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# WHO Rapid Advice Guidelines for pharmacological management of sporadic human infection with avian influenza A (H5N1) virus

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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.

## Introduction

Highly pathogenic avian influenza A (H5N1) virus causes rapid and fatal illness in many bird populations. Of all influenza A viruses circulating in birds, H5N1 is currently of greatest public-health concern because it has caused severe and fatal human infections with mortality ranging from 33% to over 50% since the first known outbreak in Hong Kong in 1997.<sup>1</sup> The spread of H5N1 in poultry and wild birds in many countries has raised concerns about the increased risk of transmission of H5N1 virus to human beings.

Clinicians, public-health officers, and policymakers worldwide are faced with uncertainty about the best pharmacological management options of human beings infected with H5N1 virus. In view of its mandate to provide international advice on public-health questions, WHO published interim clinical guidelines for the use of antivirals for H5N1 infection in February, 2004.<sup>2</sup> These interim guidelines were updated in 2005 following an expert consultation<sup>1</sup> and there has been general international agreement to stockpile antivirals for potential use during an influenza pandemic.<sup>3-5</sup>

To provide evidence-based guidelines,<sup>6</sup> WHO convened a rapid advice panel in March, 2006, on the pharmacological management of human infection with avian influenza A (H5N1) virus. Because of their public-health implications, the full guidelines were initially made available on the internet by WHO on May 20, 2006.<sup>7</sup> The guidelines are based on the current situation with sporadic H5N1 human infections and household clusters, and do not apply to a pandemic scenario.

## Methods

The methods used to develop these guidelines adhered to the suggested principles for developing transparent, evidence-based WHO guidelines.<sup>8,9</sup> The decision to convene an international rapid advice guidelines panel for the treatment and chemoprophylaxis of H5N1 virus infection was made in January, 2006; review and preparation of the evidence summaries began in February, 2006; and the panel met on March 28 and 29, 2006.

## Group composition

The group developing the guidelines included clinicians with experience in treating H5N1 patients, infectious disease experts, influenza specialists, basic scientists, public-health officers, and methodologists as shown in panel 1.<sup>10</sup>

## Formulation of questions and rating the importance of outcomes

Questions were initially identified by clinicians managing patients with H5N1 infections and refined by the panel members. An evidence profile was prepared for each question using the Grading Recommendations Assessment, Development and Evaluation (GRADE) approach.<sup>11</sup> Eight potentially important outcomes were initially identified by two reviewers (MK, ADO). This list was circulated to the panel chair (HJS), WHO staff, and the scientific reviewers by email for independent scoring of the relative importance of each outcome. Scores were rated on a scale from 1 to 9: a rating of 7-9 indicated the outcome was critical for a decision or

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recommendation, 4–6 indicated that it was important, and 1–3 indicated that it was not important. Because the relative importance of some outcomes depended on whether a drug was being used for treatment or chemoprophylaxis, these two methods were considered separately. For all ratings, the means of the panel members' ratings established the relative importance of the outcomes.

The Cochrane Consumers network was consulted and this generated four responses, but the ratings did not differ substantially from those of the panel.

### Preparation of evidence profiles

A group of independent scientific reviewers (panel 1) with expertise in the conduct of systematic reviews of the literature and preparation of evidence summaries compiled the evidence (MK, RB, LS, GEV, ADO). The clinical and public-health questions covered by the guidelines were developed from suggestions by clinicians and public-health officers and are listed in panel 2. The underlying considerations included the selection of appropriate clinical outcomes, target populations, and dosing regimens for treatment and chemoprophylaxis.

### Evidence summaries and quality ratings

The evidence summaries were based on systematic reviews supplemented with recent randomised trials (published in 2005 or 2006) for the treatment and chemoprophylaxis of any influenza virus infection; and case series, animal, and in-vitro studies for the treatment or chemoprophylaxis of H5N1 virus infection. The search strategy is described elsewhere.<sup>7</sup> Original controlled studies not included in the systematic reviews and published before 2005 or after February, 2006, were not included. However, panel members were asked to identify relevant published studies that became available between February, 2006, and the

meeting date and these were considered if provided in full to the panel 2 weeks before the meeting. Adverse event data from trials were supplemented by reports from the Uppsala Monitoring Centre and from manufacturers' reports.

Evidence summaries were created using the GRADE approach<sup>11</sup> with GRADE profiler software (v1.12, <http://www.gradeworkinggroup.org>). Evidence is classified as "high", "moderate", "low", or "very low" quality, based on its methodological characteristics for a specific health-care problem. Assessments of the quality of evidence for each important outcome took into account the study design, limitations of the studies, consistency of the evidence across studies, the directness of the evidence, and the precision of the estimate. Based on the GRADE system the overall quality of evidence is determined by the lowest quality for critical outcomes, and thus the overall quality of evidence was very low for each of the clinical questions.

### Panel meeting

One meeting of the guideline panel, chaired by a clinical epidemiologist with experience in respiratory medicine, was held to discuss the results of the evidence review and to develop recommendations. WHO was represented at the group's meeting and provided scientific input and guidance. The panel agreed recommendations would be based on a consensus of the panel and that voting would be used if agreement could not be reached. Panel members declared their potential conflicts of interest according to WHO rules in writing before and verbally at the meeting as described elsewhere.<sup>7,12</sup>

### Balance of benefits, harms, burden, and cost and developing recommendations

Formulating the recommendations included explicit consideration of the quality of evidence, benefits, harms, burdens, costs, and values. A high value was placed on antiviral resistance to specific drugs for most questions. The panel considered several different patient and exposure groups and assessed the balance of benefits and drawbacks of interventions for each group. Recommendations are classified as "strong" or "weak" recommendations, as recommended by the GRADE working group.<sup>11,13</sup> Agreement on the type and wording of the recommendations was also reached during the panel meeting by consensus. However, two recommendations required voting to decide the strength of the recommendation or whether the recommendation should be given at all.

### Results

Evidence profiles were prepared for each of the clinical questions shown in panel 2 and are available from the WHO website.<sup>7</sup> At present, no controlled clinical trial has evaluated treatment or chemoprophylaxis of human H5N1 infections. Most of the evidence used to make

#### Panel 1: Guideline panel composition for H5N1 infection rapid advice

##### Panel (voting)

- Seven clinical experts or clinicians treating patients with H5N1 virus infection
- Four virologists including influenza epidemiologists and clinical trialists
- Two methodologists with experience preparing systematic reviews and clinical practice guidelines

##### Review team

- Five reviewers including two methodologists with experience using the Grading Recommendations, Assessment, Development and Evaluation (GRADE) approach, an infectious disease specialist, and an epidemiologist with experience reviewing case studies, animal and in-vitro studies (for severe acute respiratory syndrome)

##### WHO representation

- Virologists, public-health physicians and methodologists (including the group leader)

##### Other stakeholders

- A UNICEF representative

**Panel 2: Clinical questions**

- Should oseltamivir be used for treatment or prophylaxis?
- Should zanamivir be used for treatment or prophylaxis?
- Should amantadine or rimantadine be used for treatment or prophylaxis?
- Should ribavirin be used for treatment?
- Should corticosteroids, immunoglobulin, or interferon be used for treatment?
- Should broad-spectrum antibiotics be used for the prevention of secondary pneumonia?

recommendations is derived from studies of infection with human influenza viruses during seasonal epidemics. These studies mainly included adults who were treated early in the course of uncomplicated illness. To date, many patients with H5N1 infection have been children who have presented late in the course of illness and were hospitalised after the onset of severe pneumonic disease. The evidence for the possible benefits of treatment in patients with H5N1

disease was considered indirect, because the populations, viruses, and possibly even drug effects were different. Therefore, the rating of quality of evidence—ie, confidence in the estimates of effect—for all important efficacy outcomes was lowered by two quality levels. The rate and severity of adverse effects, however, were judged to be similar. Sparse data lowered the quality of evidence for some of the other critical outcomes (eg, lower respiratory tract infections) by another level.

**Treatment**

For treatment of H5N1 infection, the final list of critical outcomes comprised mortality, duration of hospitalisation, incidence of lower respiratory tract complications, antiviral drug resistance existing before treatment, and serious adverse events. The panel placed a low value on the potential of developing resistance during therapy, adverse outcomes, and cost. In judging strength of the recommendations, the panel considered the high case fatality and the paucity of possible pharmacological alternatives in all of the recommendations.

| Duration           |   | Age groups (years)   |  |  |                                     |                                     |
|--------------------|---|--|--|--|-------------------------------------|-------------------------------------|
|                    |   | 1-6  | 7-9  | 10-12  | 13-64                               | ≥65                                 |
| <b>Oseltamivir</b> |   |  |  |  |                                     |                                     |
| Treatment          | 5 days  | Weight adjusted doses:<br>• 30 mg twice daily for ≤15 kg<br>• 45 mg twice daily for >15-23 kg<br>• 60 mg twice daily for >23-40 kg<br>• 75 mg twice daily for >40 kg | Weight adjusted doses:<br>• 30 mg twice daily for ≤15 kg<br>• 45 mg twice daily for >15-23 kg<br>• 60 mg twice daily for >23-40 kg<br>• 75 mg twice daily for >40 kg | Weight adjusted doses:<br>• 30 mg twice daily for ≤15 kg<br>• 45 mg twice daily for >15-23 kg<br>• 60 mg twice daily for >23-40 kg<br>• 75 mg twice daily for >40 kg | 75 mg twice daily                   | 75 mg twice daily                   |
| Prophylaxis        | Begin as soon as exposure identified and continue for 7-10 days after last known exposure | Dose varies by child's weight as for treatment but administered once daily   | Dose varies by child's weight as for treatment but administered once daily   | Dose varies by child's weight as for treatment but administered once daily   | 75 mg/day                           | 75 mg/day                           |
| <b>Zanamivir</b>   |   |  |  |  |                                     |                                     |
| Treatment          | 5 days  | Not licensed for use   | 10 mg (two inhalations) twice daily  | 10 mg (two inhalations) twice daily  | 10 mg (two inhalations) twice daily | 10 mg (two inhalations) twice daily |
| Prophylaxis        | Begin as soon as exposure identified and continue for 7-10 days after last known exposure | 1-4 years: NA; 5-6 years: 10 mg (two inhalations) once daily   | 10 mg (two inhalations) once daily   | 10 mg (two inhalations) once daily   | 10 mg (two inhalations) once daily  | 10 mg (two inhalations) once daily  |
| <b>Amantadine</b>  |   |  |  |  |                                     |                                     |
| Treatment          | 5 days  | 5 mg/kg per day up to 150 mg in two divided doses  | 5 mg/kg/day up to 150 mg in two divided doses  | 100 mg twice daily   | 100 mg twice daily                  | ≤100 mg/day                         |
| Prophylaxis        | Begin as soon as exposure identified and continue for 7-10 days after last known exposure | 5 mg/kg per day up to 150 mg in two divided doses <sup>7</sup>   | 5 mg/kg per day up to 150 mg in two divided doses  | 100 mg twice daily   | 100 mg twice daily                  | ≤100 mg/day                         |
| <b>Rimantadine</b> |   |  |  |  |                                     |                                     |
| Treatment          | 5 days  | Not licensed for use   | Not licensed for use   | Not licensed for use   | 100 mg twice daily                  | 100 mg/day                          |
| Prophylaxis        | Begin as soon as exposure identified and continue for 7 days after last known exposure    | 5 mg/kg per day up to 150 mg in two divided doses <sup>7</sup>   | 5 mg/kg per day up to 150 mg in two divided doses <sup>7</sup>   | 100 mg twice daily   | 100 mg twice daily                  | 100 mg/day                          |

NA=not applicable.

**Table:** The recommended dose and duration of treatment and chemoprophylaxis for management of human infection of avian influenza A (H5N1) virus

*Should H5N1 patients receive treatment with oseltamivir?*

Direct data came from the most recent case series that described 37 H5N1 patients, of whom 25 were treated with oseltamivir (19 deaths) and 12 patients did not receive oseltamivir (nine deaths).<sup>1</sup> Treatment regimens differed across these patients, beginning between days 4 to 22 of the illness. Three cases of resistance to oseltamivir developing after treatment of H5N1 patients have been published, one of whom received a prophylaxis dose.<sup>14,15</sup>

In five similarly designed studies in otherwise healthy adults with seasonal influenza (n=1644), lower respiratory tract complications (including pneumonia) were reduced (relative risk [RR] 0.15, 95% CI 0.03–0.69) but there were only 11 events.<sup>16</sup> This analysis also reported a significant reduction (RR 0.40, 95% CI 0.18–0.88) in all-cause hospitalisations within 30 days of diagnosis in oseltamivir recipients compared with placebo. Rare cases of anaphylaxis and serious skin reactions were reported during post-marketing experience, and data from regulatory trials reported nausea and vomiting as the most frequent adverse event.<sup>17,18</sup>

Even allowing for the sparse direct evidence, most panel members judged that oseltamivir should be used as treatment and made a strong recommendation (recommendation 1; see below) following a vote (one abstention and one vote for a weak recommendation out of 13 panel members). It was noted that even small relative risk reductions could lead to large net benefit in mortality. Recommended treatment regimens are shown in the table. There were no clinical data to recommend higher drug doses or more prolonged treatment, but the panel noted that two-fold higher doses did not provide greater antiviral or clinical effects in adults with uncomplicated seasonal influenza.<sup>19,20</sup>

*Should H5N1 patients receive treatment with zanamivir?*

Direct evidence for the use of zanamivir in H5N1 patients currently does not exist. Zanamivir is active in vitro and in vivo against H5N1 viruses including the oseltamivir-resistant H5N1 virus that contains the H274Y mutation.<sup>14</sup> Indirect evidence derives from zanamivir studies for treatment of seasonal influenza, but there are too few events in these studies to provide evidence of a benefit in terms of mortality or duration of hospitalisation. Lower respiratory tract complications were not significantly reduced (odds ratio [OR] 0.83, 95% CI 0.24–2.26) in three trials (n=2299 patients with 46 events) that described this outcome in otherwise healthy adults with seasonal influenza.<sup>21–24</sup> An increased incidence of bronchospasm was reported particularly for patients with airway disease.<sup>25</sup> No information on resistance of H5N1 viruses to zanamivir exists.

There was uncertainty about the adequacy of drug delivery with the commercial formulation of inhaled zanamivir in patients with viral pneumonia or possible extra-pulmonary viral spread. Although there is limited

evidence of a possible net clinical benefit of inhaled zanamivir, because H5N1 infection is associated with a high case fatality the panel made a weak recommendation for the use of zanamivir in H5N1 patients (recommendation 2; table).

*Should H5N1 patients receive treatment with M2 ion channel inhibitors?*

No controlled clinical trial has evaluated amantadine or rimantadine for the treatment of H5N1 infection, although there are published case study data for ten patients in whom amantadine was used as treatment.<sup>1</sup> All four of the patients who received amantadine within 5 days of symptom onset survived, and two of the six patients who were treated after 5 days of illness survived. Six of eight patients who did not receive amantadine survived, but no conclusions can be drawn from these uncontrolled clinical data.

There is insufficient evidence in the studies on seasonal influenza to evaluate the effects of amantadine or rimantadine on mortality or duration of hospitalisation. A Cochrane review of M2 inhibitor treatment and chemoprophylaxis reports adverse effects (gastro-intestinal and central nervous system) with both agents.<sup>26</sup> Moderate to severe central nervous system side-effects appear to be more frequent with amantadine.<sup>27,28</sup>

The development of antiviral resistance during treatment is a frequent problem with amantadine and rimantadine. Primary (pretreatment) resistance appears to be common in clade 1 H5N1 virus isolated from human beings in Thailand, Vietnam, and Cambodia,<sup>14,15,29</sup> and resistance has occurred in some clade 2 H5N1 viruses, particularly those isolated in Indonesia.<sup>14,15,29</sup> Resistance has been found in H1N1 viruses from the pre-amantadine era.<sup>30</sup>

Thus, amantadine or rimantadine do not offer greater net clinical benefit as first-line agents in the treatment of H5N1 infection compared with the neuraminidase inhibitors, and drug resistance is a major limitation. This assessment of possible net benefit under certain circumstances led to conditional and weak recommendations only when neuraminidase inhibitors are not available (recommendations 4 and 6). The recommendation includes considerations of possible development of drug resistance and the incidence of toxic effects.

*Should H5N1 patients receive combination treatment of neuraminidase inhibitors and M2 ion channel inhibitors?*

Insufficient data exist to assess the possible benefit of combination treatment of neuraminidase inhibitors and M2 ion channel inhibitors on mortality, duration of hospitalisation, complications, or resistance emergence in either seasonal influenza or H5N1 infection. Without convincing evidence of clinical benefit, combination therapy might be used only in the context of prospective

data collection (recommendation 7) at the same time as doses described for monotherapy (table).

### Chemoprophylaxis

For chemoprophylaxis, the critical outcomes were influenza cases, outbreak control, drug resistance, and serious adverse events. The panel developed risk categorisations for exposure to assist countries in prioritising use of antivirals where availability is limited and to avoid chemoprophylaxis of individuals not considered at risk (panel 3).

#### *Should oseltamivir be used for the chemoprophylaxis of H5N1 infection?*

Although oseltamivir has been used in the field for chemoprophylaxis of H5N1 infection, there are no controlled human studies. For seasonal influenza, two systematic reviews and health technology assessments have reported effects of oseltamivir (for 1–6 weeks) as chemoprophylaxis.<sup>21,31</sup> Three randomised controlled trials of the effect of oral oseltamivir on post-exposure influenza incidence found large reductions in laboratory-confirmed influenza (RR reductions of 50% to 89%).<sup>21</sup> No differences in prophylactic efficacy were found between 75 mg once-daily and 75 mg twice-daily dosing in seasonal influenza in adults. Two trials found that oseltamivir was also effective for chemoprophylaxis of household contacts of influenza cases, when taken for 7–10 days after exposure to an index case.<sup>32,33</sup>

Overall the evidence for pharmacological chemoprophylaxis of H5N1 infection with oseltamivir was rated as very low quality and indirect. However, oseltamivir has shown large effects on influenza incidence as post-exposure chemoprophylaxis for seasonal influenza and is active as pre-exposure prophylaxis in animal models of H5N1 infection.<sup>21</sup> Oseltamivir might effectively provide an important reduction in H5N1 virus transmission. The panel, therefore, recommended that chemoprophylaxis courses should begin as soon as possible after exposure status is known and be used continuously for 7–10 days after the last known exposure (recommendations 8 to 11), but the strength of the recommendation differs by risk group.

#### *Should zanamivir be used for the chemoprophylaxis of H5N1 infection?*

Two randomised controlled trials investigating the effect of inhaled zanamivir on post-exposure influenza incidence in healthy adults found large reductions in laboratory-confirmed seasonal influenza (OR 0.19, 95% CI 0.09–0.38).<sup>31</sup> A similar effect was seen in two trials of seasonal chemoprophylaxis.<sup>31</sup> Trials assessing the combination of both intranasal (not commercially available) and inhaled zanamivir in healthy adults,<sup>18</sup> and in elderly and high-risk adults showed no additive benefit for any critical outcome.<sup>31</sup>

### Panel 3: Risk stratification for the provision of chemoprophylaxis of H5N1 virus infection

Antiviral chemoprophylaxis should generally be considered according to the risk stratification described below. It is based on observational data for reported cases of human infection with avian influenza A (H5N1) virus and on high quality data from studies of seasonal human influenza virus infection.

#### High-risk exposure groups are currently defined as:

- Household or close family contacts\* of a strongly suspected or confirmed H5N1 patient, because of potential exposure to a common environmental or poultry source as well as exposure to the index case

#### Moderate-risk exposure groups are currently defined as:

- Individuals with unprotected and very close direct exposure† to sick or dead H5N1 infected animals or to particular poultry that have been implicated directly in human cases
- Persons involved in handling sick animals or decontaminating known infected animals or environments, if personal protective equipment might not have been used properly
- Health-care personnel in close contact with strongly suspected or confirmed H5N1 patients, for example during intubation or performing tracheal suctioning, or delivering nebulised drugs, or handling inadequately screened/sealed body fluids without any, or with insufficient, personal protective equipment. This also includes laboratory personnel who might have an unprotected exposure to virus-containing samples‡

#### Low-risk exposure groups are currently defined as:

- Health-care workers not in close contact (distance greater than 1 m or no direct contact with infectious material) with a strongly suspected or confirmed H5N1 patient
- Health-care workers who used appropriate personal protective equipment during exposure to H5N1 patients
- Personnel involved in culling non-infected or likely non-infected animal populations to prevent viral spread
- Personnel involved in handling sick animals or decontaminating known infected animals or environments, who used proper personal protective equipment

In the absence of sustained human-to-human transmission, the general population is currently not considered at risk.

\*A close contact may be defined as an individual sharing a household with, or remaining unprotected while within speaking distance (<1 m) of, or in the care of, a patient with confirmed or strongly suspected H5N1 infection. †Examples of high-risk exposure based on confirmed transmission to humans include: unprotected exposure to infected animal products such as consumption of blood from H5N1 infected ducks, preparation of food from infected animals (eg, plucking feathers), or prolonged exposure to infected birds in a confined space, such as playing with pets. ‡This definition of moderate risk is based on very few cases recognised under these situations to date. Because circumstances could change rapidly, it would be reasonable to consider the moderate and high-risk groups together for prophylaxis decisions. If a particular patient has been implicated in possible human-to-human transmission, then these examples of exposures could be defined as high risk.

Although the evidence for chemoprophylaxis of H5N1 infection with zanamivir is of very low quality and indirect, trials in seasonal influenza<sup>21</sup> have shown quite large reductions in the incidence of influenza cases. On the basis of extrapolation from these trials, zanamivir might provide reductions in cases of H5N1 infection (recommendations 12 to 15).

*Should M2 ion channel inhibitors be used for the chemoprophylaxis of H5N1 infection?*

No direct data on the use of M2 ion channel inhibitors in human H5N1 virus infection exist.

11 randomised controlled trials investigating the effect of oral amantadine on seasonal influenza A incidence in healthy adults found large reductions in laboratory-confirmed influenza A (RR reductions of 61%, 95% CI 35–76).<sup>21</sup> Effects on mortality were not reported. High quality evidence for the use of amantadine as post-exposure chemoprophylaxis for H5N1 infection in any population does not exist.

The effect of oral rimantadine in reducing laboratory-confirmed cases of influenza A in healthy adults in three randomised placebo controlled trials was not significant (RR 0.28, 95% CI 0.08–1.08), but head to head trials against amantadine showed no difference between the two active treatments.<sup>21</sup> Overall, amantadine and rimantadine appear not to be of greater net clinical benefit as a first-line agent for chemoprophylaxis of H5N1 infection compared with the neuraminidase inhibitors. However, based on extrapolation from trials in seasonal influenza, amantadine and rimantadine might have net clinical benefit as a first-line agent for chemoprophylaxis of H5N1 infection when neuraminidase inhibitors are not available and the virus is known or likely to be susceptible (recommendations 17 and 21).

### Recommendations for treatment of patients with confirmed or strongly suspected infection with avian influenza A (H5N1) in a non-pandemic situation

#### Recommendation 1

In patients with confirmed or strongly suspected H5N1 infection, clinicians should administer oseltamivir treatment as soon as possible (strong recommendation, very low quality evidence).

#### Remarks

This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places relatively low values on adverse reactions, the development of resistance, and costs of treatment. Despite the lack of controlled treatment data for H5N1, this is a strong recommendation, in part, because there is a lack of known effective alternative pharmacological interventions at this time. The recommendation applies to adults, including pregnant women and children. Until further

information becomes available, the current treatment regimen for H5N1 is as recommended for early treatment of adults, special patient groups (eg, those with renal insufficiency), and children with seasonal influenza.

#### Recommendation 2

In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians might administer zanamivir (weak recommendation, very low quality evidence).

#### Remarks

This recommendation places a high value on the prevention of death in an illness with high case fatality. It places a relatively low value on adverse effects (including bronchospasm), the potential development of resistance, and costs of treatment. The bioavailability of zanamivir outside of the respiratory tract is lower than that of oseltamivir. Zanamivir might be active against some strains of oseltamivir-resistant H5N1 virus. The recommendation applies to adults, including pregnant women, and children. Use of zanamivir requires that patients are able to use the diskhaler device. Until further information becomes available, the current treatment regimen for H5N1 infection is the same as recommended for early treatment of adults and children with seasonal influenza.

Although the quality of evidence when considered on a continuum is lower for the use of zanamivir compared with oseltamivir, the overall quality of evidence in the four-category grading system is very low for both interventions.

#### Recommendation 3

If neuraminidase inhibitors are available, clinicians should not administer amantadine alone as a first-line treatment to patients with confirmed or strongly suspected human infection with avian influenza H5N1 (strong recommendation, very low quality evidence).

#### Remarks

Although recognising that the illness is severe, this recommendation places a high value on the potential development of resistance and avoiding adverse effects. This is a strong recommendation in part, because of the availability of other options for treatment that might be more effective.

#### Recommendation 4

If neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible, clinicians might administer amantadine as a first-line treatment to patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus (weak recommendation, very low quality evidence).

#### Remarks

This recommendation places a high value on the prevention of death in an illness with a high case fatality.

It places a relatively low value on adverse effects and the development of resistance in a situation without alternative pharmacological treatment. Until further information becomes available, the current treatment regimen for (H5N1) infection is the same as recommended for early treatment of adults and children with seasonal influenza. The use of amantadine should be guided by knowledge about local resistance patterns, and special consideration of the benefits and harms to patients at higher risk for adverse outcomes (eg, pregnant patients).

#### Recommendation 5

If neuraminidase inhibitors are available, clinicians should not administer rimantadine alone as a first-line treatment to patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus (strong recommendation, very low quality evidence).

#### Remarks

Although recognising that the illness is severe, this recommendation places a high value on the potential development of resistance and avoiding adverse effects. This is a strong recommendation in part, because of the availability of other options for treatment that might be more effective.

#### Recommendation 6

If neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible, clinicians might administer rimantadine as a first-line treatment to patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus (weak recommendation, very low quality evidence).

#### Remarks

This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places a relatively low value on adverse effects and the development of resistance. The use of rimantadine should be guided by knowledge about local antiviral resistance patterns, and special consideration of the benefits, harms, burdens, and cost in patients at higher risk for adverse outcomes. Rimantadine has generally a more favourable side-effect profile than amantadine.

#### Recommendation 7

If neuraminidase inhibitors are available and especially if the virus is known or likely to be susceptible, clinicians might administer a combination of neuraminidase inhibitor and M2 inhibitor to patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus (weak recommendation, very low quality evidence). This should only be done in the context of prospective data collection.

#### Remarks

This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places a relatively low value on adverse effects, the potential development of resistance, and costs associated with therapy. The use of combination therapy should be guided by knowledge about local antiviral resistance patterns under special consideration for the benefits and shortcomings in patients at higher risk for adverse outcomes. Combination therapy should only be done if detailed and standardised clinical and virological data collection is in place at the start of therapy (prospective data collection). Clinicians should carefully establish which patients (eg, severely ill patients) could receive combination therapy.

### Recommendations for chemoprophylaxis of avian influenza A (H5N1)

For antiviral chemoprophylaxis, the panel devised an exposure-based assessment of risk (panel 3) developed from observational data for reported cases of H5N1 infection. These categories of risk were based on expert interpretation of existing evidence of the current situation with sporadic H5N1 infections in the prepandemic era. Decisions to initiate antiviral chemoprophylaxis should generally be guided by this risk stratification and specific recommendations for chemoprophylaxis are shown below.

#### Recommendation 8

In high-risk exposure groups oseltamivir should be administered as chemoprophylaxis continuing for 7–10 days after the last known exposure (strong recommendation, very low quality evidence).

#### Remarks

This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance, and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and be used continuously for 7–10 days after last known exposure. Oseltamivir has been used for as long as 8 weeks for chemoprophylaxis of seasonal influenza. The dose of oseltamivir for H5N1 chemoprophylaxis should be that used in seasonal influenza. This recommendation also applies to pregnant women in the high-risk exposure group.

#### Recommendation 9

In moderate-risk exposure groups oseltamivir might be administered as chemoprophylaxis, continuing for 7–10 days after the last known exposure (weak recommendation, very low quality evidence).

#### Remarks

This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low



value on adverse effects, development of resistance, and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and be used continuously for 7–10 days after last known exposure. Oseltamivir has been used for as long as 8 weeks for chemoprophylaxis of seasonal influenza. The dose of oseltamivir for H5N1 chemoprophylaxis should be that used in seasonal influenza. This recommendation applies to pregnant women in the moderate-risk exposure group.

#### **Recommendation 10**

In low-risk exposure groups oseltamivir should probably not be administered for chemoprophylaxis (weak recommendation, very low quality of evidence).

#### *Remarks*

This recommendation places a high value on avoiding adverse effects and cost. It places a lower value on preventing the low risk of H5N1 disease.

#### **Recommendation 11**

Pregnant women in the low exposure risk groups should not receive oseltamivir for chemoprophylaxis (strong recommendation, very low quality of evidence).

#### *Remarks*

This recommendation places a high value on avoiding possible but uncertain harm associated with oseltamivir chemoprophylaxis during pregnancy. It places a lower value on preventing the low risk of H5N1 disease.

#### **Recommendation 12**

In high-risk exposure groups zanamivir should be administered as chemoprophylaxis continuing for 7–10 days after the last known exposure (strong recommendation, very low quality of evidence).

#### *Remarks*

This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance, and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and be used continuously for 7–10 days after last known exposure. The dose of zanamivir should be that used for the chemoprophylaxis of seasonal influenza. The bioavailability of zanamivir outside of the respiratory tract is lower than that of oseltamivir. Zanamivir might be active against some strains of oseltamivir-resistant H5N1 virus. Consequently, it might be a reasonable choice for health-care workers with a high-risk exposure to an oseltamivir-treated H5N1 patient. This recommendation also applies to pregnant women who have high-risk exposure.

#### **Recommendation 13**

In moderate-risk exposure groups, zanamivir might be administered as chemoprophylaxis continuing for

7–10 days after the last known exposure (weak recommendation, very low quality evidence).

#### *Remarks*

This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance, and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and be continued for 7–10 days after the last known exposure. The bioavailability of zanamivir outside of the respiratory tract is lower than that of oseltamivir. Zanamivir might be active against some strains of oseltamivir-resistant H5N1 virus. This recommendation also applies to pregnant women in the moderate-risk exposure group.

#### **Recommendation 14**

In low-risk exposure groups, zanamivir should probably not be administered for chemoprophylaxis (weak recommendation, very low quality of evidence).

#### *Remarks*

This recommendation places a high value on avoiding adverse effects, possible development of resistance, and cost. It places a lower value on preventing the low risk of H5N1 disease.

#### **Recommendation 15**

Pregnant women in the low-risk exposure group should not receive zanamivir for chemoprophylaxis (strong recommendation, very low quality of evidence).

#### *Remarks*

This recommendation places a high value on avoiding possible but uncertain harm associated with zanamivir during pregnancy. It places a lower value on preventing the low risk of H5N1 disease.

#### **Recommendation 16**

If the virus is known or likely to be an M2 inhibitor-resistant H5N1 virus, amantadine should not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality evidence).

#### *Remarks*

This recommendation places a high value on avoiding adverse effects in a situation when no drug efficacy would be expected.

#### **Recommendation 17**

If neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible, amantadine might be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus in high or moderate-risk exposure groups (weak recommendation, very low quality evidence).

**Remarks**

This recommendation does not apply to pregnant women, the elderly, people with impaired renal function, and individuals receiving neuropsychiatric medication, or with neuropsychiatric or seizure disorders. It places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance, and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and be continued for 7–10 days after the last known exposure. Amantadine has been used for as long as 6 weeks for chemoprophylaxis of seasonal influenza A. This recommendation applies when neuraminidase inhibitors are not available or have limited availability.

**Recommendation 18**

If neuraminidase inhibitors are not available and even if the virus is known or likely to be susceptible, amantadine should probably not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus in low-risk exposure groups (weak recommendation, very low quality evidence).

**Remarks**

This recommendation places a high value on avoiding adverse events, development of resistance, and cost. It places a lower value on preventing the low risk of H5N1 disease.

**Recommendation 19**

In pregnant women, the elderly, people with impaired renal function, and individuals receiving neuropsychiatric medication or with neuropsychiatric or seizure disorders amantadine should not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality of evidence).

**Recommendation 20**

If the H5N1 virus is known or likely to be M2 inhibitor-resistant, rimantadine should not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality evidence).

**Remarks**

This recommendation places a high value on avoiding adverse effects in a situation when no drug efficacy would be expected.

**Recommendation 21**

If neuraminidase inhibitors are not available and especially if the virus is known or likely to be susceptible, rimantadine might be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus in high or moderate-risk exposure groups (weak recommendation, very low quality evidence).

**Remarks**

This recommendation places a high value on preventing an illness with high case fatality. It places a relatively low value on adverse effects, development of resistance, and cost. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and be continued for 7–10 days after the last known exposure. Rimantadine has been used for as long as 7 weeks for chemoprophylaxis of seasonal influenza A. This recommendation applies when neuraminidase inhibitors are not available or have limited availability. This recommendation does not apply to pregnant women.

**Recommendation 22**

If neuraminidase inhibitors are not available and even if the virus is known or likely to be susceptible, rimantadine should probably not be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus in low-risk exposure groups (weak recommendation, very low quality evidence).

**Remarks**

This recommendation places a high value on avoiding adverse events, development of resistance, and cost. It places a lower value on preventing the low risk of H5N1 disease.

**Recommendation 23**

In pregnant women rimantadine should not be administered for chemoprophylaxis of human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality of evidence).

The recommended dose and duration of treatment and chemoprophylaxis are shown in the table.

**Other recommendations**

In addition to the recommendations of antiviral use, the panel evaluated other pharmacological management options but made only one detailed recommendation (strong recommendation based on very low quality evidence against the use of ribavirin in pregnancy because of known adverse effects). Recommendations relating to antibiotic use are provided on the WHO website.<sup>7</sup> A number of research recommendations including the need for detailed prospective data collection on all H5N1 cases, exploration of combination therapy, and parenteral administration modes were also made.<sup>7</sup>

**Discussion**

This review summarises the clinical recommendations from the WHO Rapid Advice Guidelines on pharmacological management of human beings infected with avian influenza A (H5N1) virus.<sup>7</sup> These guidelines were developed by a panel involving relevant stakeholders including clinicians who cared for patients with H5N1 disease.

One of the strengths of these guidelines is the transparent, evidence-based development approach. Another strength is the explicit description of the values that influence the recommendations. The main weakness is the very limited amount of direct evidence pertaining to human H5N1 infections, and the lack of data on resource use, which render more detailed cost-effectiveness analyses infeasible.

Making strong recommendations—implying that they should be followed in most situations—in the face of evidence rated as very low quality demands explanation. First, the disease is deadly for a very high proportion of patients. Second, neuraminidase inhibitors are the most promising pharmacological treatments at present, despite the uncertainty about their efficacy. However, even a hypothetical and small reduction in the relative risk of death in the order of 10% would require only 15–30 patients to be treated to prevent one H5N1 death. Third, in the absence of important adverse outcomes, the panel judged that the potential benefits clearly outweigh the associated harm, burden, and cost during the treatment of relatively few patients worldwide. Overall, these considerations highlight the importance of separating the rating of evidence from determining the strength of recommendations in any guideline process.

Prospective clinical research is needed to assess the efficacy of neuraminidase and M2 ion channel inhibitors, the dose and duration, and the potential role of combination therapy for the treatment of H5N1 patients. The development of resistance to these drugs is a major concern and this aspect requires careful monitoring. The results of such work will help to establish whether these current recommendations will remain applicable. In view of the current uncertainty, clinicians will ask which other measures should be taken to treat H5N1 patients. Early antiviral treatment and supportive care remain key features in the management of H5N1 patients.<sup>34</sup> Policymakers will ask whether the strong recommendation for treatment with oseltamivir leads to stockpiling. Because these recommendations were developed in the context of the current pandemic alert period without sustained human-to-human transmission, extrapolation to stockpiling decisions related to pandemic preparedness is limited, since different criteria for judgment are likely to apply including changing estimates of benefit and harm.

For chemoprophylaxis, resource considerations are of even greater concern. Users of these guidelines should apply the risk stratification presented in these guidelines for allocation of oseltamivir. The panel strongly recommended chemoprophylaxis with neuraminidase inhibitors only for high-risk exposure groups and pointed out that chemoprophylaxis should be seen in the context of standard infection control measures including the proper use of adequate personal protective equipment. Zanamivir is listed as a reasonable alternative in view of the limited availability of oseltamivir and since the

evidence base for chemoprophylaxis with zanamivir is stronger than for treatment with this agent. Moreover, in certain situations of limited or no availability of neuraminidase inhibitors clinicians might consider the use of M2 inhibitors (recommendations 4, 6, 17, and 21), although no activity would be expected for resistant viruses. Guideline users must be aware, however, that the risk stratification is based on weak evidence from small observational studies as well as observations of expert clinicians.

These guidelines offer many advantages over previous advice because of the structured development process including explicit question formulation and evidence summaries. For example, the Health Evidence Network (HEN) report<sup>35</sup> provides comprehensive, evidence-based information and recommendations ranging from vaccination to stockpiling antivirals, but the report does not provide the level of detail that clinicians and other decision makers need for making decisions about the pharmacological management in exposed or infected patients.<sup>36</sup> The latter was not the mandate of the HEN report on avian influenza, and therefore the current document presents important new information.

These guidelines were developed with the aim of allowing simple implementation. The greatest barrier to implementation results from the limited availability of the neuraminidase inhibitors and the lack of resistance data. However, the clear description of the guiding principles of the panel's values and preferences will facilitate their application by clinicians treating H5N1 patients. In particular, weak recommendations will require careful evaluation of values and resources before they can be implemented. WHO will begin collecting feedback from user countries on the practicality of these guidelines. Emergence of novel human influenza A viral subtypes or a change in the pathogenicity or transmissibility of H5N1 virus strains, availability of new pharmacological agents, or important clinical research data on H5N1 will necessitate an update of these guidelines. In view of the potential for rapid change in the situation in relation to avian influenza, WHO will continue to monitor these factors carefully before deciding when to revise or update the recommendations.

**The WHO Rapid Advice Guideline Panel for the pharmacological management of humans infected with influenza A (H5N1) virus**

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For more information on the Health Evidence Network report see [http://www.euro.who.int/HEN/Syntheses/pandemicflu\\_antivirals/20060106\\_6](http://www.euro.who.int/HEN/Syntheses/pandemicflu_antivirals/20060106_6)

**Search strategy and selection criteria**

These are described in detail in the Methods section on page 21.

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#### Conflicts of interest

This guideline project was funded by WHO. Panel members made the following declarations regarding possible conflicts of interest according to WHO rules for the period 2002–2006. JB declares no personal funding, but is an investigator (through the National Institutes of Health) on trials with Roche and Biocrest; CDM declares funding for trials in unrelated therapeutic area, not in the last 4 years; FGH declares receipt of research grants for trials of antivirals and vaccines from Roche, Abbotts, Biocrest and Merck; HJS declares no personal funding, but research grants and honoraria deposited into research accounts or received by a research group that he belongs to from Pfizer, Amgen, Roche, and AstraZeneca for development or consulting regarding quality of life instruments for chronic respiratory diseases; NS declares receipt of travel grants from Roche to attend meetings on avian influenza; YY declares no personal funding, but is an investigator on trials with Tibotec Pharmaceutical, and has received travel grants from GlaxoSmithKline, Roche, Boehringer, Bristol-Myers Squibb, Pfizer, Abbot, and Gilead to attend scientific meetings. All other members of the panel declare that they have no conflicts of interest.

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