Management of Influenza A/H5N1 Infections in Humans

27 September 2007

Frederick G. Hayden, M.D.
WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

Holger J Schünemann, Suzanne R Hill, Meetal Kakad, Richard Bellamy, Timothy M Uyeki, Frederick G Hayden, Yazdan Yazdanpanah, John Beigel, Tawee Chotpitayasunondh, Chris Del Mar, Jeremy Farrar, Tran Tinh Hien, Bülent Özbay, Norio Sugaya, Keiji Fukuda, Nikki Shindo, Lauren Stockman, Gunn EVist, Alice Croisier, Azim Nagidaliyev, Cathy Roth, Gail Thomson, Howard Zucker, Andrew D Oxman, for the WHO Rapid Advice Guideline Panel on Avian Influenza

Recent spread of avian influenza A (H5N1) virus to poultry and wild birds has increased the threat of human infections with H5N1 virus worldwide. Despite international agreement to stockpile antivirals, evidence-based guidelines for their use do not exist. WHO assembled an international multidisciplinary panel to develop rapid advice for the pharmacological management of human H5N1 virus infection in the current pandemic alert period. A transparent methodological guideline process on the basis of the Grading Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to develop evidence-based guidelines. Our development of specific recommendations for treatment and chemoprophylaxis of sporadic H5N1 infection resulted from the benefits, harms, burden, and cost of interventions in several patient and exposure groups. Overall, the quality of the underlying evidence for all recommendations was rated as very low because it was based on small case series of H5N1 patients, on extrapolation from preclinical studies, and high quality studies of seasonal influenza. A strong recommendation to treat H5N1 patients with oseltamivir was made in part because of the severity of the disease. Similarly, strong recommendations were made to use neuraminidase inhibitors as chemoprophylaxis in high-risk exposure populations. Emergence of other novel influenza A viral subtypes with pandemic potential, or changes in the pathogenicity of H5N1 virus strains, will require an update of these guidelines and WHO will be monitoring this closely.

Lancet Infect Dis 2007; 7: 21-31
Italian National Cancer Institute Regina Elena, INFORMA Unit, Department of Epidemiology, Istituto Regina Elena, Rome, Italy (Prof H J Schünemann MD); Health Technology and Pharmaceuticals, WHO, Geneva, Switzerland (S R Hill MD, H Zucker MD); Norwegian Knowledge Centre for the Health Services, Oslo, Norway (M Kakad MD, G EVist PhD, A D Oxman MD); Department of Infection and Travel Medicine, James Cook University Hospital.
Oral Oseltamivir for Influenza (Adults): Effect on Antibiotic Use and Hospitalizations


LRT complications leading to use of antibiotics

- All: Placebo (10), Oseltamivir (4.5), -55%
- Bronchitis: Placebo (6), Oseltamivir (2.8), -52%
- Pneumonia: Placebo (1), Oseltamivir (0.4), -61%

All hospitalizations

- Overall: Placebo (5), Oseltamivir (2.5), -59%
- Healthy: Placebo (3), Oseltamivir (1.5), -62%
- At risk: Placebo (2), Oseltamivir (1), -50%

*P < .001 vs placebo

Epidemic and Pandemic Alert and Response

World Health Organization
Figure 1. Kaplan-Meier curve showing the effect of early oseltamivir treatment on time to discharge from hospital

- Based on 356 pts (94% Flu A)
- Median LOS: 4 vs 6 d (p<.0001)

Hospitalized Adults: Toronto Invasive Bacterial Diseases Network 1

- Prospective cohort of 322 adult patients with community-acquired influenza requiring hospital admission in Ontario, 2004-2006
- Laboratory-based surveillance
- 103 (32%) treated with oseltamivir
- In-hospital mortality rate 35/327 (10.7%)
- NAI therapy associated with reduced mortality
  - Odds ratio 0.21 (95% CI, 0.06 - 0.80)

Oseltamivir Cohort Studies: Effect on Major Outcomes

- ~50% reduction in pneumonia in treated children (Barr et al. Curr Med Res Opin. 2007;23:523-531)
The Second WHO Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus

Antalya, Turkey, 19-21 March 2007

Summary of the Second WHO Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus

BACKGROUND AND OBJECTIVES

In May 2005, WHO convened the 1st Meeting on Case Management and Research on Human Influenza A/H5 in Hanoi, Viet Nam in May 2005. Despite increased awareness at community level and efforts made by the agricultural and human health sectors to contain the disease, the number of cases of influenza A (H5N1) virus infection in humans, who die from this infection, is still high. The World Health Organization is now convening a second meeting of experienced clinical practitioners from hospitals that have treated H5N1 patients.

The objectives of the meeting:

- Summarize clinical manifestations, laboratory findings, and pathological findings associated with influenza A (H5N1) virus infections in humans,
- Summarize current knowledge about the management of H5N1 infections,
- Identify important gaps for additional research in the knowledge about, and treatment of, H5N1 infections.
Oseltamivir Therapy in H5N1, Indonesia and Turkey, 2005-6

<table>
<thead>
<tr>
<th>Oseltamivir treatment</th>
<th>No. patients</th>
<th>No. (%) survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes*</td>
<td>10</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>2 (33%)</td>
</tr>
</tbody>
</table>

*In 10 oseltamivir-treated patients, the median time from illness onset to treatment was 5 days in 6 survivors compared to 9.5 days in 4 fatal cases.

Omer et al. NEJM 2007; Kandun et al. NEJM 2007
## Oseltamivir in H5N1 Disease (1)

<table>
<thead>
<tr>
<th>Countries</th>
<th>Presumed clade</th>
<th>Survivors/treated (%)</th>
<th>Survivors/not treated (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnam (southern), Thailand, Cambodia</td>
<td>1</td>
<td>8/27 (30%)</td>
<td>2/14 (14%)</td>
<td>P = NS</td>
</tr>
<tr>
<td>Indonesia</td>
<td>2.1</td>
<td>19/65 (29%)</td>
<td>1/29 (4%)</td>
<td>P = 0.005</td>
</tr>
<tr>
<td>Turkey</td>
<td>2.2</td>
<td>4/7 (57%)</td>
<td>0/1</td>
<td></td>
</tr>
</tbody>
</table>
Pharyngeal Viral Loads during Oseltamivir Treatment of H5N1

de Jong et al. NEJM 353:25, 2005
Resistance of H5N1 Viruses to Adamantanes

Clade 1
Resistant
Asn-31

Clade 2-1
~80% resistant
Asn-31 or Ala-27

Clade 2-2
Sensitive
Ser-31

Clade 2-3
Sensitive
Ser-31

A Klimov, US CDC

Asn-31 or Ala-27
## NA Inhibitor Resistance Profiles

<table>
<thead>
<tr>
<th>NA mutation</th>
<th>NA type/ subtype</th>
<th>Susceptibility by NAI assay (fold Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Oselt</td>
</tr>
<tr>
<td>E119V</td>
<td>A/N2</td>
<td>R (&gt;50)</td>
</tr>
<tr>
<td>R292K</td>
<td>A/N2</td>
<td>R (&gt;1000)</td>
</tr>
<tr>
<td>H274Y</td>
<td>A/N1</td>
<td>R (&gt;700)</td>
</tr>
<tr>
<td>N294S</td>
<td>A/N1</td>
<td>I (12-25)</td>
</tr>
</tbody>
</table>


**Epidemic and Pandemic Alert and Response**
Influenza Antivirals in H5N1: **Summary**

- M2 inhibitors alone are not a reliable intervention due to antiviral resistance in many H5N1 viruses and rapid emergence during treatment.

- Optimal oseltamivir dose regimen is uncertain.

- Oseltamivir-resistant variants (H274Y) emerge during treatment and may compromise efficacy.
  - Variants appear less fit but associated with fatalities.
  - Retain susceptibility to zanamivir.

- Needs exist for alternative agents and study of antiviral combinations.
Clinical management of human infection with avian influenza A (H5N1) virus

15 August 2007

- Full text - English [pdf 119kb]
- WHO H5N1 Clinical Case Summary Form [pdf 41kb]
- Supplementary WHO H5N1 Clinical Case Data [pdf 22kb]

This document replaces the WHO interim guidelines on clinical management of humans infected by influenza A(H5N1) published in March 2004

The present advice is applicable for the current situation with sporadic A(H5N1) virus human infection. As more data become available or if the disease patterns change, this advice will be modified as appropriate.
Clinical Management of Human A(H5N1) Virus Infections - 1

- Oseltamivir is the primary recommended antiviral treatment.
  - Reduces A(H5N1) virus infection-associated mortality if used in the early stages of the disease
  - Treatment is also warranted at a later stage of illness.

- Consider modified regimens, especially in patients with pneumonia or progressive disease, on a case by case basis:
  - 2-fold higher dosage
  - Longer duration to 10 days
  - Combination therapy with amantadine or rimantadine (in countries where A(H5N1) viruses are likely to be susceptible to adamantanes).
Survival of mice inoculated with rg VN-1203/04

**Single-drug therapy**

- **AM 30**
- **AM 15**
- **OS 10**
- **AS 1.5**
- **Control**

**Combination therapy**

- **AM 30 + OS 10**
- **AM 15 + OS 10**
- **Control**

*Ilyushina et al. Antiviral Therapy 12:363, 2007*
Corticosteroids should not be used routinely.
- Consider for septic shock with suspected adrenal insufficiency requiring vasopressors.
- Prolonged or high dose corticosteroids → serious AEs including opportunistic infection.

Antibiotic chemoprophylaxis should not be used.
- Initial antibiotic treatment appropriate for community-acquired pneumonia
- Microbiologic studies to guide antibiotic usage for suspected bacterial co-infection.

Monitor oxygen saturation + correct hypoxemia
- At presentation and during care (e.g. pulse oximetry, ABGs)

Use evidence-based guidelines for sepsis-associated ARDS
- Lung protective mechanical ventilation strategies.
### Clinical Management of Human A(H5N1) Virus Infections – Summary 1

<table>
<thead>
<tr>
<th>Recommended Modalities</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antivirals</strong></td>
<td>Oseltamivir is the primary treatment of choice. Consider modified regimens (see text).</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>Empiric treatment for community-acquired pneumonia (CAP) per published guidelines pending microbiologic results (e.g. 2-3 days);</td>
</tr>
<tr>
<td><strong>Oxygen therapy</strong></td>
<td>Monitor oxygen saturation and maintain SaO&lt;sub&gt;2&lt;/sub&gt; over 90% with nasal cannulae or face mask.</td>
</tr>
<tr>
<td><strong>IPPV</strong> (Invasive positive pressure ventilation)</td>
<td>Early intervention recommended for ARDS. Use lung protective, low tidal volume, low pressure ventilation to prevent barotrauma and conservative fluid management.</td>
</tr>
<tr>
<td><strong>Low dose systemic corticosteroids</strong></td>
<td>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).</td>
</tr>
<tr>
<td><strong>NSAIDs, antipyretics</strong></td>
<td>Paracetamol given orally or by suppository will generally be sufficient in most cases as an anti-pyretic treatment.</td>
</tr>
<tr>
<td><strong>Infection control</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>
# Clinical Management of Human A(H5N1) Virus Infections – Summary 2

<table>
<thead>
<tr>
<th>Modalities NOT Recommended</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adamantane monotherapy</strong></td>
<td>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).</td>
</tr>
<tr>
<td><strong>Antibiotic chemoprophylaxis</strong></td>
<td>Not recommended</td>
</tr>
<tr>
<td><strong>NPPV</strong> (Non-invasive positive pressure ventilation)</td>
<td>Generally not recommended (see text).</td>
</tr>
<tr>
<td><strong>Systemic corticosteroids</strong></td>
<td>Moderate to high doses of unproven benefit and potentially harmful: not recommended;</td>
</tr>
<tr>
<td><strong>Salicylates</strong></td>
<td>Avoid administration of salicylates (such as aspirin and aspirin containing products) in children and young adults (&lt;18 years old) because of the risk of Reye Syndrome.</td>
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</tbody>
</table>
### WHO H5N1 Clinical Case Summary Form

Please fax or email to WHO Global Influenza Programme- Fax +41 22 7914878 email influenza_data@who.int

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#### Section A- Submitter Information

<table>
<thead>
<tr>
<th>Name of submitter</th>
<th>Date of submission (dd/mm/yy)</th>
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<thead>
<tr>
<th>Email/Tel. number</th>
<th>enter your email address and/or tel. n° here</th>
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#### Section B- Patient Information

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Patient Initials</th>
<th>Patient’s initials</th>
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<table>
<thead>
<tr>
<th>Country of residence</th>
<th>Place/city of residence</th>
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<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex (check one)</th>
<th>Male</th>
<th>Female</th>
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<table>
<thead>
<tr>
<th>Date of illness onset (dd/mm/yy)</th>
<th>Patient weight (kg)</th>
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#### Section C- Patient Outcome

<table>
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<th>Alive at discharge</th>
<th>Date of discharge (dd/mm/yy)</th>
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<table>
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<tr>
<th>Died</th>
<th>Date of death (dd/mm/yy)</th>
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WHO Human H5N1 Clinical - Treatment Outcomes Database

- Current WHO H5N1 database has only basic demographic, risk factor, and overall outcomes information.
  - No data on clinical presentation/course or treatment

- Need integrated database for timely risk assessments
  - Changes in clinical presentation or course
  - Prognostic features
  - Treatment effectiveness and safety
    - Antivirals, other modalities

- Proposed database
  - Retrospective and prospective data collection
  - Access restricted to WHO; no release of individual patient data
  - Regular updates on web or in WER
Mission Statement: The mission of the Southeast Asia Influenza Clinical Research Network (Network) is to advance the scientific knowledge and management of human influenza through integrated, collaborative clinical research.

Description of the Network: The Southeast Asia Influenza Clinical Research Network [SEA ICRN] is a multi-lateral, collaborative partnership of hospitals and institutions in Indonesia, Thailand, United Kingdom, United States, and Vietnam. International partners currently include US National Institute of Allergy and Infectious Diseases, Oxford University, Wellcome Trust, and WHO.
 SEA Influenza Clinical Research Network

- Collaborative partnership of hospitals and institutions in Indonesia, Thailand, Viet Nam, UK, and USA.

- International partners currently include US NIAID, Oxford University, Wellcome Trust, and WHO.

- Mission of the Network is to advance scientific knowledge and management of human influenza through integrated clinical research with the aim of improving patient care and human health.
SEA Influenza Clinical Research Network Principles

- Develop knowledge on influenza pathogenesis, therapeutics, diagnostics, and prevention through protocol-based studies

- Strong emphasis on building independent research capacity of investigators/institutions

- Compliance with international standards for clinical research

- Prompt sharing of data and isolates with approval of relevant national authorities

- Publication guidelines that are inclusive
SEA Influenza Clinical Research Network

Collaborators:
NIAID Division of Clinical Research
Oxford University
Wellcome Trust
WHO
SEA ICRN Antiviral Studies

- Loading-dose oseltamivir with probenicid (phase 1)
- Double-blind, randomized, controlled trial to compare standard and higher dose (150 mg bid) oseltamivir therapy
  - Avian influenza or severe human influenza
- IV zanamivir and oseltamivir interaction (phase 1)*
- IV zanamivir/peramivir in avian influenza (phase 2)*
- Long-term neuraminidase inhibitor prophylaxis*

*Protocol under development
SEA ICRN Diagnostic Laboratories

- 11 hospital sites in Network -
  - All have rapid antigen testing (Quickvue™)

- 5 RT-PCR diagnostic sites
  - Queen Siriraj, Bangkok; NIH-RD, Jakarta; Nat Pediatr Hosp, Hanoi; Nat Inst Infect Trop Dis, Hanoi; Oxford Univ Clin Res Unit-Hosp Trop Dis, HCMC
  - Responsible for testing, processing, and storage of specimens.
  - Culture capabilities: 2 BSL-3 laboratories (OUCRU-HTD, Queen Siriraj) and 1 BSL-2 (NIH-RD)
**SEA ICRN Reference Laboratories**

- **Virology Reference Laboratory = OUCRU-HTD**
  - Centralized measurement of virology endpoints
  - Qualitative and quantitative RT-PCR
  - Antiviral resistance testing: neuraminidase inhibition assay, sequencing
  - Training of other laboratory sites

- **Pharmacokinetics Reference Laboratory = OUCRU-Mahidol Univ, Bangkok**

- **Host Genetics Reference Laboratory – under discussion**

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Epidemic and Pandemic Alert and Response

World Health Organization
WHO Interim Protocol: Rapid operations to contain the initial emergence of pandemic influenza

Updated May 2007

English - [pdf 327kb]

Changes to this version of the protocol
This document replaces previous versions of the protocol. In brief, key changes include:

- More emphasis on rapid containment and less on rapid response (which is covered elsewhere).
- An expanded discussion of the decision-making process.
- Refinement of the containment strategy emphasizing the localized geographical approach and describing the key activities for Containment and Buffer Zones.
- A proposed approach for estimating the duration of a containment operation.
- New or updated annexes on ethical issues, non-pharmaceutical interventions, surveillance and laboratory preparedness will be added shortly.

The protocol will be updated and revised as new information becomes available and more detailed guidance and tools are developed.
WHO Antiviral Stockpiles

- For Rapid Response and Containment – 3M*
  - Virtual stockpile- 1.5 M in Switzerland, 1.5 M in USA
  - Uniquely reserved for RRC operation

- For under-resourced countries – 2M*
  - Physical stockpile in Geneva, will expire in 2011)
  - To be distributed to Member States through Regional Offices

- WHO – coordinated international stockpiles
  - Japan-ASEAN, US, and other international stockpiles

* Treatment courses – 10 capsules of 75 mg oseltamivir phosphate
SOPs for WHO Antiviral Stockpiles

- **RRC (3M)**
  - SOP as Annex to RRC protocol
  - MS to request deployment
  - Deploy, not deploy or continue preparatory actions to be decided based on technical, operational and legal/policy information

- **For developing countries (2M)**
  - ROs to work with MS on risk / needs assessment
    - Control outbreaks caused by human and non-human influenza,
    - Control severe influenza epidemics,
    - Pandemic preparedness

- **Draft - WHO SOP for utilization of collaborating international antiviral stockpiles in a pandemic influenza containment strategy**
  - First coordination meeting held in December 2006

Epidemic and Pandemic Alert and Response