Influenza

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Haemagglutinin
Neuraminidase
matrix protein M1
envelope
RNP

RNA
M1
M2
HA
NA
RNPs
NS2

PROF AMITA JAIN
Acknowledgement

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- I acknowledge help from those sites and presenters
WHO Guidelines for 
Pharmacological Management of 
Pandemic Influenza A(H1N1) 2009 
and other Influenza Viruses

Revised February 2010

Ministry of Health & Family Welfare 
Pandemic Influenza A (H1N1)

Guidelines on categorization of Influenza A H1N1 cases during screening for home isolation, testing treatment, and hospitalization
(Revised on 05.10.09)

Pandemic Influenza Risk Management 
WHO Interim Guidance

http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
What is flu?

SEVERAL NAMES: USED AS SYNONYMS

INFLUENZA
FLU
H1N1
SWINE FLU
ILI
SO IV
PDM H1N1
SEASONAL INFLUENZA
PANDEMIC INFLUENZA
Flu: the disease and the virus

- Also called Influenza
- Caused by influenza virus
- Other respiratory viral infections caused by other viruses like rhino or corona are not flu
- Swine flu is a type of flu only
- Clinical features and disease outcome is same as of any other type of flu
What is Influenza like illness?

**ILI: case definition** *(WHO)*
- An acute respiratory infection with:
  - measured *fever* of ≥ 38°C
  - and *cough/rhinorrhea*;
- with onset within the last 10 days

**SARI: case definition**
- An acute respiratory infection with:
  - history of fever or measured fever of ≥ 38°C;
  - and *cough*;
- with onset within the last 10 days;
- and requires *hospitalization*
How many types of influenza viruses? Do they all cause human illness? Is there any cross immunity among them?
Taxonomy

- Family: Orthomyxoviridae
- Genus: Influenzavirus
- Species: Influenza virus A
  - Influenza virus B
  - Influenza virus C
Influenza Virus – 3 Types

- RNA virus, Antigenically distinct 3 types (Orthomyxoviridae)
- No cross-immunity between different types

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Causes significant disease: epidemics; pandemics</td>
<td>• Causes significant disease: milder epidemics</td>
<td>• Does not cause significant disease</td>
</tr>
<tr>
<td>• Infects both humans and other species</td>
<td>• Limited to humans</td>
<td>• Limited to humans</td>
</tr>
<tr>
<td>• Frequent antigenic variations</td>
<td>• Infrequent antigenic variations!</td>
<td>• Antigenically stable</td>
</tr>
<tr>
<td></td>
<td>TYPE A</td>
<td>TYPE B</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>severity of illness</td>
<td>++++</td>
<td>++</td>
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<tr>
<td>animal reservoir</td>
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<td>no</td>
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<tr>
<td>human pandemics</td>
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<td>no</td>
</tr>
<tr>
<td>human epidemics</td>
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<tr>
<td>antigenic changes</td>
<td>shift, drift</td>
<td>drift</td>
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<tr>
<td>segmented genome</td>
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<tr>
<td>amantadine, rimantidine</td>
<td>sensitive</td>
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</tr>
<tr>
<td>zanamivir</td>
<td>sensitive</td>
<td>sensitive</td>
</tr>
<tr>
<td>surface glycoproteins</td>
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</tr>
</tbody>
</table>
Influenza virus - Structure

- Enveloped
- Envelope has two proteins
  - Hemagglutinin (HA)
  - Neuraminidase
- Nine structural proteins
- Genetic variation
- Genetic reassortment
Influenza virus - Structure

- Spherical / Pleomorphic
- Size 80 – 120nm
- Helical nucleocapsid
- Segmented genome
- Negative sense single stranded RNA
- Eight segments
The eight RNA segments

1. PB2
   - Transcriptase: cap binding

2. PB1
   - Transcriptase: elongation

3. PA
   - Transcriptase: protease activity?

4. HA
   - Haemagglutinin

5. NP
   - Nucleoprotein: RNA binding - transport of vRNA

6. NA
   - Neuraminidase: release of virus

7. M1/M2
   - Matrix protein 1: major component of virion
   - Matrix protein 2: integral membrane protein - ion channel

8. NS1/NS2
   - Non-structural protein 1: RNA transport, translation, splicing
   - Non-structural protein 2: function not known
But we talk of H1N1. What is H and N?

**HINI IS A SUBTYPE OF INFLUENZA A**

**HA AND NA ARE TWO IMP. SURFACE ANTIGENS OF INFLUENZA VIRUS WHICH ARE USED TO ANTIGENICALLY TYPE INF. A VIRUSES**
8 segmented RNA genome encodes 11 proteins

**2 surface antigens:**
- Haemagglutinin (HA)
  - Initiates infection following attachment of virus to susceptible cells
  - Antibodies to ‘H’: neutralizes the virus
- Neuraminidase (NA)
  - Release of virus from infected cell
  - Antibodies to ‘N’: modifies the infection
Hemagglutinin

- Attachment protein
- Major antigen
- Responsible for evolution of Virus
- 16 antigenic types
Neuraminidase

- Antigenic
- Receptor destroying enzyme
- Sialidase enzyme
- Removes sialic acid from glycoconjugates
- Facilitates release of virus
- Prevents self aggregation of viruses
- Helps the virus to move through mucin layer
- 9 antigenic types
How many H and N?

- 16 HA subtypes and 9 NA subtypes in nature
- A total of 144 (16 x 9) possible combinations
- 71 of which have been observed in nature
- Until 1997 only about 3 combinations affect humans
Why do pandemic and epidemic occur?
Influenza A – Antigenic Variations

**Antigenic drift: gradual antigenic change over a period;**
- Involves ‘point mutations’ in genes owing to selection pressure by immunity in host population
- Responsible for frequent influenza epidemics; necessitates reformulations of seasonal influenza vaccines

**Antigenic shift: sudden, complete or major change;**
- Results from genetic recombination of human with animal/avian virus
- Leads to a novel subtype different from both parent viruses
- If ‘novel subtype’ has sufficient genes from HI viruses which make it readily transmissible from person to person, it may cause pandemics
- Evidence suggests that human influenza viruses responsible for last 3 pandemics and latest H1N1 pandemic contained gene segments closely related to avian influenza viruses
where do “new” HA and NA come from?

HUMAN ANIMAL INTERFACE

Mixing pot
H1N1 Genetic Reassortment

N. American H1N1 (swine/avian/human) → Eurasian swine H1N1

Classical swine, N. American lineage
Avian, N. American lineage
Human seasonal H3N2
Eurasian swine lineage

Pandemic (H1N1) 2009, combining swine, avian and human viral components
Different Species Infected by Influenza A Subtypes

- All 16 H subtypes infect birds
- Most widespread epidemics & all pandemics: H1N1, H2N2, H3N2
16 HA subtypes and 9 NA subtypes in nature
- Innumerable possible combinations
- 71 of which have been observed in nature
- Until 1997 only about 3 combinations affect humans
30 September 1971- WHO Nomenclature

Consists of two parts: a strain designation, and a description of H & N Ag

Strain Designation
1. A description of the antigenic type of NP (A, B, or C)
2. Host of origin. Not indicated for strains isolated from man
3. Geographic origin
4. Strain number
5. Year of isolation

Description of H & N Ag:
1. An index describing antigenic character of hemagglutinin subtype
2. An index describing antigenic character of neuraminidase

Examples:
- 1. A/Singapore/1/57(H2N2)
- 2. A/Hong Kong/1/68(H3N2)
- 3. A/turkey/Wisconsin/1/66(Hav5N2)
- 4. A/duck/Ukraine/1/63(Hav7Neq2)
Swine Flu

• **2009 flu pandemic** was a global outbreak
• Of a new strain of a influenza A virus subtype H1N1
• officially named the "**novel H1N1**" / **pdm H1N1**
• first identified in April 2009
• commonly called "**Swine flu**"
Do pigs get flu? YES

- rarely fatal in pigs
- virus resistant to standard antiviral drugs
- Precautionary measures include use of face masks & gloves by farmers when dealing with infected animals
- cannot spread by consuming pork products
- not transmitted through food
Magnitude of Disease Burden

World-wide in distribution

- Sporadic cases every season/year round
- Outbreaks (primarily Influenza A): occur every year
- Major epidemics: at interval of 2-3 years
- Pandemics: rare; 10-15 years or more
- Attack rates during epidemics: 10-20% in general community; > 50% in closed populations
- Epidemics generally last 3-6 weeks
Influenza

Agent Factors

Reservoir of Infection:
- Humans primary reservoir for human infections
- Major reservoir – animals & birds (swine, horses, dogs, cats, domestic poultry, water birds, wild birds etc.)

Source of Infection:
- Usually a case or sub-clinical case

Communicability:
- 3-5 days from clinical onset in adults;
- Up to 7 days in young children
- Peak viral shedding occurs on day 1 of symptoms
Influenza
Host Factors

Age & Sex:
- All ages, both sexes
- Attack rates lower among adults
- High Case Fatality Ratio (CFR) during epidemic in high risk cases: (old people; children; persons with diabetes, ch. heart disease, renal & resp. diseases)

Human Immunity:
- Antibodies to ‘H’: neutralizes the virus
- Antibodies to ‘N’: modifies the infection
- Antibodies appear in 7 days after an attack; reach maximum Level in 2 weeks; drops to pre-infection level in 8-12 months
Influenza

Environmental Factors

**Seasonality:**
- Temperate zones: epidemics occur in winter
- Tropics: epidemics occur in rainy season
- Current one is ???
- Sporadic cases: any month

**Overcrowding:**
- Enhances transmission
- Higher attack rates in closed groups (schools, institutions, ships etc.)
Influenza
Disease Transmission

Mainly airborne:
- Droplet infection
- Droplet nuclei

Through direct contact

Transmission from objects possible

Incubation period:
- 18 to 72 hours
NORMAL TRACHEAL MUCOSA

3 DAYS POST-INFECTION

7 DAYS POST-INFECTION
• DECREASED CLEARANCE

• RISK BACTERIAL INFECTION

• VIREMIA RARE
RECOVERY

- INTERFERON
  - SIDE EFFECTS - FEVER, MYALGIA, FATIGUE, MALaise

- CELL-MEDIATED IMMUNE RESPONSE

- TISSUE REPAIR
  - CAN TAKE SOME TIME
After 5 days, fever and other symptoms have usually disappeared, but cough and weakness may continue.

All symptoms are usually gone within a week or two.

It can lead to pneumonia and other life-threatening complications, particularly in infants, senior citizens, and people with long-term health problems.
Flu is often confused with the common cold, but flu symptoms are usually more severe than the typical sneezing and stuffiness of a cold. Symptoms of the flu may include:

- fever
- chills
- headache
- muscle aches
- dizziness
- loss of appetite
- tiredness
- cough
- sore throat
- runny nose
- nausea or vomiting
- weakness
- ear pain
- diarrhea

Infants with the flu may simply seem sick all of a sudden or "just don't look right."
PULMONARY COMPLICATIONS

- Croup (young children)
- Primary influenza virus pneumonia
- Secondary bacterial infection
  - *Streptococcus pneumoniae*
  - *Staphylococcus aureus*
  - *Hemophilus influenzae*
NON-PULMONARY COMPLICATIONS

- Myositis (rare, > in children, > with type B)
- Cardiac complications
- Encephalopathy
- Liver and CNS
  - Reye syndrome
- Peripheral nervous system
  - Guillian-Barré syndrome
Lab diagnosis: who needs testing?

- Only those who need Oseltamivir (tamiflu)
  - at the time of epidemic we know every case is a suspect
  - No testing needed to confirm the etiology
  - Will not help in clinical management
  - Too much of burden
Lab Diagnosis: What sample to be collected?

- Respiratory specimens including:
  - **Throat and Nasal swab**
  - Bronchoalveolar lavage,
  - Tracheal aspirates,
  - Nasopharyngeal or oropharyngeal aspirates as washes,
  - Nasopharyngeal or Oropharyngeal swabs,
  - Only on swabs with a synthetic tip (such as polyester or Dacron) and aluminium or plastic shaft
  - Swabs with cotton and wooden shafts are not recommended
  - Specimens collected with swabs made of calcium alginate are acceptable
When to Collect Respiratory Specimens?

- As soon as possible after symptoms begin
- Before antiviral medications are administered
- Even if symptoms began >1 week ago
Personal Protective Equipment

- Masks (N-95)/ 3 ply surgical mask?
- Gloves
- Protective eye wear (goggles)
- Hair covers
- Boot or shoe covers
- Protective clothing (gown or apron)
Throat Swab

- Easy to do
- Highest yield in detecting H1N1
- Have the patient open his/her mouth wide open
- Patient should try to resist gagging and closing the mouth while the swab touches the back of the throat near the tonsils
Nasal / Nasopharyngeal Swab:

- Insert dry swab into nostril and back to nasopharynx
- Leave in place for a few seconds
- Slowly remove swab while slightly rotating it
- Use a different swab for the other nostril
- Put tip of swab into vial containing VTM, breaking applicator’s stick
- **Nasal Swab** is collected from the anterior turbinate

**Throat swabs can be collected into the same VTM to increase viral yield.**
How to Label Samples

- **Label**
  - Specimen No. :
  - Patient’s Name :
  - Hospital Name :
  - Unique ID No. :
  - Subject’s name
  - Subject’s unique identification number
How to Store Specimens

- Store specimens at 4 °C before and during transportation within 48 hours
- Store specimens at -70 °C beyond 48 hours
- Do not store in standard freezer –
  - keep on ice or in refrigerator
- Avoid freeze-thaw cycles
- Better to keep on ice for a week than to have repeat freeze and thaw
Transportation of specimens

- Refer to WHO guidelines for the safe transport of infectious substances and diagnostic specimens
- Coordinate with the laboratory
- Standard triple packaging system (WHO)
- Accompany with the clinical details as per proforma
- While transportation cold chain should be maintained
Waste Disposal

- Should be done as per guidelines of hospital
General Biosafety Measures

- Clinical samples should be collected by hospital staff and not by laboratory staff
- While taking samples use N95 mask
- Use Latex disposable gloves
- Wear laboratory coat/disposable apron
- Cover your hairs with head cover
Rapid tests or immunofluorescence

- Sensitivity and specificity of rapid-point-of-care or immunofluorescence tests designed for direct detection of influenza A viruses are currently unknown.
- These tests will not differentiate seasonal influenza from influenza A (H1N1)swl virus.
TREATMENT

- **Amantadine** may prevent influenza if taken continuously by high-risk persons at the time of an epidemic, but is not used widely.
- **Oseltamivir Phosphate** (TAMIFLU)
- Zanamavir
Treatment

- rarely require specific medical treatment
- Children with chronic medical conditions
- Given within 48 hours of the onset
- CDC recommends that diagnosed cases of swine influenza should be treated with oseltamivir (Tamiflu) and zanamivir (Relenza) - H1N1
- Antibiotics are used to treat the disease; although they have no effect against the virus, help prevent bacterial pneumonia and other secondary infections in influenza-weakened herds
Who needs Tamiflu?
Persons at higher risk for influenza complications recommended for antiviral treatment

- children aged younger than 2 years;
- adults aged 65 years and older;
- persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), and metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle, such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury);
- persons with immuno-suppression, including that caused by medications or by HIV infection;
- women who are pregnant or postpartum (within 2 weeks after delivery);
- persons aged younger than 19 years who are receiving long-term aspirin therapy;
- persons who are morbidly obese (i.e., body mass index is equal to or greater than 40);
- residents of nursing homes and other chronic care facilities.
## Use of antivirals for treatment of influenza

Revised February 2010

<table>
<thead>
<tr>
<th>Population</th>
<th>Pandemic influenza A (H1N1) 2009 and other seasonal influenza viruses</th>
<th>Influenza viruses known or suspected to be oseltamivir resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncomplicated clinical presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients in higher risk groups</td>
<td>Treat with oseltamivir or zanamivir as soon as possible (05)</td>
<td>Treat with zanamivir as soon as possible (05)</td>
</tr>
<tr>
<td><strong>Severe or progressive clinical presentation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (including children and adolescents)</td>
<td>Treat with oseltamivir as soon as possible (01)</td>
<td>Treat with zanamivir as soon as possible (03)</td>
</tr>
<tr>
<td>Patients with severe immunosuppression</td>
<td>Treat with oseltamivir as soon as possible. Consider higher doses and longer duration of treatment (03)</td>
<td>Treat with zanamivir as soon as possible (03)</td>
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<tr>
<td>Antiviral Agent</td>
<td>Activity Against</td>
<td>Use</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Oseltamivir Influenza A (Tamiflu®) and B</td>
<td>Treatment</td>
<td>Any age$^1$</td>
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<tr>
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<td>Chemo-prophylaxis</td>
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<td>Zanamivir Influenza A (Relenza®) and B</td>
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</table>
Oseltamivir

Oseltamivir is indicated for treatment of patients one year of age and older.

For adolescents (13 to 17 years of age) and adults the recommended oral dose (based on data from studies in typical uncomplicated influenza) is 75 mg oseltamivir twice daily for 5 days.

Zanamivir

Zanamivir is indicated for treatment of influenza in adults and children (>5 years).

The recommended dose for treatment of adults and children from the age of 5 years (based on data from studies in typical uncomplicated influenza) is two inhalations (i.e. 2 x 5mg) twice daily for 5 days.
Who needs CHEMOPROPHYLAXIS?

- CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis so as to limit the possibilities that antiviral resistant viruses could emerge.
- Indiscriminate use of chemoprophylaxis might promote resistance to antiviral medications, or reduce antiviral medication availability for treatment of persons at higher risk for influenza complications or those who are severely ill.
Antiviral chemoprophylaxis generally is not recommended if more than 48 hours have elapsed since the first exposure to an infectious person.
Chemoprophylaxis can be considered in following situations.

- Prevention of influenza in persons at high risk of influenza complications during the first two weeks following vaccination after exposure to an infectious person.
- Prevention for people with severe immune deficiencies or others who might not respond to influenza vaccination, such as persons receiving immunosuppressive medications, after exposure to an infectious person.
- Prevention for people at high risk for complications from influenza who cannot receive influenza vaccine due to a contraindication after exposure to an infectious person.
Advice for your patients

- Social distancing, It means staying away from people who might be infected
- Avoiding large gatherings, spreading out a little at work, or perhaps staying home and lying low if an infection is spreading in a community.
- Wash your hands thoroughly and frequently with soap and water or with alcohol-based hand sanitizers
- Never pick up used tissues.
- Never share cups and eating utensils
- Stay home from work or school when you're sick with the flu.
- Cover your mouth and nose with a tissue when you cough or sneeze.
Advice for your patients

- Rest in bed
- Drink lots of liquids, like water, chicken broth, and other fluids
- Take medicine to ease your fever, aches, and pains; NO ASPIRIN
- Consult doctor if you have trouble breathing, your muscles really hurt, or if you feel confused
- Most of the time, you'll feel better in a week or two
- Until then, you'll have to stay home from school and take it easy
Recommended composition of influenza virus vaccines for use in the 2014-2015 northern hemisphere influenza season (20/2/ 2014)

- trivalent vaccines for use in the 2014-2015 influenza season (northern hemisphere winter)
- an A/California/7/2009 (H1N1)pdm09-like virus;
- an A/Texas/50/2012 (H3N2)-like virus;
- a B/Massachusetts/2/2012-like virus.
- It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-like virus.
Vaccine

- **Types of Vaccine**
  - *Killed Virus* (egg based)
    - Injectable vaccine
  - *Live Virus*
    - Live Attenuated Influenza Virus strains
      - Nasal Spray
  - *Virus Subunit*
    - HA extracted from recombinant virus
People who need flu vaccine

- all kids 6 months to 18 years old
- anyone 50 years and older
- women who will be pregnant during the flu season
- anyone who lives or works with infants under 6 months old
- residents of long-term care facilities, such as nursing homes
- any adult or child with chronic medical conditions, such as asthma
- health-care personnel who have direct contact with patients such as doctors and nurses
- out-of-home caregivers and household contacts of anyone in any of the high-risk groups
People who should not get flu vaccine

- infants under 6 months old
- anyone who's severely allergic to eggs and egg products (ingredients for flu shots are grown inside eggs, so tell your doctor if your child is allergic to eggs or egg products before he or she gets a flu shot)
- anyone who's ever had a severe reaction to a flu vaccination
- anyone with Guillain-Barré syndrome (GBS)
- anyone with a fever
THANK YOU