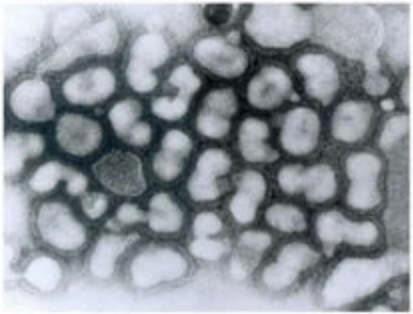
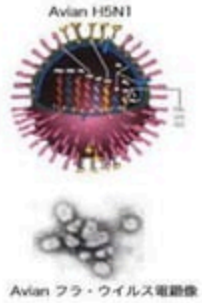
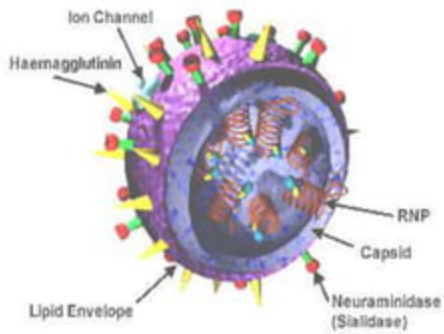
Avian Influenza/ Bird Flu





Dr. Rajesh K. Mandal
MD Resident,PG2, Internal Medicine

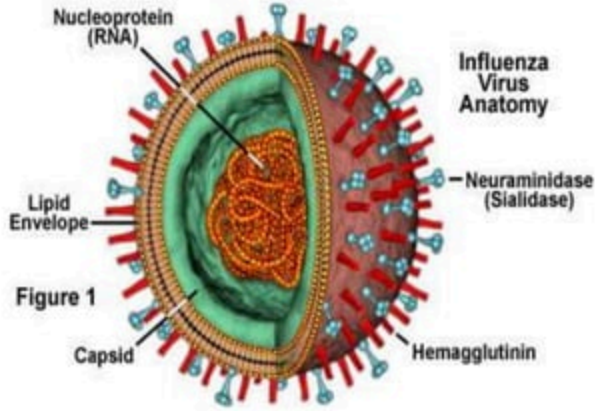
- Influenza, commonly known as "the flu", is an infectious disease caused by an influenza virus.

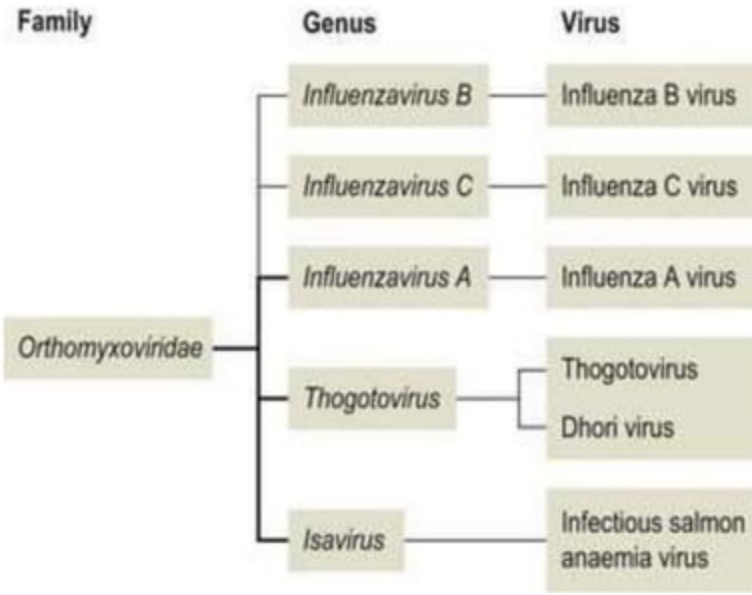


Virology

Virus classification

- Group: Group V ((−)ssRNA)
- Order: Unassigned
- Family: Orthomyxoviridae




Family
Genus
Virus
Orthomyxoviridae
Influenzavirus B
Influenza B virus
Influenzavirus C
Influenza C virus
Influenzavirus A
Influenza A virus
Thogotovirus
Thogotovirus
Dhori virus
Isavirus
Infectious salmon anaemia virus

Influenza Virus

- There are four types of influenza viruses: A, B, C and D.
- Human influenza A and B viruses cause seasonal epidemics of disease almost every winter in the United States.
- The emergence of a new and very different influenza A virus to infect people can cause an influenza pandemic.
- Influenza type C infections generally cause a mild respiratory illness and are not thought to cause epidemics.
- Influenza D viruses primarily affect cattle and are not known to infect or cause illness in people.

- The influenza A and B viruses that routinely spread in people (human influenza viruses) are responsible for seasonal flu epidemics each year.

- A pleiomorphic (non-uniform) envelope with a diameter of 50–120 nm
- Influenza type A viruses are categorized into subtypes based on the type of two proteins on the surface of the viral envelope
- H = hemagglutinin, a protein that causes red blood cells to agglutinate.
- N = neuraminidase, an enzyme that cleaves the glycosidic bonds of the monosaccharide sialic acid (previously called neuraminic acid)
- There are 18 different known H antigens (H1 to H18) and 11 different known N antigens (N1 to N11).
- All known subtypes of influenza A viruses can infect birds, except subtypes H17N10 and H18N11, which have only been found in bats.

Viral Proteins:

On the surface:

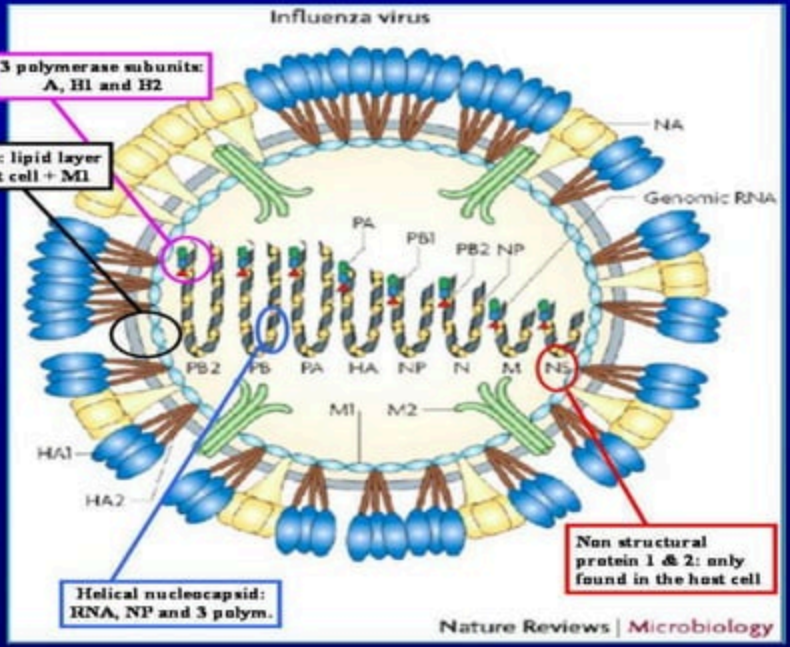
- Hemagglutinin*
- Neuraminidase*
- M2 (channel)

Internal:

- Matrix (M1) under viral envelope
- Polymerase subunits (A, B, B2,)
- Nucleoprotein

In the Host Cell:

- Non structural protein 1 & 2



- Genetic factors in distinguishing between **"human flu viruses"** and **"avian influenza viruses"** include:
- PB2: (RNA polymerase): Amino acid (or residue) position 627 in the PB2 protein encoded by the PB2 RNA gene. Until H5N1, all known avian influenza viruses had a **Glu** at position 627, while all human influenza viruses had a **lysine**.
- HA: (hemagglutinin): Avian influenza HA binds alpha **2–3** sialic acid receptors, while human influenza HA binds alpha **2–6 s**ialic acid receptors. Swine influenza viruses have the ability to bind both types of sialic acid receptors.

- The influenza A virus subtypes that have been confirmed in humans, ordered by the number of known human pandemic deaths, are:
- H1N1 caused "Spanish flu" in 1918 and the 2009 **swine flu** outbreak
- H2N2 caused "Asian flu" in the late 1950s
- H3N2 caused "Hong Kong flu" in the late 1960s
- H5N1 considered a global influenza pandemic threat through its spread in the mid-2000s
- H7N7 has unusual zoonotic potential
- H1N2 is currently endemic in humans and pigs
- H9N2, H7N2, H7N3, H5N2, and H10N7.
- H1N1,H2N2,H3N2 have been incorporated into any human adapted or pandemic influenza strain
- H7N9 potential of causing pandemic remains unknown.

Bird flu outbreak in Kathmandu

Published: May 26, 2018 9:10 am On: Kathmandu

HIMALAYAN NEWS SERVICE

Kathmandu, May 25

H5N1 influenza virus, commonly known as bird flu, has been detected in two farms in the capital.

The virus was detected in farms belonging to Hira Tamang at Dharmasthali in Tarkeshwor Municipality and Shanti Tamang at Lambagar of the same municipality. After the bird flu was detected and confirmed in ducks, the authorities culled 5,451 ducks and 180 hens, besides destroying 3,720 eggs of ducks. Up to 250 kg feed was also destroyed. "We culled ducks and hens after ducks tested positive for bird flu," said Dr

The Himalayan TIMES

Severe H5N1 bird flu reported in Chitwan

Published: May 18, 2018 5:27 pm On: Nepal

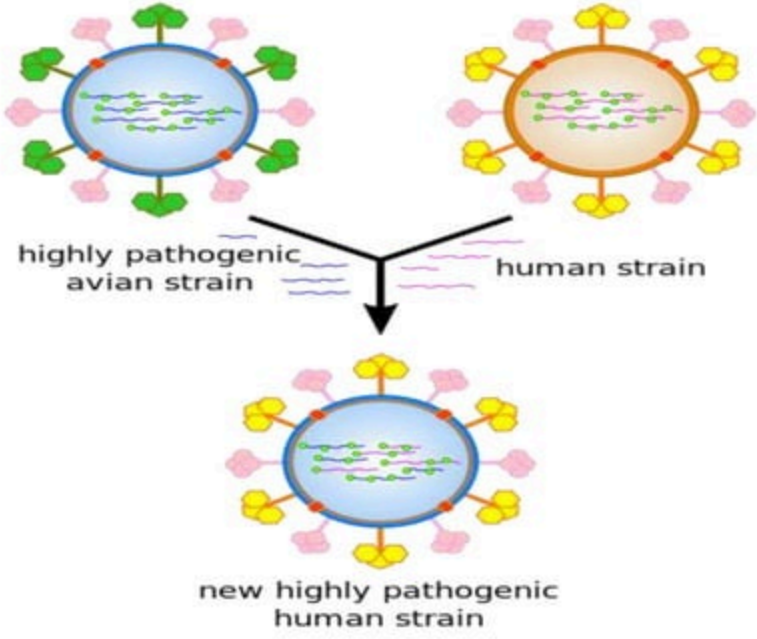
TILAK RIMAL

CHITWAN: Khairhani Municipality in Chitwan district has reported an outbreak of H5N1 bird flu, authorities said.

The virus has killed 2,500 hens exposed in two poultry farms while the remaining domestic birds including ducks, hens and pigeons were culled by the city authorities.

Antigenic Shift and Drifts

- Major changes in the envelope glycoproteins, the hemagglutinin and the neuraminidase, are referred to as antigenic shifts, and minor changes are called antigenic drifts.
- Antigenic shifts are associated with epidemics and pandemics of influenza A
- Antigenic drifts are associated with more localized outbreaks of varying extent.


highly pathogenic
avian strain
human strain
new highly pathogenic
human strain

Avian Influenza

- Avian influenza—known informally as avian flu or bird flu is a variety of influenza caused by viruses adapted to birds.The type with the greatest risk is highly pathogenic avian influenza (HPAI).
- Influenza A virus is a zoonotic infection with a natural reservoir almost entirely in birds.Avian influenza, for most purposes, refers to the influenza A virus.

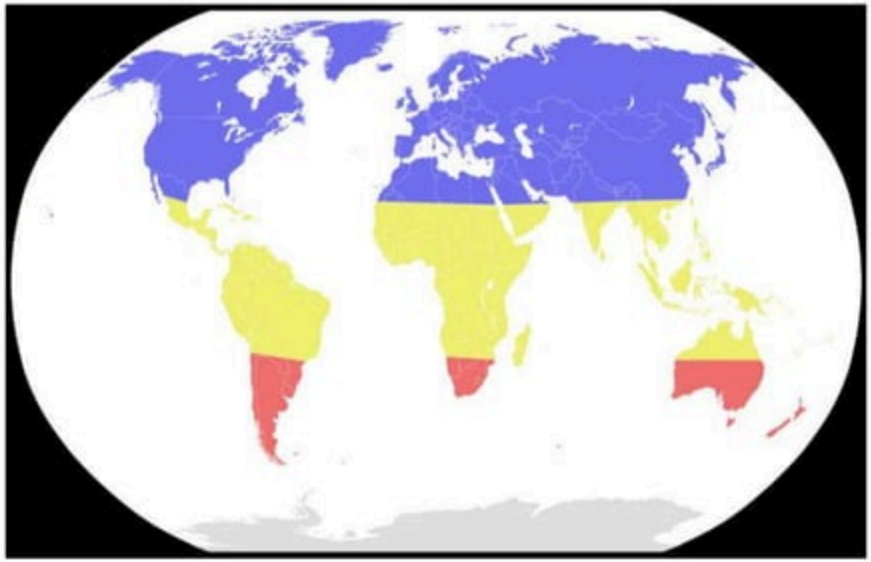
- Avian influenza strains are divided into two types based on their pathogenicity: high pathogenicity (HP) or low pathogenicity (LP).
- The most well-known HPAI strain, **H5N1**, appeared in China in 1996, and also has low pathogenic strains found in North America.
- Companion birds in captivity are unlikely to contract the virus and there has been no report of a companion bird with avian influenza since 2003. Pigeons do not contract or spread the virus

Epidemiology

- The most widely quoted date for the beginning of recorded history of avian influenza (initially known as fowl plague) was in 1878 when it was differentiated from other diseases that caused high mortality rates in birds.
- Fowl plague, however, also included Newcastle disease until as recently as the 1950s. Between 1959 and 1995, there were 15 recorded occasions of the emergence of HPAI viruses in poultry, but losses were minimal.
- Between 1996 and 2008 however, HPAI outbreaks in poultry have occurred at least 11 times and 4 of these outbreaks have involved millions of birds

- Influenza A/H5N1 was first isolated from a goose in China in 1996. **Human infections were first reported in 1997 in Hong Kong.**
- Since 2003, more than 700 human cases of Asian HPAI H5N1 have been reported to the WHO, primarily from 15 countries in Asia, Africa, the Pacific, Europe, and the Middle East, though over 60 countries have been affected
- Majority reported in main land china,additional cases reported in Hongkong,Macau,Taiwan,Malaysia and canada

Seasonal risk areas for influenza: November–April **(blue)**, April–November **(red)**, and year-round (yellow)



- Between early 2013 to early 2017, 916 lab-confirmed human cases of H7N9 were reported to the World Health Organization (WHO).
- On 9 January 2017, the National Health and Family Planning Commission of China reported to WHO 106 cases of H7N9 which occurred from late November through late December, including 35 deaths, 2 potential cases of human-to-human transmission, and 80 of these 106 persons stating that they have visited live poultry markets.

- There are many subtypes of avian influenza viruses, but only some strains of five subtypes have been known to **infect humans**: ***H5N1, H7N3, H7N7, H7N9, and H9N2.***
- At least one person, an elderly woman in Jiangxi Province, China, died of pneumonia in December 2013 from the H10N8 strain, the first human fatality confirmed to be caused by that strain.

Lineages of Influenza A Viruses

- Avian influenza (AI) viruses – influenza viruses which infect birds – have evolved into distinct genetic lineages in different geographic locations.
- AI viruses circulating in birds in Asia, called Asian lineage AI viruses, can be recognized as genetically different from AI viruses that circulate among birds in North America (called North American lineage AI viruses).
- North American lineage of H7N9 viruses could be further broken down into the North American 'wild bird' lineage versus the North American 'poultry' lineage.

Highly Pathogenic and Low Pathogenic Avian Influenza A Viruses

- Avian influenza A viruses are designated as highly pathogenic avian influenza (HPAI) or low pathogenicity avian influenza (LPAI) based on molecular characteristics of the virus and the ability of the virus to cause disease and mortality in chickens in a laboratory setting.
- HPAI and LPAI designations do not refer to the severity of illness in cases of human infection with these viruses; both LPAI and HPAI viruses have caused severe illness in humans

Influenza A H5

- There are nine known subtypes of H5 viruses (H5N1, H5N2, H5N3, H5N4, H5N5, H5N6, H5N7, H5N8, and H5N9).
- Most H5 viruses identified worldwide in wild birds and poultry are LPAI, but occasionally HPAI viruses have been detected.
- Sporadic H5 virus infection of humans has occurred, such as with Asian lineage HPAI H5N1 viruses currently circulating among poultry in Asia and the Middle East.
- Human infection of H5N1 virus infections have been reported in 16 countries, often resulting in severe pneumonia and greater than 50% mortality.

Influenza A H7

- There are nine known subtypes of H7 viruses (H7N1, H7N2, H7N3, H7N4, H7N5, H7N6, H7N7, H7N8, and H7N9).
- Most H7 viruses identified worldwide in wild birds and poultry are LPAI viruses. H7 virus infection in humans is uncommon. The most frequently identified H7 viruses associated with human infection are Asian lineage avian influenza A(H7N9) viruses, which were first detected in China in 2013.
- While human infections are rare, these have commonly resulted in severe respiratory illness and death. In addition to Asian lineage H7N9 viruses, H7N2, H7N3, H7N7 virus infections have been reported. These viruses have primarily caused mild to moderate illness in people, with symptoms that include conjunctivitis and/or upper respiratory tract symptoms.

Influenza A H9

- There are nine known subtypes of H9 viruses (H9N1, H9N2, H9N3, H9N4, H9N5, H9N6, H9N7, H9N8, and H9N9); all H9 viruses identified worldwide in wild birds and poultry are LPAI viruses.
- H9N2 virus has been detected in bird populations in Asia, Europe, the Middle East and Africa. Rare, sporadic H9N2 virus infections in people have been reported to generally cause mild upper respiratory tract illness; one infection has results in death

- Only two influenza A virus subtypes (i.e., H1N1, and H3N2) are currently in general circulation among people.
- Some subtypes are found in other infected animal species. For example, H7N7 and H3N8 virus infections can cause illness in horses, and H3N8 virus infection cause illness in horses and dogs.

Avian Influenza in Poultry (Domesticated Birds)

- Domesticated birds (chickens, turkeys, etc.) may become infected with avian influenza A viruses through direct contact with infected waterfowl or other infected poultry, or through contact with surfaces that have been contaminated with the viruses.
- Infection of poultry with LPAI viruses may cause no disease or mild illness and may only cause mild signs (such as ruffled feathers and a drop in egg production) and may not be detected.
- Infection of poultry with HPAI viruses can cause severe disease with high mortality. Both HPAI and LPAI viruses can spread rapidly through flocks of poultry. HPAI virus infection in poultry (with HPAI H5 or HPAI H7 viruses) can cause disease that affects multiple internal organs with mortality up to 90% to 100%, often within 48 hours. Some ducks can be infected without any signs of illness.

- Avian influenza outbreaks are of concern in domesticated birds for several reasons:
- the potential for low pathogenic H5 and H7 viruses to evolve into highly pathogenic viruses
- the potential for rapid spread and significant illness and death among poultry during outbreaks of highly pathogenic avian influenza
- the economic impact and trade restrictions from a highly pathogenic avian influenza outbreak
- the possibility that avian influenza A viruses could be transmitted to humans

Transmissson in Humans

- Although avian influenza A viruses usually do not infect people, rare cases of human infection with these viruses have been reported. Infected birds shed avian influenza virus in their saliva, mucous and feces.
- Human infections with virus occurs through air droplets or possibly dust inhalation or infected materials with virus on it and then touches their mouth, eyes or nose.
- Rare human infections with some avian viruses have occurred most often after unprotected contact with infected birds or surfaces contaminated with avian influenza viruses.

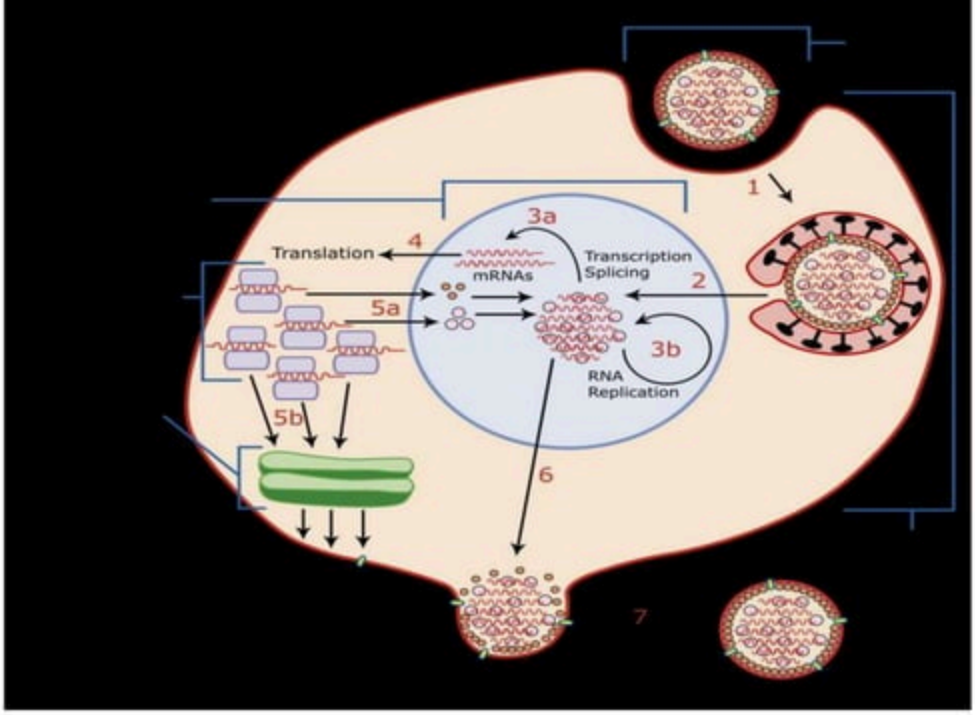
Pathogenesis

- **Receptor and Tissue Tropism**
- Tropism of avian influenza A H7N9 virus for human type (alpha 2-6 galactose) or avian type (alpha 2-3 galactose)receptors
- Human URT and Trachea has alpha 2-6 galactose receptors
- Human lungs has mixture of alpha 2-3 galactose and alpha 2-6 galactose receptors
- Avian influenza A H7N9 virus appears to bind human type receptors suggesting that they have tropim for cells in the human upper and lower respiratory tract and they may be transmissible among humans

- Epithelial cells in LRT and Type 2 pneumocytes in alveoli are susceptible to infection,evidence by viral nucleoprotein expression
- Viral titre found to be 10 folds in lung tissue than tracheal tissues
- Virus bind to both human type and avian type receptors
- Virus begin with attachment of Hemagglutin to cellular receptor
- Fusion of viral evelope and cellular endosomal membrane

- Transmembrane protease S2 (TMPRSS2) host protease is prerequisite for virus infectivity,tissue tropism and pathogenicity

- TMPRSS2 expression is associated with severe H7N9 influenza infection

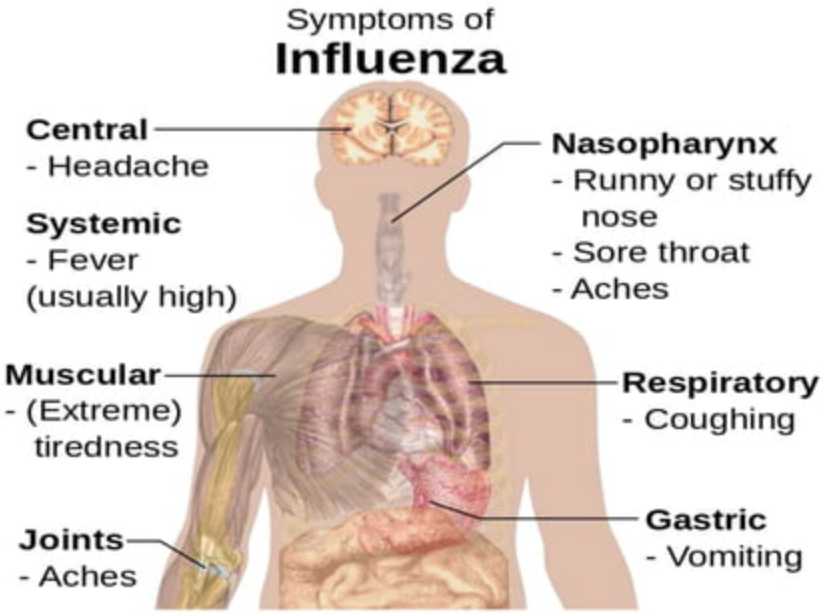

1
2
3a
3b
4
5a
5b
6
7
Translation
mRNAs
Transcription
Splicing
RNA
Replication

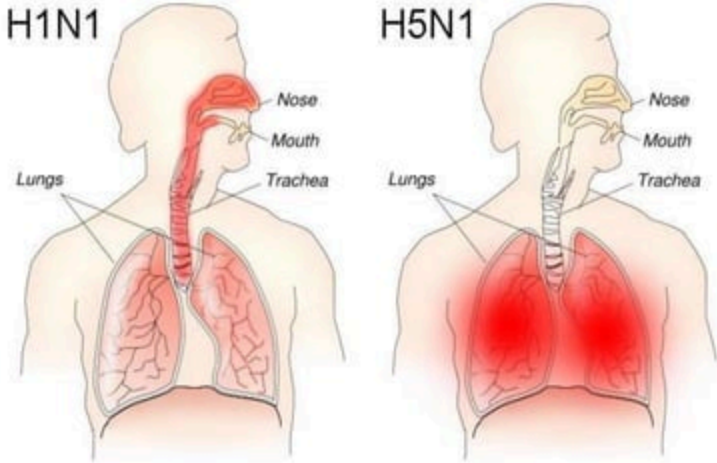
Signs and Symptoms

- Incubation period : 3 to 7 days but as long as 10 days
- Influenza is most frequently described as a respiratory illness characterized by systemic symptoms, such as headache, feverishness, chills,myalgia, and malaise, as well as accompanying respiratory tract signs and symptoms, particularly cough and sore throat.
- The patient has a fever, with temperatures of 38°–41°C (100.4°–105.8°F). A rapid temperature rise within the first 24 h of illness is generally followed by gradual defervescence over 2–3 days.

- In **uncomplicated influenza**, the acute illness generally resolves over 2–5 days, and most patients have largely recovered in 1 week,although cough may persist 1–2 weeks longer.
- **Severe Disease** : Fulminant pneumonia, acute respiratory distress, respiratory failure,seizures,septic shock, multi organ failure, Rhabdomyolysis, DIC, encephalopathy.

- **Reye's syndrome** is a serious complication in children that is associated with influenza B and—to a lesser extent—influenza A virus infection as well as with varicella-zoster virus and other viral infections. An epidemiologic association between Reye's syndrome and aspirin therapy for the antecedent viral infection has been noted.


Symptoms of
Influenza
Central
- Headache
Systemic
- Fever
(usually high)
Muscular
- (Extreme)
tiredness
Joints
- Aches
Nasopharynx
- Runny or stuffy
nose
- Sore throat
- Aches
Respiratory
- Coughing
Gastric
- Vomiting



Easily spread
Rarely fatal

Spreads slowly
Often fatal

- Most sensitive symptoms for diagnosing influenza

Symptom:	sensitivity	specificity
Fever	68–86%	25–73%
Cough	84–98%	7–29%
Nasal congestion	68–91%	19–41%

- All three findings, especially fever, are less sensitive in people over 60 years of age

- **Emergency warning signs** : Shortness of breath,Chest pain,Dizziness,Confusion,Extreme vomiting,Cyanosis,Fever and a rash,not able to drink fluids
- Flu symptoms that improve but then relapse with a high fever and severe cough (can be bacterial pneumonia)
- Signs of dehydration : (in infants) Far fewer wet diapers than regularly
- Decreased urine output
- No tears when crying(infants)

Pregnancy and teratogenecity

- Severe clinical course in 3rd Trimester and first 4weeks postpartum
- 2009 H1N1 apndemic pregnants had 5% mortality than that of general population of 1% mortality in United states
- First Trimester associated with teratogenicity, cleft lip(Odds Ratio 3.2),neural tube defect(OR 3.3),hydrocephaly(OR 5.7),congenital heart defect(OR 1.6)
- Hyperthermia is common clinical manifestation and risk factor for birth defects and infant outcome
- Spontaneous abortion,preterm delivary,LBW,Baby of small for gestation age infant,fetal death

Lactation

- Encouraged to continue breastfeeding if possible
- During seperation expressed milk can be feed to new born

Case defination

- **Confirmed case** : Avian influenza A H7N9 virus infection in patients conformed by CDC`s lab or CDC certified public lab or Lab using USFDA authorized test.
- **Probable case** : Illness compatable with influenza, lab diagnostic positive for Influenza A, negative for H1 ,Negative for H1pdm09 and negative for H3 in Real time reverse PCR (rRT-PCR)
- **Case under investigation** : illness compatable with influenza,meeting exposure criteria,lab conformation not known

Patient returned travel < 10 days of illness onset,to a area where human cases of Avian influenza A H7N9 have been detected or area where H7N9 viruses are known to be circulating in animals

or patient having contact with conformed cases of H7N9 within 10 days.

- **Close contacts** : involves coming within 6 feets/2meters or within room or care area of conformed cases are having direct contact with respiratory secretions
- Patients are likely to be infectious one day prior to illness and continues untill resolution of illness.

Diferential Diagnosis

- Influenza may be difficult to differentiate on clinical grounds alone from an acute respiratory illness caused by any of a variety of respiratory viruses or by Mycoplasma pneumoniae.
- Severe streptococcal pharyngitis or early bacterial pneumonia may mimic acute influenza, although bacterial pneumonias generally do not run a self-limited course.
- Purulent sputum in which a bacterial pathogen can be detected by Gram's staining is an important diagnostic feature in bacterial pneumonia.

Diagnosis

- Influenza A virus infection in people cannot be diagnosed by clinical signs and symptoms alone; laboratory testing is needed.
- Avian influenza A virus infection is usually diagnosed by collecting a swab from the upper respiratory tract (nose or throat) of the sick person. (Testing is more accurate when the swab is collected during the first few days of illness.)
- The laboratory looks for avian influenza A virus either by using a Real Time reverse PCR (r RT-PCR). Culture is usually not recommended.

- **Lab** : WBC normal or slightly decreased, Elevated AST,ALT,LDH,CRP,creatine kinase
- **Imaging**: On radiograph multilobar patchy consolidations and ground glass opacity.
- CT findings of airbronchogram,interlobular septal thickening,centrilobular nodules,reticular opacities,cic changes,bronchial dilatation,subpleural linear opacities.

29 yr old with H1N1 confirmed

- **Postmortem Histopathology** : Intraalveolar hemorrrhage,hyaline formation,pneumocyte hypertrophy,interstitial fibrosis,hypoxic and fatty changes in liver,kidney
- However for some patients who are no longer very sick or who have fully recovered, can show evidence of antibodies in response to the virus. It requires two blood specimens (one taken during the first week of illness and another taken 3-4 weeks later). It is done by Hemagglutination inhibition assay.

Treatment

- CDC currently recommends a **neuraminidase inhibitor** for treatment of human infection with avian influenza A viruses.
- Analyses of available avian influenza viruses circulating worldwide suggest that most viruses are susceptible to oseltamivir, peramivir, and zanamivir.
- However, some evidence of antiviral resistance has been reported in Asian H5N1 and Asian H7N9 viruses isolated from some human cases.
- The antiviral drugs amantadine and rimantadine inhibit a viral ion channel (M2 protein), thus inhibiting replication of the influenza A virus.

Treatment

Antiviral Drug	Age Group (Years)		
	Children (≤12)	13–64	≥65
Oseltamivir			
Treatment, influenza A and B	Age 1–12, dose varies by weight[a]	75 mg PO bid	75 mg PO bid
Prophylaxis, influenza A and B	Age 1–12, dose varies by weight[b]	75 mg PO qd	75 mg PO qd
Zanamivir			
Treatment, influenza A and B	Age 7–12, 10 mg bid by inhalation	10 mg bid by inhalation	10 mg bid by inhalation
Prophylaxis, influenza A and B	Age 5–12, 10 mg qd by inhalation	10 mg qd by inhalation	10 mg qd by inhalation
Amantadine[c]			
Treatment, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥10, 100 mg PO bid	≤100 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥10, 100 mg PO bid	≤100 mg/d
Rimantadine[c]			
Treatment, influenza A	Not approved	100 mg PO bid	100–200 mg/d
Prophylaxis, influenza A	Age 1–9, 5 mg/kg in 2 divided doses, up to 150 mg/d	Age ≥10, 100 mg PO bid	100–200 mg/d

- Zanamivir is administered via an oral inhalation device and may exacerbate bronchospasm in asthmatic patients.
- Oseltamivir has been associated with nausea and vomiting, whose frequency can be reduced by administration of the drug with food.
- Amantadine causes CNS side effects, primarily jitteriness, anxiety, insomnia, or difficulty concentrating. These side effects disappear promptly upon cessation of therapy.
- Rimantadine appears to be equally efficacious and is associated with less frequent CNS side effects than is amantadine.

- Antibacterial drugs should be reserved for the treatment of bacterial complications of acute influenza, such as secondary bacterial pneumonia.
- The choice of antibiotics should be guided by Gram's staining and culture of appropriate specimens of respiratory secretions, such as sputum.

Prevention

- The best way to prevent infection with avian influenza A viruses is to avoid sources of exposure. Most human infections with avian influenza A viruses have occurred following direct or close contact with infected poultry.
- People who have had contact with infected birds may be given influenza antiviral drugs preventatively.
- When used to prevent seasonal influenza, antiviral drugs are 70% to 90% effective.

- Chemoprophylaxis with oseltamivir or zanamivir has been 84–89% efficacious against influenza A and B.
- Chemoprophylaxis with Amantadine or Rimantadine is no longer recommended because of widespread resistance to these drugs.

Vaccination

- Since 1975, influenza vaccines have been trivalent—i.e., they have contained two influenza A subtypes (H3N2 and H1N1) and one influenza B component.
- However, two antigenically distinct lineages of influenza B virus have circulated since the 1980s, and a quadrivalent vaccine that includes both B lineages is now available (2013–2014) as well.
- Quadrivalent vaccines are available in both inactivated and liveattenuated vaccine formulations.

- The United States government maintains a stockpile of vaccines to protect against some Asian avian influenza A H5N1 viruses.
- The stockpiled vaccine could be used if similar H5N1 viruses were to begin transmitting easily from person to person.
- Since influenza viruses change, CDC continues to make new candidate vaccine viruses as needed. Creating a candidate vaccine virus is the first step in producing a vaccine.

- WHO recommends annual vaccination for:

- pregnant women at any stage of pregnancy
- children aged between 6 months to 5 years
- elderly individuals (aged more than 65 years)
- individuals with chronic medical conditions
- health-care workers.

References

- 1. Harrisons principle of internal medicine.19ed
- 2. Centers for Disease Control and Prevention.www.cdc.gov
- 3. World Health Organization
- 4. uptodate

- Thank you