INFLUENZA-1

VL – 6
Dec. 8th 2013
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Importance of Influenza

- One of the most important Emerging and Reemerging infectious diseases
- Causes high morbidity and mortality in communities (epidemics) and worldwide (pandemics)
- Epidemics are associated with excess mortality
Discovery of Influenza Virus

- First isolated from a pig in 1931 (swine flu)
- Isolated from human in 1933
Myxoviruses

Orthomyxoviruses
- Smaller
- Segmented RNA genome
- Liable to Agic variation

Paramyxoviruses
- Larger
- Single piece of RNA
- Not liable to Agic variation

Influenza viruses
- Parainfluenza
- Mumps virus
- Measles virus
- Respiratory syncytial virus

Myxo = affinity to mucin
Characteristics of Influenza Virus

- Pleomorphic
- Types A, B, C
- Diameter 80 - 120 nm
- Pleomorphic, spherical, filamentous particles
- Single-stranded RNA
- Segmented genome, 8 segments in A and B
- Hemagglutinin and Neuraminidase on surface of the virion
Influenza Viruses

- Replicate in mucus membranes
- Target tissue: upper & lower respiratory tract
- Cause influenza: acute respiratory disease that may occur in epidemics or even pandemics
Virus Structure and Replication
Influenza Structure

- 8 segments of single-stranded RNA
- Segments combine with nucleoprotein (NP) to form the ribonucleoprotein core
- M1 matrix protein surrounds the core
- Lipid coat surrounds the matrix
- Embedded in the lipid membrane are 2 important viral proteins: hemaglutinin (HA) and neuraminidase (NA)
- RNA segments + nucleocapsid = a nucleocapsid with helical symmetry
Influenza A Virus Structure

- Lipid Bilayer
- NA (Neuraminidase)
- HA (Hemagglutinin)
- M₂ (Ion channel)
- M₁ (Matrix protein)
- Infected cell protein NS₁
- PB1, PB2, PA (Transcriptase complex)
- NP (Nucleocapsid)
Antigenic structure & Classification

I- Type Specific Ag (core Ag):
- Three serotypes: A, B & C according to internal structure patterns (nucleocapsid & matrix). These patterns don't cross react

II- Strain (subtype) specific Ag:
- Two surface glycoproteins, HA & NA are used to subtype the virus
- Influenza strains are named after their types of HA & NA surface patterns e.g. H1N1
Neuraminidase (N)
Cleaves neuraminic acid to release virus progeny from infected cells

Haemagglutinin (H)
Binds to host cell surface receptor
The flu virus binds onto sugars on the surfaces of epithelial cells such as nose, throat, and lungs of mammals and intestines of birds.
Influenza virus Replication cycle

1. Virus (structure shown in a cutaway view) adsorbs to a respiratory epithelial cell by hemagglutinin spikes and fuses with the membrane.

2. The virus is endocytosed into a vacuole and uncoated to release its 8 nucleocapsid segments into the cytoplasm.

3. The nucleocapsids are transported into the nucleus. There the (−) sense RNA strand (black) is transcribed into a (+) sense strand (red) that will be translated into viral proteins that make up the capsid and spikes.

4. (+) Sense RNA is used to synthesize glycoprotein spikes inserted into the host membrane.

5. The (+) sense RNA strands are used to synthesize new (−) sense RNA strands. These are assembled into nucleocapsids and transported out of the nucleus to the cell membrane.

6. Release of mature virus occurs when viral parts gather at the cell membrane and are budded off with an envelope containing spikes.
Influenza Viral Budding

- Matrix protein (M) interacts with HA and NA
  - HA are glycoproteins on envelope
  - Interaction occurs at the level of their cytoplasmic tail
- M protein also interacts with helical nucleocapsid proteins RNP
Viral Types and Pathogenicity
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
Types of Influenza virus

II- Type B virus:
- Causes milder disease
- Infects human only
- Only undergo antigenic drift
- Not known to undergo antigenic shift

III- Type C virus:
- Antigenically stable
- Known to cause only minor respiratory disease; probably not involved in epidemics
Pathogenesis

Viral NA degrades the protective mucin layer
Allowing the virus to enter the cells

Epithelial cells of respiratory tract

Replication inside the cells
Cilia damage
Epithelial desquamation

The infection is limited to the respiratory tract

There are proteases there essential for HA to be active

Despite systemic symptoms, no viremia

Those symptoms are due to cytokines production
Pathogenesis

- A person becomes infected when they inhale microdroplets containing the virus
- Upper and lower respiratory tract epithelial cells have sialic acid molecules to which the HA binds
- As the virus causes the cells to die, inflammation occurs – a cough reflex results thereby spreading the virus again
- Additional “flu-like” symptoms (sneezing, fever, chills, muscle aches, headaches, fatigue) occur as a result of interferon production triggered by the presence of dsRNA during viral replication
Pathogenicity

- Acute, highly contagious respiratory illness
- Seasonal, pandemics; among top 10 causes of death in some countries
- Most commonly among elderly and small children
- Causes rapid shedding of cells, stripping the respiratory epithelium; severe inflammation
- Weakened host defenses predispose patients to secondary bacterial infections, especially pneumonia
Immunology
Surface Antigens and Immunity

- Immunity reduces likelihood of infection and severity of disease
- Antibodies are specific to different types of surface antigens
- Changes in H and N antigens allow the virus to evade previously developed immune responses
- Antigenic changes: drift and shift
Hemagglutinin

- **Structure**: trimer of "lollipops" with fibrous stem anchored in the membrane and globular protein sphere containing the sialic acid receptor site

- **Function**: Sialic acid receptor sites bind to host cell’s glycoproteins allowing for infection to occur
Neuraminidase

- **Structure**: Box-shaped tetramer with stalk that anchors it to the cellular membrane
- **Function**: Cleaves off sialic acid molecules from the surface of cells thereby preventing infected cells from “recapturing” budding virus molecules.
Surface Antigens

**Haemagglutinin**
- Binds to host cell surface receptor
- The target of neutralizing Abs
- Haemagglutinates RBCs from various animal species

**Neuraminidase**
- Cleaves neuraminic acid to release virus progeny from infected cells
- Degrades the protective layer of mucin in the respiratory tract
- Plays a minimal role in immunity to influenza
Antigenic Variation

- Ag Variations occurs only in influenza 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 viruses and 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.
Antigenic Variation

1- antigenic shift

- 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.

- **Genetic reassortment**: the exchange of genetic material between viruses inside a host cell.
Antigenic Shift event

This is responsible for appearance of completely new strains to which no one is immune & not covered by annual vaccinations.

Duck Influenza Virus

Human Influenza Virus

Immune system has no recall for Duck HA

Human Influenza Virus with Duck HA

HA RNA

NA RNA

HA RNA

NA RNA
Example of antigenic shift

H2N2 virus circulated in 1957-1967
H3N2 virus appeared in 1968 and completely replaced H2N2 virus
Host and Lineage Origins For The Gene Segments of 2009 A(H1N1) Virus
Influenza Antigenic Changes

- **Antigenic Drift**
  - Minor change, same subtype
  - Caused by point 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 shifts
    - May result in epidemic

- **Example of antigenic drift**
  - 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
Influenza Antigenic Changes

- **Antigenic Shift**
  - Major change, new subtype
  - Caused by exchange of gene segments
  - May result in pandemic

- **Example of antigenic shift**
  - H2N2 virus circulated in 1957-1967
  - H3N2 virus appeared in 1968 and completely replaced H2N2 virus
Clinical Findings and Diagnosis
Mode of transmission

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

- Droplet
- Air-Borne
- Contact
  - Direct
  - Indirect

Short Incubation Period 1-3 days
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.
Clinical Findings

- High fever
- Non-productive as well as productive cough
- Shortness of breath
- Dyspnoea
- Hypoxia
- 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
Primary influenza pneumonia

- Primary influenza pneumonia occurs when influenza virus infection directly involves the lung, typically producing a severe pneumonia.

- 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
Host Defenses

- Interferon signals for cells to inhibit protein synthesis
- Anti-HA antibodies bind and stay with the virus as it makes its way through the cell and somehow interferes with the replication process
- Anti-NA antibodies stop the molecule from shaving off the sialic acid residues
Complications

- Septic shock,
- Respiratory failure,
- Acute respiratory distress syndrome,
- Refractory hypoxemia,
- Acute renal dysfunction,
- Multiple organ dysfunction,
- Rhabdomyolysis,
- Encephalopathy,
- Bacterial and fungal infections such as ventilator-associated pneumonia and blood-stream infection sometimes by multi-drug resistant bacteria
### Groups at high risk for influenza complication

- **Children <2 years***
- **Adults ≥65 years of age**
- **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**
Diagnosis

- Nose and throat swabs are used and then examined by:
  - Direct Immunofluorescent
  - Cell culture and embryonated egg inoculation

- Serum tests can also be performed to test for HA antibodies
Lab Tests

- Leukocyte counts have been normal or low
- Leukopenia
- Lymphopenia
- Moderate thrombocytopenia in some cases
Epidemiology
WHO Definitions

- **Epidemic**: Human-to-human spread of the virus into at least two countries in one WHO region
- **Pandemic**: Human-to-human spread of the virus with community level outbreaks in at least one other country in a different WHO region than initial epidemic
- **Attack rate**: Numbers of cases of infection per unit of population
- **Virulence**: Severity of illness caused by a particular virus

Influenza Epidemiology

- **Reservoir**: Human, animals (type A only)
- **Transmission**: Respiratory Probably airborne
- **Temporal pattern**: Peak December - March in Temperate area
  May occur earlier or later
- **Communicability**: Maximum 1-2 days before to 4-5 days after onset
Natural History of Influenza Viruses

- Serum antibody
- Prevalence
- Virus isolation

### Hemagglutinin Subtypes of Influenza A Virus

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Human</th>
<th>Swine</th>
<th>Horse</th>
<th>Bird</th>
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<tbody>
<tr>
<td>H1</td>
<td></td>
<td></td>
<td>🐴</td>
<td>🐥</td>
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<tr>
<td>H2</td>
<td></td>
<td>🐺</td>
<td></td>
<td>🐥</td>
</tr>
<tr>
<td>H3</td>
<td></td>
<td>🐺</td>
<td>🐴</td>
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<tr>
<td>H4</td>
<td></td>
<td>🐺</td>
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<tr>
<td>H5</td>
<td></td>
<td>🐺</td>
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<tr>
<td>H6</td>
<td></td>
<td>🐺</td>
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<tr>
<td>H7</td>
<td></td>
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<td>H8</td>
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<td>🐺</td>
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<tr>
<td>H9</td>
<td></td>
<td>🐺</td>
<td>🐴</td>
<td>🐥</td>
</tr>
<tr>
<td>H10</td>
<td></td>
<td>🐺</td>
<td>🐴</td>
<td>🐥</td>
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<tr>
<td>H11</td>
<td></td>
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<td>H15</td>
<td></td>
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<td>🐴</td>
<td>🐥</td>
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</table>

Adapted from Levine AJ. *Viruses*. 1992;165, with permission.
# History: Known Flu Pandemics

<table>
<thead>
<tr>
<th>Name of pandemic</th>
<th>Date</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asiatic Flu</td>
<td>1889–1890</td>
<td>1 million</td>
</tr>
<tr>
<td>Spanish Flu</td>
<td>1918–1920</td>
<td>40 –100 million</td>
</tr>
<tr>
<td>Asian Flu</td>
<td>1957–1958</td>
<td>1 – 1.5 million</td>
</tr>
<tr>
<td>Hong Kong Flu</td>
<td>1968–1969</td>
<td>0.75 – 1 million</td>
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</table>

Information taken from en.wikipedia.org/wiki/influenza
## Human Influenza Virus Type and Variant Forms

<table>
<thead>
<tr>
<th>Type</th>
<th>H/N Subtype</th>
<th>Strain/History</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>H1N1</td>
<td>Spanish Flu Pandemic 1918</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/ New Jersey/76 swine flu</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/ USSR /77 / 90</td>
</tr>
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<td></td>
<td></td>
<td>A/Texas/36/91</td>
</tr>
<tr>
<td></td>
<td>H2N2</td>
<td>A/Singapores/57/Avian flu</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/ Japan/62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/ Taiwan/64</td>
</tr>
<tr>
<td></td>
<td>H3N2</td>
<td>A/Hong Kong/68 Pandemic</td>
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<tr>
<td></td>
<td></td>
<td>A/Johanasseburg/33/94</td>
</tr>
<tr>
<td>B</td>
<td>None</td>
<td>B/Harbin/07/94</td>
</tr>
<tr>
<td>C</td>
<td>None</td>
<td>JHB/2/66</td>
</tr>
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</table>
Pandemic Influenza Viruses

<table>
<thead>
<tr>
<th>Pandemic</th>
<th>Subtype</th>
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<tbody>
<tr>
<td>1889</td>
<td>H2N?</td>
</tr>
<tr>
<td>1899</td>
<td>H3N8</td>
</tr>
<tr>
<td>1918</td>
<td>H1N1</td>
</tr>
<tr>
<td>1957</td>
<td>H2N2</td>
</tr>
<tr>
<td>1968</td>
<td>H3N2</td>
</tr>
<tr>
<td>1977</td>
<td>H1N1</td>
</tr>
</tbody>
</table>
Geographical location

Confirmed human cases of avian influenza A(H7N9) reported to WHO

- HEBEI: 1 Case, 1 Death
- HENAN: 4 Cases, 2 Deaths
- SHANDONG: 2 Cases, 2 Deaths
- BEIJING: 2 Cases, 0 Deaths
- ANHUI: 2 Cases, 2 Deaths
- HUNAN: 2 Cases, 1 Death
- JIANGXI: 6 Cases, 1 Death
- JIANGSU: 28 Cases, 9 Deaths
- SHANGHAI: 33 Cases, 18 Deaths
- ZHEJIANG: 48 Cases, 11 Deaths
- FUJIAN: 5 Cases, 1 Death
- TAIWAN: 1 Case, 0 Deaths

Data as of 25 October 2013, 8:00 GMT+1
Source: WHO/GIP
Epidemiological curve of confirmed cases of avian influenza A(H7N9) reported to WHO, by day, 2013

Cumulative number of confirmed cases of avian influenza A(H7N9) reported to WHO, by month, 2013

Total number of cases includes number of deaths
WHO reports only laboratory cases
All dates refer to onset of illness

Data in WHO/HQ as of 25 October 2013, 08:00 GMT+1
Source: WHO/GIP
Treatment and Prevention
Influenza Vaccines

- Whole virus vaccines: inactivated forms of virus with the predicted HA, are grown in embryonated eggs
- Subunit vaccine: uses both HA and NA subunits extracted from recombinant virus forms
- 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
Influenza Vaccines

- Inactivated subunit (TIV)
  - Intramuscular
  - Trivalent
  - Annual

- Live attenuated vaccine (LAIV)
  - Intranasal
  - Trivalent
  - Annual
## Inactivated Vaccine Effectiveness by Age and Risk Group

<table>
<thead>
<tr>
<th>Age/Risk group</th>
<th>Outcome</th>
<th>Effectiveness*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6m-16 years, healthy</td>
<td>Influenza</td>
<td>50-90%</td>
</tr>
<tr>
<td>18-64 years, healthy</td>
<td>Influenza</td>
<td>50-90%</td>
</tr>
<tr>
<td>≥65 years, community</td>
<td>Influenza</td>
<td>30-70%</td>
</tr>
<tr>
<td>Elderly, nursing home</td>
<td>Influenza</td>
<td>30-40%</td>
</tr>
<tr>
<td>Elderly, nursing home</td>
<td>Hospitalization</td>
<td>30-60%</td>
</tr>
</tbody>
</table>

*Effectiveness may be lower when vaccine and circulating strains antigenically different.

Source: CDC.
## Approved Monovalent Vaccines for Novel H1N1 Influenza

<table>
<thead>
<tr>
<th>Route</th>
<th>Manufacturer</th>
<th>Formulation</th>
<th>Thimerosal</th>
<th>Age</th>
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<tbody>
<tr>
<td>IM</td>
<td>sanofi pasteur</td>
<td>0.25/mL prefilled syringe</td>
<td>0</td>
<td>6 – 35 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5/mL prefilled syringe or single-dose vial</td>
<td>0</td>
<td>&gt;36 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.0 mL multidose vial</td>
<td>25 mcg/0.5 mL</td>
<td>&gt;36 months</td>
</tr>
<tr>
<td>IM</td>
<td>CSL</td>
<td>0.5 mL prefilled syringe</td>
<td>None</td>
<td>≥18 years</td>
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<tr>
<td></td>
<td></td>
<td>5.0 multi-dose vial</td>
<td>25 mcg/0.5 mL</td>
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<tr>
<td>IM</td>
<td>Novartis Vaccine</td>
<td>0.5 mL prefilled syringe</td>
<td>&lt;1.0 mcg Hg</td>
<td>≥4 years</td>
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<tr>
<td></td>
<td></td>
<td>5.0 multi-dose vial</td>
<td>25 mcg/0.5 mL</td>
<td></td>
</tr>
<tr>
<td>Intranasal</td>
<td>MedImmune</td>
<td>Single-dose sprayer</td>
<td>0</td>
<td>2-49 years</td>
</tr>
</tbody>
</table>
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 two years
Antiviral Treatment Recommendations

- 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
- 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
Healthy Habits

- **When Healthy:**
  - Avoid close contact with those who are sick
  - Wash your hands often
  - Avoid touching your eyes, nose and mouth to decrease the spread of germs

- **When Ill:**
  - Cover your mouth and nose with a tissue (or upper sleeve) when you sneeze or cough
  - Stay home from work or school when you are sick
Key facts

- Influenza is an acute viral infection that spreads easily from person to person.
- Influenza circulates worldwide and can affect anybody in any age group.
- Influenza causes annual epidemics that peak during winter in temperate regions.
- Influenza is a serious public health problem that causes severe illnesses and deaths for higher risk populations.
- An epidemic can take an economic toll through lost workforce productivity, and strain health services.
- Vaccination is the most effective way to prevent infection.