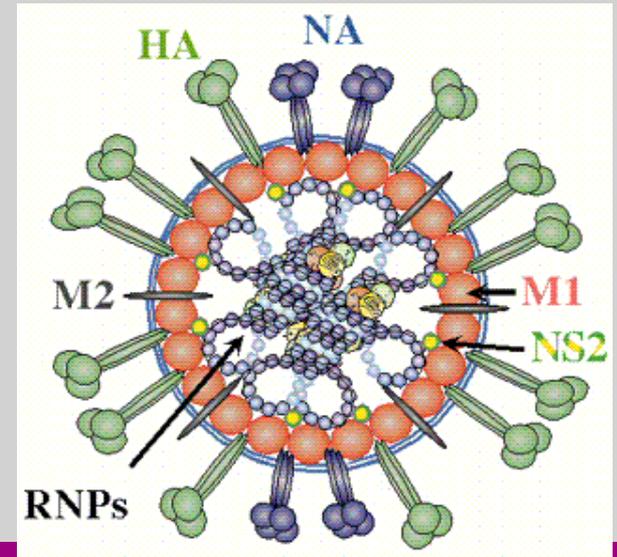
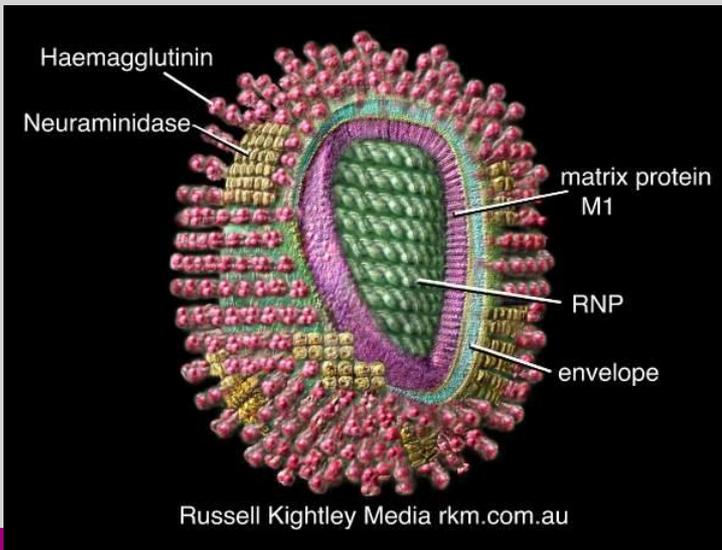


Influenza



PROF AMITA JAIN



Acknowledgement

- Some of the pictures in this series are taken from open access material on web.
- Some of the material was provided by colleagues and friends in the field.
- 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**

**WHO Guidelines for
Pharmacological Management of
Pandemic Influenza A(H1N1) 2009
and other Influenza Viruses**

<http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm>

Revised February 2010



What is flu?

**SEVERAL NAMES: USED
AS SYNONYMS**

INFLUENZA

FLU

H1N1

SWINE FLU

ILI

SO IV

PDM H1N1

SEASONAL INFLUENZA

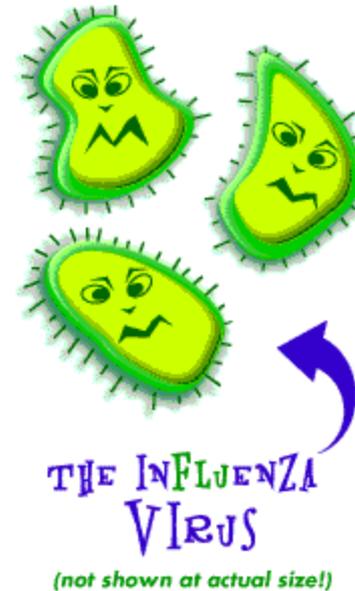
PANDEMIC INFLUENZA



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 $\geq 38\text{ C}^\circ$
- and cough/ rhinorrhoea;
- with onset within the last 10 days
- **SARI: case definition**
- An acute respiratory infection with:
- history of fever or measured fever of $\geq 38\text{ C}^\circ$;
- 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

Type A

- Causes significant disease: epidemics; pandemics

- Infects both humans *and* other species

- Frequent antigenic variations

Type B

- Causes significant disease: milder epidemics

- Limited to humans

- Infrequent antigenic variations!

Type C

- Does not cause significant disease

- Limited to humans

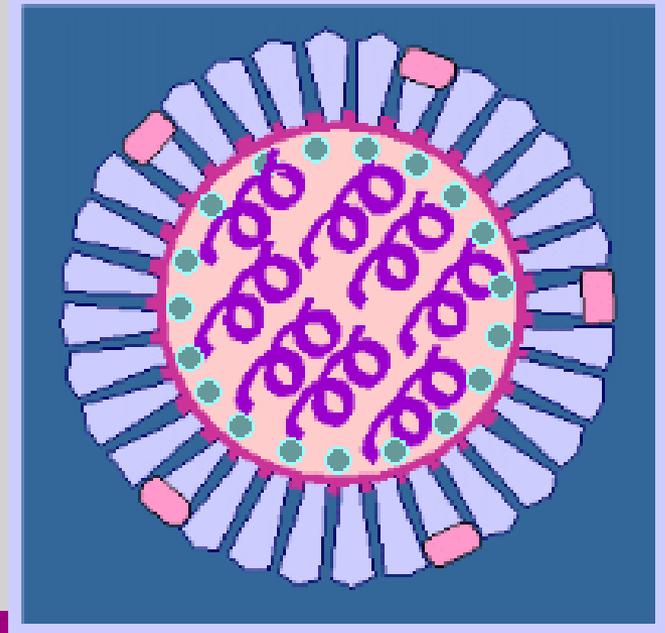
- Antigenically stable

	TYPE A	TYPE B	TYPE C
severity of illness	++++	++	+
animal reservoir	yes	no	no
human pandemics	yes	no	no
human epidemics	yes	yes	no (sporadic)
antigenic changes	shift, drift	drift	drift
segmented genome	yes	yes	yes
amantadine, rimantidine	sensitive	no effect	no effect
zanamivir	sensitive	sensitive	
surface glycoproteins	2	2	(1)

Influenza virus- Structure



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

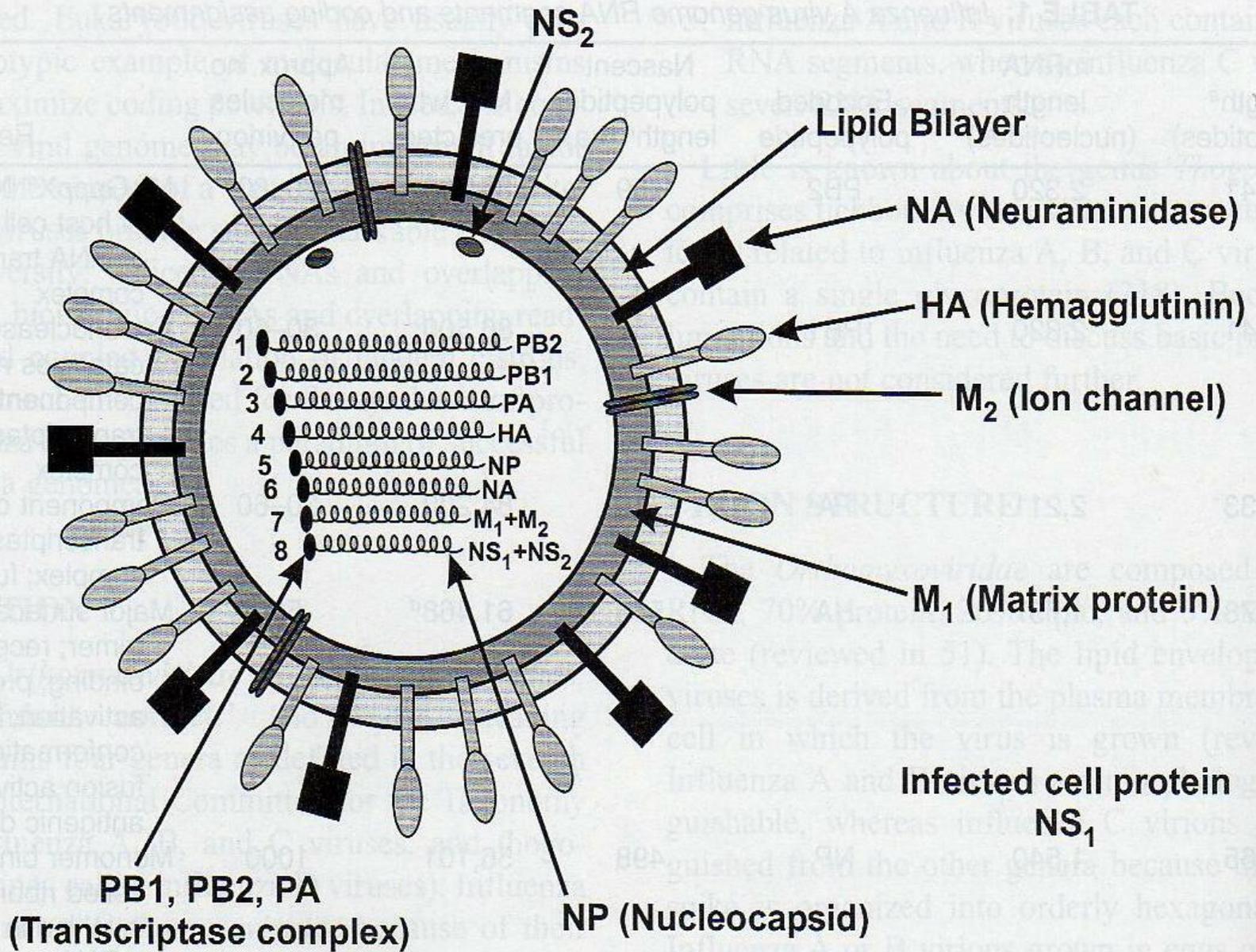


Influenza virus- Structure



- **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?



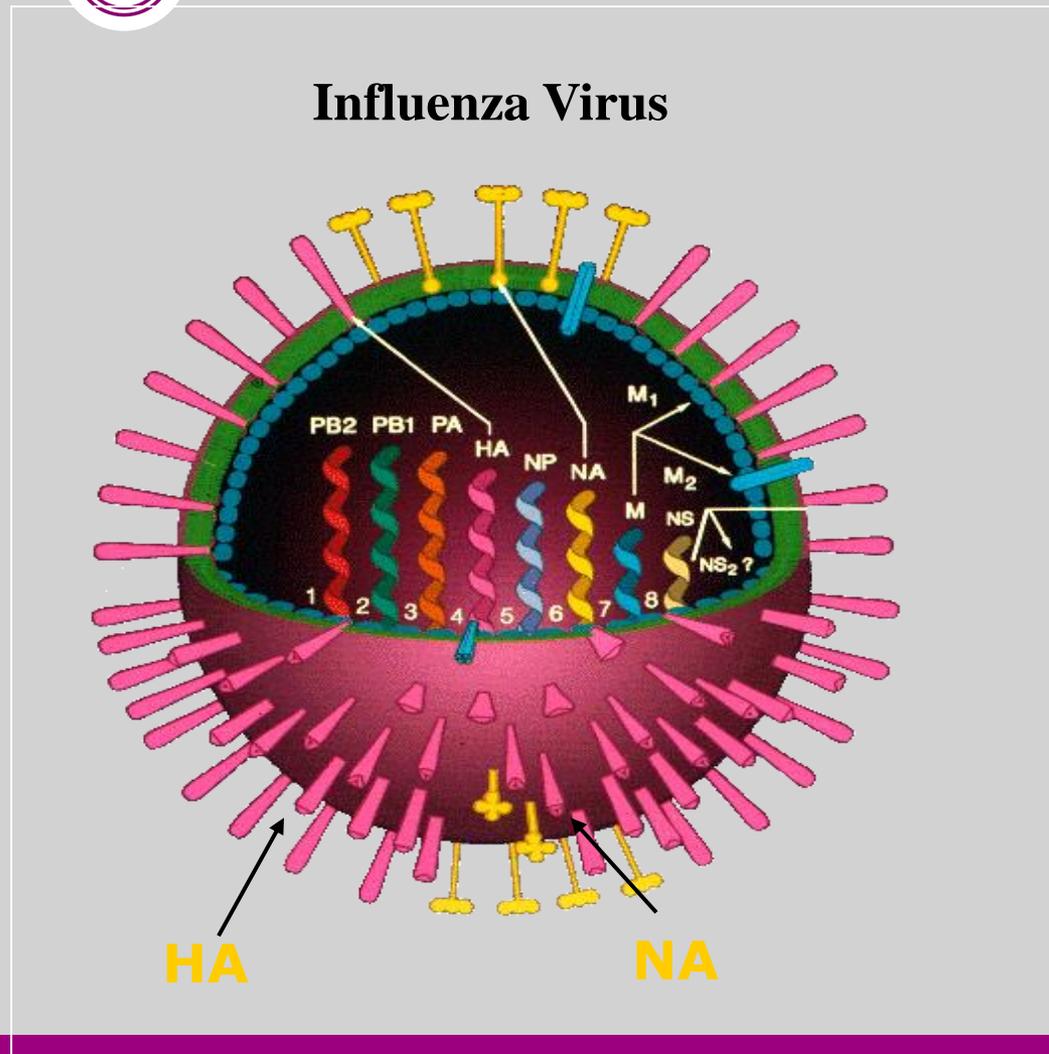
H₁N₁ IS A SUBTYPE OF INFLUENZA A

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:

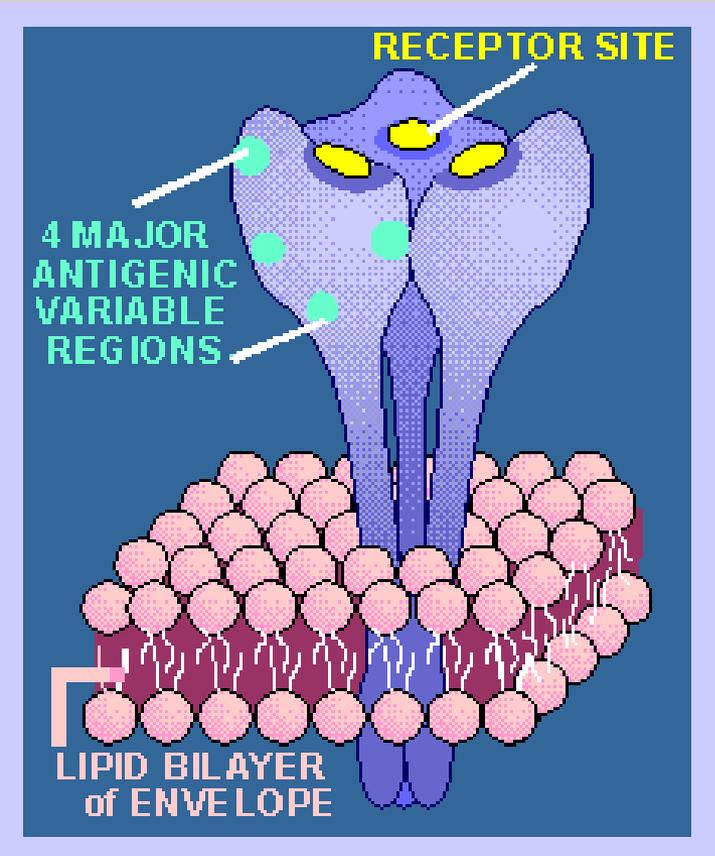
- Haemagglutinin (HA)
 - Initiates infection following attachment of virus to susceptible cells
 - Antibodies to 'H': neutralizes the virus
- Neuraminidase (NA)
 - Release of virus from infected cell
 - Antibodies to 'N': modifies the infection



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

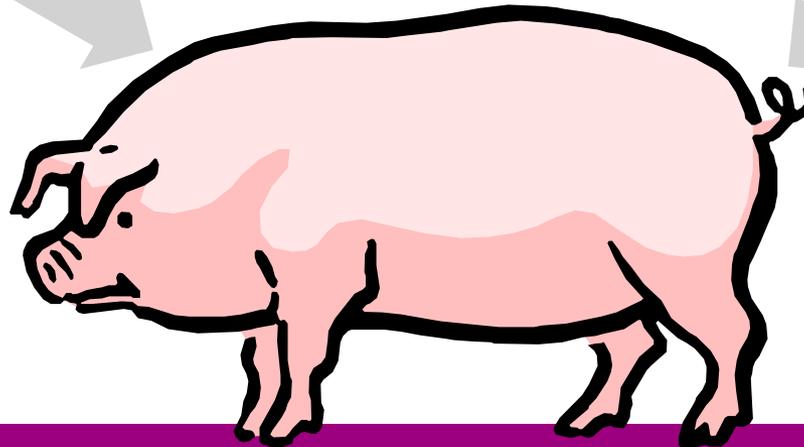
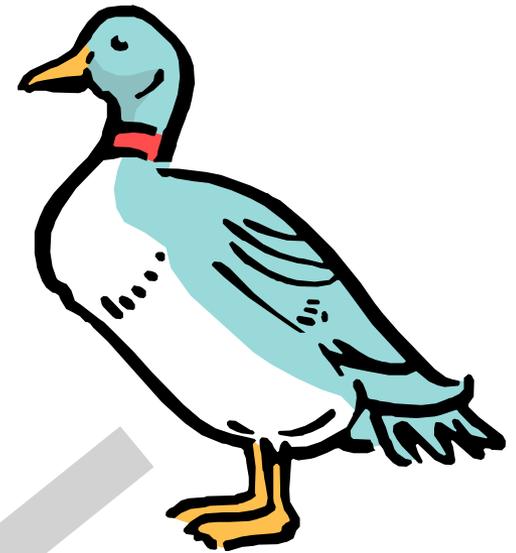
where do “new” HA and NA come from?



HUMAN ANIMAL INTERFACE



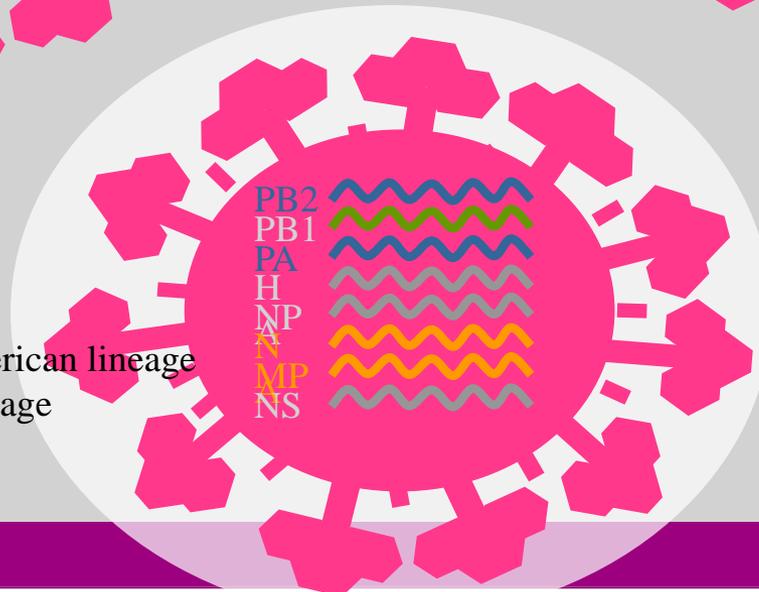
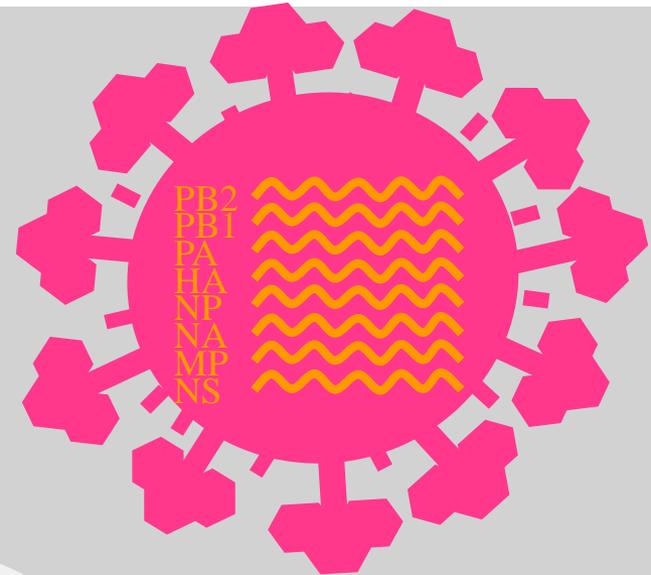
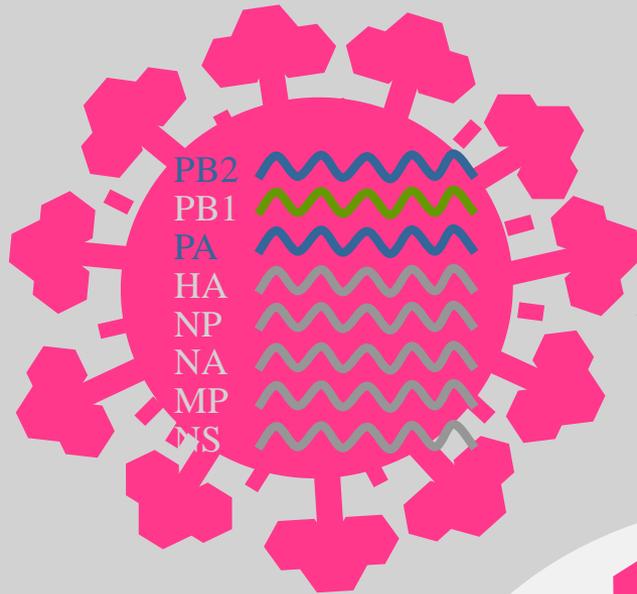
Mixing pot



H1N1 Genetic Reassortment

N. American H1N1
(swine/avian/human)

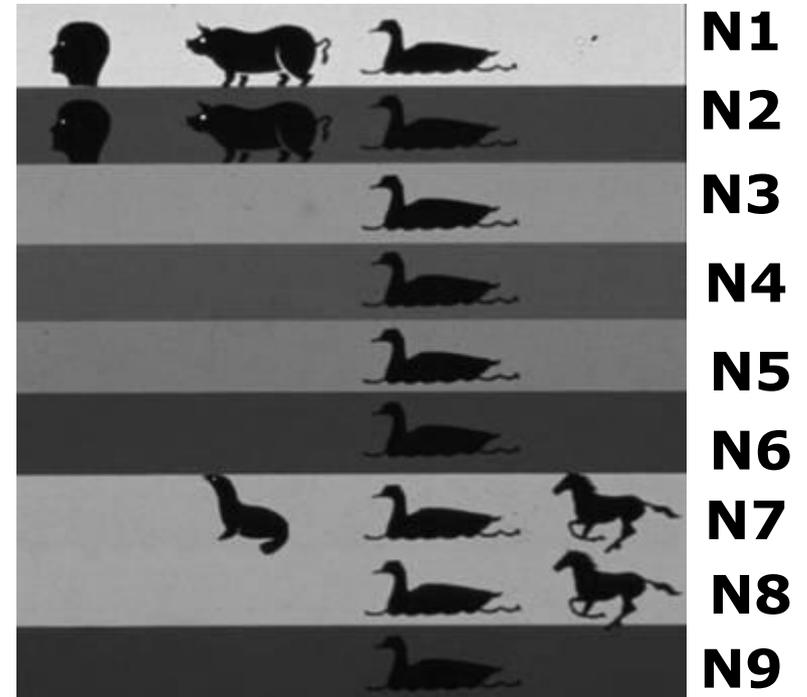
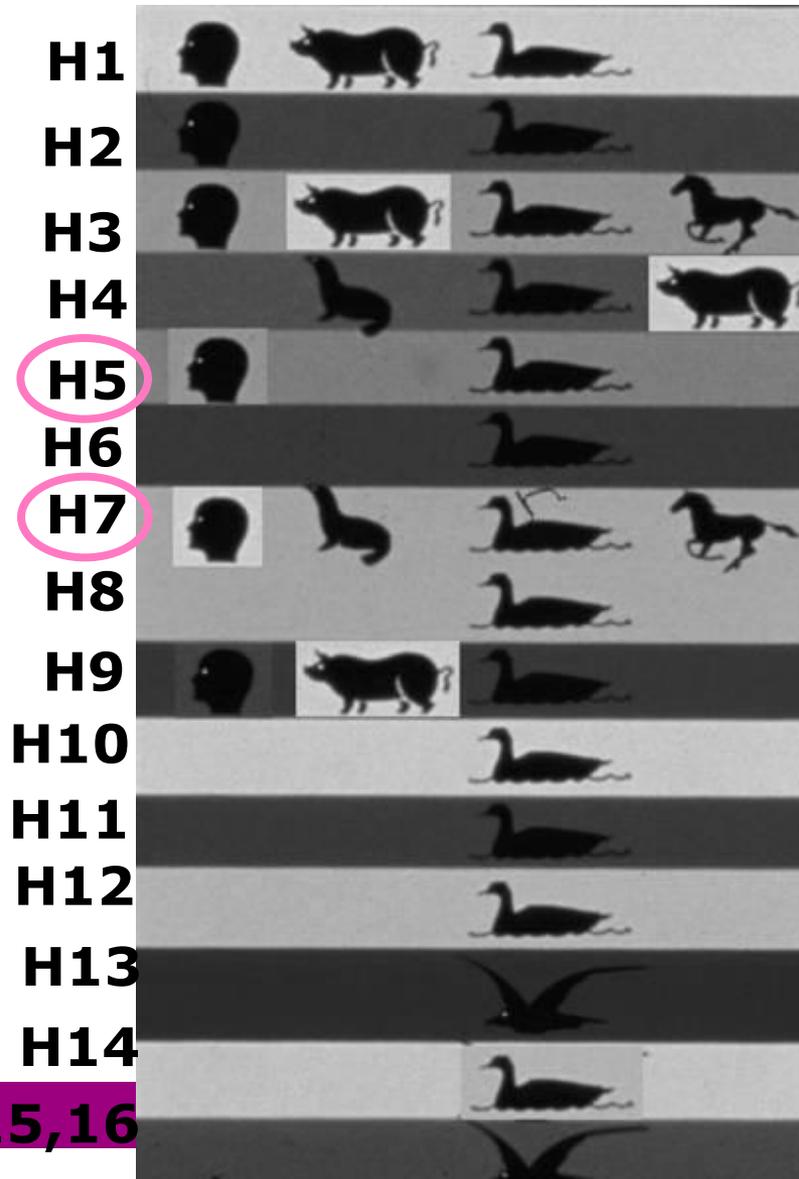
Eurasian swine H1N1



- 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

How many H and N?



- ∞ 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)

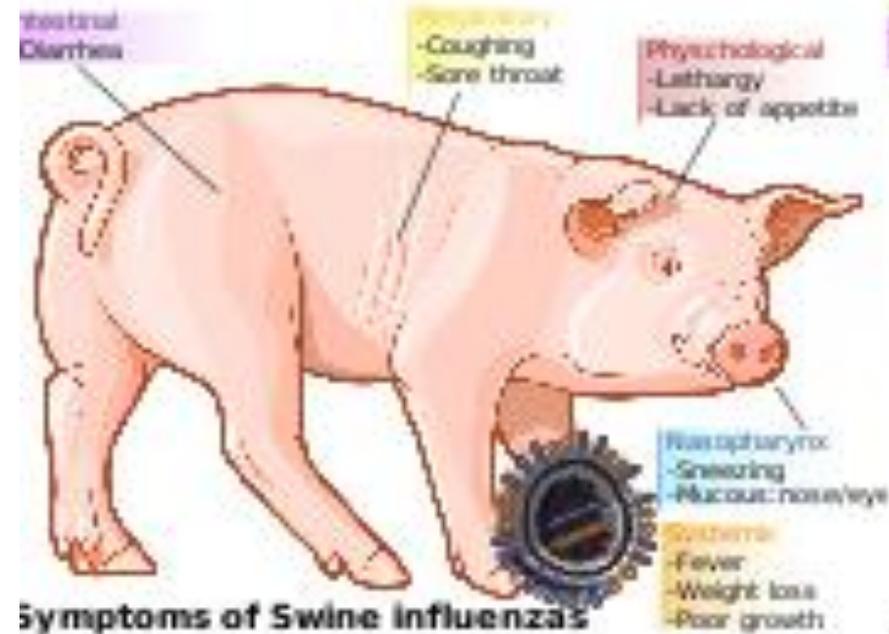
Swine Flu

- **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:

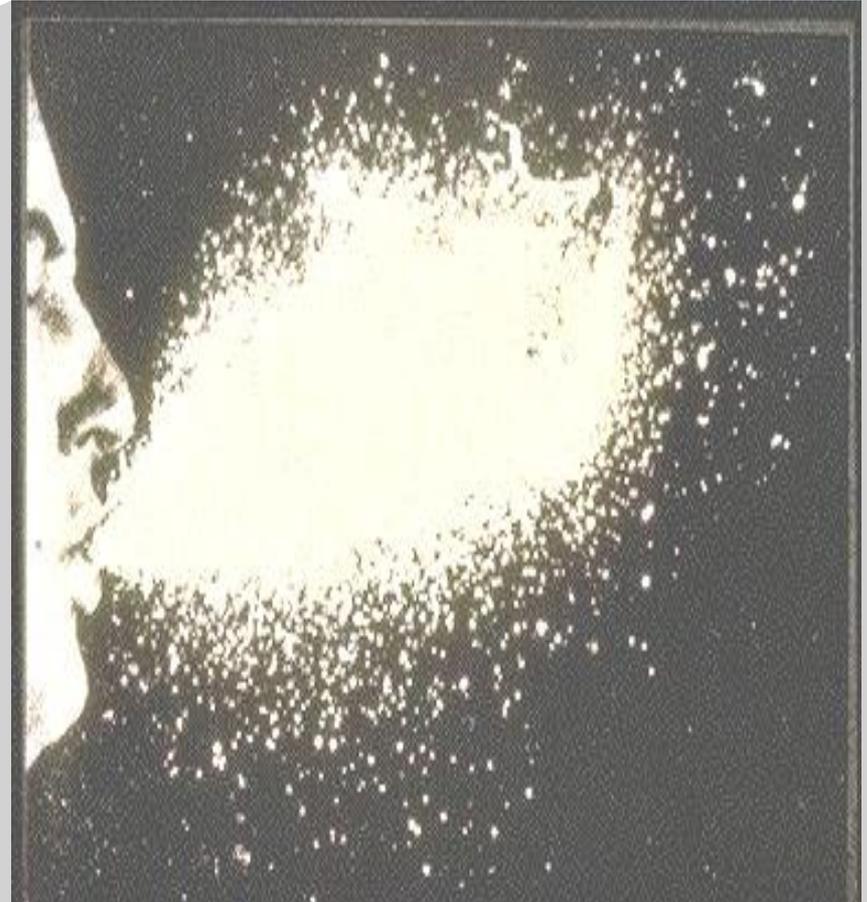
- Droplet infection
- Droplet nuclei

Through direct contact

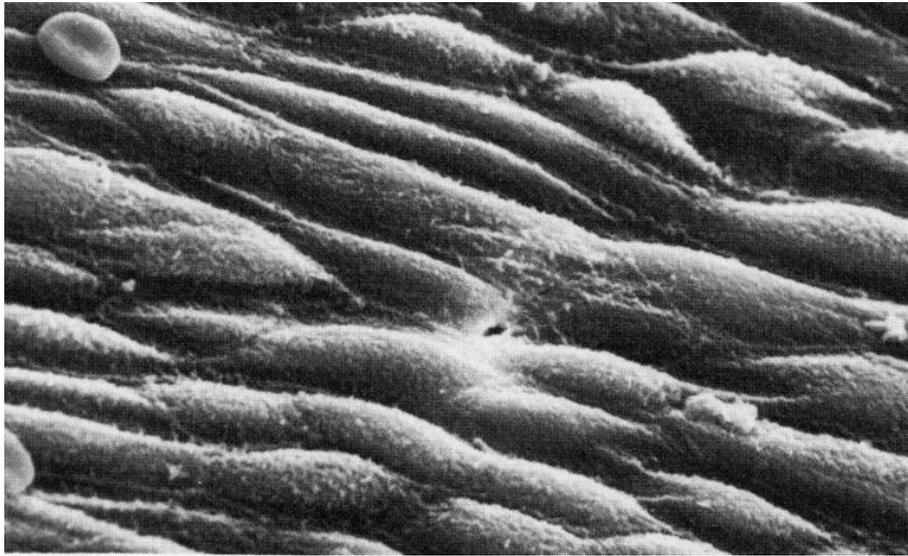
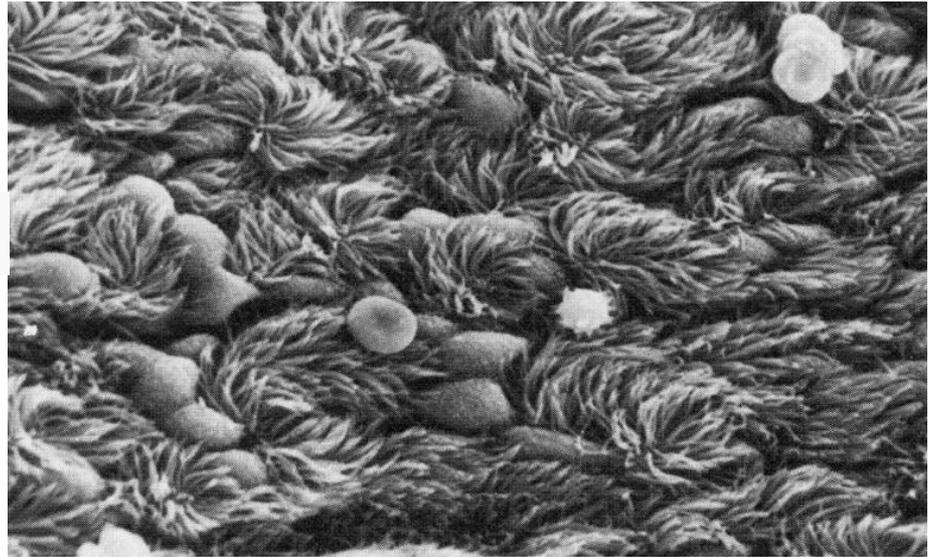
Transmission from objects possible

Incubation period:

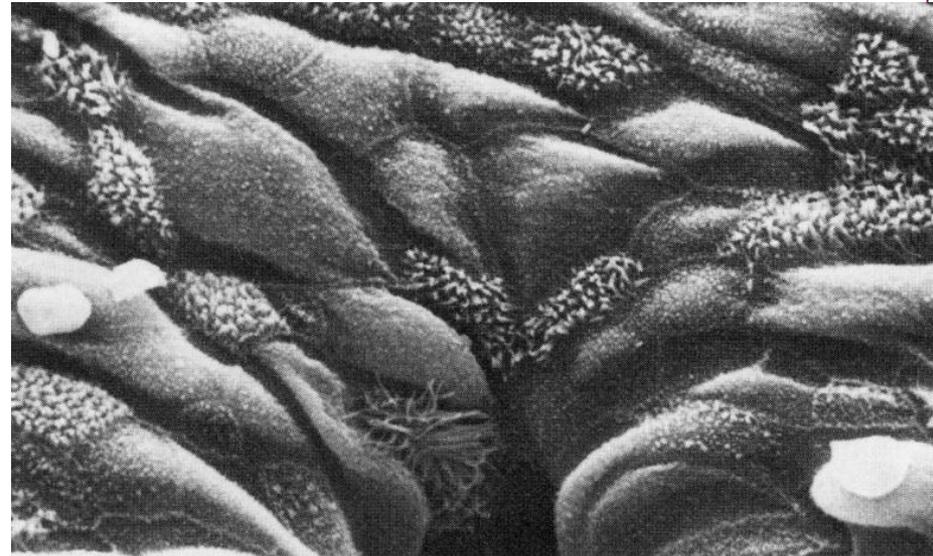
- 18 to 72 hours



NORMAL TRACHEAL MUCOSA

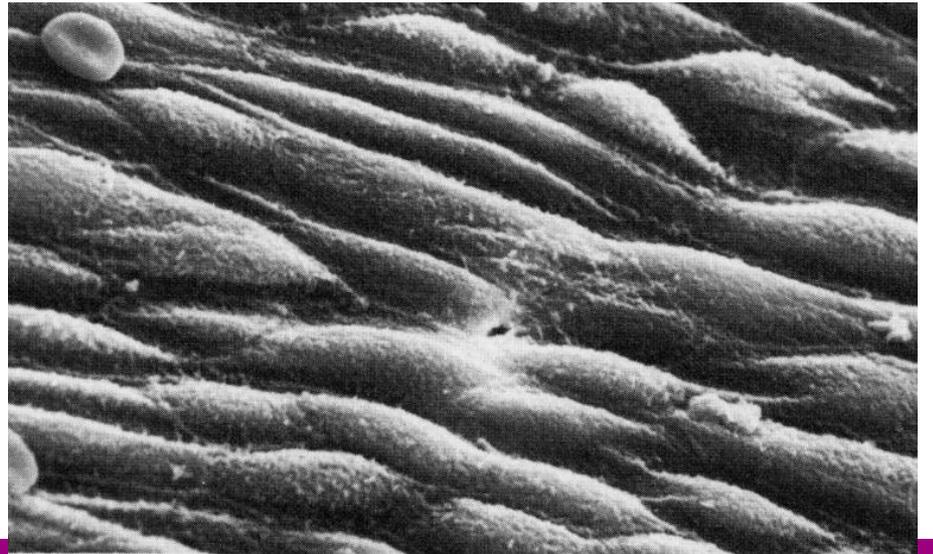
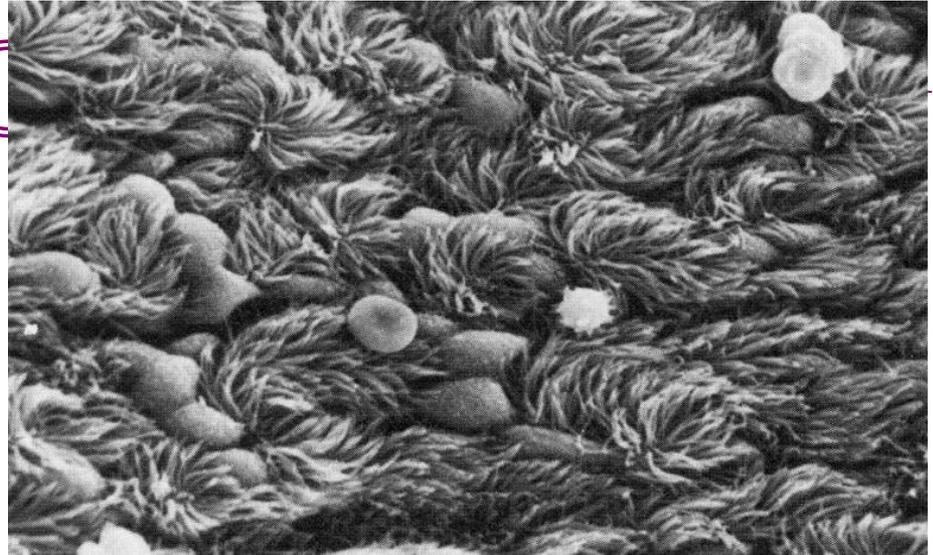


3 DAYS POST-INFECTION



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

Duration



- 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.

Signs and Symptoms



- 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

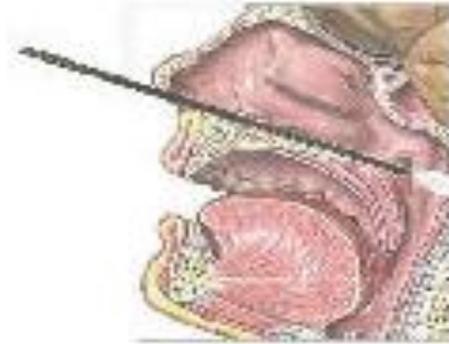


- Easy to do
- Highest yield in detecting H1N1
- Have the patient open his/her mouth wide open
- Patient should try to resist gagging and closing the mouth while the swab touches the back of the throat near the tonsils

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?



Influenza Antiviral Medications: Summary for Clinicians

On this Page

- Table 1. Antiviral Medications Recommended for Treatment and Chemoprophylaxis of Influenza
- Summary of Influenza Antiviral Treatment Recommendations
- Table 2. Persons at higher risk for influenza complications who are recommended for antiviral treatment
- Treatment Considerations for Patients Hospitalized with Suspected or Confirmed Influenza
- Diagnostic Testing for Influenza
- Table 3. Recommended Dosage and Duration of Treatment or Chemoprophylaxis for Influenza Antiviral Medications
- Table 4. Duration of Treatment or Chemoprophylaxis
- Chemoprophylaxis
- Dosing in Adult Patients with Renal Impairment
- Table 5. Recommended Oseltamivir and Peramivir Dose Adjustments for Treatment or Chemoprophylaxis of Influenza in Adult Patients with Renal Impairment or End Stage Renal Disease (ESRD) on Dialysis
- Adverse Events
- Selected References

The information on this page should be considered current for the 2014-2015 influenza season for clinical practice regarding the use of influenza antiviral medications.

This page contains excerpts from [Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza – Recommendations of the Advisory Committee on Immunization Practices](http://www.cdc.gov/flu/antivirals/summary-clinicians.htm) (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6001a1.htm>). [PDF Version](http://www.cdc.gov/mmwr/pdf/rr/rr6001a1.pdf) [1 MB, 28 pages] (<http://www.cdc.gov/mmwr/pdf/rr/rr6001a1.pdf>)

Previously, the neuraminidase inhibitors oseltamivir and zanamivir were the only recommended influenza antiviral drugs. On December 19, 2014, the U.S. Food and Drug Administration approved Rapivab® (peramivir) to treat influenza infection in adults. The antiviral content on the CDC website is in the process of being updated to reflect that change.

Influenza antiviral medications with activity against influenza viruses are an important adjunct to influenza vaccine in the control of influenza.

- Influenza antiviral prescription drugs can be used to **treat** influenza or to **prevent** influenza.
- Five licensed prescription influenza antiviral agents are available in the United States.

<http://www.cdc.gov/flu/antivirals/summary-clinicians.htm>

Persons at higher risk for influenza complications recommended for antiviral treatment



- children aged younger than 2 years;¹
- 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.

**WHO Guidelines for
Pharmacological Management of
Pandemic Influenza A(H1N1) 2009
and other Influenza Viruses**

Use of antivirals for treatment of influenza

Revised February 2010

Population	Pandemic influenza A (H1N1) 2009 and other seasonal influenza viruses	Influenza viruses known or suspected to be oseltamivir resistant
Uncomplicated clinical presentation		
Patients in higher risk groups	Treat with oseltamivir or zanamivir as soon as possible (05)	Treat with zanamivir as soon as possible (05)
Severe or progressive clinical presentation		
All patients (including children and adolescents)	Treat with oseltamivir as soon as possible (01) (zanamivir should be used if oseltamivir unavailable) (02)	Treat with zanamivir as soon as possible (03)
Patients with severe immunosuppression	Treat with oseltamivir as soon as possible. Consider higher doses and longer duration of treatment (03)	Treat with zanamivir as soon as possible (03)

Antiviral Medications Recommended for Treatment and Chemoprophylaxis of Influenza

Antiviral Agent	Activity Against	Use	Recommended For	Not Recommended for Use in
Oseltamivir (Tamiflu®) and B	Influenza A and B	Treatment	Any age ¹	N/A
		Chemo-prophylaxis	3 months and older ¹	N/A
Zanamivir (Relenza®) and B	Influenza A and B	Treatment	7 yrs and older	people with underlying respiratory disease (e.g., asthma, COPD) ²
		Chemo-prophylaxis	5 yrs and older	people with underlying respiratory disease (e.g., asthma, COPD) ²
Peramivir (Rapivab®) and B	Influenza A and B	Treatment	18 yrs and older	N/A
		Chemo-prophylaxis	N/A	N/A

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

Does the current Vaccine work? yes



- **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



SURVEILLANCE

