# VI PANDEMIC INFLUENZA COURSE
# REGIONAL HEALTH CARE TRAINNING CENTER
## FIRST WEEK
### PROGRAM
### MORNING SESSIONS

| Monday 02th June | Tuesday 03th June | Wednesday 04th June |
|---|---|---|
| 8:00 to 9:00 am | 8:00 To 9:00 a.m. | 8:00 to 10:00 |
| Welcome Remarks and Introduction to the Course<br>**Dr. Jorge Motta**<br>GMI Director | Laboratory diagnostic approaches.<br>**Dr. Marshall Monteville.**<br>Navy Environmental Health Center. | Seasonal Influenza 2,008: The Global and the Latin American perspective.<br>**Dr. Enrique Mendoza**<br>Academic Director |
| 9:00 to 10:00 am<br>Baseline Evaluation.<br>**Dr. Enrique Mendoza**<br>Academic Director | 9:00 to 10:00 a.m.<br>Laboratory diagnostic approaches.<br>**Dr.Marshall Monteville.**<br>Navy Environmental Health Center. | Seasonal Influenza 2,008<br>**Dr. Enrique Mendoza**<br>Academic Director |
| 10:00 to 10:30 am<br>Coffe Break | 10:00 to 10:30 am<br>Coffe Break | 10:00 to 10:30 am<br>Coffe Break |
| 10:30 to 12:00 pm | 10:30 to 12:00 pm. | 10:30 to 12:00 |
| Basic Virology<br>**Evelia Quiróz.**<br>Professor<br>University of Panama | Infection control in the hospital and in the community settings. Isolation, quarantine and restriction of movement.<br>**Dr. Christopher Clagett.**<br>Navy Environmental Health Center. | Avian Influenza 2,008 The global perspective<br>**Dr. Enrique Mendoza**<br>Academic Director |
| 12:00 to 2:00 p.m.<br>Lunch Break | 12:00 to 2:00 p.m.<br>Lunch Break | 12:00 to 2:00pm<br>Lunch Break |

### PRELIMINARY PROGRAM
### AFTERNOON SESSIONS

| Monday 02th June | Tuesday 03th June | Wednesday 04th June |
|---|---|---|
| 2:00 to 3:00 pm<br>Seasonal, Pandemic and Avian Influenza: molecular and cellular perspective.<br>**Dr. Evelia Quiroz**<br>Univ. of Panama | 2:00 to 3:00 pm.<br>Infection control in the hospital and in the community settings. Isolation, quarantine and restriction of movement.<br>**Dr. Christopher Clagett.**<br>Navy Environmental Health Center. | 2:00 to 3:30 pm<br>Seasonal Influenza: Clinical Manifestations, Diagnostic and Treatment.<br>**Dr. Nestor Sosa**<br>International Affairs Director |
| 3:00 to 3:30 p.m.<br>Coffe Break | 3:00 to 3:30 pm<br>Coffe Break | 3:30 to 4:00 pm<br>Coffe Break |
| 3:30 to 5:00 p.m. | 3:30 to 5:00p.m. | 4:00 to 5:00 p.m. |
| Influenza A (H5N1) in Humans<br>**Dr. Michael Callahan** | Seasonal and Pandemic Influenza virus and the immune system.<br>**Dr. Juan Miguel Pascale**<br>GMI-University of Panama | Pandemic and Avian Influenza: Clinical Manifestations, Diagnostic and Treatment.<br>**Dr. Nestor Sosa**<br>International Affairs Director |

**PRELIMINARY PROGRAM**
**MORNING SESSIONS**
**FIRST WEEK**

| Thursday 05th June | Friday 06th June | Saturday 07th June |
|---|---|---|
| 8:00 to 10:00 a.m. | 8:00 to 10:00 a.m. | 8:00 to 12:00 a.m. |
| Public Health and Epidemiology aspects of influenza.<br>**Dr. Michael Tapper.**<br>Lennox Hill Hospital. | The lesson learned from SARS<br>**Dr. Michael Tapper.**<br>Lennox Hill Hospital. | First week Evaluation |
| 10:00 to 10:30 am<br>Break | 10:00 to 10:30 am<br>Break | |
| 10:30 to 12:00 am | 10:30 to 12:00 pm | |
| Public Health and Epidemiology aspects of influenza.<br>**Dr. Michael Tapper.**<br>Lennox Hill Hospital. | The lessons learned from past pandemics<br>**Dr. Michael Tapper.**<br>Lennox Hill Hospital. | |
| 12:00 to 2:00pm<br>Lunch Break | 12:00 to 2:00pm<br>Lunch Break | 12:00 to 2:00pm<br>Lunch . |

**PRELIMINARY PROGRAM**
**AFTERNOON SESSIONS**

| Thursday 05th June | Friday 06th June | Saturday 07th June |
|---|---|---|
| 2:00 to 4:00 pm<br>Seasonal and pandemic Vaccines 2,008<br>**Dr. Enrique Mendoza**<br>Academic Director | 2:00 to 4:00 pm<br>Influenza pandemic community mitigation strategy<br>**Dr. Enrique Mendoza**<br>Academic Director | FREE AFTERNOON AND EVENING |
| 4:00 to 6:00 pm | 4:00 to 5:00 pm | |
| Influenza in birds and in other animals.<br>**Dr. Olga Bravo**<br>**Dr. Enrique Samudio**<br>School of Veterinary Medicine<br>University of Panama | Non-pharmaceutical measures in a pandemic scenario<br>**Dr. Vicente Bayard**<br>Gorgas Memorial Institute<br>. | |

## SECOND WEEK
### PROGRAM
### MORNING SESSIONS

| Monday 09th June | Tuesday 10th June |
|---|---|
| 8:00 to 10:00 am | 8:00 To 9:00 a.m. |
| Computing Modeling of Pandemic Influenza<br>**Dr. Roy Wong**<br>Costa Rica | Neuroaminidase inhibitors<br>**Dr. Steven Toovey**<br>Roche |
| 10:00 to 10:30 am<br>Break | 10:00 to 10:30 am<br>Break |
| 10:30 to 12:00 pm | 10:30 to 12:00 pm. |
| The people and the family In the pandemic scenario<br>**Dr. Rosana Sánchez**<br>Honduras | Infections Diseases outbreaks in Central America<br>**Dr. Steven Toovey**<br>Roche |
| 12:00 to 2:00 p.m.<br>Lunch Break | 12:00 to 2:00 p.m.<br>Lunch Break |

### PRELIMINARY PROGRAM
### AFTERNOON SESSIONS

| Monday 09th June | Tuesday 10th June |
|---|---|
| 2:00 to 4:00 pm | 2:00 to 4:00 pm |
| Personal Protective Equipment<br>Lecture and Worshop<br>**Dr. Soraya Solano Acuña**<br>Costa Rica | 2:00 to 4:00 pm.<br>The school system in the Pandemic Influenza<br>**Msc. Marvin Cervantes**<br>Costa Rica |
| 4:00 to 5:00 p.m. | 4:00 to 6:00p.m. |
| Personal Protective Equipment<br>Lecture and Worshop<br>**Dr. Soraya Solano Acuña**<br>Costa Rica | H5n1 Human Cases<br>**Dr.Lei Yung-Chao**<br>Taiwan |

**Oficina Regional de los CDC para Centroamérica, Panamá y República Dominicana (CDC-CAP), el Centro de Estudios en Salud de la UVG, el Instituto Conmemorativo Gorgas de Panamá (ICG) y el Centro Regional de Capacitación en Salud**

| Miércoles 11 | Jueves 12 | Viernes 13 |
|---|---|---|
| 8:00 – 8:15<br>**Introducción al Taller**<br>(Dr. Nivaldo Linares)<br><br>8:15 – 9:15<br>**Sesión 1**<br>*(Conferencia)*<br>**Vigilancia de la influenza**<br>(Dr. Wilfrido Clará, CDC/CAP-UVG/CES)<br><br>9 :15 – 10:15<br>**Sesión 2**<br>*(Mesa de Discusión)*<br>**Vigilancia de la influenza en los países de la Región**<br>(Moderador: Dr. Wilfrido Clará, CDC/CAP-UVG/CES)<br><br>10 :15 – 10:30 RECESO<br><br>10:30 – 13:00<br>**Sesión 3**<br>*(Estudio de caso)*<br>**Vigilancia de influenza**<br>(Dr. Wilfrido Clará, CDC/CAP-UVG/CES) | 8:00 – 12:30<br>Sesión 5 Continuación…<br>*(Estudio de Caso)*<br>**Investigación de caso sospechoso de influenza aviar en humanos (H5N1)**<br><br>8:00 -9:00<br>Parte 3.<br>*Búsqueda de caso e identificación de contactos*<br>(Dr. Nivaldo Linares, CDC/CAP-UVG/CES)<br><br>9:30 -10:30<br>Parte 4.<br>*Manejo de datos de casos y contactos*<br>(Dr. Rafael Chacón, CDC/CAP-UVG/CES)<br><br>10:30 – 10:45<br>RECESO<br><br>10:45 – 13:00<br>Parte 5.<br>*Evaluando la transmisión de humano a humano, conclusión de estudio de caso y escritura del reporte final*<br>(Dr. Rafael Chacón, CDC/CAP-UVG/CES) | 8:00 – 9:00<br>Sesión 10<br>*(Conferencia)*<br>**Centro de Operaciones de Emergencias**<br>(Dr. Carter Stone, CDC/CAP-UVG/CES)<br><br>9:00 – 10:15<br>**Sesión 11**<br>*(Conferencia)*<br>**Equipos de Respuesta Rápida y Escenarios para el ejercicio de campo**<br>(Dr. Jorge Jara, CDC/CAP-UVG/CES)<br><br>10:15 – 10:30 RECESO<br>10:30 – 15:30<br>**Sesión 11**<br>*(Trabajo de grupo)*<br>**Ejercicio de campo**<br>(Coordinador: Dr. Jorge Jara, CDC/CAP-UVG/CES)<br>• Escenario 1. Centro de Operaciones<br>(Lic. Carter Stone, CDC/CAP-UVG/CES y Dr. Raúl González, CISED, MINSA, Panamá)<br>• Escenario 2. ERR investigación de caso en comunidad<br>(Dr. Nivaldo Linares, CDC/CAP-UVG/CES y Dr. Jorge Jara, CDC/CAP-UVG/CES)<br>• Escenario 3. ERR Vigilancia, Triage y manejo de casos en Hospital<br>(Dr. Wilfrido Clara, CDC/CAP-UVG/CES y Dr. Rafael Chacon, CDC/CAP-UVG/CES) |
| 13:00 – 14:00 Almuerzo | 13:00 – 14:00 Almuerzo | 13:00 – 14:00 Almuerzo en Escenarios |

| Miércoles 11 | Jueves 12 | Viernes 13 |
|---|---|---|
| **14:00 – 14:30**<br>**Sesión 4**<br>*(Conferencia)*<br>**Respuesta Rápida: Investigación de caso sospechoso de influenza aviar en humanos (H5N1)**<br>(Dr. Nivaldo Linares, CDC/CAP-UVG/CES)<br><br>**14:30 – 17:00**<br>**Sesión 5**<br>*(Estudio de Caso)*<br>**Investigación de caso sospechoso de influenza aviar en humanos (H5N1)**<br><br>14:30 -15:45<br>Parte 1.<br>*Introducción a la investigación de casos, preparativos antes de la investigación y definición de casos*<br>(Dr. Rafael Chacón, CDC/CAP-UVG/CES)<br><br>**15:45 – 16:00**<br>**RECESO**<br><br>16:00 – 18:00<br>Parte 2.<br>*El laboratorio en la investigación de casos Colección de muestras clínicas*<br>(Lic. Jenny Lara, NIC, INCIENSA, Costa Rica) | **14:00 – 15:00**<br>**Sesión 6**<br>*(Conferencia)*<br>**La operación de respuesta rápida y contención**<br>(Dr. Nivaldo Linares, CDC/CAP-UVG/CES)<br><br>**15:00 – 15:45**<br>**Sesión 7**<br>*(Conferencia)*<br>**Medidas farmacológicas**<br>(Dr. Rafael Chacón, CDC/CAP-UVG/CES)<br><br>**15:45 - 16:00**<br>**RECESO**<br><br>**16:00 – 17:00**<br>**Sesión 8**<br>*(Conferencia)*<br>**Medidas no farmacológicas**<br>(Dr. Rafael Chacón, CDC/CAP-UVG/CES)<br><br>**17:00 – 18:00**<br>**Sesión 9**<br>*(Discusión grupal)*<br>**¿Estamos preparados en para el desarrollo de una operación de respuesta rápida y contención en los países de la región?**<br>(Dr. Nivaldo Linares, CDC/CAP-UVG/CES) | **15:30 – 16:30**<br>**Sesión 12**<br>*(Conferencia)*<br>Integración de los proceso de alerta-respuesta frente a la influenza<br>Dr. Jorge Jara, CDC/CAP-UVG/CES)<br><br>**16:30 - 17:00**<br>**Cierre**<br>(Dr. Nivaldo Linares, CDC/CAP-UVG/CES) |

# Clinical management of human infection with avian influenza A (H5N1) virus

**Yung-Chao, Lei. M.D.**
**Centers for Disease Control, Taiwan**
**June 10, 2008**

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## Outline

- Current cases H5NI situation
- General considerations
- Case management
  1. Epidemiology and demographic characteristics
  2. Clinical features
  3. Diagnosis
  4. Site of care
  5. Antiviral Treatment
  6. Other pharmacological interventions
  7. Supportive therapy for critically ill patients
  8. Special considerations
- Summary & Conclusion

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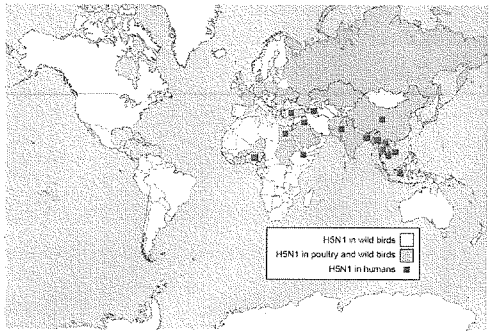
## Nations With Confirmed Cases H5N1 Avian Influenza

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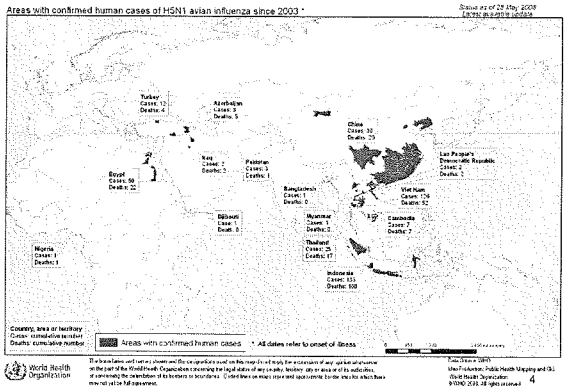


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## Current Situation

Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO

**28 May 2008**

| Country | 2003 | | 2004 | | 2005 | | 2006 | | 2007 | | 2008 | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | cases | deaths | cases | deaths | cases | deaths | cases | deaths | cases | deaths | cases | deaths | cases | deaths |
| Azerbaijan | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 5 | 0 | 0 | 1 | 0 | 8 | 5 |
| Bangladesh | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| Cambodia | 0 | 0 | 4 | 0 | 4 | 4 | 2 | 2 | 1 | 1 | 0 | 0 | 7 | 7 |
| China | 1 | 1 | 0 | 0 | 8 | 5 | 13 | 8 | 5 | 3 | 3 | 3 | 30 | 20 |
| Djibouti | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| Egypt | 0 | 0 | 0 | 0 | 0 | 0 | 18 | 10 | 28 | 9 | 7 | 3 | 53 | 22 |
| Indonesia | 0 | 0 | 0 | 0 | 20 | 13 | 55 | 45 | 42 | 37 | 16 | 13 | 133 | 108 |
| Iraq | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 0 | 0 | 3 | 2 |
| Lao People's Democratic Republic | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 2 | 2 |
| Myanmar | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 |
| Nigeria | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 |
| Pakistan | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 3 | 1 | 0 | 0 | 3 | 1 |
| Thailand | 0 | 0 | 17 | 12 | 5 | 2 | 3 | 3 | 0 | 0 | 0 | 0 | 25 | 17 |
| Turkey | 0 | 0 | 0 | 0 | 0 | 0 | 12 | 4 | 0 | 0 | 0 | 0 | 12 | 4 |
| Viet Nam | 3 | 3 | 29 | 20 | 61 | 19 | 0 | 0 | 8 | 8 | 8 | 5 | 109 | 55 |
| Total | 4 | 4 | 51 | 32 | 98 | 43 | 115 | 79 | 99 | 59 | 32 | 24 | 393 | 141 |

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

63%

## General considerations - transmission

- Direct avian-to-human H5N1 virus transmission is the predominant means of human infection
- The most commonly recognized risk factor: Handling of sick or dead poultry during the week before the onset of illness
- 90% of case clusters have occurred among blood-related family members
  - possible genetic susceptibility

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## General considerations - WHO

- **Respiratory failure** is the major complication in patients hospitalized with influenza A(H5N1) virus infection.
- **No standardized approach** exists for the clinical management of A(H5N1)-infected humans, and many patients progress rapidly to ARDS and multi-organ failure.
- After exposure to infected poultry, the **incubation period** generally appears to be 7 days or less, and in many cases this period is 2 to 5 days



## Case Management

- Epidemiology and demographic characteristics
- Clinical Features
- Diagnosis
- Site of care
- Antiviral Treatment
- Other pharmacological interventions
- Supportive therapy for critically ill patients
- Special considerations

WHO – Updated advice 15 August 2007
http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage07/en/index.html



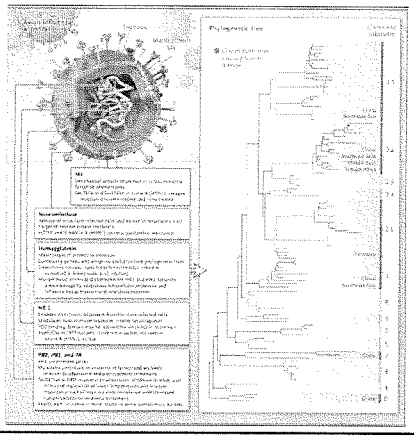



Table 1. Case Fatality Proportion According to Clade or Subclade and Median Time from Onset of Illness to Hospitalization or Death in Patients with Confirmed Influenza A (H5N1) Illness.

| Country | Predominant Clade or Subclade* | Case Fatality Proportion | Onset of Illness to Hospitalization | | Onset of Illness to Death | |
|---|---|---|---|---|---|---|
| | | no. of patients/ total no. (%) | days | no. of patients | days | no. of patients |
| Cambodia, Thailand, Vietnam† | 1 | 66/123 (54) | 4 | 109 | 8 | 65 |
| Indonesia | 2.1 | 76/96 (79) | 5 | 64 | 9 | 72 |
| Azerbaijan, Djibouti, Egypt, Iraq, Nigeria, Turkey | 2.2 | 28/58 (44) | 3 | 16 | 9 | 24 |
| China, Laos | 2.3 | 17/26 (65) | 5 | 16 | 10 | 17 |

1. The cumulative case-fatality proportion is approximately **61%**
2. The time from the onset of illness to presentation (median, **4 days**) or to death (median, **9 to 10 days**) has remained unchanged from 2003 through 2006

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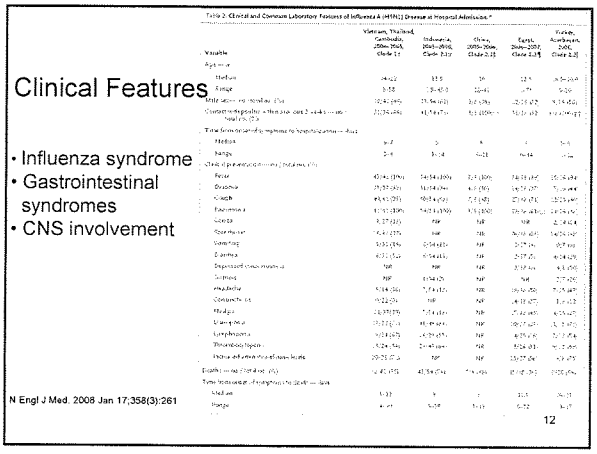
## Epidemiology and demographic characteristics

- The median age of patients: approximately 18 years
- 90% of patients: 40 years of age or younger
- Most patients with influenza A (H5N1) virus infection were previously healthy.
- Six affected pregnant women, four have died, and the two survivors had a spontaneous abortion
- No cases have been identified among short-term travelers visiting countries affected by outbreaks among poultry or wild birds



## Clinical Features

- Influenza syndrome
- Gastrointestinal syndromes
- CNS involvement



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## Clinical Features – symptoms and signs

- Most patients with H5N1 influenza present with an **influenza syndrome**
  - fever, cough and shortness of breath
  - radiological evidence of pneumonia
- Gastrointestinal symptoms
  - diarrhoea, vomiting, and abdominal pain
- CNS involvement
  - similar to the occasional reports of CNS manifestations associated with seasonal human influenza A and B virus infections

→ **Nonspecific clinical presentation !!!**

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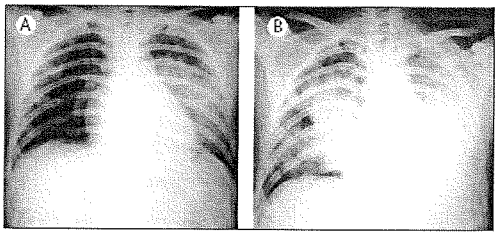


*Figure 2:* H5N1 influenza pneumonia
Chest radiographs of a 24-year-old man with H5N1 influenza virus infection showing rapid progression from left-sided pneumonia at admission (A) to bilateral pneumonia 4 days later (B).

- Rapidly progressive bilateral pneumonia, requiring ventilatory support within days of onset
- Most patients dying of progressive respiratory failure.

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## Clinical Features - lab

- Leukopenia, lymphopenia, mild-to-moderate thrombocytopenia, and elevated levels of aminotransferases are common but not universal
- **Poor prognosis:** Lymphopenia and increased levels of lactate dehydrogenase
- **Early onset of lymphopenia**: might be secondary to virus-induced apoptosis as suggested by in-vitro and murine experiments with H5N1 influenza viruses

Lancet 2007; 371: 1464–75

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## Differential Diagnosis

- The presenting signs and symptoms of A(H5N1) illness are non-specific
- Differential diagnosis of all persons presenting with **acute febrile respiratory illness**
- **Detailed exposure history**
  - any close/direct contact with sick or dead poultry, wild birds, other severely ill persons
  - travel to an area with A(H5N1) activity
  - work in laboratory handling samples possibly containing A(H5N1) virus

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## Diagnosis

- **NOT recommend**: commercially available, rapid site-of-care influenza detection tests **(rapid antigen test)** for individual patient diagnosis
  - low sensitivity (0% - 36%)
  - a negative rapid test result does **not** exclude human infection
  - a positive test does **not** distinguish from infection by other influenza viruses
  - require 1000 times higher levels of virus than viral cultures to be positive

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## Diagnosis

The best method for the initial diagnosis

- **Detection of viral RNA** by means of conventional or real-time reverse-transcriptase polymerase chain reaction **(RT-PCR)**
  - provide results within 4 to 6 hours
  - under biosafety level 2 conditions
- Collection of multiple respiratory specimens (nasal, throat, endotracheal aspirates from intubated patients)
  - feces or blood or CSF
- Preferably before antiviral treatment

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## Diagnosis

- Detection of **anti-H5 antibodies**
  - epidemiologic investigations
  - seroconversion generally occurs 2 to 3 weeks after infection
- **Microneutralization assays**
  - labor-intensive
  - require biosafety level 3 facilities

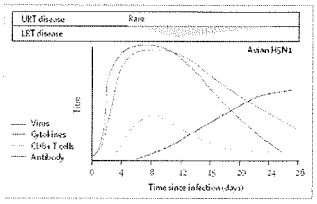



Figure 1: Course of human infection with highly pathogenic H5N1 influenza virus



## Site of care

- **Hospital care** in the initial stages of the disease to monitor clinical status, including oxygenation, is warranted whenever possible.
- **Follow-up of discharged patients** with home visits or telephone contact
  - ensure there is no deterioration or occurrence of new illness in contacts
  - infected persons probably cease to excrete the infectious virus **3 weeks** after illness onset



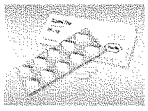
## Antiviral Treatment

- **Oseltamivir**
  - Agent of choice for treatment of A(H5N1) virus infections
  - Optimal regimens
    - Clinical status
    - Child/Adolescent or Adult
    - Gastrointestinal dysfunction
- **Neuraminidase inhibitors**: Zanamivir/peramivir
- **Adamantanes** ( amantadine and rimantadine)
- Combination therapy
- Immunotherapy

Drug Metab Dispos. 2002 Jan;30(1):13-9.
N Engl J Med. 2008 Jan 17;358(3):261



## Oseltamivir



- Available only in **oral** formulations
- the primary antiviral agent of choice for the treatment of A(H5N1) virus infections
- No controlled clinical trials
  - Limited observational evidence
  - early oseltamivir administration may be associated with reduced mortality in patients
- **As early as possible** based on clinical suspicion and before confirmation of etiology
  - **standard 5-day course** of therapy



TAMIFLU Dosage by Age and Weight

| Age and Weight | Pill Dosage | Liquid Dosage (using oral dosing dispenser) |
|---|---|---|
| Adults and Children 13 yrs. and older | 1 Dose= One 75 mg pill | 1 Dose= 75 mg |
| Children 1 – 12 yrs. | | |
| 33 lbs. or less (15 kg or less) | 1 Dose= One 30 mg pill | 1 Dose= 30 mg |
| 34 lbs – 51 lbs (16 kg – 23 kg) | 1 Dose= One 45 mg pill | 1 Dose= 45 mg |
| 52 lbs – 88 lbs (24 kg – 40 kg) | 1 Dose= Two 30 mg pills | 1 Dose= 60 mg |
| 89 lbs or more (41 kg or more) | 1 Dose= One 75 mg pill | 1 Dose= 75 mg* |

*The 75 mg dose can be measured out using a combination of 30 mg and 45 mg.

◆ the optimal treatment regimen is not currently known in A(H5N1) virus infections.



## Oseltamivir

- The standard dose and duration (**1 dose, twice daily, for 5 days)** are derived from treatment studies of outpatients with uncomplicated seasonal influenza.
- If continued fever and clinical deterioration
  - ongoing viral replication
  - bacterial superinfection
  - other nosocomial complications
- If no clinical improvement after a standard 5-day course
  → therapy may be extended for **a further 5 days**

## Oseltamivir – higher doses

- In adults with uncomplicated seasonal influenza, higher doses (**150 mg twice daily in adults**) were tolerated as well as the approved regimen but provided no greater clinical or virological benefit.
- Whether higher doses might reduce **oseltamivir resistance emergence** is unknown
- the safety of higher doses has not been examined in **children**
  - rarely, severe neuropsychiatric effects in adolescents

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## Oseltamivir – Gastrointestinal dysfunction

- **In critically ill patients** with gastric stasis, placement of **a naso-jejunal tube** is a consideration
  - no data are available on the absorption of oseltamivir oral preparations administered through a nasogastric tube
  - an invasive and technically demanding procedure of uncertain value
  - collection of several timed plasma for later determination of oseltamivir carboxylate levels would be helpful

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## Oseltamivir - summary

- Oseltamivir remains the **primary recommended** antiviral treatment.
- **Early treatment** with oseltamivir is recommended
- Antiviral treatment should **NOT** be withheld when patients are presenting late
- Consider **modified regimens**
  - the optimal dose and duration of therapy are still uncertain.
- No definitive conclusions about its efficacy can be made

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## Neuraminidase inhibitors

- Zanamivir/peramivir
- Highly active in vitro and in animal models of A(H5N1) virus infection, including that due to oseltamivir-resistant virus
- Topically applied (inhaled) zanamivir has not been studied in human A(H5N1) illness
- Parenterally administered neuraminidase inhibitors now in clinical development (e.g. intravenous zanamivir or peramivir)
- Stringent hospital infection control measures

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## Adamantanes

- amantadine and rimantadine
- **Monotherapy**: a high frequency of rapid resistance emergence
- Globally many A(H5N1) virus isolates now show primary resistance.
- When neuraminidase inhibitors are available, **monotherapy with amantadine or rimantadine is NOT recommended.**

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## Combination therapy

- In an area where A(H5N1) viruses are likely to be adamantane-susceptible, combination therapy with oseltamivir and an adamantane at standard doses may be considered if there is pneumonic disease or clinical progression
- Should only be considered when the locally circulating A(H5N1) viruses (**Clade 2.2 and 2.3**) are likely to be susceptible to adamantanes
  - **Clade 1** (Cambodia, Thailand, Viet Nam) and the majority of **clade 2.1** (Indonesia) A(H5N1) virus isolates are adamantane-resistant

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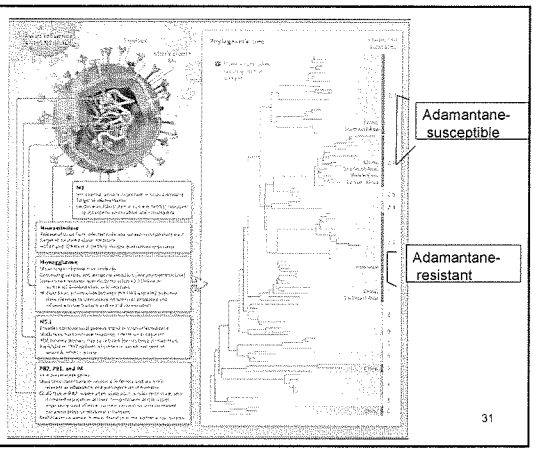




## Immunotherapy

- Administration of **anti-H5N1 specific antibodies** in the form of neutralizing monoclonal antibodies or of polyclonal sera (convalescent or post-immunization) shows efficacy in animal models
- Two patients who were treated with both oseltamivir and convalescent plasma from A(H5N1) virus-infected patients survived
- Close clinical and serial virological monitoring



## Virological monitoring

- Real-time therapeutic monitoring of the virological response by **RT-PCR** testing would be desirable to help guide therapy
- Not routinely available at present
- collection of serial respiratory samples (throat swabs and, if available, tracheal aspirates) for detection of virus
- **Collect time**: before treatment, day 4–5, and day 7–8 after treatment is initiated
- WHO can assist



## Other pharmacological interventions

- Antibiotics
- Immuno-modulators
  - systemic corticosteroids
  - other immunomodulating agents
- Haemophagocytosis and intravenous immunoglobulin (IVIG)



## Antibiotics

- **Start empiric treatment** with antibiotics according to the latest published national, international or expert group CAP treatment guidelines
- ICU:
  include a combination of a **β-lactam** (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either **azithromycin** or a **fluoroquinolone**
- The use of fluoroquinolone monotherapy in such patients is **not** recommended
- Tailored by taking into consideration the likely pathogens and local susceptibility patterns



**Table 7. Recommended empirical antibiotics for community-acquired pneumonia.**

- Antibiotics
  - Prophylactic use not recommended
  - Empirical use for Community-acquired pneumonia.

Inpatients, non-ICU treatment
A respiratory fluoroquinolone (strong recommendation; level I evidence)
A β-lactam **plus** a macrolide (strong recommendation; level I evidence)
Inpatients, ICU treatment
A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence) or a respiratory fluoroquinolone (level I evidence) (strong recommendation)
(for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)
Special concerns
If Pseudomonas is a consideration
An antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg)
or
The above β-lactam plus an aminoglycoside and azithromycin
or
The above β-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for above β-lactam)
(moderate recommendation; level III evidence)
If CA-MRSA is a consideration, add vancomycin or linezolid (moderate recommendation; level III evidence)

Clin Infect Dis. 2007 Mar 1;44 suppl 2:S27-72

## Antibiotics

- Diagnostic workup for CAP:
  **blood culture** and **sputum** for Gram stain & culture
- If no bacteriological cause of CAP and diagnostic testing **confirms A(H5N1)** virus infection
  → empiric antibiotic treatment may be **stopped**
- If suspicion of A(H5N1) virus infection but **both negative** of diagnostic testing for A(H5N1) virus and pathogens of CAP
  → **continued therapy for both possibilities**
  → pending further microbiological studies

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## Antibiotics

- **Prophylactic antibiotics** is **NOT** recommended
  - unproven benefit
  - may select for resistant bacteria
  - cause side effects
- If clinical deterioration after initial improvement, be careful to choose the antibiotics
  - should cover likely pathogens based on local etiologic and susceptibility patterns including *Staphylococcus, Streptococcus and nosocomial Gram negative organisms.*

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## Systemic Corticosteroid (I)

- Role in **Sepsis**
  - IV hydrocortisone (<300mg daily) only to adult **septic shock** patients after it has been confirmed that their BP is poorly responsive to fluid resuscitation and vasopressor therapy
  - Daily addition of oral fludrocortisone (50ug) if hydrocortisone is not available and the steroid that is substituted has no significant mineralocorticoid activity. *(Fludrocortisone is considered optional if hydrocortisone is used)*
  - Hydrocortisone be reserved for use in **children** with catecholamine resistance and suspected or proven adrenal insufficiency

Crit Care Med. 2008 Jan;36(1):296-327.

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## Systemic Corticosteroid (II)

- Role in **ALI/ARDS**
  - Routine use of methylprednisolone for persistent ARDS (>=7 days) is **not** supported despite the improvement in cardiopulmonary physiology
  - No clear benefit in treating A(H5N1) virus – associated pneumonia or ARDS with high-dose corticosteroid
  - Unproven benefit and potential harmful of moderate to high doses of steroid

  **→Systemic corticosteroid: Not recommended**

  **→Corticosteroids should not be used routinely**

N Engl J Med. 2005 Sep 29;353(13):1374-85.
N Engl J Med. 2006 Apr 20;354(16):1671-84.

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## Systemic Corticosteroid - summary

- To date no consistent survival benefit has been found
- **High-dose corticosteroids** increase the risks of
  - enhanced A(H5N1) viral replication
  - secondary infections, opportunistic infection.
  - musculoskeletal side effects
- High dose steroids should **NOT** be given for treatment of A(H5N1) disease.
- **Lower dose steroids** should be considered in the treatment of refractory septic shock according to current best-practice guidelines, but the benefit in paediatric septic shock is unknown

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## Cytokines and A(H5N1)

- High plasma levels of pro-inflammatory cytokines and chemokines that correlate with the levels of virus in the upper respiratory tract
- Cytokine dysregulation has also been invoked in the pathogenesis of sepsis and septic shock

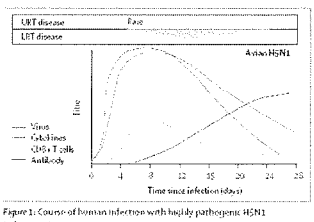


Figure 1: Course of human infection with highly pathogenic H5N1

## Other immunomodulating agents

- Multiple immuno-modulating agents, including **NSAIDs, growth hormone, anti-TNF** modalities amongst other therapies, have **NO** proven benefit in the treatment of sepsis
  → immune modulating agents of unproven value should **NOT** be used at present in the treatment of A(H5N1) disease.
- **Aspirin (salicylic acid)** or salicylate-containing products should not be administered to suspected influenza or A(H5N1) patients under 18 years old because of the risk of **Reye Syndrome**

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## Haemophagocytosis and intravenous immunoglobulin

- Reactive haemophagocytosis in fatal A(H5N1) virus-infected cases
- **Haemophagocytic lymphohistocytosis (HLH)**
  - fever, splenomegaly, bicytopenia, hypertriglyceridenia, hypofibrinogenemia, haemophagocytosis in bone marrow, spleen or lymph nodes, low/absent NK-cell activity, hyperferritinemia and increased soluble CD25 levels
  - intravenous immunoglobulin (ivIG) (if available) may be considered as a treatment option
  - consider and monitor any complications of ivIG

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## Supportive therapy for critically ill patients

- Oxygen therapy
- Ventilatory support
- Non-ventilatory treatments for ALI/ARDS
- Resuscitation
- Fluid therapy
- Vasopressor
- Blood product administration
- Glucose control
- Bicarbonate therapy
- Deep vein thrombosis prophylaxis
- Stress ulcer prophylaxis

Crit Care Med. 2008 Jan;36(1):296-327

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## Oxygen therapy

- Recognize and treat hypoxemia early
- **Pulse oximeters** should be used for initial evaluation and followed by frequent serial monitoring
- **Clinical signs:**
  - raised respiratory rate (corrected for age)
  - altered conscious
- SaO2 should be maintained over **90%.**

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## Oxygen therapy

- **Nasal cannulae:**
  only effective for management of mild hypoxemia
- **Face mask**
  - need high flow oxygen (e.g. 10 litres per minute)
  - close involvement of nursing staff
- If medical oxygen is not available, then industrial oxygen can be used (e.g. delivered by face mask) provided it conforms with national guidelines

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## Ventilatory Support

- **Non-invasive positive pressure ventilation ( NPPV)**
  - suggested as a bridging strategy for patients with early ALI without hemodynamic instability
  - hemodynamic instability and multiorgan failure are contra-indications
  - increased risk of potentially infectious aerosols
- use NPPV and the clinical condition has not improved **within 2 hours** or satisfactory oxygenation levels have not been achieved with NPPV, then invasive positive pressure ventilation (IPPV) should be started as soon as possible

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## Invasive positive pressure ventilation (IPPV)

- Preferred mode of ventilatory support for patients with A(H5N1) virus infection complicated by ARDS
- Transferred to a well-trained facility
- In techniques for personal protection
- A **low-volume, low-pressure** strategy for ventilation
- Lung-protective ventilation

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## Invasive positive pressure ventilation (IPPV)

- Lung-protective ventilation:
  - minimizing tidal volume (goal of maximum 6 ml/kg of predicted body weight) and plateau pressures (maximum 30cm H2O)
  - saturation (SaO2, measured by pulse oximetry) of **> 88 %** or a partial pressure of arterial oxygen (PaO2) **> 55** mmHg
  - fractional inspired oxygen (FiO2) with appropriate level of positive end-expiratory pressure (PEEP) to recruit atelectatic alveoli

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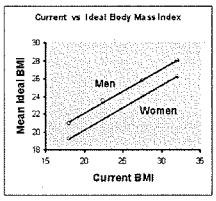
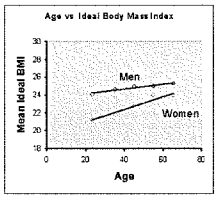
## Predicted Body Weight

- Male=50+2.3(height in inch-60)
- Male=50+0.91(height in cm -152.4)
- Female=45.5+2.3(height in inch-60)
- Female=45.5+0.91(height in cm-152.4)

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## Other Supportive Therapy

- Resuscitation
- Fluid therapy
- Vasopressor
- Blood product administration
- Glucose control
- Bicarbonate therapy
- Deep vein thrombosis prophylaxis
- Stress ulcer prophylaxis

Crit Care Med. 2008 Jan;36(1):296-327.

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## Resuscitation

- Goals of resuscitation when a patient develops septic shock:
  - **CVP** : 8~12 mmHg or (12~15mmHg)#
  - **MAP**>=65 mmHg
  - **Urine output** >=0.5ml/kg/hr
  - **Central venous ( SVC) oxygen saturation** >=70% or mixed venous >=65%
- If venous oxygen saturation target is not achieved
  - Further fluid
  - PRBC transfusion to Hct>=30%
  - Dobutamine, maximum 20 ug/kg/min

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## Fluid therapy

- Conservative or liberal approach to fluid therapy?
  - Prompt resuscitation of hemodynamically unstable patients improves outcome
  - Fluid resuscitation with either **colloids** or **crystalloids** is recommended
  - A **conservative fluid strategy** for patients with ALI who do not have evidence of tissue hypoperfusion
  - **Albumin** and **furosemide** therapy may improve lung physiology measures in the subset of hypoproteinemic patients with lung injury

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## Vasopressor

- **Maintain MAP>=65mmHg**, titrated with supplementing end points
- Either **norepinephrine** or **dopamine** as the first choice of vasopressor agent although **norepinephrine is more potent**
- **Dopamine** as the first choice of support for the pediatric patient with hypotension refractory to fluid resuscitation
  - Dopamine–refractory shock may be reversed with norepinephrine or epinephrine infusion
  - No clear evidence for the use of vasopressin in pediatric sepsis

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## Blood product administration

- **RBC transfusion**:
  when Hb<7.0g/dl to a target Hb of 7.0~9.0 g/dl in adults in the absence of extenuating conditions
- **FFP**: should **NOT** be used to correct lab clotting abnormalities in the absence of bleeding or planned invasive procedures.
- **Platelet transfusion** in patients with severe sepsis:
  - Platelet counts < 5000/$mm^3$
  - Platelet counts: 5,000~30,000/$mm^3$ with a significant risk of bleeding
  - Platelet counts > 50,000/$mm^3$ for surgery or invasive procedure

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## Glucose control

- Following initial stabilization, patients with severe sepsis and hyperglycemia who are admitted in ICU should receive **IV insulin** therapy
- A validated protocol for insulin dose adjustments and targeting glucose level to **<150 mg/dl**
- The optimal goal glucose is not known in children

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## Bicarbonate therapy and IVIG

- **Sodium bicarbonate** for the purpose of improving hemodynamics in patients with hypoperfusion-induced lactic acidemia with pH>=7.15 is **NOT** recommended.
- **IVIG** for cases of A(H5N1) virus infection complicated by haemophagocytosis
- IVIG may be considered in children with severe sepsis.

Crit Care Med. 1991 Nov;19(11):1352-6.
J Trop Pediatr. 2005 Oct;51(5):271-8.

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## DVT and stress ulcer prophylaxis

- Patients (and postpubertal children) with severe sepsis are recommended to receive DVT prophylaxis with either **low dose UFH** (bid or tid) or **daily LMWH** unless contraindicated
- Septic patients with contraindications for heparin → **mechanical prophylaxis**
- In very high risk patients → may combine pharmacologic and mechanical therapy
- **LMWH** is preferred for patients with very high risk
- **H2 blockers** or **PPI** are recommended to be given to patients with severe sepsis to prevent UGIB

Chest. 2007 Feb;131(2):507-16.
Chest. 2008 Jan;133(1):149-55.
N Engl J Med. 1996 Sep 5;335(10):701-7.

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## Special considerations

- A(H5N1) combined with **HIV** infection:
  Limited case experience is available
- Four of six **pregnant women** with confirmed A(H5N1) disease died, one of whom had received corticosteroids without antiviral therapy
- Pregnant women should be treated with **antiviral therapy** and appropriate supportive care should be administered.

Table1 . Summary of treatment modalities for clinical management of human A(H5N1) virus infection.

| Recommended Modalities | Strategies |
|---|---|
| Antivirals | Oseltamivir is the primary treatment of choice. Consider modified regimens (see text). |
| Antibiotics | Empiric treatment[1] for community-acquired pneumonia (CAP) per published guidelines pending microbiologic results (e.g. 2-3 days); |
| Oxygen therapy | Monitor oxygen saturation and maintain $SaO_2$ over 90% with nasal cannulae or face mask. |
| IPPV (Invasive positive pressure ventilation) | Early intervention recommended for ARDS. Use lung protective, low tidal volume, low pressure ventilation to prevent barotrauma and conservative fluid management. |
| Low dose systemic corticosteroids | Appropriate for refractory septic shock complicating ARDS (e.g. hydrocortisone intra venous 200mg per day in divided doses (50 mg every 6 hours) in adults). |
| NSAIDs, antipyretics (Non-steroidal anti-inflammatory drugs) | Paracetamol given orally or by suppository will generally be sufficient in most cases as an anti-pyretic treatment. |
| Infection control | Whenever risk of infectious aerosols, use particulate respirator (N95, FFP2 or equivalent), eye protection, gowns, gloves and an airborne precaution room or negative pressure room. |

| Modalities NOT Recommended | Strategies |
|---|---|
| Adamantane monotherapy | When neuraminidase inhibitors are available, monotherapy with amantadine or rimantadine is not recommended. Combination therapy is consideration in areas where A(H5N1) virus is likely susceptible (see text). |
| Antibiotic chemoprophylaxis[1] | Not recommended |
| NPPV (Non-invasive positive pressure ventilation) | Generally not recommended (see text). |
| Systemic corticosteroids | Moderate to high doses of unproven benefit and potentially harmful; not recommended; |
| Salicylates | Avoid administration of salicylates (such as aspirin and aspirin containing products) in children and young adults (<18 years old) because of the risk of Reye Syndrome. |

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# Conclusion

- Collaborative sharing of **clinical** and **treatment data** from affected patients is essential to refine optimal case management
- **Standardization** of clinical care and antiviral management is fundamental to improve understanding of the disease course and to identify the appropriate therapy.
- **Reporting** clinical findings and treatment outcomes to WHO will greatly help its work in risk assessment and in the development of management guidance.

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***Thanks for your attention***

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