertwined HA1 and HA2 dimers.

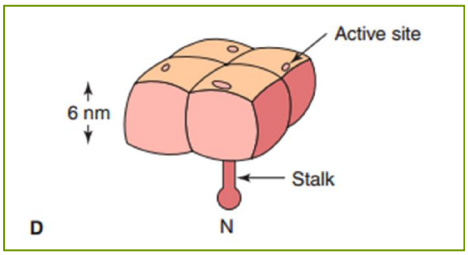
The **(HA)** protein binds to sialic acid residues on the respiratory epithelium. (for entrance)

The **cleavage** of **(HA)** is necessary for the virus particle to be infectious and is mediated by **cellular** proteases.

Influenza viruses remain confined to the RT (respiratory tract) because the proteases that cleave (**HA**) are most common at those sites.

Examples have been noted of **more** virulent **influenza** viruses that have adapted to use **a more ubiquitous enzyme**, such as plasmin, to cleave **(HA)** and promote **widespread** infection of cells. **Therefore, they can infect the lower respiratory tract and are associated with pneumonia**.

(NA) protein structure:



The spike on the virus particle is a **tetramer** composed of four identical monomers.

The (NA) functions at the end of the viral replication cycle. It is a sialidase , an enzyme that removes sialic acid (virus receptors), from glycoconjugates.

(NA) facilitates **release** of virus particles from infected cell surfaces during the budding process and helps prevent **self-aggregation** of virions by removing **sialic acid residues** from viral **glycoproteins**.

It is possible that (NA) helps the virus **negotiate** through the mucin layer in the respiratory tract to reach the target epithelial cells.

The standard nomenclature system for influenza virus isolates includes the following information: **type**, **host of origin (swine, bird…), geographic origin (e.g. Iowa in US)**, **strain**, **number**, and **year** of **isolation**.

Antigenic descriptions of the (HA) and the (NA) are given in parentheses for **type A**.

The host of origin is not indicated for human isolates, such as:

A/Hong Kong/03/68(H3N2), but it is indicated for others, such as: A/swine/Iowa/15/30(H1N1).

So far, **15** sub-types of (HA) (H1–H15) and **nine** sub-types of NA (N1–N9), in many different combinations, have been recovered from birds, animals, or humans.

Four (HA) (**H1–H3, H5**) and **two** (NA) (**N1, N2**) sub-types have been recovered from humans, such as: H1N1, H2N2, H3N2…What about H1N3?

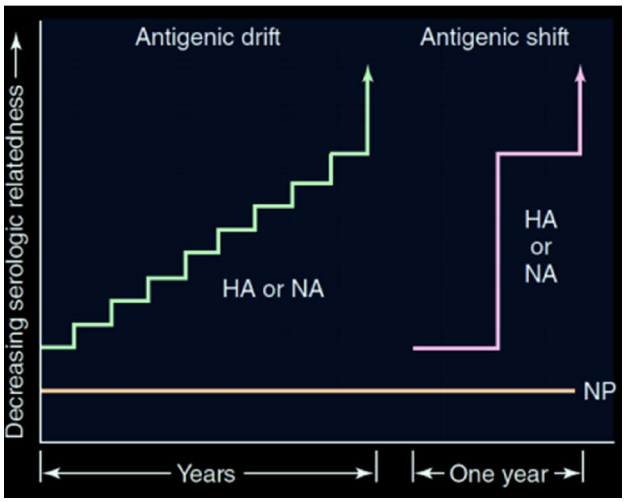
SEASONS OF INFLUENZA:

The two surface antigens (HA and NA) of influenza undergo antigenic variation independent of each other.

Minor antigenic changes are termed **antigenic drifts,** and **major antigenic changes** are called **antigenic shifts**; resulting in the appearance of new subtypes.

Antigenic **drift** is caused by the accumulation of point **mutations** in the gene, resulting in amino acid **changes** in the protein.

Antigenic **drift** allows for evasion of the host immune system by small mutations in the (HA) and (NA) genes, making the protein **less recognizable to pre-existing host immunity.**



This is why you get the Flu every other year or so. It is because of these minor changes that your body will mount an immune reaction against these similar, but newly combined, antigens.

Antigenic drift is responsible for the seasonal influenza per 2-3 years.

Genetic re-assortment: the exchange of complete gene segments, producing new (novel) viruses.

Antigenic shift reflects drastic changes in the sequence of a viral surface protein. These changes are too extreme to be explained by mutations. ***Antigenic shifts*** are produced by genetic re-assortment between human, swine, and avian influenza viruses.

WHAT REALLY HAPPENS IN AN ANTIGENIC SHIFT:

1* an Influenza A infected patient that interacts with animals might come across an already infected animal with Influenza A

2* The infected animal transfers the virus to the infected patient. The patient now has 2 different influenza Types in jis body.

3* The 2 viruses inside the patient with exchange RNA segments (re-assortment), producing a new novel virus, a virus that is never seen before.

This process causes the genetic shift.

This novel virus is new to the human population. No vaccines have been made against its new antigens. No one has humoral immunity against it. This is when a **Pandemic** arises.

This novel virus, upon infecting people, even **immunocompetent** individuals, will cause an immune reaction called **CYTOKINE STORM.**

This reaction is what usually kills people. People who are **immunocompromised** are the most affected, but this reaction could also mill immunocompetent individuals.

Influenza **B and C** viruses do **NOT** exhibit antigenic shift because few related viruses exist in animals.

Antigenic shift is responsible for influenza pandemics per 20-30 years.

CLINICAL FEATURES:

Influenza attacks mainly the **upper respiratory tract.**

It poses a serious risk for **elderly** adults, **very** young children, and people with underlying medical conditions such as **lung, kidney, or heart problems, diabetes, or cancer.**

Symptoms of classic influenza usually appear **abruptly** (sudden onset) and include chills, headache, and dry cough followed closely by high fever, generalized, muscular aches, malaise, and anorexia.

*The fever usually lasts 3–5 days, as do the systemic symptoms.

*Respiratory symptoms typically last another 3–4 days. The cough and weakness may persist for 2–4 weeks after major symptoms subside. Mild or asymptomatic infections may occur.

*These symptoms may be induced by any strain of influenza **A or B**. In contrast, **influenza C rarely causes the influenza syndrome, causing instead a common cold illness**. *Coryza* (inflammation of the mucos membranes of the nose) and cough may last for several weeks.

COMPLICATIONS:

Serious **complications** usually occur only in **elderly** adults and debilitated individuals, especially those with underlying **chronic** disease.

Pneumonia complicating influenza infections can be **viral (flu pneumonia, usually by Influenza A virus), secondary bacterial**, or a **combination of the two**.

One of the most causes of post-flu pneumonia in hospitalized people is S.aureus infections. Yet it could also be caused by Viral Pneumonia.

This is attributed to **loss of ciliary clearance**, **dysfunction of phagocytic** cells, and provision of a rich **bacterial growth** medium by the alveolar exudate.

Bacterial pathogens are most often **Staphylococcus aureus**, **Streptococcus pneumoniae**, and **H**. **influenza**.

EPIDEMIOLOGY:

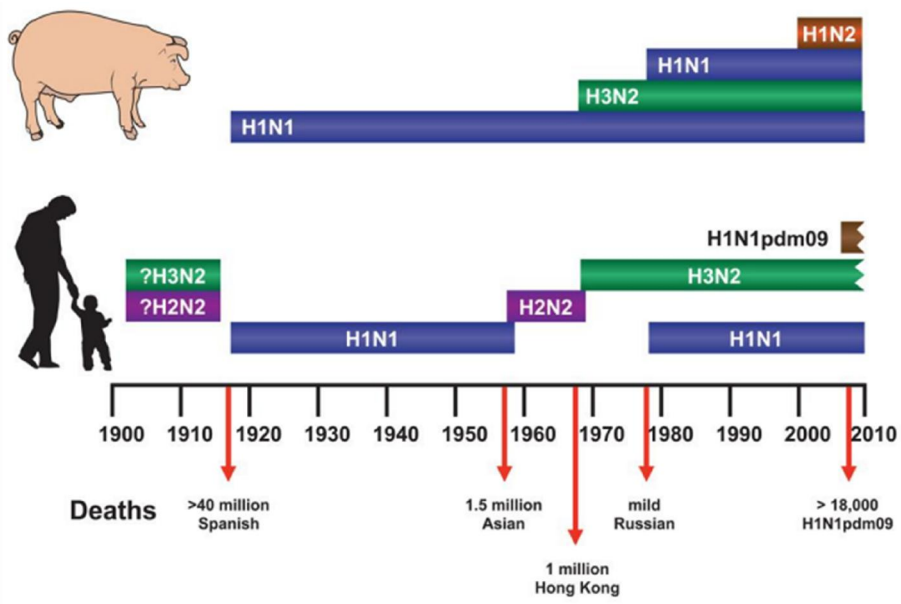
Influenza viruses occur worldwide and cause **annual outbreaks** of variable intensity. It is estimated that **annual epidemics of seasonal influenza** cause 3 –5 million cases of severe illness and 250,000–500,000 deaths worldwide.

The incidence of influenza peaks during the **winter.** However, continuous person-to-person chain of **transmission** must exist throughout the year for maintenance of the agent between epidemics.

Influenza outbreaks occur in waves, the experience in any given year will reflect the interplay between extent of antigenic **drift** of the predominant virus and waning immunity in the population.

The period between epidemic **waves of influenza A** tends to be 2–3 years.

Every 10–40 years, when a **new subtype of influenza A** appears, a **pandemic** result.



Spanish pandemic (1918): It was though that people died from secondary bacterial infections found in their specimens –**specifically Haemophilus influenzae and streptococci Pneumonia**-. However, using reverse genetics, it was found that what killed people in Spanish pandemic was an influenza virus (H1N1).

Hong Kong Pandemic → H2N2

Avian flu→ H5N1

Swine flu → H1N2

DIAGNOSIS:

Definitive diagnosis cannot be made on clinical grounds except in an epidemic situation.

Rapid diagnosis can be made by the demonstration of **viral antigens** in respiratory tract secretions (low sensitivity).

PCR (molecular diagnosis) provides **definitive** diagnosis of flu (higher sensitivity).

TREATMENT:

First-generation antiviral agents effective against influenza A include two related drugs, **amantadine** and **Rimantadine**. Both drugs stop viral un-coating by inhibition of the viral **M2** membrane protein. These agents reduce both the duration and the severity of flu symptoms**, but only if given early in infection.**

Second-generation antiviral agents effective against influenza A and B include **Zanamivir** and **Oseltamivir** (***Tamiflu***). They inhibit viral neuraminidase (**NA**) (which is not present in Influenza C).

Resistant viruses emerge more frequently during therapy with 1st line generation antiviral agents than with 2nd generation agents.

VACICINES:

Inactivated viral vaccines are the primary means of prevention of influenza.

A live-virus vaccine must be **attenuated** so as not to induce the disease it is designed to prevent.

Many types of Influenza vaccine are usually prepared in embryonated eggs, and therefore people with egg intolerance shouldn't take these types of vaccines.

The vaccine is usually a cocktail containing one or two type A viruses (usually H1N1 and H3N2) and one type B virus of the strains isolated in the previous winter's outbreaks.

Existing vaccines are continually being rendered obsolete as the viruses undergo **antigenic drift and shift.**

PRECAUTIONS:

Although **transmission** of influenza virus occurs primarily by aerosol spread, **hand transmission** also is potentially important.

Studies have shown that hand washing with soap and water or the use of alcohol-based hand rubs is highly effective at reducing the amount of virus on human hands.

The end.