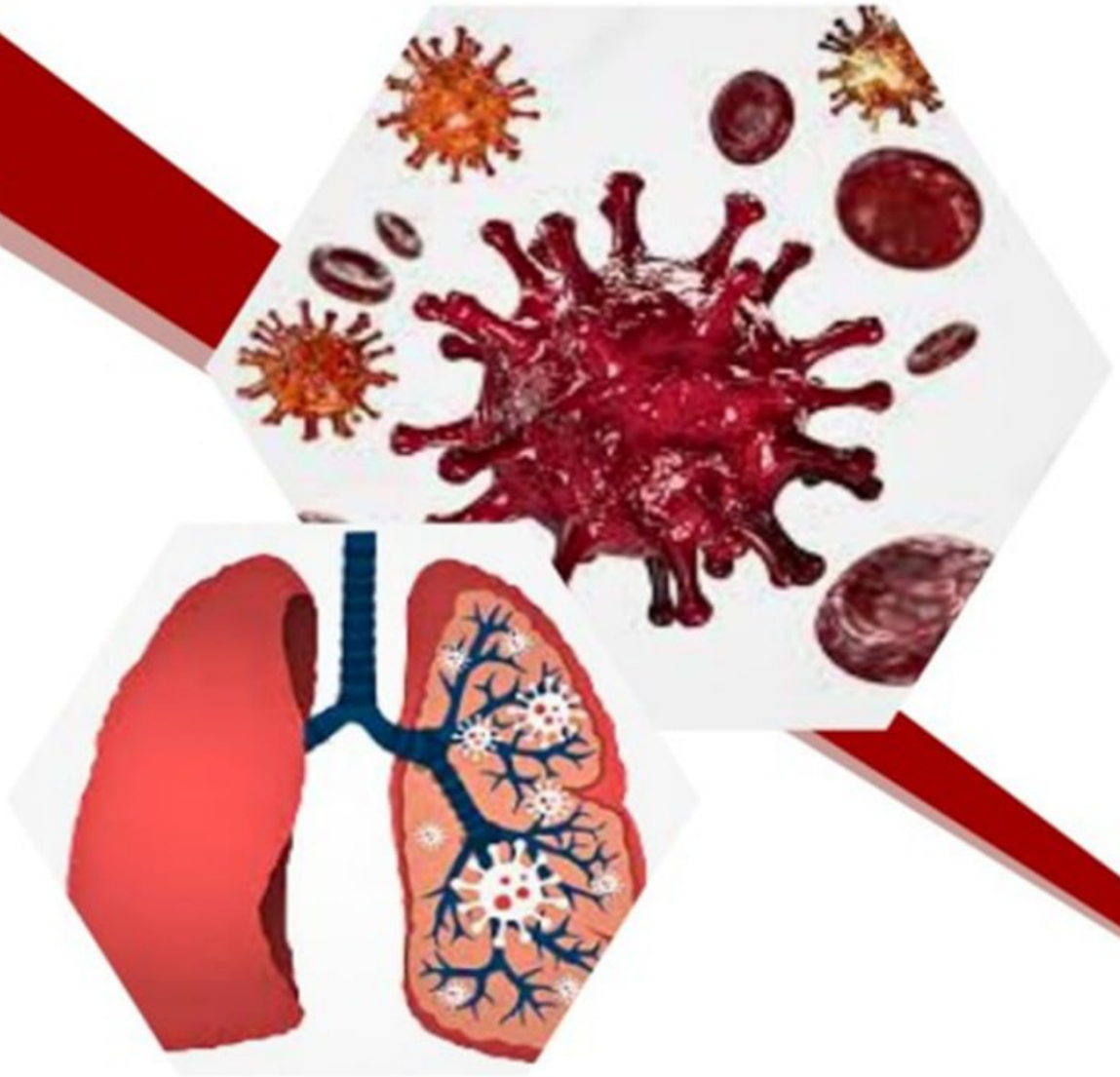
Doctor.021

no. 1

RS MICROBIOLOGY



Writer: Noor Abu Hantash

Corrector: Naim Alsharif

Doctor: Nader Alaridah

INFLUENZA

-It is a winter season disease, economic toll, and health services stress. (common in hospitals)

-The upcoming waited pandemic! And WHO fear!

-It is defined as acute respiratory tract illness caused by the influenza virus, then usually and most often results in a sudden onset of fever and constitutional symptoms (headache, myalgia, malaise, and arthralgia) and MIGHT be accompanied by localized upper respiratory tract symptoms (rhinorrhoea (runny nose), sneezing, and coughing) in contrast to common cold (that is caused by rhinoviruses and adenoviruses causing nasal obstruction, and nasal discharge).

-**Important note:** there is no viremia phase for the influenza virus (antigens are rarely recovered in the blood culture) though these systemic constitutional symptoms are caused by cytokines releasing (immune response).

-General Consideration

• Acute viral respiratory illnesses are among the most common of human diseases, accounting for one-half or more of all acute illnesses.
• Influenza is an acute respiratory illness caused by infection with influenza viruses.
• One of the most important *Emerging and Reemerging* infectious diseases.
-Due to the antigenic variation, which we discussed in African Trypanosoma, but here in influenza, there are 2 types of antigenic variation: shift (the pandemic cause) and drift.

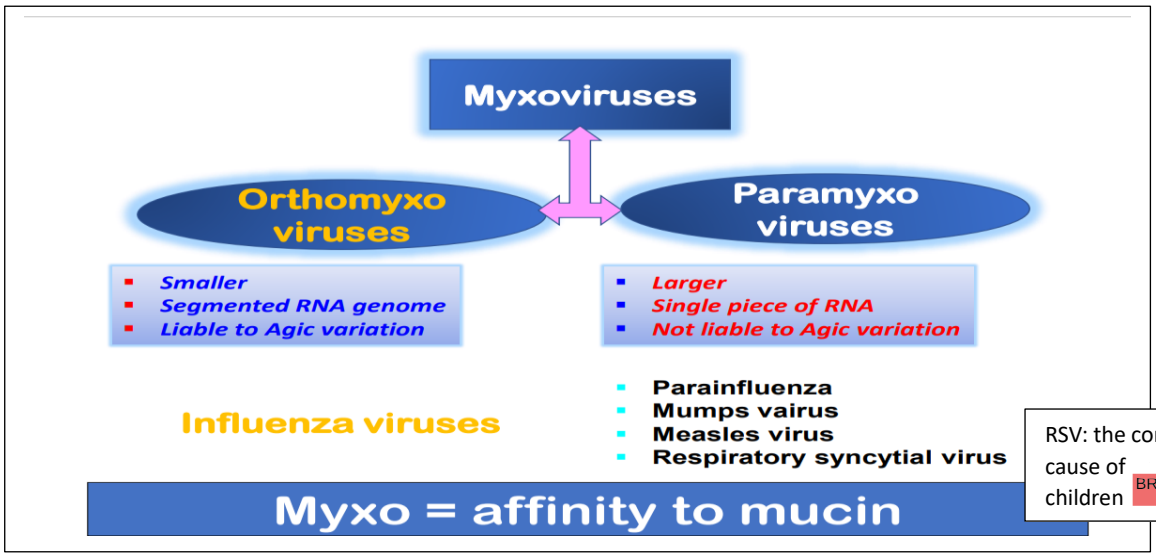
-It is also the reason that's why seasonal vaccines are given against.

-Medical students should take this vaccine not for age reasons but to decrease the vulnerability to the high-risk patients they treat.

• The illness affects the upper and/or lower respiratory tract and is often accompanied by systemic signs and symptoms such as fever, headache, myalgia, and weakness.

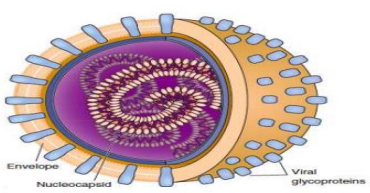
• Outbreaks of illness of variable extent and severity occur nearly every year.

-Such outbreaks result in significant morbidity rates in the general population and in increased mortality rates among certain high-risk patients, mainly as a result of pulmonary complications.



-Orthomyxoviruses are of segmented RNA, which leads to the occurrence of the antigenic variation phenomenon, its shift type happens by the exchange of genetic material, so if the same host cell gets infected with 2 different strains of the influenza virus from 2 different species, a genetic exchange may happen due to its –ve sense SEGMENTED RNA, opposite to paramyxoviruses that are non-segmented single piece of RNA, so they are not labile to antigenic variation.

-Myxo: means affinity to mucin, which is found in the upper respiratory tract and to a lesser extent in the lower respiratory tract in humans and other mammals, also it is found in the GIT of birds, so they shed it in their feces.



Characteristics of Influenza Virus

- Pleomorphic

-There are 4 types of influenza virus:

- Types A, B, C, D

-Since type D primarily affects cattle, and the documented cases of human infection with this type don't induce a disease, it is not under the scope. (D causes infection but doesn't cause a disease)

-So there are 3 types that cause a human disease (A, B, C)

Diameter 80 - 120 nm

Pleomorphic, spherical, filamentous particles

Single-stranded RNA

Segmented genome, 8 segments in A and B

-enveloped, has glycoprotein spike proteins:

Hemagglutinin (HA) and Neuraminidase (NA) on surface of the virus

-HA is used in virus A subtyping only.

-While B and C are least liable to Ag variation, so we use for them lineage description.

Influenza Structure

• **8 segments of single-stranded RNA** in type A and B,
7 segs in type C

• **Segments combine with nucleoprotein (NP) to form the ribonucleoprotein core**

• **M1 matrix protein surrounds the core**

-Typing is based on 2 things:

1. Nucleocapsid (ribonucleoprotein)

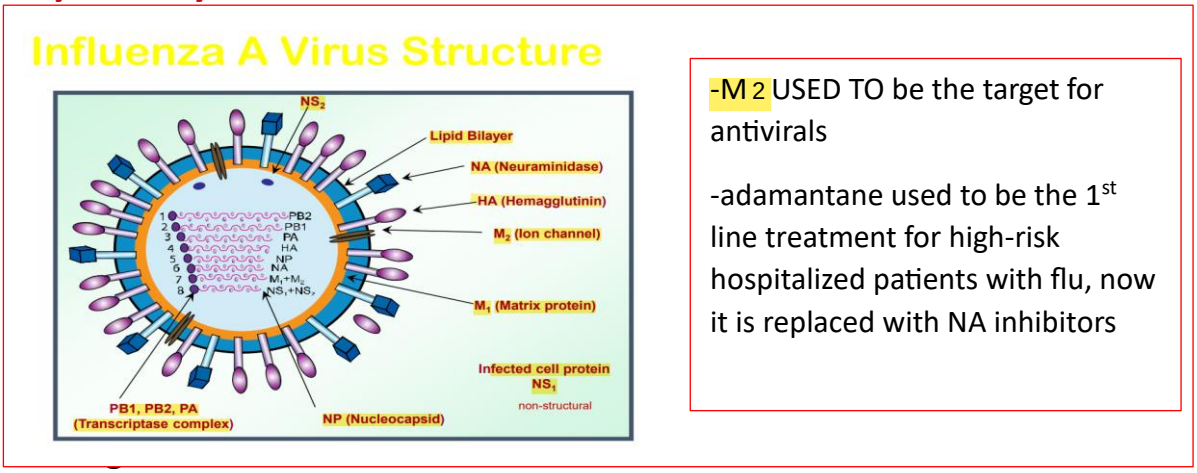
2. Matrix protein (M1)

-They are antigen-unrelated, with no cross-reaction between them, meaning if one host cell gets infected with type A and B, NO REASSORTMENT may happen between A and B Ags.

• **Lipid coat surrounds the matrix**

• **Embedded in the lipid membrane are 2 important viral proteins: hemagglutinin (HA) and neuraminidase (NA),** type C lacks NA segs.

• **RNA segments + nucleocapsid = a nucleocapsid with helical symmetry**



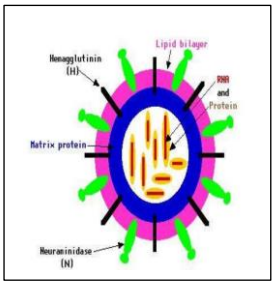
-M 2 USED TO be the target for antivirals

-adamantane used to be the 1st line treatment for high-risk hospitalized patients with flu, now it is replaced with NA inhibitors

Antigenic structure& Classification

I- Type Specific Ag (core Ag):

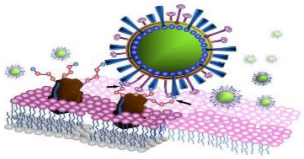
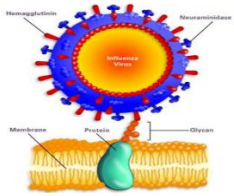
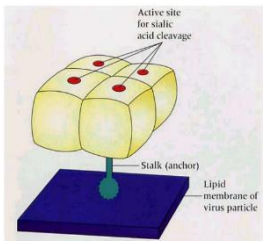
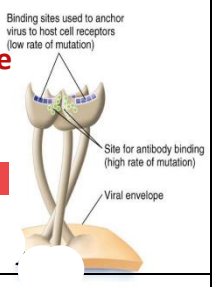
⍰ Three serotypes: A, B & C
according to internal structure proteins (nucleocapsid & matrix). These ptns don't cross-react



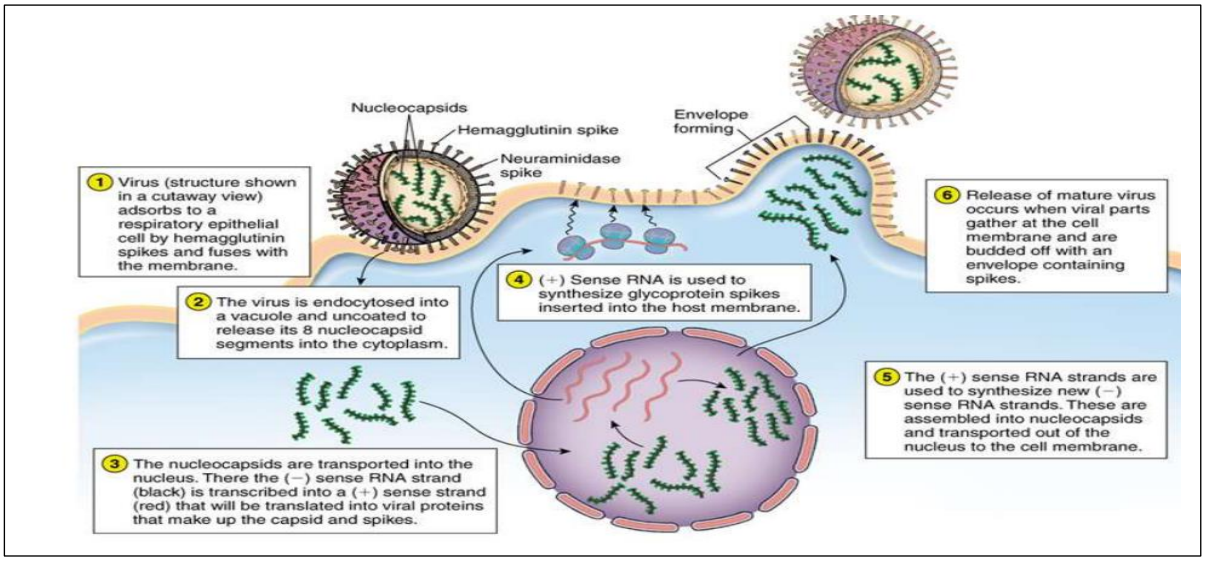
II- Strain (subtype) specific Ag:

⍰ Two surface glycoptns, HA & NA are used to subtype the virus

⍰ Influenza strains are named after their types of HA & NA surface ptns e.g. H1N1

NA 	HA 
- Cleaves neuraminic acid to release virus progeny from infected cells **- Degrades the protective layer of mucin in the respiratory tract**	**- Binds to host cell surface receptor**
1-Acts on neuraminic acid (a type of sialic acid) 2-it eases the navigation and negotiation of the virion through the mucus secretion in respiratory tract transporting it to lower respiratory tract, and here becomes the fear of direct rapid progression pneumonia(1ry pneumonia) -**Minimal role in immunity**(doesn't produce neutralizing antibodies).	**Has the ability to agglutinate RBCs from Various animal species.** **It's the target of neutralizing antibodies.** -it induces immunity, however, the influenza virus immunity is short, that's there are seasonal vaccines.
Function: Cleaves off sialic acid molecules from the surface of cells thereby preventing infected cells from "recapturing" budding virus molecules. works **at the end** of the replicative cycle of the virus to prevent the recapturing of the virion and allowing its spread to infect adjacent cells. -NA=Nice to meet you=at the end!	**-Function: Sialic acid receptor sites bind to host cell's glycoproteins allowing for infection to occur** Fusion and **initiation** (at the beginning of the replicative cycle) of infection because it binds with a glycoprotein on epithelial cells (mucus-secreting cells)– the sialic acid(receptor).HA is synthesized as a precursor Protein and requires cleavage by host cell proteases to gain its fusion capacity. These proteases are mainly Found in the upper respiratory tract. That's why Influenza viruses usually infect upper respiratory tract -HA =Hello!(at the beginning)
• Structure: Box-shaped tetramer with stalk that anchors it to the cellular membrane 	**Structure: trimer of "lollipops" with Fibrous stem anchored in the membrane and globular protein sphere containing the sialic acid receptor site**  the binding site on hemagglutinin with Host cell Sialic receptor is not changing frequently however the site of binding for Antibody generated against hemagglutinin is highly variable.
11 known NAs.	18 known HAs.

Influenza virus Replication cycle



1- The virus enters the cell by receptor-mediated endocytosis, the HA binds with the sialic acid (sugar moieties on the host cell surface mainly epithelial cells also mucus-secreting cells, gland cells, and alveolar macrophages so it is found on the upper respiratory tract, to a lesser extent lower respiratory tract, and in the intestinal tract of the birds which shed the virus in their feces)

2- HA needs activation through fusion and cleavage by the proteases and the acidic environment of the cytoplasm in the infected host cells.

3- Influenza viruses are -ve sense RNA that are transported and to the nucleus after uncoating from their lipid membranes, so the transcription and replication of flu viruses happen in the nucleus

4 - —ve sense RNA transcribed to +ve sense RNA segments, some of these +ve sense segments transcriped to mRNA then translated to spike proteins (NA, HA), the other +ve sense RNA segs become templates (return -ve sense) to be the genetic material of the newly formed virion.

5-final assembly between the genetic material and spikes happens on the plasma membrane and then the virion dissociates from the plasma membrane by NA, allowing its spread to infect adjacent cells.

*transcription and replication→nucleus///final assembly→on plasma membrane

*replicating cycle takes around 6hrs

Types of Influenza virus

I- Type A virus:

- Infects humans as well as animals
- Undergoes continuous Antigenic variations
- Many animal species have their own influenza A virus
- Pigs & birds are the reservoirs playing a role in occurrence of influenza epidemics

-Only type A causes shifts so pandemics, that's because of its wide host reservoir, it can infect humans, birds, swine, horses, ducks, geese, domesticated birds, pigs, poultry and wide exotic birds (especially water migratory birds).

-The shift occurs due to a major drastic change in Ag variation→pandemic.

-so, what are the characteristics of the pandemic?

1)new subtype of type A influenza

2)significant disease induction (not just infection)

3)retain and sustain transmissibility between infected and susceptible humans)

II- Type B virus:

- Causes milder disease
- Infects human only
- Only undergo antigenic drift
- Not known to undergo antigenic shift

III- Type C virus:

- most Agntigenically stable, very mild disease in human
- Known to cause only minor respiratory disease; probably not involved in epidemics

-B and C types **primarily** infect human, however, B can also infect seals

-they don't cause pandemics because of a wide reservoir lack property, type B may cause epidemics.

-type C only causes outbreak sporadic cases of flu.

	Severity	Stability	Number of segments	Animals and humans	Shifting and drifting	Pandemics and epidemics
Type A	Most severe	Least stable	8	Both	Both	Both
Type B	Intermediate	Intermediate	8	Just humans	Only drifting	Only epidemics
Type C	Least severe	Most stable	7 (lacks NA)	Just humans	Only drifting	Sporadic cases

Antigenic Variation

Ag Variations occurs only in infuenza A because it has a wide host range, giving influenza A the opportunity for a major reorganization of its genome & hence its surface Ags

Pigs are susceptible to avian, human & swine influenza virusesand they potentially may be infected with influenza viruses from different species. If this happens, it is possible for the genes of these viruses to mix and create a new virus, pigs called mixing bowl, when swine gets infected by both human and avian influenza viruses, it may reassort different segs from different species creating a new subtype and hence shift, it may cause a pandemic if the previous 3 characteristics are achieved.

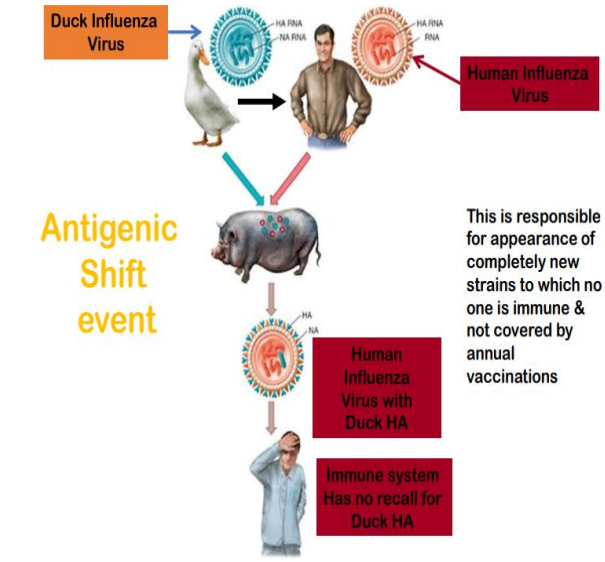
1- antigenic shift=only A

It is the process in which the genetic segment encoding for envelope glycoproteins (HA&NA) is replaced by another one from a different strain through genetic reassortment causing replacement of the original HA or NA by a new one

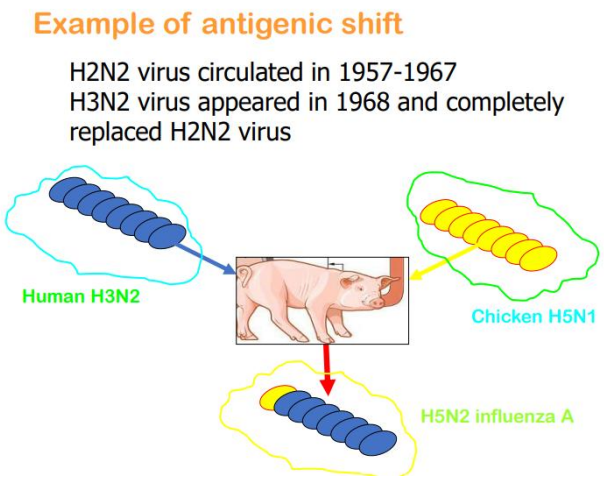
Major change, new subtype, May result in pandemic.

Genetic reassortment: the exchange of genetic material between viruses inside a host cell

examples:



Here duck and human influenza viruses infect a swine cell, and a new reassorted subtype produced by NA from the human flu virus and HA from the duck flu virus, this HA is foreign immunogenic antigen in the new infected human (no previous immunity, and no available vaccine so if the 3rd characteristic of transmissibility achieved this subtype will cause a pandemic



Avian and human reassortment →H5 from the chicken and N2 from human→H5N2:new subtype

But it doesn't cause pandemics bcz of its inability to sustain transmissibility

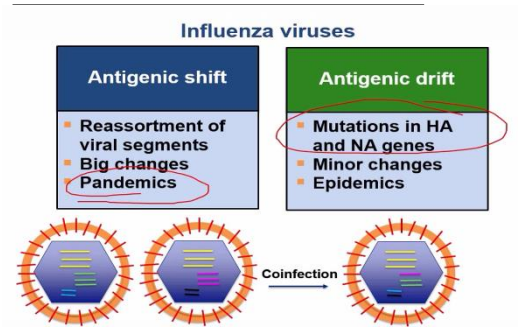
2) Antigenic Drift: A, B, C

• Minor change, same subtype

• Caused by point (SPONTANEOUS) mutations in gene, minor change of an amino acid sequence of HA or NA. Occurs in influenza A & B produce new strains are referred to as antigenic drifts

• May result in epidemic

-This antigenic mutation may result in a new subtype over long period, but somehow, there are populations partially immune, so no pandemics!

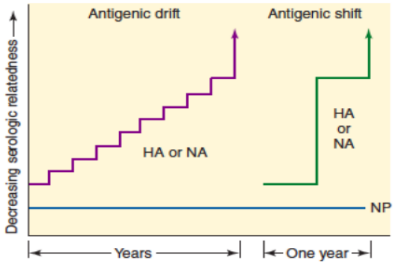


- **Example of antigenic drift:**

-year, A type, place of isolation, strain number, subtype

- **In 2003-2004, A/Fujian/411/2002-like (H3N2) virus was dominant**
- **A/California/7/2004 (H3N2) began to circulate and became the dominant virus in 2005**

-here just the place of isolation that differs with the same subtype so it is a drift, no pandemics due to partial immunity that makes a phenomenon called original antigenic sin



Notice that the antigenic drift(minor changes)is very

Slow and takes many years to result in a new subtype.(10-40 yrs)

While antigenic shift (major changes) on a sudden onset

Which results in a new subtype immediately.(within 1 yr)→pandemic of high mortality and morbidity

Classification and Nomenclature

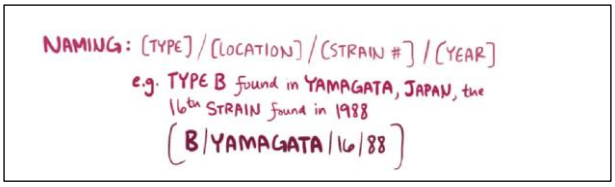
Type A: NAMING: (TYPE) / (ORIGINAL HOST) / (LOCATION) / (STRAIN #) / (YEAR OF ORIGIN) (SUBTYPE)

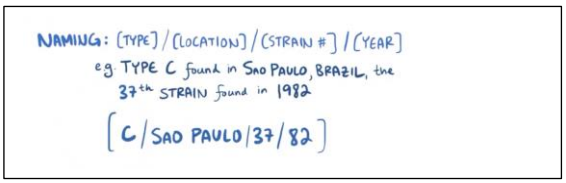
- **The standard nomenclature system for influenza virus isolates includes the following information: type, host of origin(if human we don't mention it), geographic origin, strain number, and year of isolation. Antigenic descriptions of the HA and the NA are given in parentheses for type A.**
- **The 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, 18 subtypes of HA (H1–H18) and eleven subtypes of NA (N1–N11), in many different combinations, have been recovered from birds, animals, or humans. Six HA (H1–H3, H5, H7, H9) and Three NA (N1, N2,N7) subtypes have been recovered from humans.**

-H1, H2, H3, N1,N2→Circulating between humans

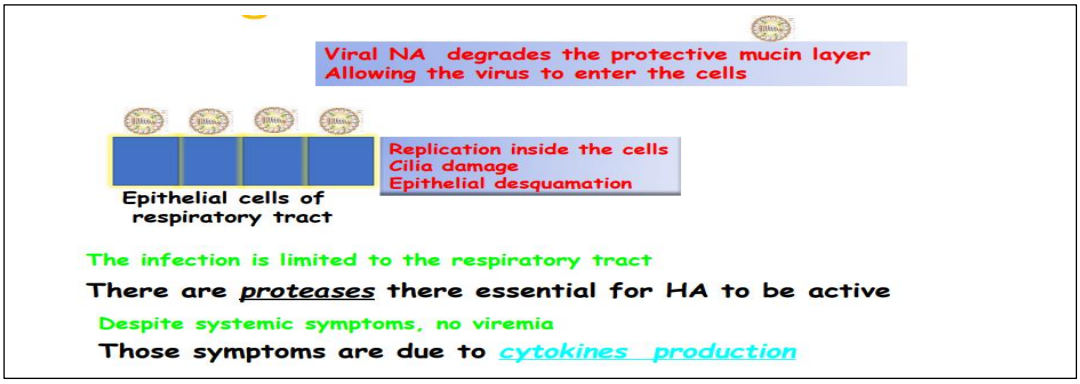
-the above+H5,H7,H9, N7,N9→highly medical important, they infect avians and humans who deal with these avians, so an acquired mutation in transmissibility gene may happen.

-however the nomenclature of B and C are different →lineage nomenclature.





Pathogenesis

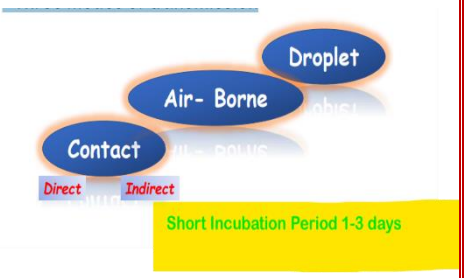


1. Viral NA degrades the protective mucin layer, allowing the virus to enter the cells. 2. Replication inside the cells. 3. Cilia damage. 4. Epithelial desquamation, direct psychopathic effect for flu infection, infiltration to cells and edema.
   - Symptoms appear due to cytokines production. (symptoms are systemic, like fever, chills, myalgia, in addition to minor respiratory symptoms like a runny nose, cough). In influenza infection, we have no viremia – no infection in the blood, those symptoms are due to cytokines release (IL1,6,8, TNF-a, INF-a)
   -there are proteases essential for HA activation, before PCR, culture was the standard test for Dx, they tended to add trypsin (protease) to achieve suitable growth media.

Mode of transmission

- **Highly contagious disease with person to person transmission**
- **Three modes of transmission**

-Air-borne :with direct contact with 2 or less meter far.



-Contact:

-Paras object(hands,..):the virus remains viable and infectious up to 6 hrs

-Non-paras objects: (table,..):the virus remains viable and infectious up to 48hrs

Duration of shedding

- **In otherwise healthy adults with influenza infection, viral shedding can be detected 24 to 48 hours before illness onset, but is generally at much lower titers than during the symptomatic period**
- **In a review of 56 studies of 1280 healthy adults who were experimentally challenged with influenza virus, shedding of influenza virus increased sharply one-half to one day following exposure, peaked on the second day, and then rapidly declined**
- **The average duration of shedding was 4.8 days Shedding ceased after six or seven days in most studies but occurred for up to 10 days in some. Studies of natural infection in healthy adults have shown similar results**

-Incubation period is about 2-3 days after exposure

-Shedding = indicator for infectivity:

1)Before 2-3 days of symptoms onset

2)Shedding peaks on 1-2days after symptoms onset then declines, after 5-7 days on average, shedding will stop and it may continue up to 10 days.

-However, the flu virus correlates very well with the flu symptoms of the affected person, which means if the patient is still coughing and sneezing on day 8, there is shedding.

Clinical Findings

- **High fever**
- **Non-productive as well as productive cough**
- **Shortness of breath= Dyspnoea**
- **Hypoxia, cyanosis**
- **Evidence of lower respiratory tract disease with opacities, consolidation, and infiltrates noted on chest imaging**
- **More severe infections (i.e. pneumonia) are sometimes associated with Influenza because of the increased susceptibility to other infections as a result of a damaged airway,** extrapulmonary complications, superimposed bacterial infection, and in high-risk groups of children and elderly those on ventilators superimposed fungal infection may happen.

Pulmonary complications

-with high mortality in risk group

1)Primary influenza pneumonia=direct rapid progression

- **Primary influenza pneumonia occurs when influenza virus infection directly involves the lung, typically producing a severe pneumonia.** (it was in the upper respiratory tract then spreads to lower respiratory tract)
- **Clinical suspicion for primary influenza pneumonia should be raised when symptoms persist and increase instead of resolving in a patient with acute influenza.**
- **High fever, dyspnea, and even progression to cyanosis can be seen.**

2)Secondary bacterial pneumonia = superimposed bacterial infection (Streptococcus pneumoniae, Staphylococcus aureus, and gram-ve Haemophilus influenzae).

3)Mixed viral and bacterial pneumoni (most common cause of pneumonia post-influenza virus)

-How to differentiate between 1ry vs 2ry influenza pneumonia:

1ry: persistent worsening symptoms
2ry: there is a window of recovery, when the patient feels better for days then the symptoms come again and worse than before, and if the cough was non-productive, it returns as productive.

Complications

- **Septic shock,**
- **Respiratory failure,**
- **Acute respiratory distress syndrome,**
- **Refractory hypoxemia,**
- **Acute renal dysfunction, (**hemodynamic instability, immune response)
- **Multiple organ dysfunction,**
- **Rhabdomyolysis,** (indirect muscle injury, bcz of immune response rather than the virus, the myoglobin is high in the blood)
- **Encephalopathy (Reye syndrome)**

-Reyes syndrome= rare complication of encephalopathy and liver degenerative changes), more likely to occur in a 5-15-year-old patient who has recovered from influenza and is taking salicylate acid(aspirin), the mechanism is unknown

-the solution is to avoid aspirin ingestion in flu and even flu-like patients between 5-15 years.

- **Bacterial and fungal infections(superimposed infections) such as ventilator-associated pneumonia and blood-stream infection sometimes by multi-drug resistant bacteria**

Groups at high risk for influenza complication

-The same population that is highly recommended to take the seasonal vaccine

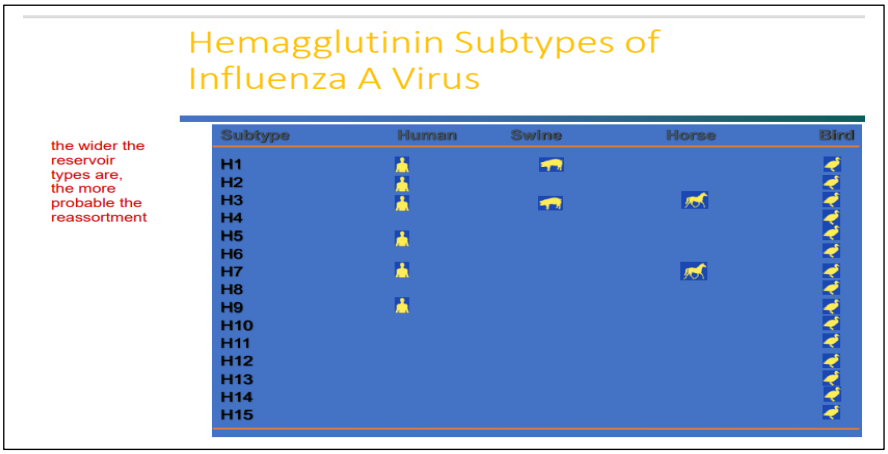
Pregnant women and immunosuppressed people are given inactivated killed vaccine rather than live attenuated.

- Children <2 years*
- Adults ≥65 years of age — may need admission to the hospital
- Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic (including sickle cell disease), metabolic (including diabetes mellitus), neurologic, neuromuscular, and neurodevelopmental disorders (including disorders of the brain, spinal cord, peripheral nerve and muscle such as cerebral palsy, epilepsy, stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury)
- Immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus)
- Women who are pregnant or postpartum (within 2 weeks after delivery)
- Children <19 years of age and receiving long-term aspirin therapy
- Native Americans and Alaskan Natives
- Morbidly obese (body mass index [BMI] ≥40 for adults or BMI >2.33 standard deviations above the mean for children)
- Residents of nursing homes and other chronic care facilities

Laboratory Diagnosis

A. Polymerase Chain Reaction **Gold standard for dx, highly specific and sensitive, within hrs the result will be available**	**• Rapid tests based on the 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.**
B. Isolation and Identification of Virus **-used to be used before pcr**	**• Viral culture procedures take 3–10 days. Classically, embryonated eggs and primary monkey kidney cells have been the isolation methods of choice for influenza viruses, although some continuous cell lines may be used. in the presence of trypsin, which cleaves and activates the HA so that replicating virus will spread throughout the culture. Cell cultures can be tested for the presence of virus by hemadsorption 3–5 days after inoculation, or the culture fluid can be examined for *virus after 5–7* days by hemagglutination**
C. Serology **-retrospective dx** **-**	**• Antibodies to several viral proteins (hemagglutinin, neuraminidase, nucleoprotein, and matrix) are produced during infection with influenza virus. The immune response against the HA glycoprotein is associated with resistance to infection.** **• Routine serodiagnostic tests in use are based on haemagglutination inhibition (HI) and enzyme-linked immunosorbent assay. *Paired acute and convalescent sera are necessary because normal individuals usually have influenza antibodies. A fourfold or greater increase in titer must occur to indicate influenza infection*. Human sera often contain nonspecific mucoprotein inhibitors that must be destroyed before testing by HI**

-**Important note:** past question:- there are no detected antigens in serology (no Ag in blood)but in the RT-PCR, we are looking for them, they are found in the taken respiratory specimen (nasopharyngeal, oropharyngeal, nasal swab)



History: Known Flu Pandemics

H1N1 and H3N2 are the circulating subtypes between humans, and they are in the vaccine

Name of pandemic	Date	Deaths
Spanish Flu H1N1	1918-1920	40 -100 million
Asian Flu H2N2	1957-1958 in China	1 - 1.5 million
Hong Kong Flu H3N2	1968-1969	0.75 - 1 million
Swine Flu H1N1	2009-2010 in Russa	0.15-0.6 million

Treatment and Prevention

Influenza Vaccines

Influenza Vaccines=the best way for prevention, it is seasonal, bcz of antigenic variation

1• Whole virus vaccines: inactivated forms of virus with the predicted HA, are grown in embryonated eggs

-live attenuated vaccine grows in embryonated eggs, so for those -who are allergic to eggs, the benefit of the vaccine for them will reduce.

2• Subunit vaccine: uses both HA and NA subunits extracted from recombinant virus forms

3• Split-virus vaccines: purified HA (lessens the side-effects)

• Recommended for health care workers, elderly/ people in nursing homes, asthmatics, chronic lung disease patients, some pregnant women, and anyone who is susceptible to infection

-elderly and children>2yrs are with high mortality =high priority for vaccination and hospital admission need.

• Inactivated subunit (TIV) =killed	• Live attenuated vaccine (LAIV) flu mist
Intramuscular, injectable	• Intranasal
• Trivalent	• Trivalent
Annual	Annual

-they are both in Jordan

-before 2004 they were trivalent but now they are quadrivalent, (H1N1, H3N2 and 2 lineages of type B ((Victorea and Yamagata))

WHO recommends annual vaccination for (in order of priority)

Nursing-home residents (the elderly or disabled)

Elderly individuals

People with chronic medical conditions

Other groups such as pregnant women, health care workers, those with essential functions in society, as well as children from ages six months to five years

Antiviral Treatment Recommendations

M2 inhibitors (adamantanes): rimantadine and amantadine were the 1st line management, but because they don't work on type B &C, and bcz the circulating subtypes H1N1, H3N2 start to show resistance, the NA inhibitors become the 1st line management:

• Treatment with oseltamivir (Tamiflu) or zanamivir is recommended for:

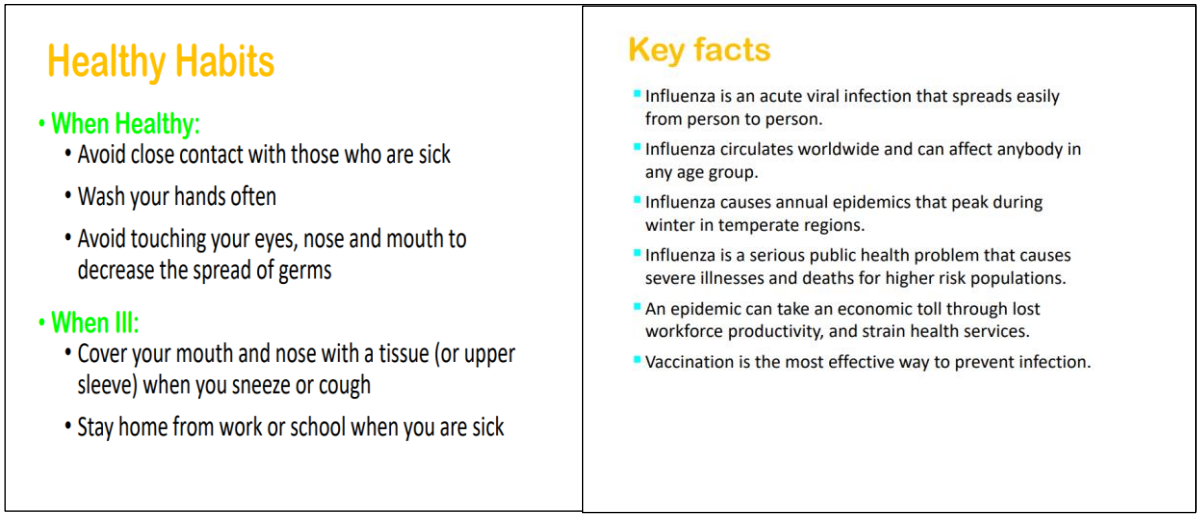
• All patients requiring hospitalization

• Patients at increased risk of complications

- **Children 0-4 years**
- **Pregnant women**
- **Persons with immune suppression, chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological (including sickle cell disease), neurologic, neuromuscular, or metabolic disorders (including diabetes mellitus)or > 65 years**
- **Early treatment is the key**

-we initiate the dose within 48 hrs of symptoms onset, to gain significant recovery.

- **Clinicians should not wait for confirmatory tests to treat**
- **Postexposure prophylaxis should generally not be used**
- **Consider for high-risk person with close unprotected exposure**
- **Do not use if more than 48 hours after exposure**



Avian Influenza

- **A contagious viral infection and/or disease of many avian species including poultry, wild and exotic birds, ratites, shore birds and migratory waterfowl.**

-it is a silent infection in exotic birds and they shed the virus in their feces for 2 weeks, while domesticated birds(poultry, geese, ducks)show the disease by showing:

• The highly pathogenic form of the disease is characterized by severe depression, decrease in egg production, high mortality, edema, hemorrhage, and frank necrosis.
• All H5 and H7 infections are reportable to the World Organization for Animal Health (OIE)

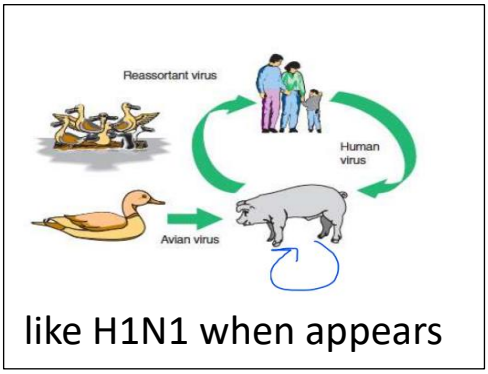
Where does AI virus come from?

• All known subtypes of influenza A viruses circulate among wild birds, especially migratory waterfowl (e.g. ducks and geese) which are considered *natural reservoirs* for influenza A viruses
-because of these natural reservoir, eradication of influenza is impossible!

• Domestic poultry like chickens and turkeys are not natural reservoirs for AI virus and usually develop clinical disease when infected with AI virus

How does AI virus spread?

• Exposure of poultry to migratory waterfowl
• Exposure of commercial poultry to AI-infected backyard, game bird, or hobby flocks
• Contact with AI-infected live bird markets
• Bird to bird contact (through feces)
• Aerosol droplets
• Manure(bird feces), equipment, vehicles, egg flats, crates, contaminated shoes and clothing
• Wildlife vectors/scavengers



like H1N1 when appears

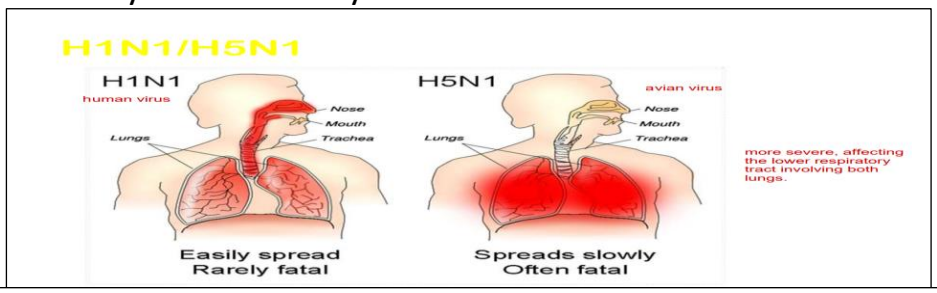
-humidity and low temp, keep the virus viable and infectious up to 3 months.
-avian influenza can be transmitted to humans but its cycle terminates shortly, it infects up to 3 people then stops.

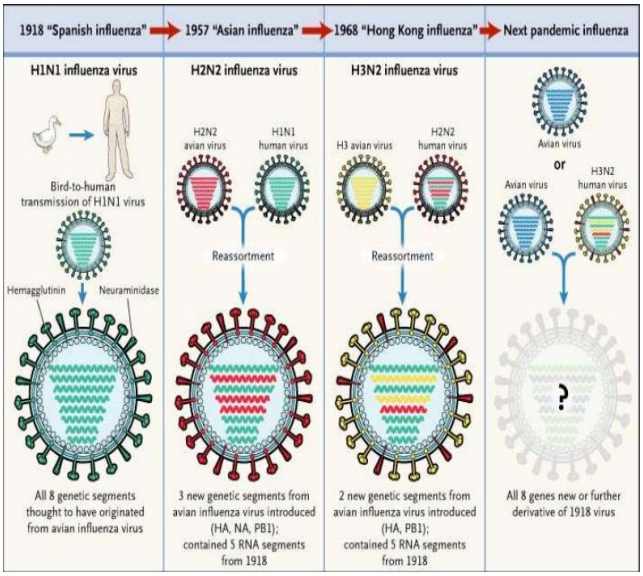
What are the types of Avian Influenza in domestic poultry?

• Low pathogenic avian influenza (LPAI)
• Mild or no clinical signs
• Low to moderate mortality

- **However, the low pathogenic H5 and H7 strains are capable of mutating under field conditions into highly pathogenic strains**
- **Highly pathogenic avian influenza (HPAI)**
- **Sudden onset**
- **Severe clinical signs**
- **High mortality**

-important note:past question:these low and high pathogenic are in avians, but if the human is infected by either LPAI or the HPAI, it will always be severe with high mortality and morbidity.





They used mathematical models to predict the next pandemic! Also, they used poultry and seasonal vaccines benefiting from seasonal variation in continents

-but it is really hard, bcz of triple, or even 5, 6, 7 segs reassortment

-which may happen between 7 segs from 7 species!

WHAT IS SWINE FLU ?

Swine Influenza (swine flu) is a respiratory disease of pigs caused by type A influenza viruses (H1N1 subtype) that causes regular outbreaks in pigs. People do not normally get swine flu, but human infections can and do happen Swine flu viruses have been reported to spread from person-to person, but in the past, this transmission was limited and not sustained beyond three people

-always a disease, no silent infection

The end

Recap page:

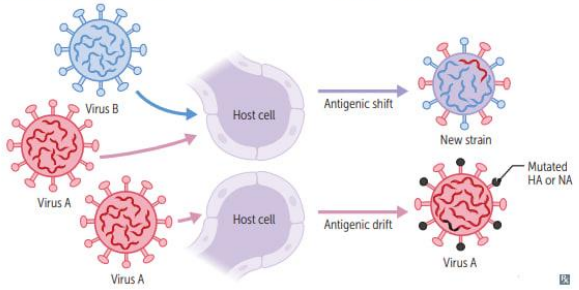
Otrhomyxovirus – Night Shift at the Orthodontist's

1. Moon w/ orange hues – RNA NEG Single Strand virus
2. All RNA Negs Bring along their own Polymerase
3. Babies in the helmet - Replicates in the nucleus
4. Orthodontist in the coat – Enveloped
5. FIU-oride poster w/ ABC – most common cause of the flu, strains ABC
6. Octopus w/ 8 arms – 8 segments, so there is 8 places where it can mutate. Antigenic shift and drift
7. DOKTAR DRIFT- **Antigenic drift** is **point mutations** in the viral genome leading to changes in the hemagglutinin (HA) and neuraminidase (NA) molecules. Seasonal flu and epidemics
8. Night Shift, h is falling down to symbolize assortment of genes. - **Antigenic shift** is when segments are shared to form a new species. Segment changes and pandemics.
9. Multiple color curtains – antigenic shift
10. Three main influenza viruses – A causes epidemics and pandemics (Antigenic shift) – B causes epidemics (antigenic drift)
11. Heme Aquarium, Octopus sitting on RBC's, and sialic chains on the helmet – Hemagglutinin (HA), this is a glycoprotein that binds to sialic acid found in membranes in Upper respiratory and RBCs causing them to clump.
12. HA Antigens, H1, H2, H3, - define cell tropism (cells that can be affected) – HA molecule will bind to sialic acid on the cell membrane, then endocytosed into the cell, pH needs to be changed by M2 protein to allow for uncoating.
13. Shell with octopus and 2 M's – M2 Protein
14. Manta ray – Amantadine, Rimantadine inhibit M2 so no uncoating. But allows increased dopamine release in CNS
15. Octopus w/ knife that is missing from Nurse Assistants tray - Neuraminidase (NA) – allows break virus free from sialic acid inside the host cell
16. Nurse name is TamV(Tamiflu) she is capping all of the scalpel trade name for Oseltamivir/Anamivir: NA inhibitors blocking release of virus
17. Droplets coming off the aquarium – Flu spread by respiratory droplets
18. Pirates skeleton – killed virus IM
19. Bubbles in nose – Live vaccine
20. Orthodontist inspecting mouth w/ gold staff - Staph aureus pneumonia
21. Sun with rays - Reyes syndrome – aspirin associated with treatment causing encephalitis, and hepatomegaly. Will uncouple mitochondria proton gradient along the electron transport chain in the hepatic cells.
22. Stuffed bear on boys back - Guillen Barre syndrome – ascending paralysis – Finding high protein with low WBC's

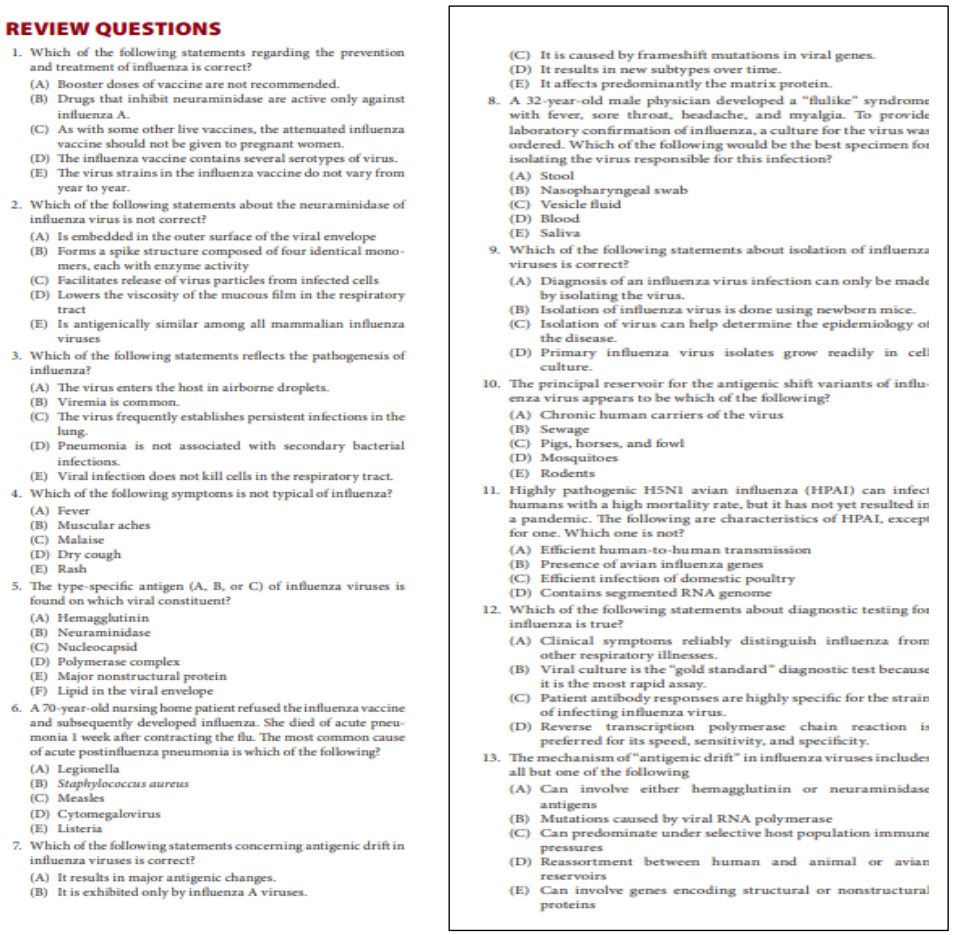
- Influenza viruses are major respiratory pathogens.
- Influenza type A is highly variable antigenically and causes most epidemics and all global pandemics.
- Influenza type B sometimes undergoes antigenic changes and can cause epidemics.
- Influenza type C is antigenically stable.
- Influenza A strains are also found in aquatic birds, ducks, domestic poultry, pigs, and horses.
- The viral genome is single-stranded, negative-sense RNA consisting of eight separate segments.
- Surface glycoproteins, HA and NA, determine influenza virus antigenicity and host immunity.
- Minor antigenic changes in HA and NA, termed **antigenic drift**, occur independently and are caused by accumulation of point mutations.
- A major antigenic change in HA or NA, called **antigenic shift**, results in a new influenza virus subtype and is caused by genetic reassortment of genome segments between human and animal viruses.
- Because many different viruses can cause respiratory infections, diagnosis of influenza infection cannot reliably be made clinically and relies on laboratory assays.
- Immunity to influenza is long lived and subtype specific. Only antibodies to HA and NA are protective.
- Both inactivated and live-virus vaccines exist but are continually being rendered obsolete as new antigenic variants of influenza viruses arise.
- Antiviral drugs exist, but resistant viruses emerge frequently, especially to M_2 ion channel inhibitors.
- Avian influenza A viruses, H5N1, H7N9, and H9N2 cause sporadic human infections but have not acquired the ability for sustained human-to-human transmission.

Influenza vi uses	Orthomyxoviruses. Enveloped, ⊖ ssRNA viruses with segmented genome. Contain hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly *S aureus*, *S pneumoniae*, and *H influenzae*. Treatment: supportive +/– neuraminidase inhibitor (eg, oseltamivir, zanamivir).
Genetic/antigenic shift	Infection of 1 cell by 2 different segmented viruses (eg, swine influenza and human influenza viruses) → RNA segment reassortment → dramatically different virus (genetic shift) → major global outbreaks (pandemics).
Genetic/antigenic drift	Random mutation in hemagglutinin (HA) or neuraminidase (NA) genes → minor changes in HA or NA protein (drift) occur frequently → local seasonal outbreaks (epidemics).

Hemagglutinin: lets the virus in
Neuraminidaways: sends the virus away
Reformulated vaccine ("the flu shot") contains viral strains most likely to appear during the flu season, due to the virus' rapid genetic change.
Killed viral vaccine is most frequently used.
Live attenuated vaccine contains temperature-sensitive mutant that replicates in the nose but not in the lung; administered intranasally.
Sudden shift is more deadly than gradual drift.



Past questions from Jawetz book



REVIEW QUESTIONS

1. Which of the following statements regarding the prevention and treatment of influenza is correct?
   (A) Booster doses of vaccine are not recommended.
   (B) Drugs that inhibit neuraminidase are active only against influenza A.
   (C) As with some other live vaccines, the attenuated influenza vaccine should not be given to pregnant women.
   (D) The influenza vaccine contains several serotypes of virus.
   (E) The virus strains in the influenza vaccine do not vary from year to year.
2. Which of the following statements about the neuraminidase of influenza virus is not correct?
   (A) Is embedded in the outer surface of the viral envelope
   (B) Forms a spike structure composed of four identical monomers, each with enzyme activity
   (C) Facilitates release of virus particles from infected cells
   (D) Lowers the viscosity of the mucous film in the respiratory tract
   (E) Is antigenically similar among all mammalian influenza viruses
3. Which of the following statements reflects the pathogenesis of influenza?
   (A) The virus enters the host in airborne droplets.
   (B) Viremia is common.
   (C) The virus frequently establishes persistent infections in the lung.
   (D) Pneumonia is not associated with secondary bacterial infections.
   (E) Viral infection does not kill cells in the respiratory tract.
4. Which of the following symptoms is not typical of influenza?
   (A) Fever
   (B) Muscular aches
   (C) Malaise
   (D) Dry cough
   (E) Rash
5. The type-specific antigen (A, B, or C) of influenza viruses is found on which viral constituent?
   (A) Hemagglutinin
   (B) Neuraminidase
   (C) Nucleocapsid
   (D) Polymerase complex
   (E) Major nonstructural protein
   (F) Lipid in the viral envelope
6. A 70-year-old nursing home patient refused the influenza vaccine and subsequently developed influenza. She died of acute pneumonia 1 week after contracting the flu. The most common cause of acute postinfluenza pneumonia is which of the following?
   (A) Legionella
   (B) *Staphylococcus aureus*
   (C) Measles
   (D) Cytomegalovirus
   (E) Listeria
7. Which of the following statements concerning antigenic drift in influenza viruses is correct?
   (A) It results in major antigenic changes.
   (B) It is exhibited only by influenza A viruses.
   (C) It is caused by frameshift mutations in viral genes.
   (D) It results in new subtypes over time.
   (E) It affects predominantly the matrix protein.
8. A 32-year-old male physician developed a "flulike" syndrome with fever, sore throat, headache, and myalgia. To provide laboratory confirmation of influenza, a culture for the virus was ordered. Which of the following would be the best specimen for isolating the virus responsible for this infection?
   (A) Stool
   (B) Nasopharyngeal swab
   (C) Vesicle fluid
   (D) Blood
   (E) Saliva
9. Which of the following statements about isolation of influenza viruses is correct?
   (A) Diagnosis of an influenza virus infection can only be made by isolating the virus.
   (B) Isolation of influenza virus is done using newborn mice.
   (C) Isolation of virus can help determine the epidemiology of the disease.
   (D) Primary influenza virus isolates grow readily in cell culture.
10. The principal reservoir for the antigenic shift variants of influenza virus appears to be which of the following?
    (A) Chronic human carriers of the virus
    (B) Sewage
    (C) Pigs, horses, and fowl
    (D) Mosquitoes
    (E) Rodents
11. Highly pathogenic H5N1 avian influenza (HPAI) can infect humans with a high mortality rate, but it has not yet resulted in a pandemic. The following are characteristics of HPAI, except for one. Which one is not?
    (A) Efficient human-to-human transmission
    (B) Presence of avian influenza genes
    (C) Efficient infection of domestic poultry
    (D) Contains segmented RNA genome
12. Which of the following statements about diagnostic testing for influenza is true?
    (A) Clinical symptoms reliably distinguish influenza from other respiratory illnesses.
    (B) Viral culture is the "gold standard" diagnostic test because it is the most rapid assay.
    (C) Patient antibody responses are highly specific for the strain of infecting influenza virus.
    (D) Reverse transcription polymerase chain reaction is preferred for its speed, sensitivity, and specificity.
13. The mechanism of "antigenic drift" in influenza viruses includes all but one of the following
    (A) Can involve either hemagglutinin or neuraminidase antigens
    (B) Mutations caused by viral RNA polymerase
    (C) Can predominate under selective host population immune pressures
    (D) Reassortment between human and animal or avian reservoirs
    (E) Can involve genes encoding structural or nonstructural proteins
14. Each of the following statements concerning the prevention and treatment of influenza is correct *except*
    (A) The inactivated influenza vaccine contains H1N1 virus but the live, attenuated influenza vaccine contains H3N2 virus.
    (B) The vaccine is recommended to be given each year because the antigenicity of the virus drifts.
    (C) Oseltamivir is effective against both influenza A and influenza B viruses.
    (D) The main antigen in the vaccine that induces protective antibody is the hemagglutinin.
15. Each of the following statements concerning the antigenicity of influenza A virus is correct *except*
    (A) Antigenic shifts, which represent major changes in antigenicity, occur infrequently and are caused by the reassortment of segments of the viral genome.
    (B) Antigenic shifts affect both the hemagglutinin and the neuraminidase.
    (C) The worldwide epidemics caused by influenza A virus are caused by antigenic shifts.
    (D) The protein involved in antigenic drift is primarily the internal ribonucleoprotein.
16. Which of the following infectious agents is most likely to cause a pandemic?
    (A) Influenza A virus
    (B) *Streptococcus pyogenes*
    (C) Influenza B virus
    (D) Respiratory syncytial virus
    (E) Influenza C virus

Answers

1. D	5. C	9. C	13. D
2. E	6. B	10. C	14. A
3. A	7. D	11. A	15. D
4. E	8. B	12. D	16. A

Past paper

8- A patient with egg allergy and should not be given influenza vaccine, to protect them from Influenza A and B you can use:

Answer: Oseltamivir or zanamivir

1)Outbreak of pneumonia takes place in nursing home, and can be treated with zanamivir and adamantanes effectively, the most likely pathogen is...

A. Influenza A
B. Influenza B
Legionella pneumophelia
D. Metapneumo

Answer: A

2) the live attenuated vaccine of influenza virus is administered:

A. Oraly
B. Deep Intramuscular
C. Intravenous
D. Intranasal (Ans)
E. Subcutaneous

Answer: D

V2 check the highlighted

V3 check red highlights