

Clinical Features, Diagnosis and Management of Avian Influenza

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Presentation

- Clinical presentation
 - Seasonal Influenza
 - Human cases of H5N1 influenza
 - Pandemic influenza
- Laboratory Diagnosis
- Case Definitions
- Case Management
 - Chemotherapy
 - Admission and Discharge Policy
 - Isolation of Cases and Infection Control Practices in health facilities

Clinical Presentation Seasonal Influenza

Influenza - Transmission

Person-to-person

- **droplets**: Due to coughing, sneezing
- Highly contagious to susceptible persons
- Replicates in large airway epithelial cells
- Viremia has rarely been reported

Incubation period: 1- 4 days (*typically 2-3 days*)

- Viral shedding can begin before symptom onset
- Peak viral shedding on first day of symptoms
- Adults may shed for 4-6 days, **Children longer**
- Immunosuppressed, immunocompromised can shed for months

High-risk groups for Complications of Influenza

- **Infants and young children**
- **Elderly**
- **Persons of any age with chronic conditions**
 - Chronic pulmonary or cardiovascular conditions
 - Chronic neurological conditions that impair breathing or clearance of respiratory secretions
 - Chronic metabolic diseases
 - Renal dysfunction
 - Hemoglobinopathies
 - Immunosuppressed, immunocompromised
 - Children 6 months -18 years on chronic aspirin therapy
 - Pregnant women
 - Nursing home residents, chronic care facility residents

Signs and Symptoms of Uncomplicated Influenza

- **Infants and young children:**
 - Diarrhea, rhinorrhea, congestion, high fever alone
- **School-age children:**
 - Sudden onset of febrile upper respiratory disease (fever, chills, rhinorrhea, congestion, sore throat, non productive or productive cough), chest discomfort
 - Abdominal pain, vomiting, diarrhea
 - Myalgia
- **Adults:**
 - Sudden onset of febrile upper respiratory disease (fever, chills, rhinorrhea, congestion, sore throat, non productive or productive cough), chest pain
 - Vomiting
 - Myalgia
- **Elderly:**
 - Low grade fever or afebrile upper respiratory disease (rhinorrhea, congestion, sore throat, non productive or productive cough), chest pain
 - Myalgia, fatigue, malaise

Frequency of baseline symptoms*

Symptom	(%)
• Fever $\geq 38^{\circ}\text{C}$	68
• Feverishness**	90
• Cough	93
• Nasal congestion	91
• Weakness	94
• Loss of appetite	92
• Sore throat	84
• Headache	91
• Myalgia	94

*In 2,470 patients with laboratory-confirmed influenza (Monto 2000)

**Defined as the patient's subjective feeling that they had a fever or chill

Monto AS. Arch Intern med 2000;160: 3243-47.

Physical findings of Influenza

- **Fever:** rapid onset, peaking at 38.40°C (up to 41°C, especially in children), typically lasting 3 days (up to 4-8 days), gradually diminishing
- **Face:** flushed
- **Skin:** hot and dry
- **Eyes:** watery, reddened
- **Nose:** nasal discharge
- **Ear:** otitis
- **Mucous membranes:** hyperemic
- **Cervical lymph nodes:** (especially in children)

Influenza v/s common cold

Symptoms	Influenza	Cold
• Fever	Usually high, lasts 3-4 days	Unusual
• Headache	Yes	Unusual
• Fatigue/ weakness	Can last up to 2-3 weeks	Mild
• Pains, aches	Usual and often severe	Slight
• Exhaustion	Early and sometimes severe	Never
• Stuffy nose	Sometimes	Common
• Sore throat	Sometimes	Common
• Cough	Yes	Unusual
• Chest discomfort	Common, maybe severe	Mild / moderate
• Complications	Bronchitis, pneumonia; In severe cases life-threatening	Sinus congestion

Differential Diagnosis

Virus	Most frequent	Occasional
Rhino virus	Common cold	Worsening of underlying lung disease
Corona virus	Common cold	Worsening of underlying lung disease
RSV	Pneumonia & bronchiolitis in young	Common cold in adults
Para influenza virus	Croup & LRTI in young	Pharyngitis & common cold in adults
Adino virus	Common cold & Pharyngitis in young	Outbreak of URI in military camps
Influenza B virus	Influenza	Rhinitis and Pharyngitis
Enterovirus	Acute febrile illness	Rhinitis and Pharyngitis

Course of illness

- **Severity varies from afebrile symptoms mimicking common cold to severe prostration without major respiratory signs and symptoms, especially in the elderly.**
- **Fever and systemic symptoms typically last 3 days, occasionally 5-8 days, and gradually diminish**
- **Cough and malaise may persist > 2 weeks.**
- **Second fever spikes are rare.**
- **Full recovery may take 1-2 weeks or longer, especially in the elderly.**

Complications of Influenza

- **Exacerbation of chronic illness**
 - Cardiac (congestive cardiac failure, coronary artery disease)
 - Chronic pulmonary disease (COPD)
 - Metabolic disease (diabetes)
- **Bronchitis, Sinusitis**
- **Dehydration**
- **Reactive airway disease**
- **Viral Pneumonia: more with mitral stenosis & pregnancy.**
- **Cardiac: myocarditis, pericarditis**
- **Musculoskeletal: myositis, rhabdomyolysis**
- **Invasive bacterial co-infection like sepsis, toxic shock syndrome due to:**
 - **Bacterial pathogens**
 - Staphylococcus aureus: MRSA, MSSA,
 - Streptococcus pneumoniae, Group A Streptococcus,
 - Hemophilous influenzae

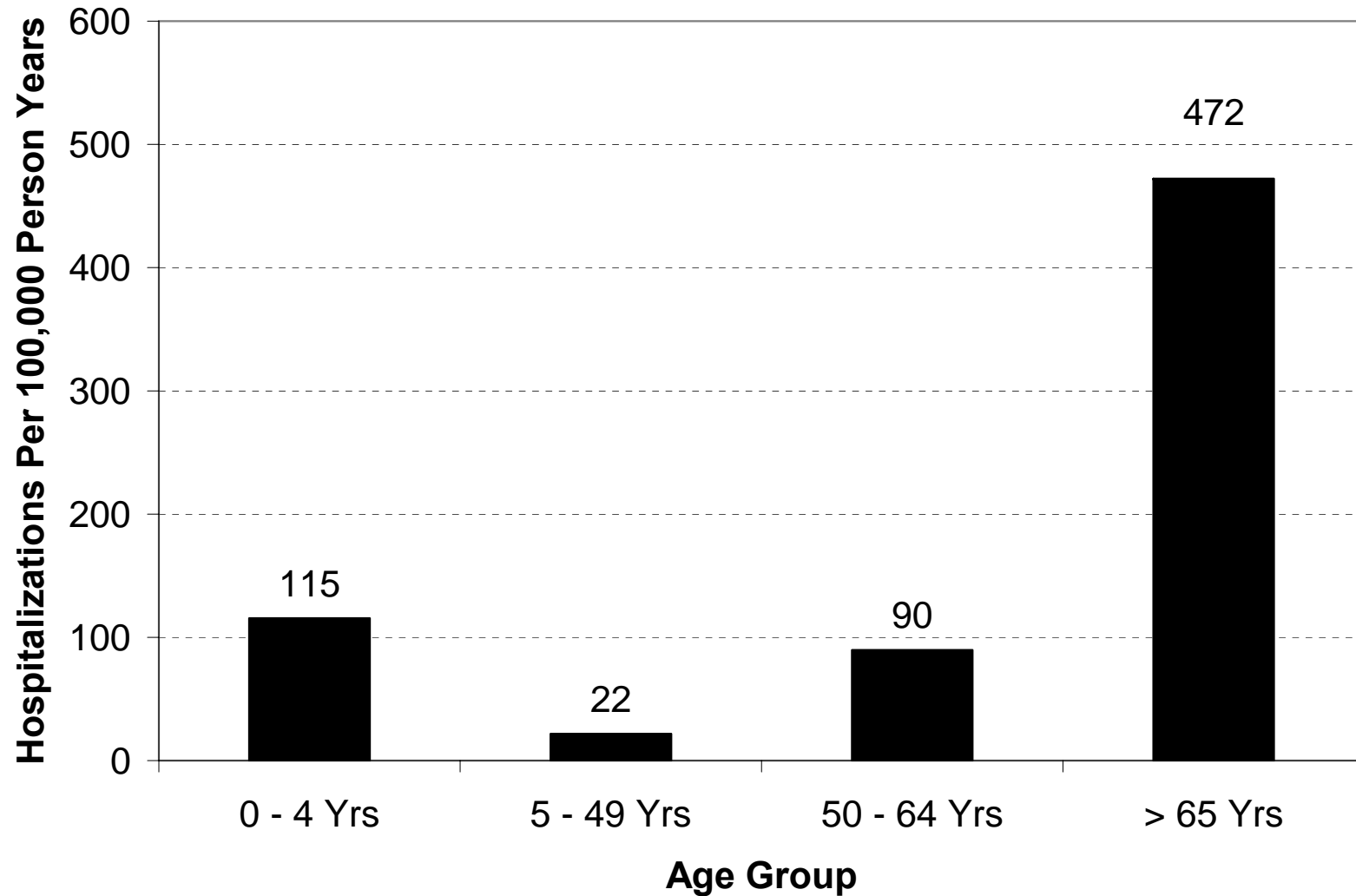
Neurological Complications Associated with Influenza

- **Febrile seizures**
 - Sporadically reported in U.S.
 - More frequently reported in Hong Kong
- **Encephalopathy or encephalitis**
- **Transverse myelitis**
- **Guillain Barre Syndrome (relationship uncertain)**

Reye syndrome

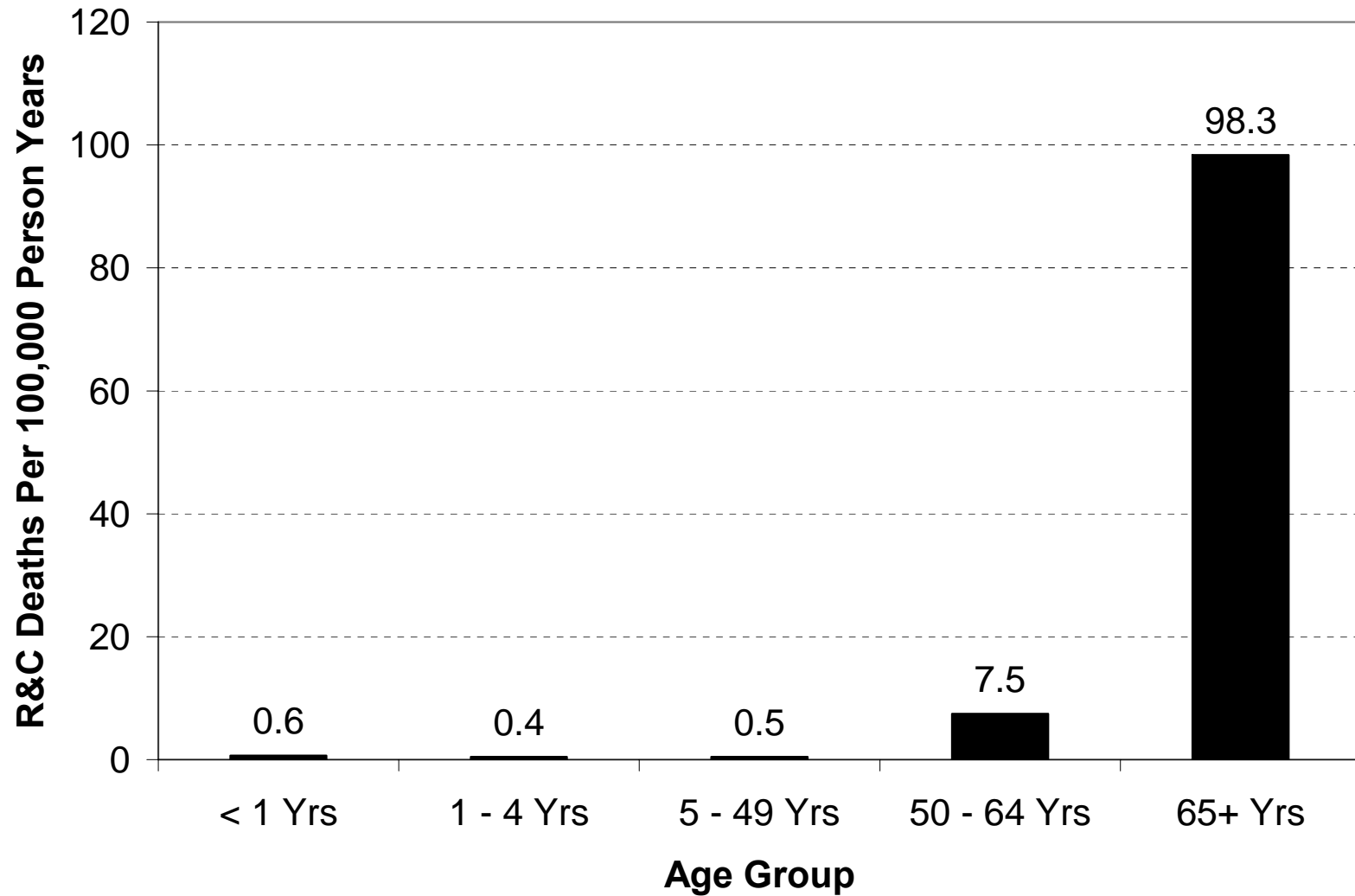
- **Combination of liver disease and non inflammatory encephalopathy.**
- **Associated with previous viral infections, such as influenza (more common with B), cold, or chickenpox.**
- **Particularly associated with Influenza B.**
- **Strong link between the administration of aspirin and Reye syndrome.**

Influenza-Associated Hospitalizations By Age Group*



*Thompson, CDC, 2004, unpublished data

Influenza-Associated Deaths By Age Group*



*Thompson, et al. JAMA 2003

Summary: Human (Seasonal) Influenza

- **Signs and symptoms vary by:**
 - Patient age, immune status, and underlying chronic conditions
- **Uncomplicated influenza generally presents as an acute febrile upper respiratory tract illness**
- **Complications of influenza vary by age and underlying conditions**
- **The most common reason for hospitalization due to complications from influenza is exacerbation of chronic underlying disease (cardiopulmonary)**
- **Invasive bacterial co-infection can occur**

Clinical Presentations of Human Infections with Avian Influenza A Viruses

Transmission of H5N1 Virus

- **Avian-to-human transmission**
 - Predominant mode of transmission
 - Exposure to infected poultry
 - Direct contact with sick or dead poultry (touching, slaughtering, cleaning, defeathering, preparing for cooking; ingestion of H5N1 virus-infected poultry (undercooked meat, uncooked duck blood)
 - Exposure to dead wild birds (dead swans)
- **Indirect animal-to-human transmission**
 - Contact with surfaces contaminated with infected poultry feces and H5N1 virus
- **Other animal-to-human transmission**
 - Contact with other infected animals (not reported)

Transmission of H5N1 Virus

- **Limited, non-sustained human-to-human transmission***
 - Close, prolonged unprotected contact with a sick H5N1 case
 - Very rare, but documented
 - Most cases in blood-related family members
 - Reported in health care workers
 - Hospital transmission documented

**No evidence of sustained human-to-human transmission of H5N1 viruses*

Environment to Humans

- Theoretically possible H5N1 virus exposures:
 - Oral ingestion of contaminated water during swimming and direct intranasal inoculation during exposure to water
 - Contamination of hands from infected fomites and subsequent self-inoculation
 - Use of untreated poultry feces as fertilizer is another possible risk factor

WHO Case Definition for Influenza A/H5N1 - 1

Suspected/Possible H5N1 case:

- A person presenting with unexplained acute lower respiratory illness with fever (body temperature of $> 38^{\circ}\text{C}$) and cough, shortness of breath or difficulty in breathing; AND
- One or more of the following exposure in the 7 days prior to symptom onset:
 - Close contact (within 1 meter) with a person who is suspected, probable, or confirmed H5N1 cases;
 - Exposure (e.g. handling, slaughtering, defeathering, butchering, preparation for consumption) to poultry or wild birds or their remains or to environments contaminated by their faeces in an area where H5N1 infections in animals or humans have been suspected or confirmed in the last month;
 - Consumption of raw or undercooked poultry products in an area where H5N1 infections in animals or humans have been suspected or confirmed in the last month;
 - Close contact with a confirmed H5N1 infected animal other than poultry or wild birds (e.g. cat or pig)
 - Handling samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting.

WHO Case Definition for Influenza A/H5N1 - 2

Probable H5N1 case (notify WHO)

Probable Case definition 1:

- A person meeting the criteria for a suspected case, AND
- Infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (hypoxemia, severe tachypnea), OR positive laboratory confirmation of an influenza A infection but insufficient laboratory evidence for H5N1 infection.

Probable Case definition 2:

- A person dying of an unexplained acute respiratory illness who is considered to be epidemiologically linked by time, place, and exposure to a probable or confirmed H5N1 case.

WHO Case Definition for Influenza A/H5N1 - 3

Confirmed H5N1 Case (notify WHO)

- A person meeting the criteria for a suspected or probable case, AND
- One of following positive results conducted in a national, regional or international influenza laboratory whose H5N1 test results are accepted by WHO as confirmatory:
 - Isolation of an H5N1 virus;
 - Positive H5 PCR results from tests using two different PCR targets, e.g. primers specific for influenza A and H5 HA;
 - A fourfold or greater rise in neutralization antibody titre for H5N1 based on testing of an acute serum specimen (collected 7 days or less after symptom onset) and a convalescent serum specimen. The convalescent neutralizing antibody titre must also be 1:80 or higher;
 - A microneutralization antibody titre for H5N1 of 1:80 or greater in a single serum specimen collected at day 14 or later after symptom onset and a positive result using a different serological assay, for example, a horse red blood cell HI titre of 1:160 or greater or an H5-specific western blot positive result.

H5N1 Clinical Findings 2003-09

Incubation period: usually 2-5 days but maybe longer.

➤ **Presenting signs**

- Fever, cough, shortness of breath, dyspnea, diarrhea

➤ **Laboratory findings:**

➤ **Admission:**

- *Leukopenia, lymphopenia*

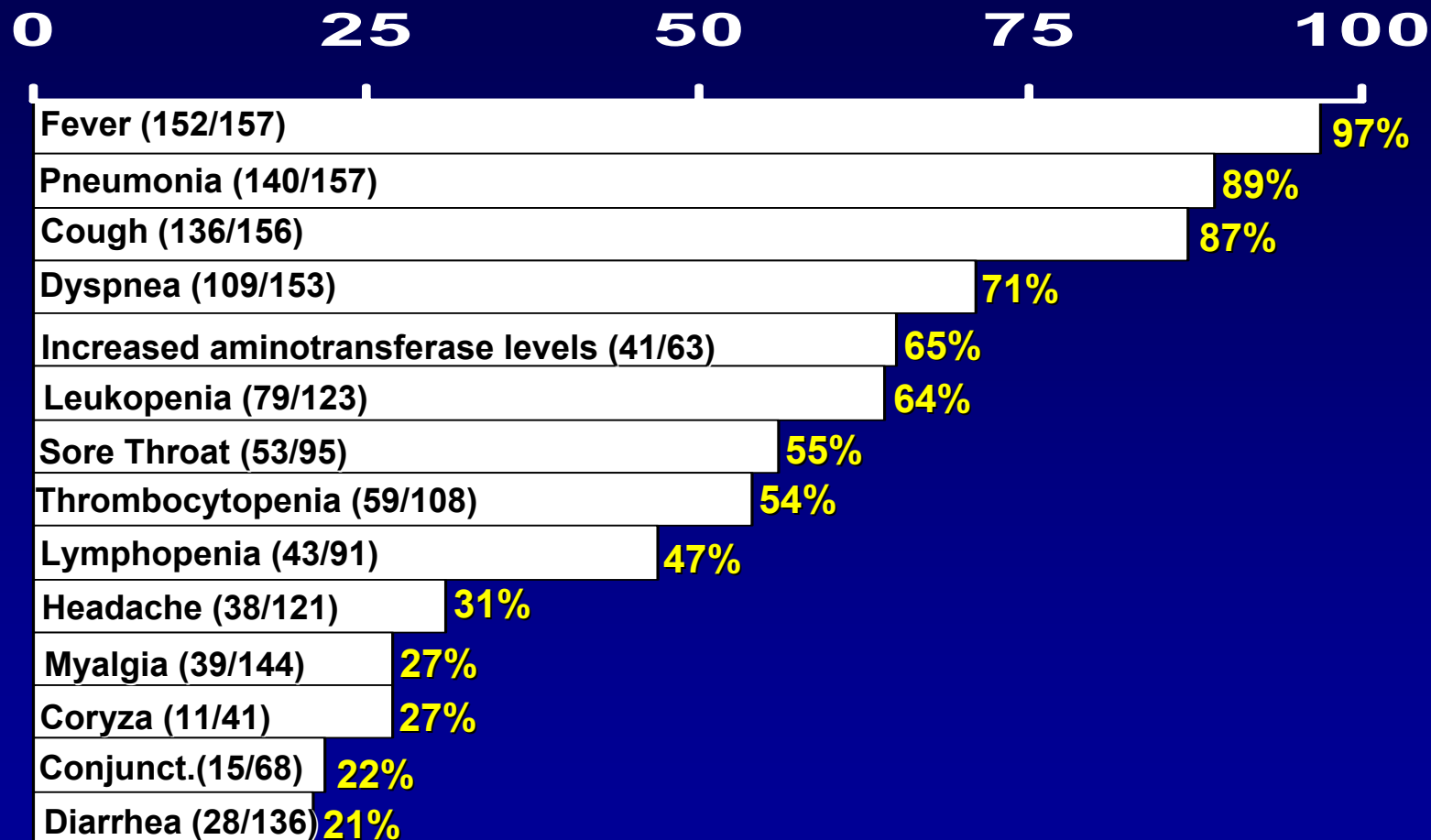
- *Moderate thrombocytopenia*

➤ **Clinical findings during hospitalization**

- Bilateral pneumonia, hypoxia requiring oxygen
- Respiratory failure, ARDS

Clinical and Laboratory Features of Influenza A (H5N1) Disease at Hospital Admission

Percent of Cases with Sign/Symptom



Source: Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus
N Engl J Med 2008; 358:261-73

Clinical Presentations

Country	Vietnam	Indonesia	China	Egypt	Turkey
Clad	1	2.1	2.3	2.2	2.2
Fever(in %)	100	100	100	89	94
Dyspnoea	89	94	50	37	44
Cough	98	93	88	71	80
Pneumonia	100	100	100	61	88
Coryza	33	0	0	0	14
Sore Throat	32	0	0	68	88
Vomiting	16	11	0	8	0
Diarrhea	52	11	0	5	29
Drowsiness	0	0	0	8	50
Seizure	0	2	0	0	0
Headache	36	13	0	45	27
Conjun..	0	0	0	37	12
Myalgia	30	13	0	45	27

CXR findings in confirmed H5N1 cases, Vietnam 2004

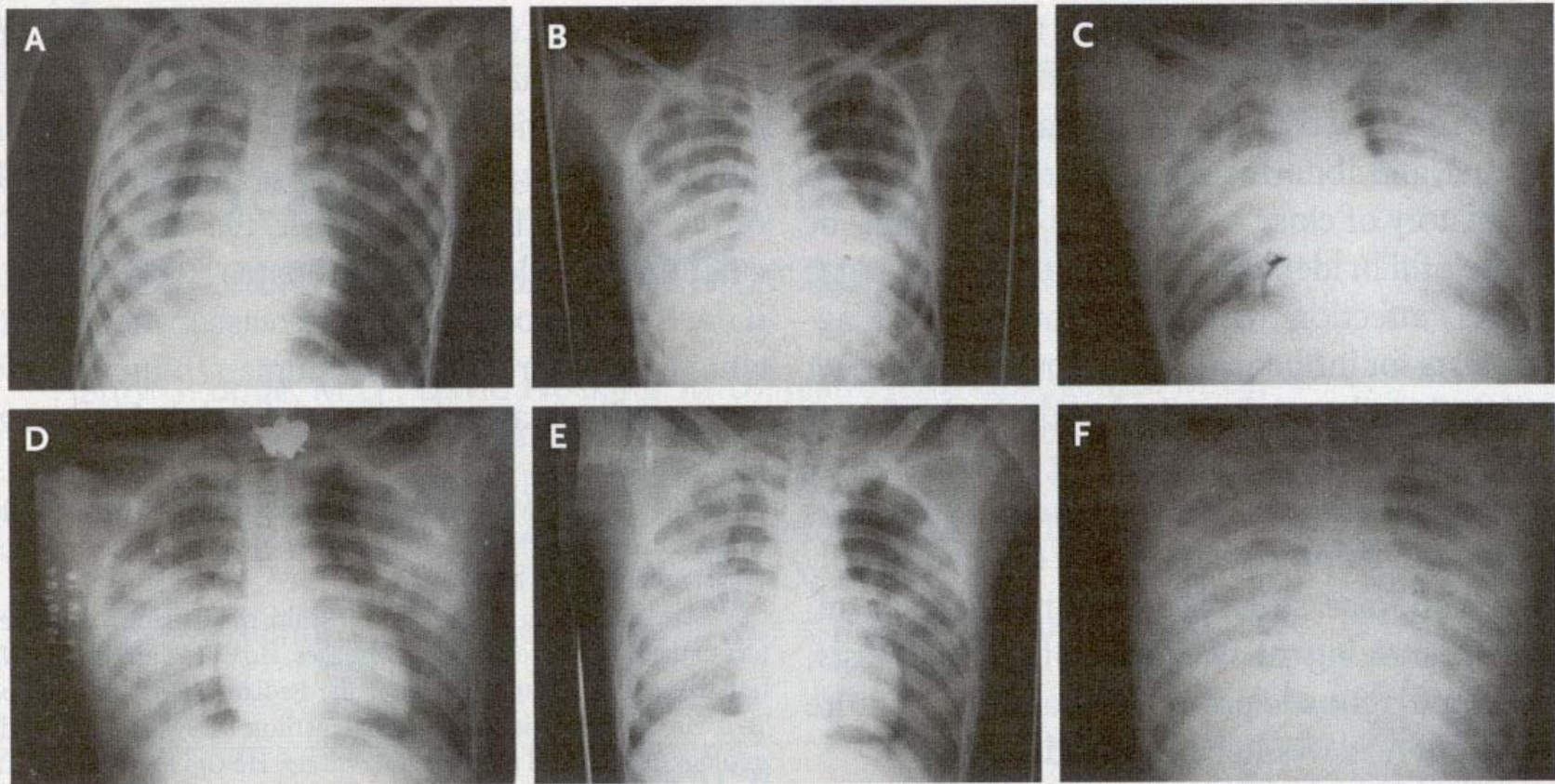


Figure 3. Chest Radiographs.

Radiographs from Patient 5 (Panel A), Patient 7 (Panel B), and Patient 9 (Panel C) show widespread consolidation, collapse, and interstitial shadowing. In Panels D, E, and F, three chest radiographs show the progression in Patient 8 on days 5, 7, and 10 of illness, respectively.

**14 year-old
female H5N1
fatal case,
Turkey, 2006**

*Oner AF et al., NEJM 2006;
355:2179-85*

CXR findings in confirmed H5N1 case, Vietnam 2005

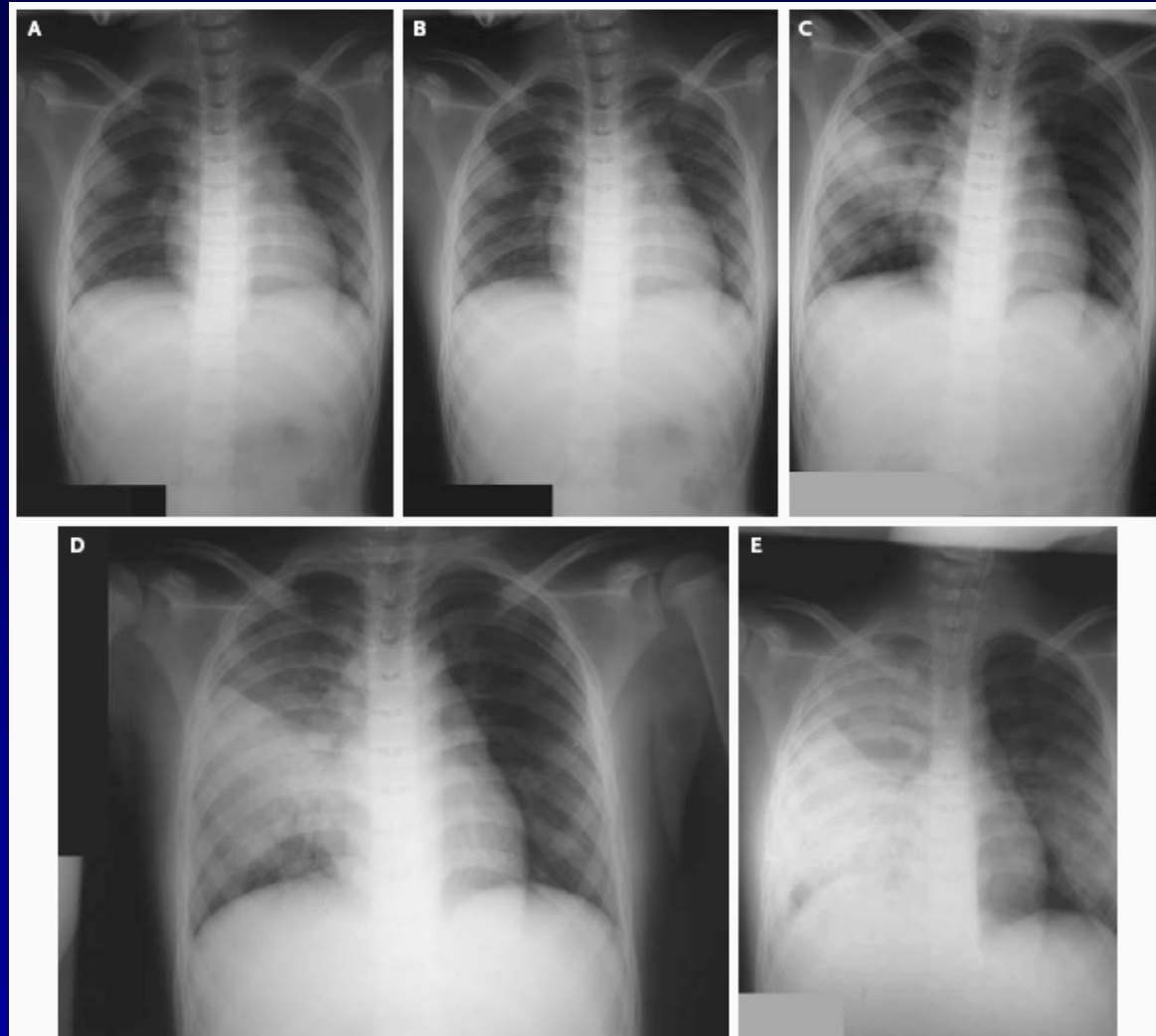


Figure 1. Serial Chest Radiographs Obtained from Patient 1.

A chest radiograph obtained at admission revealed a small focal pulmonary infiltrate in the right middle zone (Panel A). A chest radiograph obtained two days later showed minimal progression of the infiltrate (Panel B). On day 3, the pneumonia had progressed to involve most of the right middle zone (Panel C), and further progression was noted on day 4 (Panel D) and day 6 (Panel E), the day the patient died.

Table 3. Initial Diagnosis in Patients with Confirmed Influenza A (H5N1) Virus Infection.*

Diagnosis	Indonesia (N = 52)	Thailand (N = 25)
	<i>number (percent)</i>	
Pneumonia	24 (46)	11 (44)
Dengue virus infection	6 (12)	4 (16)
Typhoid fever	2 (4)	0 (0)
Upper respiratory illness	14 (27)	4 (16)
Avian influenza	6 (12)	2 (8)
Other	0 (0)	4 (16)†

* Data are from Chotpitayasunondh T and Soeroso S (unpublished data).

† Tuberculosis was diagnosed in one patient, diarrhea in one patient, dizziness in one patient, and leptospirosis in one patient.

Need for high suspicion for H5N1

- **Nonspecific presentation often results in misdiagnosis**
- **Keep H5N1 infection in differential diagnosis in cases presenting with epidemiological risk factors and unusual course of illness (eg rapidly progressing pneumonia)**

Complications of H5N1 Virus Infection

- **Most common complication: pneumonia**
 - **Progresses to respiratory failure**
 - requiring mechanical ventilation
- **Acute respiratory distress syndrome (ARDS)**
- **Multi-organ failure**
 - **Cardiac and renal dysfunction**
 - **Gastrointestinal involvement**
- **Encephalitis has been reported**
- **Sepsis-like syndrome, DIC, shock**

Summary: Human Infections with Avian Influenza A Viruses

- **Signs and symptoms vary by:**
 - Avian influenza A virus subtype, and pathogenicity classification
- **Low pathogenic avian influenza A viruses typically cause mild clinical illness (H7N7 & H9N2)**
 - Conjunctivitis
 - Uncomplicated influenza-like illness with mild respiratory symptoms.
- **Highly pathogenic avian influenza A viruses can cause mild to severe and fatal disease**
 - Conjunctivitis
 - Pneumonia, respiratory failure
 - H5N1 virus has caused severe and fatal disease

Clinical Presentation Pandemic Influenza

Pandemic Influenza (1)

- **Depends upon virulence of virus**
 - 1918 H1N1 was severe
 - 1957 H2N2 was moderately severe
 - 1968 H3N2 was mild
- **Impact is not limited to the year when the pandemic virus emerges**
 - **Strains evolve through antigenic drift and continue to circulate**

Pandemic Influenza (2) - Possible Complications

- **Cannot be predicted in advance of pandemic**
- **Most affected groups can vary and cannot be predicted in advance**
- **High incidence of uncomplicated influenza-like illness**
- **Complications associated with seasonal influenza, including exacerbation of chronic conditions**
- **Severe viral pneumonia**
- **Severe secondary bacterial pneumonia**
- **Cardiopulmonary complications in pregnant women**
- **Possible neurological complications (encephalopathy, encephalitis)**
- **Severe complications in immunocompromised, immunosuppressed**
- **Sudden death**

Laboratory Diagnosis

Laboratory Diagnosis (1)

- Any of following lab tests confirms the diagnosis:
 - Isolation of an H5N1 virus;
 - Positive H5 PCR results from tests using two different PCR targets, e.g. primers specific for influenza A and H5 HA;
 - A fourfold or greater rise in neutralization antibody titre for H5N1 based on testing of an acute serum specimen (collected 7 days or less after symptom onset) and a convalescent serum specimen. The convalescent neutralizing antibody titre must also be 1:80 or higher;
 - A microneutralization antibody titre for H5N1 of 1:80 or greater in a single serum specimen collected at day 14 or later after symptom onset and a positive result using a different serological assay, for example, a horse red blood cell HI titre of 1:160 or greater or an H5-specific western blot positive result.

Laboratory Diagnosis (2)

- Every suspect or probable human case of avian influenza must be investigated to confirm the diagnosis
- Respiratory and blood specimens are collected for laboratory testing as clinically indicated with appropriate precautions
- Collect both nose and throat swabs in viral transport medium
 - Diagnostic yields higher with throat specimens
 - Nasal swabs are appropriate for detecting human influenza A and B
 - Collect tracheal aspirates, if available – higher viral titres and yields
- Repeated collection of multiple respiratory samples recommended - Negative single sample does not rule out H5N1 infection

Laboratory Diagnosis (3)

- Samples should be transported in cold chain at 2-8°C to the designated laboratory quickly
- Packing of samples should conform to WHO bio-hazardous guidelines and should also conform to safe transportation in a civilian aircraft
- Each sample should be accompanied with clinical details and the identification data of the case
- Lab should be informed before sending the samples

Laboratory Diagnosis (4)

- Detection of viral RNA by conventional or real-time RT-PCR is best method for initial diagnosis of influenza A H5N1
 - Test can be performed in BSL-2 Lab
 - Results are available in 4-6 hours
 - Frequent updating of primers and probes is needed due to genetic variability of influenza A H5N1
- Commercially available rapid assays for influenza antigen detection
 - do not differentiate between human and avian subtypes of influenza A viruses
 - require 1000 times higher levels of virus than virus culture to be positive

Case Management

Case Management - Presentation

- Specific Treatment (Antivirals)
- Other treatments
- Admission and Discharge Policy
- Infection control in health care facilities

Antiviral drugs

- M2 ion channel inhibitors
 - Amantadine (Amantrel, Cipla Protec Division) (oral)
 - Rimantadine (Flumadine, Forest Laboratories) (oral)
- Neuraminidase inhibitors
 - Oseltamivir (Tamiflu, Roche Laboratories) (oral)
 - Zanamivir (Relenza, Glaxo Wellcome) (oral inhalation)
- Ribavirin (low doses ineffective, efficacy modest even with very high doses)

Antiviral drugs (2)

- M2 inhibitors effective against type A viruses, Neuraminidase inhibitors effective against both A and B viruses
- Effective for prevention and treatment, given in dose of: **100mg twice daily for prophylaxis & treatment both.**
- M2 inhibitors have CNS and GIT side effects
- Side effects more with Amantadine than with Rimantadine
- Oseltamivir has less, primarily GIT side effects
- Zanamivir may produce bronchospasm
- Drug resistance viruses more with M2 inhibitors
- Overall Neuraminidase inhibitors are superior to M2 inhibitors
- Combination therapy (Oseltamivir+amantadine) may be considered in seriously ill cases where c&s shows sensitivity to adamantanes.

Oseltamivir

- Early treatment (within 2 days of onset of symptoms) improves survival
- Optimal doses of oseltamivir and duration of therapy are uncertain
- Suggested Doses
 - Children 1 year of age or older
 - < 15 kg (30 mg twice daily)
 - 15-23 kg (45 mg twice daily)
 - 23-40 kg (60 mg twice daily)
 - >40 kg (75 mg twice daily)
 - Adults (75 mg twice daily)
- Duration of treatment - 5 days
- Higher dose for increased duration may be considered if there is pneumonia or evidence of clinical progression - 150 mg twice daily in adults for 10 days

Neuraminidase Inhibitors cont..

- For prophylaxis: Tamiflu 75mg per day till 7-10 days after last exposure.
- **Zanamivir:**
- For treatment 10mg (2 inhalations)x 2times x 5 days.
- For prophylaxis: 10mg once daily till 7-10 days after last exposure.

Other Treatments

- Correction of hypoxemia (Oxygen)
- Antibiotics
 - When bacterial infection is suspected
 - Treat according to published evidence-based guidelines
 - Antibiotic prophylaxis should be avoided
- Corticosteroid should not be used routinely - not shown to be effective
- Role of immunomodulators not determined
- Mechanical ventilation for respiratory failure, if needed
- Supportive care

Discharge of cases

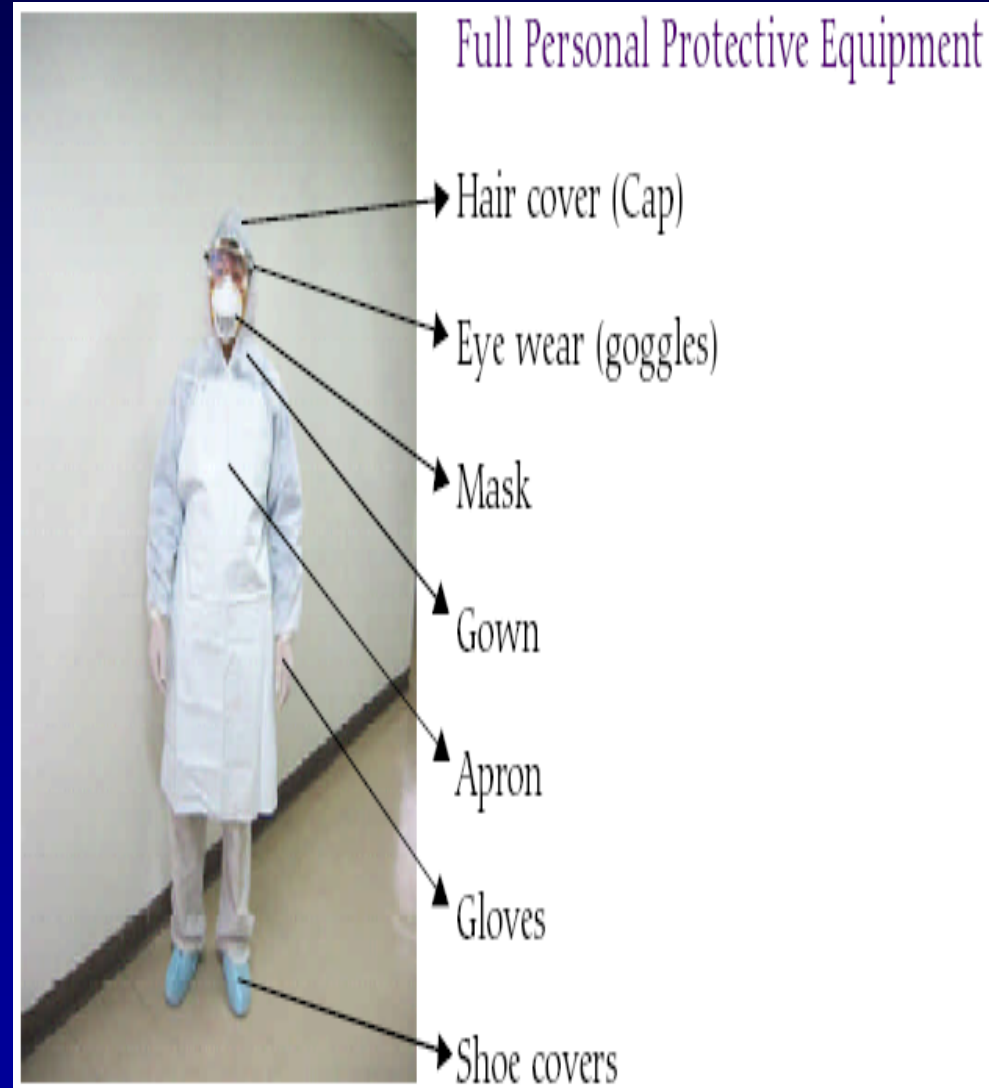
- Adult cases are discharged if they remain afebrile for 7 days and X-Ray chest is normal
- Children below 12 years are discharged 21 days after the onset of illness provided they also fulfill the discharge criteria for adults.

Infection control in health facilities

- Isolation of cases
 - Negative-pressure room, or
 - Single well ventilated rooms.
 - Cohort in ward with beds at least 1 meter apart, preferably separated by physical barrier
- Take standard, contact, droplet and airborne isolation precautions
- Only limited health care workers should have access to cases. If possible, they should not look after other patients
- Cases should also use N-95 masks (three layer surgical masks, if N-95 masks not available)
- Visitors should not be allowed. Otherwise give them proper PPE

Prevent Health Care Workers Exposure

- All health care workers involved in the management of cases are given appropriate PPE and pre-exposure chemoprophylaxis
- Oseltamivir – 75 mg daily
- They should wash hands frequently
- They should monitor their temperature twice daily and report any febrile event immediately



Summary of Case Management

- Treatment in isolation with standard, droplet, contact precautions
- Cases should be provided separate rooms or cohorted with at least 3 feet distance
- Anti-viral drugs (recent H5N1 viruses are resistant to Amantadine and rimantadine, but susceptible to Oseltamivir)
- Supportive therapy including mechanical ventilation if needed
- Good infection control practices in health settings
- All health care workers involved in the management of cases are given oseltamivir chemoprophylaxis and appropriate PPE
- Cases should also use N-95 masks (three layer surgical masks, if N-95 masks not available)

Thank You