

Influenza

Influenza is one of the most important diseases that affect us, and it gained much more concern in the past few years.

First of all let's look at some definitions:

What is the difference between pandemic and epidemic?

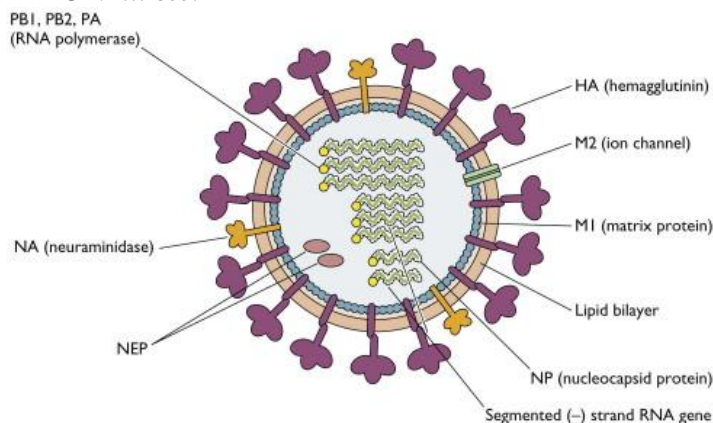
Pandemic: a global outbreak of disease that occurs with new influenza type A (influenza is just an example) that emerges in the human population.

Every time a new influenza type A virus emerges it makes a pandemic and causes serious illness and spreads easily between people worldwide.

Epidemic: seasonal outbreaks. For example we hear that in Jordan in December hundred people were affected by a virus.

Virology of influenza

- It's an **RNA** virus which has 8 gene segments.
- Influenza can be classified into 3 types: Type A, Type B, Type C.
- Have two kinds of spikes:
 1. **Hemagglutinin spikes** and its function is to attach to surface receptor.
 2. **Neuraminidase spikes** and its function is to cut the connection between the HA and the infected cell which allows the release of the virus thus allowing it to infect other cells.
- Type A is further classified according to the type of hemagglutinin HA (1-15 subtypes) and neuraminidase NA (1-9 subtypes). For example: H1N1, H2N2, H5N1... etc.



- Nomenclature : the name should include the following:
Type A, for example,

1. from where it was isolated. (Example: chicken)
 2. Form which city, ex: Hong Kong
 3. Year, ex: (1997)
- Influenza is present in animals in addition to humans; some strains are restricted to humans while others are restricted to animals, some of Type A subtypes affect humans only, animals only or both. Most of type B and Type C affect humans.
 - The most important causes of Viral Pneumonia are Type A and B Influenza (Type C is rarely involved in pneumonia).

Influenza viruses are constantly changing. They can change in two different ways.

Shifting and drifting

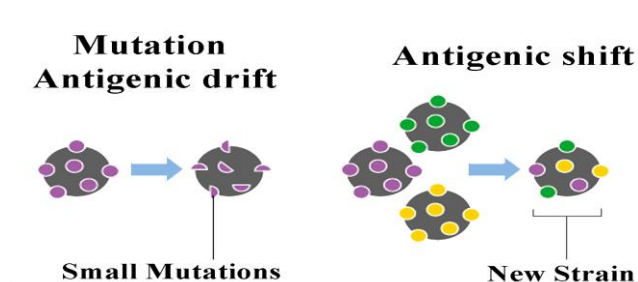
Antigenic shift is the process by which two or more different strains of a virus, or strains of two or more different viruses, combine to form a new subtype having a mixture of the surface antigens of the two or more original strains. (Wikipedia)

Antigenic drift is a mechanism for variation in viruses that involves the accumulation of mutations within the genes that code for antibody-binding sites. (Wikipedia)

Difference between shifting and drifting: shifting occurs on a **larger scale** however drifting occurs on a **smaller scale**, for example the river shifted means that it totally changed its course but when we say that the river drifted this means that it slightly changed its course.

Now what **distinguishes** the influenza virus that it continuously changes. If this change occurs on the level of point mutation we call it **antigenic drift**, which is responsible for the annual **epidemics**, but why doesn't it cause pandemics? Because of **herd immunity and cross protection**.

But if antigenic shift occurred, in this case we'll get cheerily assortment: the virus will gain new genes and segments of RNA so shifting is responsible for **pandemics**. The new gene segments and the new genetic material which the virus gained is usually taken from **non** human viruses (for example viruses that infect birds)

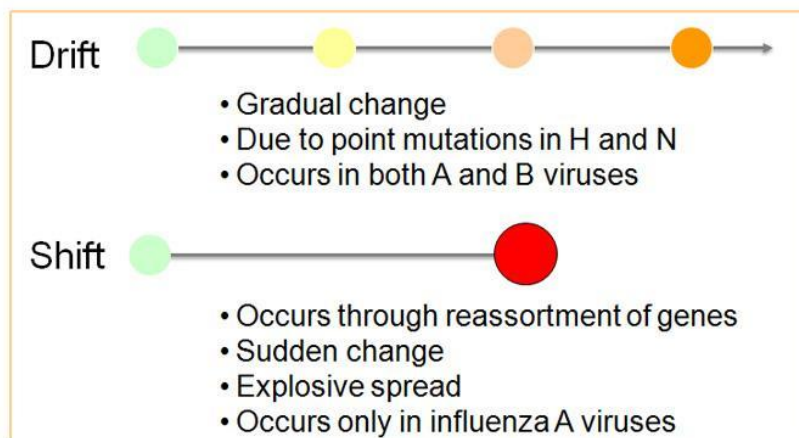


Take for an example a new influenza virus called HxNx, when it appears people have no immunity against it, thus it will spread dramatically worldwide causing a pandemic, in the following year of the virus appearance and number of infected people will drop because people started developing immunity against it. I.e. in the first year of its appearance it will cause a pandemic then in the following years it will be seasonal or epidemic. In average every 30 years we have a pandemic or a new virus, meaning that in 100 years approximately 3 pandemics occur. However, recently this **interpandemic period** (period between two pandemics) started to decrease.

Last 300 years, there are 4 pandemics per century

This is a very useful link about antigenic shift and drift:

<http://www.cdc.gov/flu/about/viruses/change.htm>



Pandemics over the years:

- 1890 due to H2N2
- 1900 due to H3N8
- 1918 due to H1N1, it's also called the Spanish pandemic but its thought that it emerged in America. However it was clear in Spain, 40 million people died due to H1N1.
- Asian (H2N2), 1957 , 1 million died
- Hong Kong 1968-1977, 1 million died
- Russian, 1977
- 2009 due to H1N1 (its different from the H1N1 in 1918, they are similar on some aspects but **50%** of the genetic material is different) used to be called swine influenza however now it's called new H1N1 2009(combination of the human virus with the swine virus). Its mortality rate is below 1%.

Thus H1N1 wasn't one of the major pandemics; add to that its sensitive to its drug.

Avian influenza (أنفلونزا الطيور): **H5N1**, one of the major outbreaks that occurred recently. It was in birds but they do not show symptoms and then it crossed the

species barrier and humans caught it due to birds' migration. In Jordan we reported only **one** case, Egypt was also affected, and the center of the outbreak was china.

It's a very bad disease with a mortality rate is 50%, but fortunately it didn't outbreak outrageously because it's hardly transmitted between people(low infectivity).

It's worth mentioning that H5N1 is still circulating in the world until this moment. But we don't hear about it that much because reported cases are minimal and in certain countries, because as we already said that it's hardly transmitted between people.

Typically we get flu in winter however in pandemics it will occur in a season which isn't usual, for example flu outbreak will occur in summer and it will affect young people. in a study on People who are affected by H5N1 it has been found that people affected are typically aged from 5-24. 9 of them had direct contact with chickens and they had fever, shortness of breath, cough, diarrhea, in lab work they turned to have pancytopenia, 8 have died.

The doctor showed us a chest X-Ray

H5N1 → Chest X-Ray: The lung might become white within few days.

Symptoms of influenza:

- 1) Fever
- 2) Cough
- 3) Sore throat
- 4) Runny Nose
- 5) Headache
- 6) muscle ache
- 7) some may lead to vomiting and diarrhea
- 8) It's possible in some influenza viruses for things to get complicated as in **N1N1** which may lead to severe respiratory disease, pneumonia, ARDS , severe inflammatory reactions(acute respiratory distress syndrome)
(remember in H1N1 the mortality rate late is low, below 1%)

Influenza may lead to super infection, for example it can start with a flu then inflammation in the lungs then an infection by strep. Pneumonia or staph aureus.

How do we diagnose influenza?

1. First we look at the typical symptoms such as fever myalgia nasal congestion.
2. PCR (using tracheal aspirate/ throat or nasal swab).
3. Rapid antigen, but it has poor sensitivity and there are recommendations not to use it. In this method, we take nasal swab, and then look for the antigen in the sample.
4. Antibody antigen > not diagnostic because Serum Antibodies appear late, and by the time they appear you might have already been cured.

Questions asked by students:

Why there is a difference in the capability of these viruses to infect people?

Some viruses are transmitted easily, while others are not, and this is due to presence of specific receptors in humans. Thus people having these receptors are more prone to get infected.

Are all the spikes on these viruses are the same?

As we said there are subtypes for HA and NA, thus in the same virus for example in H1N1 the spikes are the same and they are different from H2N2 but due to point mutations and drifting they will differ, new H1N1 2009 in USA might be different than new H1N1 2009 in France.

How do we treat influenza?

If you have a patient that has influenza and he is stable (no shortness of breath or cyanosis or hypoxia, diabetes, COBD) only typical fever and myalgia then there is no need for antibiotics.

Group of neuraminidase inhibitors such as oseltamivir, zanamivir can be used for the treatment of influenza given in the first 48 hours, early in the course of the disease.

Delayed therapy might be useless, and you should double the dose and the duration of treatment.

Q) How will we differentiate between common cold or flu and judge if we should give the patient antibiotic, since the patient might be first stable and having flu then deteriorate. Giving him an antibiotic from the beginning, will it be better?

There is no simple answer however if the symptoms are severe and the person who is suspected to have flu or a common cold is around someone who is for sure affected by flu then most probably it is flu. Recommend to give the antibiotic from the beginning.

- **Zanamavir (inhaler)**

- **Oseltamivir (oral)** (Tamiflu is the name available in the market) with oral bioavailability over 80%

unfortunately, Resistance for Oseltamivir was reported, with fatal outcomes.

- Vaccines should be taken every once in a while.

They should be administrated as soon as possible (from 24-72 hours)

Vaccines are Available for circulating strains, and need to be manufactured for each new stain

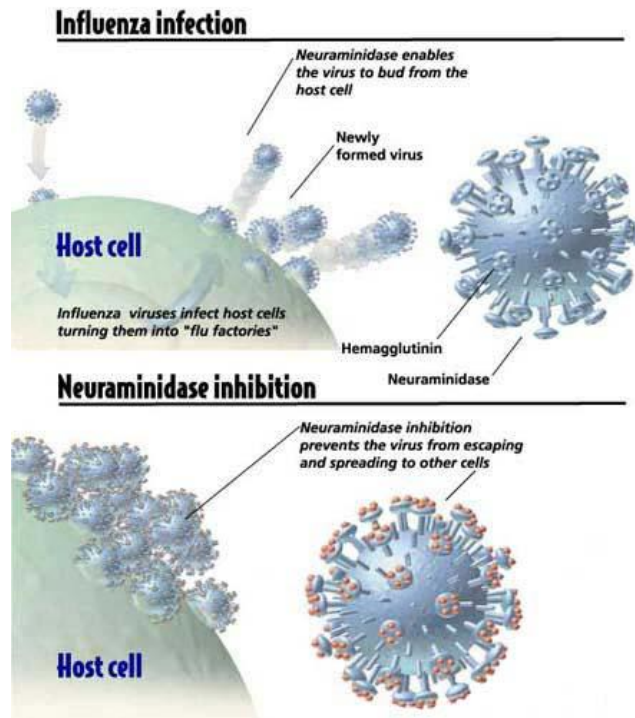
(Vaccines will be discussed in details in lecture #4)

Mechanism of neuraminidase inhibitors:

The virus is attached to the receptor and in order for this virus to exit the cell and be able to infect other cells it should be attached to the neuraminidase present at the surface of the virus so by using neuraminidase inhibitors we block this attachment thus the virus will stay inside the infected cell and won't be able to escape and infect other cells, so the propagation of the disease will not continue.

Zanamavir inhaler and Oseltamivir oral but it's easier to give a patient a drug orally since inhaler could be irritating for some patients and can be hard to use.

The concept of neuraminidase inhibition



- *If you have flu try to sneeze or cough in a tissue so you don't spread the virus.
- cover your nose and mouth when coughing using a tissue
- * Strangely influenza virus doesn't live on clothes or tissues, only on skin.
- *Keep you hands clean and wash them with soap.
- *If you examine a patient with influenza you should wear a mask.
- *If you have flu and you need to examine a patient you should wear a mask.
- *Bone marrow transplant and immunocompromised patients shouldn't be in contact with people having flu.

Done by Ala'a Arafah.