WHO/PSM/PAR/2006.6

WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus

Contents

Executive summary

The recent geographical spread of highly pathogenic avian influenza A (H5N1) virus in poultry and wild waterfowl has increased opportunities for transmission of the virus to humans. Outbreaks in poultry have now been accompanied by human cases in nine countries. To date, human cases have remained rare and sporadic, but the disease is very severe and the case fatality is high. With the H5N1 virus now confirmed in birds in more than 50 countries, additional sporadic human cases should be anticipated. Although international experts agree that antiviral drugs should be considered for treatment of H5N1 patients and also for chemoprophylaxis, the efficacy and effectiveness of these management options have not been systematically assessed. Guidance on their use is needed worldwide.

From 28–29 March 2006, the World Health Organization (WHO) assembled an international panel of clinicians experienced in the treatment of H5N1 patients, infectious disease experts, public health officers and methodologists to develop rapid advice for the pharmacological management of patients with H5N1 infection. To develop evidence-based guidelines, the panel used a transparent methodological guideline process, based on the GRADE approach, that included evaluation of existing systematic reviews, literature searches and expert consultation. The resulting guidelines separate strong from weak recommendations for or against a specific action and assign four categories of quality of evidence (high, moderate, low and very low).

The panel considered several different specific patient and exposure groups and made a number of strong recommendations for or against specific actions regarding the treatment and chemoprophylaxis of H5N1 virus infection. All recommendations are specific to the current pre-pandemic situation. Recommendations were based on careful consideration of the benefits, harms, burdens and cost of interventions. Risk categorizations for exposure were developed to assist countries in prioritizing the use of antiviral drugs where their availability is limited. Overall, the quality of the underlying evidence for all recommendations was very low. No data from controlled clinical trials of H5N1 infection are available. The existing evidence is based on small observational case series of H5N1 patients, results from in vitro and animal model studies of H5N1, or the extrapolation of data from high quality studies conducted to evaluate the treatment and chemoprophylaxis of normal, or "seasonal", influenza. These shortcomings highlight the need for further research. While the quality of the evidence for some of the critical outcomes was moderate or low, the overall quality of evidence on which to base a summary assessment was very low for all antiviral drugs. Differences exist in the quality of evidence for individual critical outcomes among the various antiviral drugs (see annex 3 for gradings and ratings).[1]

[1] Based on the GRADE approach to grading the quality of evidence, the critical outcome with the lowest quality of evidence determines the overall quality assessment.

Brief summary of recommendations

This advice pertains only to influenza A (H5N1) infections in the current pre-pandemic situation. Recommendations will be updated as new information becomes available or if there is evidence for sustained human-to-human transmission of H5N1 or another novel avian influenza virus emerges. Whenever feasible, sequential clinical data collection and virological sampling (for analysis at WHO-designated laboratories) should be performed during treatment or should apparent failures of chemoprophylaxis occur.

Self-medication in the absence of appropriate clinical or public health advice is discouraged. When considering chemoprophylaxis for H5N1 infection, priority should be given to standard infection control practices. This includes protection of health care workers and individuals involved in eradication of animals infected with H5N1 virus as well as household contacts of H5N1 patients.

As stated above, the quality of the evidence for the following recommendations is very low and this is mainly the result of the availability of only very indirect data from high quality studies in seasonal influenza. For treatment of patients with confirmed or strongly suspected human infection with the H5N1 virus, where neuraminidase inhibitors are available for therapy:

- Clinicians should administer oseltamivir treatment (strong recommendation); zanamivir might be used as an alternative (weak recommendation). The quality of evidence if considered on a continuum rather than in four categories is lower for the use of zanamivir compared to oseltamivir.
- In these patients, clinicians should not administer amantadine or rimantadine alone as a first-line treatment (strong recommendation).
- Clinicians might administer a combination of a neuraminidase inhibitor and an M2 inhibitor if local surveillance data show that the H5N1 virus is known or likely to be susceptible (weak recommendation), but this should only be done in the context of prospective data collection.

For treatment of patients with confirmed or strongly suspected H5N1 infection, where neuraminidase inhibitors <u>are not</u> available for therapy:

- Clinicians might administer amantadine or rimantadine as a first-line treatment if local surveillance data show that the H5N1 virus is known or likely to be susceptible to these drugs (weak recommendation).

In general, decisions to initiate antiviral chemoprophylaxis should be guided by the risk stratification described below. Stratification is based on observational data for reported cases of human H5N1 infection and on high quality data from studies of seasonal influenza.

High risk exposure groups are currently defined as:

- Household or close family contacts[1] 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:

- Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal) if personal protective equipment may not have been used properly.
- Individuals with unprotected and very close direct exposure[2] to sick or dead animals infected with the H5N1 virus or to particular birds that have been directly implicated in human cases.
- 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 group also includes laboratory personnel who might have an unprotected exposure to virus-containing samples.[3]

Low risk exposure groups are currently defined as:

- Health care workers not in close contact (distance greater than 1 metre) with a strongly suspected or confirmed H5N1 patient and having no direct contact with infectious material from that 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 as a control measure.
- Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal), who used proper personal protective equipment.

[1] A close contact may be defined as an individual sharing a household with, or remaining unprotected whilst within speaking distance (< 1 metre) of, or in the care of, a patient with confirmed or strongly suspected H5N1 infection.

[2] 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 or other products from infected animals (e.g. plucking feathers); or prolonged exposure to infected birds in a confined space, such as playing with pets.

[3] This definition of moderate risk is based on very few cases recognized under these situations to date. As circumstances may 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.

Where neuraminidase inhibitors are available:

- In high risk exposure groups, including pregnant women, oseltamivir should be administered as chemoprophylaxis, continuing for 7–10 days after the last exposure (strong recommendation); zanamivir could be used in the same way (strong recommendation) as an alternative.
- In moderate risk exposure groups, including pregnant women, oseltamivir might be administered as chemoprophylaxis, continuing for 7-10 days after the last exposure (weak recommendation); zanamivir might be used in the same way (weak recommendation).
- In low risk exposure groups oseltamivir or zanamivir should probably **not** be administered for chemoprophylaxis (weak recommendation). Pregnant women in the low risk group should not receive oseltamivir or zanamivir for chemoprophylaxis (strong recommendation).
- Amantadine or rimantadine should not be administered as chemoprophylaxis (strong recommendation).

Where neuraminidase inhibitors are not available:

- In high or moderate risk exposure groups, amantadine or rimantadine might be administered for chemoprophylaxis if local surveillance data show that the virus is known or likely to be susceptible to these drugs (weak recommendation).
- In low risk exposure groups, amantadine and rimantadine should not be administered for chemoprophylaxis (weak recommendation).
- In pregnant women, amantadine and rimantadine should not be administered for chemoprophylaxis (strong recommendation).
- In the elderly, people with impaired renal function and individuals receiving neuropsychiatric medication or with neuropsychiatric or seizure disorders, amantadine should not be administered for chemoprophylaxis (strong recommendation).

The panel also considered the question of antibiotic use in H5N1 patients and made the following general recommendations:

- In patients with severe community-acquired pneumonia regardless of the geographical location, clinicians should follow appropriate clinical practice guidelines (strong recommendation).
- In patients with confirmed or strongly suspected H5N1 infection who do not need mechanical ventilation and have no other indication for antibiotics, clinicians should not administer prophylactic antibiotics (strong recommendation).
- In patients with confirmed or strongly suspected H5N1 infection who need mechanical ventilation, clinicians should follow clinical practice guidelines for the prevention or treatment of ventilator-associated or hospital-acquired pneumonia (strong recommendation).

Other co-interventions considered were: routine use of corticosteroids, use of immunoglobulin and interferon, and also of ribavirin. There was no basis to make a recommendation for use of any of these medicines outside the context of a randomized trial, but ribavirin particularly should not be used in pregnant women (strong recommendation).

Generally, the recommendations have been developed to be as specific and detailed as possible without losing sight of the user-friendliness of this document and the individual recommendations. The panel encourages feedback on all aspects of these guidelines, including their applicability in individual countries.

The panel developed a number of clinical and basic research recommendations that could help augment the currently sparse direct evidence. Emergence of new influenza A viral subtypes or a change in the pathogenicity or transmissibility of the H5N1 virus, the development of new pharmacological agents or the availability of important clinical research data will necessitate an update of these guidelines.

Summary of clinical recommendations

Brief description of methodology used for grading the quality of evidence and strength of recommendations (see the section on methods)

The evidence was assessed according to the methodology described by the GRADE working group. Briefly, in this system the quality of evidence is classified as "high", "moderate", "low" or "very low" based on methodological characteristics of the available evidence for a specific health care problem. The definition of each is provided below.

- ***High:*** Further research is very unlikely to change confidence in the estimate of effect.
- ***Moderate:*** Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
- ***Low:*** Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
- ***Very low:*** Any estimate of effect is very uncertain.

Recommendations are classified as "strong" or "weak" recommendations, as delineated in the GRADE methodology. "Strong" recommendations can be interpreted as:

- Most individuals should receive the intervention.
- Most well informed individuals would want the recommended course of action and only a small proportion would not.
- The recommendation could unequivocally be used for policy making.

"Weak" recommendations can be interpreted as:

- The majority of well informed individuals would want the suggested course of action, but an appreciable proportion would not.
- Values and preferences vary widely.
- Policy making will require extensive debates and involvement of many stakeholders.

While the quality of the evidence for some of the critical outcomes was moderate or low, the overall quality of evidence on which to base a summary assessment was very low for all antiviral drugs. Differences in the quality of evidence exist for individual critical outcomes among the various antiviral drugs (see annex 3 for gradings and ratings).[1]

[1] Based on the GRADE approach to grading the quality of evidence, the critical outcome with the lowest quality of evidence determines the overall quality assessment.

Recommendations

Self-medication in the absence of appropriate clinical or public health advice is discouraged.

Context: Treatment of patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus in a non-pandemic situation where neuraminidase inhibitors are available for therapy.

Rec 01: 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 (e.g. those with renal insufficiency) and children with *seasonal* influenza.

Rec 02: 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 may 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 to oseltamivir, the overall quality of evidence in the four category grading system is very low for both interventions.

Rec 03: If neuraminidase inhibitors <u>are available</u>, clinicians should <u>not</u> 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 recognizing 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 may be more effective.

Rec 04: If neuraminidase inhibitors are <u>not available</u> 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 in patients at higher risk for adverse outcomes (e.g. pregnant patients).

Rec 05: 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 recognizing 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 may be more effective.

Rec 06: If neuraminidase inhibitors are <u>not available</u> 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 favorable side effect profile than amantadine.

Rec 07: 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 downsides in patients of higher risk for adverse outcomes. Combination therapy should only be carried out if detailed and standardized clinical and virological data collection is in place at the start of therapy (prospective data collection). Clinicians should carefully determine which patients (e.g. severely ill patients) could receive combination therapy.

Chemoprophylaxis

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

High risk exposure groups are currently defined as:

- Household or close family contacts[1] 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:

- Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal) if personal protective equipment may not have been used properly.
- Individuals with unprotected and very close direct exposure[2] to sick or dead animals infected with the H5N1 virus or to particular birds that have been directly implicated in human cases.
- 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 group also includes laboratory personnel who might have an unprotected exposure to virus-containing samples.[3]

Low risk exposure groups are currently defined as:

- Health care workers not in close contact (distance greater than 1 metre) with a strongly suspected or confirmed H5N1 patient and having no direct contact with infectious material from that 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 as a control measure.
- Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal), who used proper personal protective equipment.

---

[1] A close contact may be defined as an individual sharing a household with, or remaining unprotected whilst within speaking distance (< 1 metre) of, or in the care of, a patient with confirmed or strongly suspected H5N1 infection.

[2] 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 or other products from infected animals (e.g. plucking feathers); or prolonged exposure to infected birds in a confined space, such as playing with pets.

[3] This definition of moderate risk is based on very few cases recognized under these situations to date. As circumstances may 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.

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

Rec 08: 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 to 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.

Rec 09: 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 to 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.

Rec 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, potential development of resistance and cost. It places a lower value on preventing the low risk of H5N1 disease.

Rec 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.

Rec 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 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 to 10 days after last known exposure. The dose of zanamivir should be that used for seasonal influenza chemoprophylaxis. The bioavailability of zanamivir outside of the

respiratory tract is lower than that of oseltamivir. Zanamivir may 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.

Rec 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 continued for 7 to 10 days after last known exposure. The bioavailability of zanamivir outside of the respiratory tract is lower than that of oseltamivir. Zanamivir may be active against some strains of oseltamivir resistant H5N1 virus. This recommendation also applies to pregnant women in the moderate risk exposure group.

Rec 14: In low risk exposure groups zanamivir should probably <u>not</u> 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.

Rec 15: Pregnant women in the low risk exposure group should <u>not</u> 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.

Rec 16: If the virus is known or likely to be an M2 inhibitor <u>resistant</u> H5N1 virus, amantadine should <u>not</u> 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.

Rec 17: If neuraminidase inhibitors are <u>not available</u> 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 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.

Rec 18: If neuraminidase inhibitors are <u>not available</u> and even if the virus is known or likely to be susceptible, amantadine should probably <u>not</u> 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.

Rec 19: In pregnant women, the elderly, people with impaired renal function and individuals receiving neuropsychiatric medication or with neuropsychiatric or seizure disorders amantadine should <u>not</u> be administered as chemoprophylaxis against human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality of evidence).

Rec 20: If the virus is known or likely to be M2 inhibitor <u>resistant</u> H5N1 virus, rimantadine should <u>not</u> 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.

Rec 21: If neuraminidase inhibitors are <u>not available</u> 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 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.

Rec 22: If neuraminidase inhibitors are <u>not available</u> and even if the virus is known or likely to be susceptible, rimantadine should probably <u>not</u> 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.

Rec 23: In pregnant women rimantadine should <u>not</u> be administered for chemoprophylaxis of human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality of evidence).

Rec 24: In patients with severe community acquired pneumonia regardless of the geographical location, clinicians should follow appropriate clinical practice guidelines (strong recommendation, the panel has not judged the quality of the evidence for this recommendation).

Remarks: The choice of antibiotics should be based on knowledge of local pathogens, other co-morbidities and resistance patterns. Hospitals should have local antimicrobial surveillance data that can be used to inform the choice. Further advice about monitoring antimicrobial resistance is available in the WHO Global Strategy for Containment of Antimicrobial Resistance, at http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf. Local standard treatment guidelines should be updated regularly.

Rec 25: In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus who do not need mechanical ventilation and have no other indication for antibiotics, clinicians should not administer prophylactic antibiotics (strong recommendation, the panel has not judged the quality of the evidence for this recommendation).

Remarks: This is a strong recommendation in part because there is no evidence that antibiotic chemoprophylaxis reduces the risk of bacterial superinfection in H5N1 or seasonal influenza, whether or not the patients require mechanical ventilation. Antibiotics are likely to select for resistant bacteria, if superinfection occurs. Thus, at present there are no known clinical net benefits from chemoprophylaxis with antibiotics.

Rec 26: In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus who need mechanical ventilation, clinicians should follow clinical practice guidelines for the prevention or treatment of ventilator associated or hospital acquired pneumonia (strong recommendation, the panel has not judged the quality of the evidence for this recommendation).

Remarks: As the risk for bacterial infection in mechanically ventilated patients is increased, this recommendation places a high value on avoiding consequences of proven or suspected bacterial infection and a low value on adverse effects of antibiotics, the development of resistance, and cost. Appropriate broad spectrum antibiotic therapy should be instituted with a commitment to tailor antibiotics as soon as possible on the basis of serial clinical and anti-microbiologic data.

Rec 27: In pregnant patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians should not administer ribavirin as treatment or chemoprophylaxis (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on avoiding the high risk of teratogenic effects of ribavirin during pregnancy.

1. Background

Human cases of infection with the H5N1 avian influenza virus were first reported in Hong Kong SAR in 1997 (18 cases) and again in 2003 (2 cases). In the present outbreak of human cases, which began in December 2003, more than 200 cases have been reported from nine countries in Asia, Europe, northern Africa, and the Middle-East. Human cases are directly linked to the presence of the virus in birds, and this geographical presence is now considerable. An updated record of cases and their outcomes and of affected countries can be found at http://www.who.int/csr/disease/avian_influenza/country/en/.

Of all influenza A viruses that circulate in birds, the H5N1 virus is of greatest present concern for human health for two main reasons. First, the H5N1 virus has caused by far the greatest number of human cases of very severe disease and the greatest number of deaths. A second implication for human health, of far greater concern, is the risk that the H5N1 virus – if given enough opportunities – could develop the characteristics to start another influenza pandemic. The virus has met all prerequisites for the start of a pandemic save one: an ability to spread efficiently and sustainably among humans. While H5N1 is presently the influenza A virus of greatest concern, the possibility that other avian influenza A viruses, known to infect humans, might cause a pandemic cannot be ruled out.

At present, infection with influenza A(H5N1) virus is primarily a disease of birds. The species barrier is substantial: the virus does not easily infect humans. Nonetheless, with the virus now reported in domestic or wild birds in more than 50 countries, sporadic human cases will almost certainly continue to occur. Few guidelines for the clinical management of such patients have been published. In February 2004, WHO published interim clinical guidelines. These guidelines were updated in September 2005 (WHO Writing Committee 2005) following an expert consultation. The purpose of the present document is to review and update recommendations on clinical case management of patients infected with the H5N1 virus as well as to review and update recommendations on the use of antiviral drugs as chemoprophylaxis. The guidelines apply to the current situation in which no efficient or sustained human-to-human transmission of the virus is known to be occurring.

The document is addressed primarily to clinicians managing H5N1 cases or advising on management of specific populations potentially at risk of the disease. It is likely that it will be used by health care managers and policy makers. It has been prepared as a "rapid advice" document, and therefore has a defined scope, based on clinical questions that have been raised by health care teams managing H5N1 patients. While it does not cover all interventions that may be relevant, it will be updated and expanded as experience and evidence accumulate from reported cases and from formal clinical trials or animal research. In addition, the current picture could change given the propensity of all influenza A viruses to mutate rapidly and unpredictably. Such a change would also necessitate updating of the guidelines.

A fundamental first-line approach to the clinical management of patients with H5N1 avian influenza is to ensure that appropriate infection control procedures are in place in health care systems and are used by all involved in managing animal or human disease or suspected cases. Specific guidelines for infection control procedures are described in a parallel document: Influenza A (H5N1): WHO Interim Infection Control Guidelines for Health Care Facilities, 2004) (http://www.who.int/csr/disease/avian_influenza/guidelines/Guidelines_for_health_care_facilities.pdf) and are therefore not included here. However, it should be assumed that for all recommendations about pharmacological treatments that are described here, the recommendations on infection control procedure and practice apply and are critical to the management of H5N1 patients.

2. Scope

The target audience of these guidelines is primarily health care professionals managing H5N1 patients or advising on management of specific populations potentially at risk of the disease, but health care policy makers and public health officers have also been considered. National programmes and treatment guideline groups may also wish to use the document as the basis for implementation or development of locally adapted guidelines (see annex 1 – Adaptation of guidelines).

The clinical questions covered by this document were developed in consultation with clinicians from a variety of countries involved in the management of H5N1 patients. They can be summarized briefly as:

- Should clinicians use the antiviral drugs that are currently available for the treatment of H5N1 patients? What are the benefits, harms, burdens and cost of each currently available alternative? Can all patient groups be treated in the same way? What dose of the medicine should be used and for how long?
- Should clinicians use the antiviral drugs that are currently available for chemoprophylaxis in persons who may be at risk of contracting avian influenza? In the context of prevention, what are the benefits, harms, burdens and cost of each currently available alternative? Are there particular population groups who are at greater or lesser risk of the disease, and if so, should the use of the medicines be modified?
- If there is limited availability of antiviral drugs, should the use of these medicines be prioritized and should other medicines be used?
- What additional pharmacological treatments might be of benefit in the treatment of H5N1 patients? Should antibiotics be used prophylactically? What is the role of corticosteroids, immunoglobulin and interferon? What is the role of ribavirin?

These questions have been considered in the context of the current situation in which no efficient or sustained human-to-human transmission of the H5N1 virus is known to be occurring, and no evidence indicates that a pandemic is imminent. A change in this situation would require modification of the recommendations. The recommendations in this document do not apply to treatment or chemoprophylaxis of seasonal influenza.

These guidelines do not provide recommendations on use of ventilators, isolation procedures, vaccination and other public health interventions, although these will be included in later versions. However, recommendations on the use of particular therapies that are covered in the document must be considered together with infection control, which remains a primary strategy for the control of outbreaks.

3. Methods

This document was prepared according to a modification of the WHO Guidelines for Guidelines (WHO 2003), as a "rapid advice" guideline document, taking into account the need for advice to be provided urgently. Complete details of the methods are provided in annex 2; a brief summary is provided below.

The clinical questions and scope of these guidelines were defined in consultation with clinicians managing H5N1 patients. WHO commissioned an independent academic centre to compile summaries of evidence, based on systematic reviews and health technology assessments (see annex 3) according to the GRADE methodology described in the WHO Guidelines for Guidelines. Published animal and in vitro studies were also summarized. The summaries of evidence were then peer reviewed and corrections and comments incorporated by the expert panel. If no relevant systematic reviews were found for specific interventions, evidence summaries could not be completed in the time available. In such cases, recommendations which graded the quality of the evidence could not be made (antibiotics, other co-interventions).

A guideline panel comprising international scientists and experts in clinical treatment of avian and seasonal influenza, guideline methodology, basic research, policy making, pharmacology and virology was convened from 28–29 March 2006 (see annex 4 for list of participants and annex 5 for conflict of interest declarations). The panel was asked to identify critical clinical outcomes as a basis for making the recommendations. Mortality, duration of hospitalization, incidence of lower respiratory tract complications, antiviral drug resistance and serious adverse effects were rated as critical outcomes in the assessment of treatment interventions for H5N1 patients. For chemoprophylaxis, influenza cases, outbreak control, drug resistance and serious adverse effects were rated as critical outcomes. The impact of chemoprophylaxis on these outcomes formed the basis of considerations used when reaching conclusions. All outcomes reported in the clinical trials are summarized in the evidence profiles set out in annex 3.

The evidence was assessed according to the methodology described in GRADE (GRADE Working Group 2004) In this system evidence is classified as "high" , "moderate", "low" or "'very low". Definitions are as follows:

- ***High:*** Further research is very unlikely to change confidence in the estimate of effect.
- ***Moderate:*** Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
- ***Low:*** Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
- ***Very low:*** Any estimate of effect is very uncertain.

Factors considered when classifying evidence are the study design and rigour of its execution, the consistency of results, how well the evidence can be directly applied to the patients, the interventions, the outcomes, the comparator, whether the data are sparse or imprecise and whether a potential for reporting bias exists. No controlled clinical trials are presently available for H5N1 patients. In addition it is uncertain whether the evidence that is available for seasonal influenza can be directly applied to patients infected with the H5N1 virus, as the biology of this disease appears to be different from infection with seasonal influenza virus. The data available from pre-clinical studies of H5N1 infection were used to inform this consideration. It is important to note that a group of trials may constitute "high quality" evidence for one question, but because of uncertainty about their applicability or directness, can be regarded as "very low" quality evidence for a different question. While the quality of the evidence for some of the critical outcomes was moderate or low, the overall quality of evidence on which to base a summary assessment was very low for all antiviral drugs. Differences exist in the quality of evidence for individual critical outcomes among the various antiviral drugs (see annex 3 for gradings and ratings).[1]

The panel reviewed the evidence summaries and the draft guidelines and made recommendations. Consensus was reached on nearly all recommendations, but one recommendation required voting about the strength of the recommendation (weak as opposed to strong) and one required voting about whether a weak recommendation or no recommendation should be made.

Formulating the recommendations included explicit consideration of the quality of evidence, benefits, harms, burdens, costs and values and preferences, described in the "Remarks" for each recommendation. "Values" are the desirability or preference that individuals exhibit for a particular health state. Individuals usually assign less value to and have less preference for more impaired health states (e.g. death or dependency after a stroke) compared to other health states (e.g. full health or having a very mild stroke without serious sequelae). In this document, the term "values" refers to the relative worth or importance of a health state or consequences (benefits, harms, burdens and costs) of a decision.

Very little information about costs of treatment or chemoprophylaxis of H5N1 was available to the panel. For this guideline the main cost consideration was the acquisition cost of the antiviral drugs. Estimates of current acquisition costs are set out in section 8 on drug supply.

Recommendations are classified as "strong" or "weak" recommendations, as recommended in the GRADE methodology. "Strong" recommendations can be interpreted as:

- Most individuals should receive the intervention, assuming that they have been informed about and understand its benefits, harms and burdens.
- Most individuals would want the recommended course of action and only a small proportion would not.
- The recommendation could unequivocally be used for policy making.

[1] Based on the GRADE approach to grading the quality of evidence, the critical outcome with the lowest quality of evidence determines the overall quality assessment.

"Weak" recommendations can be interpreted as:

- The majority of individuals would want the suggested course of action, but an appreciable proportion would not.
- Values and preferences vary widely.
- Policy making will require extensive debates and involvement of many stakeholders.

Specific recommendations about antiviral drugs are presented in two sections: recommendations for treatment of H5N1 patients and recommendations for chemoprophylaxis of H5N1 infection. For recommendations pertaining to chemoprophylaxis, an exposure-based assessment of risk was developed, based on observational data for reported cases of H5N1 infection and corresponding information on viral transmission. General recommendations about the use of co-interventions are given in a separate section. Full details of the methods are set out in annex 2.

Rapidly changing information about this disease may require frequent updating of the guidelines. The first revision may occur in not more than 12 months following publication of this document. The main factors that will influence the timing of the update include: whether significant new scientific evidence becomes available, the availability of new antiviral medicines or a change in the pathogenicity or transmissibility of H5N1 viruses, including the emergence of a pandemic virus.

4. Case description

Assessment of possible cases[1]

Investigations of most laboratory-confirmed cases of human H5N1 infection have identified direct contact with infected birds as the most likely source of exposure. When assessing possible cases, the level of clinical suspicion should be heightened for persons showing influenza-like illness, especially with fever and symptoms in the lower respiratory tract, who have a history of direct contact with poultry or wild birds (generally sick or dead unvaccinated poultry) in an area where confirmed outbreaks of highly pathogenic H5N1 avian influenza are occurring.

Case description/clinical features

Like most emerging diseases, H5N1 avian influenza virus infections in humans are poorly understood. Clinical data from H5N1 cases in 1997 and the current outbreak are beginning to provide a picture of the clinical features of disease, but much remains to be learned. In many patients, the disease caused by the H5N1 virus follows an unusually aggressive clinical course, with rapid deterioration and high fatality.

The incubation period for H5N1 in people may be longer than that for seasonal influenza, which is around two to three days. Current data for H5N1 virus infection suggest a similar incubation period but ranging up to eight days and rarely longer (periods as long as 17 days have been reported). However, the possibility of multiple exposures to the H5N1 virus makes it difficult to define the incubation period precisely. WHO currently recommends that an H5N1 incubation period of seven days be used for field investigations and the monitoring of patient contacts.

Initial symptoms include a high fever, usually with a temperature higher than 38°C, and influenza-like symptoms. Diarrhoea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums have also been reported as early symptoms in some patients. Watery diarrhoea without blood appears to be more common with H5N1 virus infection than in seasonal influenza.

However, in many patients the rapid development of lower respiratory tract symptoms is a common feature that causes them to first seek treatment. On present evidence, difficulty in breathing develops around five days following the first symptoms. Respiratory distress, a hoarse voice, and a crackling sound when inhaling are commonly reported. Sputum production is variable and sometimes bloody. Recently, blood-tinted respiratory secretions have been observed in Turkey. Almost all H5N1 patients develop pneumonia. During the 1997 Hong Kong SAR outbreak, all severely ill patients had primary viral pneumonia, which

[1] Adapted from the WHO Fact sheet on Avian Influenza
http://www.who.int/mediacentre/factsheets/avian_influenza/en/index.html

did not respond to antibiotics. Limited data on patients in the current outbreak suggest a primary viral pneumonia with H5N1 virus infection, usually without microbiological evidence of bacterial superinfection at presentation. Turkish clinicians have also reported pneumonia as a consistent feature in severe cases; as elsewhere, these patients did not respond to treatment with antibiotics.

The spectrum of clinical symptoms may, however, be broader, and not all confirmed H5N1 patients have presented with respiratory symptoms. In two patients from southern Viet Nam, the clinical diagnosis was acute encephalopathy; neither patient had respiratory symptoms at presentation. In another case, from Thailand, the patient presented with fever and diarrhoea, but no respiratory symptoms. However, all patients had radiographic evidence of lower respiratory tract disease and a recent history of direct exposure to infected poultry.

In patients infected with the H5N1 virus, clinical deterioration is rapid. In Thailand, the time between onset of illness to the development of acute respiratory distress was around six days, with a range of four to 13 days. In severe cases in Turkey, clinicians have observed respiratory failure three to five days after symptom onset. Another common feature is multiorgan dysfunction. Common laboratory abnormalities include leukopenia (mainly lymphopenia), mild-to-moderate thrombocytopenia, elevated aminotransferases, and some instances of disseminated intravascular coagulation.

According to reports from Viet Nam, Thailand and Turkey, chest radiograph (CXR) findings have been consistently abnormal on admission. Chest radiographs have typically shown consolidation, often bilateral and multifocal. In addition, patchy lobar and interstitial infiltrates have been described a median of 7 days after onset of symptoms (range 3-17 days) (Chotpitayasunondh 2005; Hien and Farrar, personal communication). Pleural effusions have been less commonly reported with cavitation, in the absence of superinfection, being an occasional finding in Vietnamese patients.

5. Treatment of H5N1 patients: recommendations for use of antiviral drugs

The following recommendations for use of antiviral drugs for the treatment of H5N1 patients apply to the current situation defined by the absence of efficient or sustained human-to-human transmission.

At present, no controlled clinical trials have evaluated treatment or chemoprophylaxis of H5N1 patients. The evidence on which the recommendations are based is predominantly derived from studies of infection with human influenza viruses during seasonal epidemics, and is thus indirect. In addition, the majority of these studies focus on early treatment of uncomplicated human influenza in otherwise healthy adults in which infection has been acquired following human-to-human transmission. So far, most patients with H5N1 infection have presented late in the course of illness and were hospitalized after the onset of severe disease. Many of those infected with the H5N1 virus have been children. This patient profile increases uncertainty about the generalizability of the evidence to H5N1 patients. Summaries of evidence used to make the recommendations are set out in Annex 3. Where a GRADE evaluation of the available literature has been possible, this is displayed in evidence profiles and a corresponding summary of findings.

The panel rated mortality, duration of hospitalization, incidence of lower respiratory tract complications, resistance and serious adverse effects as critical outcomes for the assessment of treatment interventions for H5N1 patients. While the quality of the evidence for some critical outcomes was moderate or low, the overall quality of evidence on which to base a summary assessment was very low for all antiviral drugs. Differences in the quality of evidence exist for individual critical outcomes between the various antiviral drugs (see annex 3 for gradings and ratings).[1]

Self-medication with antivirals, in the absence of appropriate clinical or public health advice, is discouraged.

5.1 Should H5N1 patients receive treatment with oseltamivir?

Summary of findings

No clinical trial has evaluated oseltamivir in the treatment of H5N1 patients.

Four systematic reviews and health technology assessments (HTA) reporting 5 studies of the use of oseltamivir in seasonal influenza were identified (see annex 3). These studies examined the use of oseltamivir in otherwise healthy adults, high risk adults or children for treatment of seasonal influenza. In these trials, oseltamivir treatment was generally started

[1] Based on the GRADE approach to grading the quality of evidence, the critical outcome with the lowest quality of evidence determines the overall quality assessment.

early in the disease (within 48 hours of symptom onset). Children up to 1 year of age were not included. The duration of treatment was up to 5 days. The studies were conducted in several countries in the northern and southern hemispheres, but resource-poor countries were not represented.

There are three published case series describing H5N1 patients treated with oseltamivir (Beigel 2005, Hien 2004, Chotpitayasunondh 2005).[1]

There are many in vitro and animal studies of the effects of oseltamivir on the H5N1 virus (see annex 3).

Benefits

There are too few events in the reported studies to provide evidence of benefit of oseltamivir on mortality or duration of hospitalization in either seasonal influenza or H5N1 infection. In seasonal influenza lower respiratory tract complications (including pneumonia) were reduced (RR 0.15, 95% CI 0.03 to 0.69) in a series of 5 similarly designed trials (n = 1644) that addressed this outcome in otherwise healthy adults with seasonal influenza (Kaiser et al, 2003), but there were only 11 events. This same analysis also reported a significant reduction (RR 0.40, 95% CI 0.18 to 0.88) in all-cause hospitalizations within 30 days of diagnosis in oseltamivir recipients compared to placebo, but this finding was based on a total of 27 events (18 out of 1063 patients treated with placebo compared with 9 out of 1350 treated with oseltamivir).[2] The most recent case series describes 37 H5N1 patients, of whom 25 were treated with oseltamivir (19 deaths) and 12 described as not being treated with oseltamivir (9 deaths) (Beigel 2005). Treatment regimens differed across these patients beginning between day 4 to 22 of illness.

Harms

Serious adverse events and drug resistance were generally not reported in systematic reviews of oseltamivir use in adults with seasonal influenza. There have been 2 trials in paediatric populations that reported very few adverse events (RR 2.00, 95% CI 0.61 to 6.61). However, reporting of harms is often complicated by withdrawals of patients from trials due to adverse events that are not fully described in published reports. Data from regulatory trials submitted by the manufacturer to the US Food and Drug Administration included nausea and vomiting as the most frequent adverse event in both children and adults (FDA label information, Dutkowski 2003). Rare cases of anaphylaxis and serious skin reactions were also reported during post-marketing experience with oseltamivir. Spontaneous reports to WHO of adverse reactions listed 644 reports of adverse reactions, but there is no assessment of causality or severity of these events in relation to oseltamivir. The most commonly reported adverse event was nausea (n = 110 cases). There were 86 reports of exposure to oseltamivir in pregnancy (maternal exposure) recorded on the Roche Drug Safety database as at 31 March 2005. Twenty-five of these women were either lost to follow up or the outcome of the pregnancy was unknown. For 33 women, the pregnancy was still

[1] There has been an additional published fatal case report of a pregnant woman with human infection of avian influenza H5N1, who did not receive antiviral therapy (Shu 2006).

[2] A recent report of 8 cases (6 of these had complete data) described that 3 H5N1 patients who had cleared pharyngeal viral RNA by the end of 5 days treatment with oseltamivir survived. Three patients whose pharyngeal samples remained positive despite therapy died, two of whom had emergence of osletamivir-resistant variants (de Jong NEJM 2005).

ongoing. Among the remainder there were 2 reports of birth defects and 4 cases of spontaneous abortion. Three cases of resistance to oseltamivir developing after treatment of H5N1 patients have been published (Le 2005, De Jong 2005).

Treatment considerations

Available formulations:

Oseltamivir phosphate is available as a capsule containing 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension.

Treatment regimen:
Patients with renal impairment, i.e. a creatinine clearance between 10 and 30 ml/min, who are being considered for oseltamivir treatment require dose reduction. Based on unpublished pharmacokinetic data from the manufacturer, a dose of 75 mg once daily could be used in these patients. There is no recommendation for dose reduction in patients with hepatic disease. Patients with severe gastrointestinal symptoms may have reduced oral absorption of oseltamivir but this has not been studied. There is currently no empirical evidence to suggest the use of a loading dose or higher doses of oseltamivir in patients with severe disease but increased doses and duration of treatment have been suggested as a strategy to reduce the risk for development of drug resistance. Patients who vomit within one hour of ingestion might be given an additional dose of 75 mg, but this is based on physiological considerations. There are no documented differences in the metabolism of the drug for different ethnic groups.

The recommended dose for seasonal influenza is 75 mg twice daily in adults or the following weight-adjusted doses in children for 5 days (CDC 2006a, CDC 2006b and appropriate FDA label).

- Children 1 year of age or older: weight-adjusted doses
- 30mg twice daily for ≤ 15 kg
- 45mg twice daily for >15 to 23 kg
- 60mg twice daily for >23 to 40kg
- 75mg twice daily for >40kg

Currently there is a single published observational study that reported use of oseltamivir in 47 children under one year of age and showed no significant adverse effects (Tamura 2005).

Other research and basic research findings for H5N1 patients

One study has evaluated the effect of oseltamivir on neuraminidase and viral replication using H5N1 isolates from humans. Two additional studies using H5N1 isolated from ducks evaluated the effect of oseltamivir on viral replication (see annex 3). Consistent animal data from three studies in mice indicate that high-dose oseltamivir treatment increased survival in this animal model.

Conclusion

Oseltamivir treatment may be of net clinical benefit in H5N1 patients. However, there are no clinical trials directly dealing with human H5N1 infection; based on the GRADE quality criteria, the evidence is of very low quality. This assessment of possible net benefit is based on extrapolation from studies performed in populations with seasonal influenza and consideration of other research data.

Clinical recommendation[1]

Rec 01: 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 (e.g. those with renal insufficiency) and children with seasonal influenza.

5.2. Should H5N1 patients receive treatment with zanamivir?

Summary of findings

No clinical trial or case study has evaluated zanamivir in the treatment of H5N1 patients.

There were 4 systematic reviews and HTAs (annex 3) that examined the use of zanamivir in otherwise healthy adults, high risk adults or children for treatment of seasonal influenza. The doses of inhaled zanamivir in the studies were 10 mg twice and four times daily in adults and children for up to 5 days. There were 3 studies evaluating both inhaled and intranasal zanamivir in combination; however the intranasal formulation is not available for clinical use. The studies were conducted in several countries in the northern and southern hemispheres.

There are very few studies describing animal and in vitro data about the effects of zanamivir on the H5N1 virus. Zanamivir is active in vitro and in vivo against oseltamivir-resistant H5N1 virus that contains the H274Y mutation (Le 2005).

[1] The panel voted on whether this recommendation should be strong or weak and there was one abstention and one dissenting vote out of thirteen.

Benefits

There are too few events in the reported studies to provide evidence of a benefit of zanamivir treatment on mortality or duration of hospitalization in either seasonal influenza of H5N1 infection. Lower respiratory tract complications (pneumonia) were not significantly reduced (OR 0.83, 95% CI 0 .24 to 2.26) in 3 trials (n = 2299 patients with 46 events) that described this outcome in otherwise healthy adults with seasonal influenza (Jefferson 2006, Monto 1999, Puhakka 2003, MIST 1998).

Harms

The identified systematic reviews did not provide informative evidence on serious adverse events. Data submitted by the manufacturer to the US Food and Drug Administration reported headache and nausea as the most frequent adverse events in both children and adults. This report also included warnings regarding an increased incidence of bronchospasm; patients with airway disease appear to be at increased risk for this severe adverse reaction (FDA note. JAMA Sept 13 2003). Spontaneous reporting of adverse reactions to the WHO listed 253 cases of adverse reactions, but there is no assessment of causality or severity of these events in relation to zanamivir. Headache was one of the most frequently reported biologically plausible adverse reactions (n = 22). There are four case reports of use of zanamivir during pregnancy that report three spontaneous abortions and one death but there was no assessment of causality. No information on resistance of H5N1 viruses to zanamivir exists.

Treatment considerations

Available formulations:

Zanamivir is available for oral inhalation only, using a diskhaler device.

Zanamivir has been approved by the US Food and Drug Administration for treatment of influenza in individuals aged ≥ 7 years. No dose adjustment for patients with hepatic or renal impairment is recommended.

The recommended treatment dose for inhaled zanamivir in seasonal influenza is 10 mg twice daily for 5 days, in adults and children ≥ 7 years (CDC 2006a, CDC 2006b).

The ability to deliver inhaled zanamivir to sites of viral replication in the context of pneumonia or serious lower respiratory tract disease is uncertain. It is also unknown whether inhaled zanamivir achieves sufficient blood and tissue levels to inhibit virus replication outside the respiratory tract. The bioavailability of inhaled zanamivir in adults ranges from 4% to 17%, compared to an average of 2% after ingestion (Glaxo Wellcome 2001, FDA approved label). Inhaled zanamivir might be appropriate in those patients unable to take oral medications, including oseltamivir.

Other research and basic research findings

Two studies have evaluated the effect of zanamivir on neuraminidase inhibition and viral replication using H5N1 virus isolate from humans. An additional study using H5N1 viruses isolated from ducks evaluated the effect of zanamivir on viral replication (see annex 3).

Consistent animal data from three studies in mice indicate that zanamivir treatment increased survival in this animal model. Zanamivir is active in vitro and in vivo against oseltamivir-resistant H5N1 virus that contains the H274Y mutation. Inhaled zanamivir may have lower bioavailability in organ systems other than the respiratory tract (Wong and Yuen 2006).

Conclusion

No direct data are available on the use of zanamivir to treat H5N1 patients. While there is evidence of net clinical benefit of ***inhaled*** zanamivir in patients with seasonal influenza**,** the quality of evidence when considered on a continuum is lower for the use of zanamivir compared to oseltamivir**.** However, based on the four category GRADE approach, the overall quality of evidence is very low for both interventions.

Clinical recommendations

Rec 02: 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 may 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 to oseltamivir, the overall quality of evidence in the four category grading system is very low for both interventions.

5.3 Should H5N1 patients receive treatment with amantadine?

Summary of findings

No controlled clinical trial has evaluated amantadine for the treatment of H5N1 infection.

There were 3 systematic reviews and HTAs (annex 3) that examined the use of amantadine in otherwise healthy adults, high risk adults or children for treatment of seasonal influenza A. The doses of amantadine in the studies were 100 mg once daily and 100 mg twice daily in adults for up to 10 days. The studies were conducted in several countries in the northern hemisphere, but resource-poor countries were not represented.

There are case study data for 10 patients in whom amantadine was used for the treatment of H5N1 infection (Beigel 2005). 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 the eight patients who did not receive amantadine survived. No conclusions can be reached from these uncontrolled clinical data.

Two studies reported clade 1 H5N1 viruses isolated from humans in Thailand and from birds in South-east Asia carrying M2 inhibitor resistance mutations. Few in vitro studies were found that described the effects of amantadine on H5N1 virus and no animal studies about the effects of amantadine on H5N1 virus were identified.

Benefits

There is insufficient evidence in the reported studies to evaluate the benefit of amantadine on mortality or duration of hospitalization in either seasonal influenza or H5N1 infection. Data obtained from 3 small trials of individuals with seasonal influenza A suggest no reduction in influenza A viral shedding associated with amantadine treatment (RR 0.96, 95% CI 0.72 to 1.27).

Harms

There are limited data on serious adverse events described in the systematic reviews highlighting the limitations of systematic reviews and published randomized controlled trials in reporting adverse events. The Cochrane review of amantadine treatment and chemoprophylaxis in seasonal influenza reports no significant difference in the number of mild adverse effects (gastrointestinal and central nervous system) between the treatment and placebo groups but it focused on randomized controlled trials. The data submitted by the manufacturer to the US Food and Drug Administration reported nausea, dizziness (lightheadedness) and insomnia as the most frequent adverse events in both children and adults. Observational studies and case reports have documented increased frequencies of moderate to severe central nervous system side effects, including hallucinosis, delirium, psychosis, altered mentation, and coma in elderly subjects, those with renal insufficiency, and those receiving concurrent psychoactive medications, as well as increased seizure activity in those patients with pre-existing disorders. Spontaneous reporting to WHO of adverse reactions listed 1863 reports of adverse reactions, but there is no assessment of causality or severity of these events in relation to amantadine. The most commonly reported adverse event was hallucinations (n = 389 cases). There are two case reports of use of amantadine during pregnancy. In one of these cases spontaneous abortion occurred although the mother was also receiving two other additional medications; no assessment of causality was carried out.

The development of resistance is a frequent problem with amantadine.

Treatment considerations

Available formulations:

Amantadine is available in tablet 100 mg, capsule and syrup form.

The recommended treatment dose of amantadine in seasonal influenza A is 100 mg twice daily in adults and children between 10 and 65 years of age, for 5 days (CDC 2006a). In the elderly over 65 and in other populations in some jurisdictions, a once-daily dose of 100 mg is recommended.[1]

In children under 10 (CDC 2006a (table 1))

- 1–9 years: 5mg/kg/day (not to exceed 150 mg per day, in 2 divided doses)
- 10–12 years: 100mg twice daily

In patients with renal impairment (See FDA approved label):

Creatinine clearance (ml/min/1.73 m2)	**Dose**
• 30–50	200 mg 1st day and 100 mg each day thereafter
• 15–29	200 mg 1st day and 100 mg on alternate days
• <15	200 mg every 7 days

The recommended dosage for patients on haemodialysis is 200 mg every 7 days.

Amantadine should be used with caution in patients receiving treatment with neuropsychiatric drugs and patients with seizure disorders, where the potential risks outweigh the benefits. This drug should not be used by women who are breastfeeding. Poor adherence rates secondary to adverse effects have been reported with amantadine use.

Other research and basic research findings

Clade 1 H5N1 virus isolated from humans in Thailand and from birds in South-east Asia carries mutations associated with resistance to M2 inhibitors. However. these mutations have not yet been identified in clade 2 H5N1 viruses isolated from the People's Republic of China.

High-level resistance is readily selected by growth of human influenza A virus in the presence of amantadine in vitro and in vivo and confers cross-resistance to other M2 inhibitors. While all contemporary pandemic strains of human influenza A virus have been susceptible, the frequency of resistance in community H3N2 isolates has increased dramatically, now exceeding 90% in North America (Bright JAMA CDC), and many clade 1 H5N1 virus also show de novo resistance. Resistance has been found in H1N1 viruses from the pre-amantadine era (Hayden 1996, Bean 1992, Abed 2005, Hay 1996).

No animal studies of H5N1 virus and the effects of amantadine were identified.

[1] The recommended regimen in the British National Formulary (BNF) and in Japan is 100mg od for patients > 10yrs of age.

Conclusion

Amantadine appears *not* to be of greater net clinical benefit as a first-line agent in the treatment of H5N1 infection compared to the neuraminidase inhibitors where these medicines are available. Drug resistance is a major limitation. However, amantadine may have net clinical benefit as a first-line agent in the treatment of H5N1 infection when neuraminidase inhibitors are not available and the H5N1 virus is known or likely to be susceptible to amantadine. There are no clinical trials dealing with amantadine treatment in H5N1 patients. This assessment of possible net benefit under certain circumstances is based on extrapolations from studies performed in populations with seasonal influenza A and includes consideration of likely development of drug resistance and the incidence of toxic effects.

Clinical recommendations

Rec 03: If neuraminidase inhibitors <u>are available</u>, clinicians should <u>not</u> 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 recognizing 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 may be more effective.

Rec 04: If neuraminidase inhibitors are <u>not available</u> 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 in patients at higher risk for adverse outcomes (e.g. pregnant patients).

5.4 Should H5N1 patients receive treatment with rimantadine?

Summary of findings

No clinical trial or case study has evaluated rimantadine treatment of H5N1 infection.

Two systematic reviews (annex 3) were identified that examined the use of rimantadine for the treatment of seasonal influenza A in otherwise healthy adults, high risk adults or children. The doses of rimantadine in the studies were 200 mg once daily and 150 mg twice daily in adults for up to 10 days. The studies were conducted in the USA.

Two studies reported clade 1 H5N1 viruses isolated from humans in Thailand and from birds in South-east Asia carrying M2 inhibitor resistance mutations. There are few in vitro studies about the effects of rimantadine on H5N1 virus and no animal studies describing the effects of rimantadine on H5N1 virus. Animal and in vitro studies have shown the development of cross-resistance to the M2 inhibitors in human influenza A virus grown in the presence of these compounds (Abed 2005, Hay 1996, Hayden 1996**)**.

Benefits

There is insufficient evidence in the reported studies to evaluate the benefit of rimantadine on mortality or duration of hospitalization in either seasonal influenza A or H5N1 infection. Data from 3 small trials of individuals with seasonal influenza A suggest there is no evidence of a statistically significant reduction in influenza A viral shedding associated with rimantadine treatment (RR 0.67, 95% CI 0.22 to 2.07).

Harms

Similarly to the description of adverse events with amantidine use, there are very limited data on serious adverse events described in the systematic reviews. The Cochrane review of rimantadine use in influenza A shows no significant difference in the number of adverse effects (gastrointestinal and central nervous system) occurring in the treatment or placebo groups but the data from randomized trials are limited. In addition, the review showed no significant difference in the number of adverse effects when rimantadine was compared with amantadine. The data submitted by the manufacturer to the US Food and Drug Administration reported nausea, vomiting, dizziness and insomnia as the most frequent adverse events. Spontaneous reporting to WHO of adverse reactions includes 182 reports of adverse reactions, but there is no assessment of causality or severity of these events in relation to rimantadine. The most commonly reported adverse event was convulsions (n = 21), with a further 17 reported with grand mal convulsions. However, observational studies have shown that the incidence of adverse central nervous system effects was significantly less with rimantadine than with amantadine (Dolin 1982). No case reports on the use of rimantadine during pregnancy exist.

Treatment considerations

Available formulations:

Rimantadine is available in tablet and syrup form.

The recommended treatment dose of rimantadine in seasonal influenza A is 100 mg twice a day for adults and children over 12 years of age (CDC 2006a, CDC 2006b). In patients with severe hepatic dysfunction, renal failure (creatinine clearance of 10 ml/min) and elderly nursing home patients, a dose reduction to 100 mg daily is recommended. There are currently no data available regarding the safety of rimantadine in patients with renal or hepatic impairment (see FDA approved label)

Other research and basic research findings

One study evaluated the effect of rimantadine on viral replication using H5N1 isolates from humans, and demonstrated no effect. One additional study using multiple strains of H5N1 virus also evaluated the effect of rimantadine on viral replication. High-level resistance is readily selected by growth of human influenza A virus in the presence of amantadine in vitro and in vivo and confers cross-resistance to other M2 inhibitors. No data were available from animal studies of H5N1 virus and rimantadine.

Conclusion

Although there are no comparative clinical trials, rimantadine appears *not* to be of greater net clinical benefit as a first-line agent in the treatment of H5N1 infection than the neuraminidase inhibitors, when these drugs are available. However, rimantadine may be of net clinical benefit as a first-line agent in the treatment of H5N1 infection when neuraminidase inhibitors are **not** available and the virus is known or likely to be susceptible. In this situation the use of rimantadine may be preferable to amantadine, given the more favourable side-effect profile (Dolin 1982). There are no clinical trials dealing with rimantadine treatment in H5N1 patients. This assessment of possible net benefit is based on extrapolations from studies performed in populations with seasonal influenza A and includes consideration of likely development of drug resistance and the incidence of toxic effects.

Clinical recommendations

Rec 05: 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 recognizing 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 may be more effective.

Rec 06: If neuraminidase inhibitors are <u>not available</u> 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 favorable side effect profile than amantadine.

5.5 Should H5N1 patients receive combination treatment of M2 inhibitors and neuraminidase inhibitors?

Summary of findings

No clinical trial or case study has evaluated the combination of M2 inhibitors and neuraminidase inhibitors in the treatment of H5N1 infection.

No systematic review has examined the combination of M2 inhibitors and neuraminidase inhibitors in the treatment of H5N1 infection. The review identified one small randomized controlled trial that compared nebulized zanamivir (16 mg four times daily) and rimantadine (100 mg once or twice daily administered to hospitalized patients with seasonal influenza A only) to rimantadine and placebo in the USA. The study was terminated after enrollment of 41 patients and approximately 40 percent of patients were lost to follow-up (9 of 20 in the combined treatment group and 7 of 21 in the rimantadine group) (Ison 2003, Madren 1995, Leneva 2000, Govorkova 2004). Nebulized zanamivir is not currently available.

Few animal and in vitro studies describe the effects of combination treatment of H5N1 infection. Oral administration of oseltamivir, in combination with rimantadine in mice infected with avian influenza A (H9N2) virus reduced the number of deaths. In vitro and animal model studies with human influenza A (H1N1 and H3N2) viruses suggest that combining neuraminidase inhibitors and rimantadine exerts an additive or synergistic anti-influenza effect for viruses that are susceptible to both agents (see annex 3).

Benefits

There are too few data to assess any benefit of combination treatment on mortality or duration of hospitalization in either seasonal influenza or H5N1 infection. There are no published case reports of H5N1 infection treated with a combination of M2 inhibitors and neuraminidase inhibitors. Thus, there is no evidence beyond what is known for monotherapy with either of these agents to evaluate any effect on H5N1 infection.

Harms

The harms seen for monotherapy are described in the relevant sections and are likely to apply to combination therapy. Based on the known pharmacology, no additive effect on adverse effects might be expected, although increased gastrointestinal intolerance is a possibility with combinations of M2 inhibitors and oseltamivir. In addition, the severity of H5N1 illness must be taken into account when considering possible benefits and harms. The one small randomized control trial in patients with seasonal influenza suffered from large numbers of drop outs, but it is not possible to determine whether these were due to adverse effects. No information on resistance of H5N1 virus to combination therapy exists, but H5N1 virus resistant to the M2 inhibitors is known to exist.

Treatment considerations

Treatment considerations and available formulations for monotherapy have been described in the relevant sections. These apply for combination therapy.

Other research and basic research findings

Animal studies of human influenza viruses, examining combinations of oseltamivir and M2 inhibitors, showed synergistic effects (see annex 3).

Conclusion

There are no direct data from the use of combination therapy of M2 inhibitors and neuraminidase inhibitors in H5N1 patients. There is no evidence of net clinical benefit of combination therapy in patients with seasonal influenza A.

Clinical recommendations[1]

Rec 07: 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 downsides in patients of higher risk for adverse outcomes. Combination therapy should only be carried out if detailed and standardized clinical and virological data collection is in place at the start of therapy (prospective data collection). Clinicians should carefully determine which patients (e.g. severely ill patients) could receive combination therapy.

[1] The panel voted on whether a weak recommendation or no recommendation should be given and there were three dissenting votes out of thirteen.

6. Chemoprophylaxis of H5N1 infection: recommendations for use of antiviral drugs

An exposure-based assessment of risk has been devised to evaluate the net clinical benefits of antiviral chemoprophylaxis. Decisions to initiate antiviral chemoprophylaxis should generally be guided by the risk stratification described below. The stratification is based on observational data for reported cases of H5N1 infection and on high quality data from studies of seasonal influenza.

High risk exposure groups are currently defined as:

- Household or close family contacts[1] 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:

- Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal) if personal protective equipment may not have been used properly.
- Individuals with unprotected and very close direct exposure[2] to sick or dead animals infected with the H5N1 virus or to particular birds that have been directly implicated in human cases.
- 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 group also includes laboratory personnel who might have an unprotected exposure to virus-containing samples.[3]

Low risk exposure groups are currently defined as:

- Health care workers not in close contact (distance greater than 1 metre) with a strongly suspected or confirmed H5N1 patient and having no direct contact with infectious material from that patient.

---

[1] A close contact may be defined as an individual sharing a household with, or remaining unprotected whilst within speaking distance (< 1 metre) of, or in the care of, a patient with confirmed or strongly suspected H5N1 infection.

[2] 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 or other products from infected animals (e.g. plucking feathers); or prolonged exposure to infected birds in a confined space, such as playing with pets.

[3] This definition of moderate risk is based on very few cases recognized under these situations to date. As circumstances may 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.

- 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 as a control measure.
- Personnel involved in handling sick animals or decontaminating affected environments (including animal disposal), who used proper personal protective equipment.

In the present absence of sustained human-to-human transmission of the H5N1 virus, the general population is not considered at risk. The observed clustering of some H5N1 cases within families has raised the possibility of genetic susceptibility to the virus. Once an H5N1 patient has been identified, an urgent epidemiological field investigation should be undertaken and follow up of close contacts should be initiated.

The panel rated outbreak control, drug resistance and serious adverse effects as critical outcomes in the assessment of prophylactic interventions for H5N1 infection. While the quality of the evidence for some of the critical outcomes was moderate or low, the overall quality of evidence on which to base a summary assessment was very low for all antiviral drugs. Differences exist in the quality of evidence for individual critical outcomes among the various antiviral drugs (see annex 3 for gradings and ratings).[1]

6.1 Should oseltamivir be used for the chemoprophylaxis of H5N1 infection?

Summary of findings

No clinical trial has evaluated oseltamivir for chemoprophylaxis of H5N1 infection.

Two systematic reviews and HTAs (annex 3) have examined chemoprophylaxis of seasonal influenza with oseltamivir for 1 to 6 weeks in otherwise healthy adults, high risk adults or children including household contacts. The doses of oseltamivir in the individual studies varied between the trials. The studies were conducted in the northern hemisphere and resource-poor countries were not represented.

The animal and in vitro data about the effects of oseltamivir on H5N1 infection were described above in the section on treatment of H5N1 infection.

Benefits

Three randomized controlled trials investigating the effect of oral oseltamivir on post-exposure influenza incidence found large reductions in laboratory-confirmed influenza (relative risk reductions of 50% to 89%). No differences in prophylactic efficacy were found between 75 mg once daily and 75 mg twice daily dosing in seasonal influenza in adults (Hayden 1999). One trial in the elderly found a relative risk reduction of 92% but included only 13 events. No significant effect on influenza-like illnesses was seen in these three trials.

[1] Based on the GRADE approach to grading the quality of evidence, the critical outcome with the lowest quality of evidence determines the overall quality assessment.

Two trials studied the effects of oseltamivir used as chemoprophylaxis, in which household contacts of influenza cases received chemoprophylaxis for 7 to 10 days after exposure to an index case (Welliver 2001, Hayden 2004). Effects on mortality were not reported, nor were effects on viral shedding and outbreak control, but prevention of influenza illness would be expected to reduce likelihood of influenza-associated complications, hospitalizations, and mortality. No information on potential cost savings from effective chemoprophylaxis of seasonal influenza was reported and therefore potential cost savings in chemoprophylaxis of H5N1 cannot be inferred. There is no controlled trial evidence about the effects of post-exposure chemoprophylaxis in health care workers potentially exposed to the H5N1 virus or workers handling dead or diseased birds or engaged in the decontamination of animal environments.

Harms

Information about resistance to oseltamivir and serious adverse events was not reported in the systematic reviews. Information reported by the manufacturer to the US Food and Drug Administration included an increased incidence of nausea in patients receiving chemoprophylaxis (7% versus 3%). As described in the section on treatment with oseltamivir, three cases of resistance to oseltamivir developing after treatment in patients with avian influenza A (H5N1) have been described.

Other harms relating to treatment with oseltamivir are reported in section 5.1.

Considerations for chemoprophylaxis

Available formulations:

Oseltamivir phosphate is available as a capsule containing 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension.

When considering chemoprophylaxis of H5N1 infection, high priority should be given to standard infection control practices. These practices can protect health care workers and household contacts as well as individuals involved in decontamination of animals. The recommended chemoprophylaxis dose is 75 mg once daily in adults and the following weight-adjusted doses in children, for 7–10 days:

- Children 1 year of age or older: weight-adjusted doses
- 30 mg once daily for ≤ 15 kg
- 45 mg once daily for >15 to 23 kg
- 60 mg once daily for >23 to 40 kg
- 75 mg once daily for >40 kg

There is no evidence available for the chemoprophylactic use of oseltamivir in children under 1 year of age.

Chemoprophylaxis courses should begin as soon as possible after exposure status is known and be used continuously for 7 to 10 days after the last known exposure. Although based on indirect evidence from seasonal influenza, chemoprophylaxis with oseltamivir for periods of up to 8 weeks is considered safe.

Other research and basic research findings

These findings have been described in section 5.1.

Conclusion

The evidence for pharmacological chemoprophylaxis of H5N1 infection with oseltamivir in exposed and unexposed individuals is of 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. Oseltamivir might effectively provide an important reduction in H5N1 virus transmission. This view is based on extrapolation from studies performed in populations with seasonal influenza.

Clinical recommendations

Rec 08: 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 to 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.

Rec 09: 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 to 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.

Rec 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, potential development of resistance and cost. It places a lower value on preventing the low risk of H5N1 disease.

Rec 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.

6.2 Should zanamivir be used for the chemoprophylaxis of H5N1 infection?

Summary of findings

No clinical trial has evaluated zanamivir for chemoprophylaxis of H5N1 infection.

Three systematic reviews and HTAs (annex 3) have examined chemoprophylaxis of seasonal influenza with inhaled zanamivir for 5 to 28 days in otherwise healthy adults and high risk groups, including close contacts of index cases. The studies were conducted in the northern hemisphere and resource-poor countries were not represented.

The animal and in vitro data about the effects of zanamivir on H5N1 virus were described above in the corresponding section on treatment of human infection with avian influenza A (H5N1) virus.

Benefits

Two randomized controlled trials investigating the effect of inhaled zanamivir on post-exposure influenza incidence in healthy adults found large reductions in laboratory-confirmed influenza (OR 0.19, 95% CI 0.09 to 0.38). A similar effect was seen in 2 trials of seasonal chemoprophylaxis.

Influenza-like illnesses was not reported as an outcome in the post-exposure chemoprophylaxis trials and there was no significant reduction in the number of cases of influenza-like illness with chemoprophylaxis using inhaled zanamivir.

Another trial assessing the combination of both intranasal and inhaled zanamivir in healthy adults showed no additive benefit. A similar study of combined inhaled and intranasal chemoprophylaxis in elderly and high-risk adults showed no significant reduction in the number of laboratory-confirmed cases of seasonal influenza or influenza-like illness.

Effects on mortality were not reported in any of the studies. Information on viral shedding and outbreak control was not reported although this outcome was considered critical for the evaluation of zanamivir as chemoprophylaxis.

No information on potential savings of chemoprophylaxis of H5N1 infection was reported. There is no evidence about the effects of post-exposure chemoprophylaxis in health care workers potentially exposed to the H5N1 virus or workers involved in decontamination of avian influenza A (H5N1) virus.

Harms

No prophylaxis failures due to drug-resistant virus have been recognized to date, including when zanamivir has been used for both treatment and post-exposure prophylaxis in the same households (Hayden 2000). The number of trial withdrawals was reported in one study of chemoprophylaxis of seasonal influenza with inhaled zanamivir. This study showed no significant difference between the number of withdrawals in treatment and placebo arms. As described in the section on treatment with zanamivir, no information on resistance of H5N1 virus to zanamivir exists.

Other harms relating to treatment with zanamivir are reported in section 5.1.

Considerations for chemoprophylaxis

Available formulations:

Zanamivir is available for oral inhalation only, using a diskhaler device. Nebulized and intranasal formulations of zanamivir have been used in clinical trials but are not available for clinical use.

When considering chemoprophylaxis of infection with avian influenza A (H5N1) virus, high priority should be given to standard infection control practices. These practices protect health care workers and individuals involved in disposal of animals as well as household contacts. The recommended dose of inhaled zanamivir in individuals aged 5 years and over is 10 mg once daily as chemoprophylaxis (FDA press release 2006[1]). The duration of use of zanamivir has ranged from 5 to 28 days in healthy adults. Courses should begin as soon as possible after exposure status is known and be used continuously for 7 to 10 days after last known exposure.

Other research and basic research findings

These findings have been described in section 6.2.

Conclusion

The evidence for pharmacological chemoprophylaxis of H5N1 infection with zanamivir in exposed and unexposed individuals is of very low quality and indirect. However, zanamivir, when used as post-exposure chemoprophylaxis against seasonal influenza, has shown relatively large reductions in the incidence of influenza cases. Zanamivir might effectively provide an important reduction in cases of H5N1 infection. This view is based on extrapolation from studies performed in populations with seasonal influenza.

[1] US Food and Drug Administration (2006). FDA News: FDA Approves a Second Drug for the Prevention of Influenza A and B in Adults and Children http://www.fda.gov/bbs/topics/NEWS/2006/NEW01341.html.

Clinical recommendations

Rec 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 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 to 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 may 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.

Rec 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 to 10 days after the last known exposure. The bioavailability of zanamivir outside of the respiratory tract is lower than that of oseltamivir. Zanamivir may be active against some strains of oseltamivir-resistant H5N1 virus. This recommendation also applies to pregnant women in the moderate risk exposure group.

Rec 14: In low risk exposure groups, zanamivir should probably <u>not</u> 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.

Rec 15: Pregnant women in the low risk exposure group should <u>not</u> 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.

6.3 Should amantadine be used for the chemoprophylaxis of H5N1 infection?

Summary of findings

No clinical trial has evaluated amantadine for post-exposure chemoprophylaxis of H5N1 infection.

Three systematic reviews and HTAs (annex 3) have examined chemoprophylaxis of seasonal influenza A with amantadine for 20 days to 6 weeks in otherwise healthy adults, the elderly, children with learning difficulties and high-risk children (data for the elderly and children came from studies conducted in a residential environment). The dose of amantadine was typically 100 mg twice daily. The studies were conducted in the northern hemisphere and resource-poor countries were not represented.

Observational studies have shown transmission of resistant human influenza A viruses from treated persons to close contacts in nursing homes due to failures of drug prophylaxis (Houck 1995, Mast 1991).

As stated previously, clade 1 H5N1 viruses isolated from humans in Thailand and from birds in South-east Asia have been shown to carry M2 inhibitor resistance mutations for amantadine. The animal and in vitro data about the effects of amantadine on H5N1 virus were described above in the section on treatment of H5N1 infection.

Benefits

Eleven randomized controlled trials investigating the effect of oral amantadine on seasonal influenza A incidence in healthy adults found large reductions in laboratory-confirmed influenza A (relative risk reductions of 35% to 76%). A significant effect on influenza-like illnesses in healthy adults was seen in fifteen trials reporting this outcome, with a relative risk reduction of 13% to 36%. Effects on mortality were not reported. Only one trial reported on viral shedding, showing a relative risk reduction of 13% to 47%.

No information on potential savings of chemoprophylaxis of H5N1 infection was reported. There is no evidence for the use of amantadine as post-exposure chemoprophylaxis for H5N1 infection in any population, including health care workers or workers involved in decontamination of H5N1 virus.

Harms

Use of amantadine is associated with adverse effects on both the central nervous system and gastrointestinal tract. Six trials of chemoprophylaxis in healthy adults reported a relative risk of withdrawal due to adverse effects of between 1.5 and 3.7 in the group receiving amantadine. The risk of adverse effects is higher in chemoprophylaxis arms and they occur earlier. Further harms relating to treatment with amantadine are reported in section 5.3.

Considerations for chemoprophylaxis

Available formulations:

Amantadine is available in tablet 100 mg, capsule and syrup form.

When considering chemoprophylaxis of H5N1 infection, high priority should be given to standard infection control practices. These practices protect health care workers and household contacts as well as individuals involved in decontamination of animals.

The recommended chemoprophylactic dose of amantadine in seasonal influenza A is 100 mg twice daily in adults and children between the ages of 10 and 65 years for 7 to 10 days after the last known exposure (CDC 2006a, CDC 2006b). In the elderly over 65 years of age, a once daily dose of 100 mg is recommended.

In children under 10 years of age (CDC 2006a table 1)

- 1–9 years: 5 mg/kg/day (not to exceed 150mg per day, in 2 divided doses)
- 10–12 years: 100 mg twice daily

In patients with renal impairment (See FDA approved label):

Creatinine clearance (ml/min/1.73 m2)	**Dose**
• 30–50	200 mg 1st day and 100 mg each day thereafter
• 15–29	200 mg 1st day and 100 mg on alternate days
• <15	200mg every 7 days

The recommended dosage for patients on haemodialysis is 200 mg every 7 days.

Amantadine should be used in caution in patients receiving treatment with neuropsychiatric drugs and patients with seizure disorders, where the potential risks outweigh the benefits. The drug should not be used by women who are breastfeeding. Poor adherence rates secondary to adverse effects have been reported with amantadine use.

Other research and basic research findings

These findings have been described in section 5.3.

Conclusion

The evidence for pharmacological chemoprophylaxis of H5N1 infection with amantadine in exposed and unexposed individuals is of very low quality because it is indirect. While studies of amantadine chemoprophylaxis have shown a reduction in the number of seasonal influenza A cases, there is a possibility of antiviral resistance developing rapidly where amantadine treatment is used in conjunction with amantadine chemoprophylaxis. In addition, there is a higher incidence of adverse effects associated with amantadine use.

Amantadine appears *not* to be of greater net clinical benefit as a first-line agent for chemoprophylaxis of H5N1 infection compared to the neuraminidase inhibitors when these medicines are available. However, amantadine may 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. This view is based on extrapolation from studies performed in populations with seasonal influenza A.

Clinical recommendations

Rec 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.

Rec 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 to 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.

Rec 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.

Rec 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).

6.4 Should rimantadine be used for the chemoprophylaxis of H5N1 infection?

Summary of findings

No clinical trial has evaluated rimantadine for post-exposure chemoprophylaxis of H5N1 infection.

Two systematic reviews (annex 3) have examined chemoprophylaxis of seasonal influenza A with rimantadine for up to 6 weeks in otherwise healthy adults (no data were reported for the elderly, high risk groups or children). The studies were conducted in the northern hemisphere and resource-poor countries were not represented.

A randomized controlled trial by Hayden et al in seasonal influenza H3N2 showed transmission of resistant human influenza A viruses from treated persons to household contacts due to failure of drug prophylaxis (Hayden et al 1989).

As stated previously, clade 1 H5N1 viruses isolated from humans in Thailand and from birds in South-east Asia have been shown to carry M2 inhibitor resistance mutations for rimantadine. The animal and in vitro data about the effects of rimantadine on H5N1 virus were described above in the section on treatment of H5N1 infection.

Benefits

Three randomized controlled trials investigating the effect of oral rimantadine on seasonal influenza A incidence in healthy adults found no significant reduction in laboratory-confirmed cases of influenza A cases or influenza-like illness. Effects on mortality were not reported. No trial reported on viral shedding or provided information on potential savings of chemoprophylaxis of H5N1 infection. There is no evidence for the use of rimantadine as post-exposure chemoprophylaxis for H5N1 infection in any population, including health care workers potentially exposed to the H5N1 virus or workers involved in decontamination of H5N1 virus.

Harms

Three trials of chemoprophylaxis in healthy adults showed no significant difference in terms of withdrawals due to adverse effects between the group receiving rimantadine and the placebo arm. Further harms relating to treatment with rimantadine are reported in section 5.4.

Considerations for chemoprophylaxis

Available formulations:

Rimantadine is available in tablet and syrup form.

When considering chemoprophylaxis for H5N1 infection, high priority should be given to standard infection control practices. These practices protect health care workers, household contacts and individuals involved in decontamination of animals.

Rimantadine has been used for as long as 7 weeks for chemoprophylaxis of seasonal influenza A at doses of 100 mg twice daily in adults and children over 10 years of age. In patients with severe hepatic dysfunction, renal failure (creatinine clearance of 10 ml/min) and elderly nursing home patients, a dose reduction to 100 mg daily is recommended. There are currently no data available regarding the safety of rimantadine during multiple dosing in subjects with renal or hepatic impairment (see FDA approved label). In children less than 10 years of age, rimantadine should be administered once a day, at a dose of 5 mg/kg but not exceeding 150 mg, in two divided doses.

Other research and basic research findings

These findings have been described in section 5.4.

Conclusion

The evidence for pharmacological chemoprophylaxis of H5N1 infection with rimantadine in exposed and unexposed individuals is of very low quality and very indirect. Studies of rimantadine chemoprophylaxis have not shown a reduction in the number of cases of seasonal influenza A. There is a possibility of antiviral resistance developing rapidly where rimantadine treatment is used in conjunction with rimantadine chemoprophylaxis.

Rimantadine appears **not** to be of greater net clinical benefit as a first-line agent for chemoprophylaxis of H5N1 infection compared to neuraminidase inhibitors when these medicines are available. However, rimantadine could have net clinical benefit as a first-line agent for prophylaxis of H5N1 infection when neuraminidase inhibitors are not available and the H5N1 virus is known or likely to be susceptible. This view is based on extrapolation from studies performed in populations with seasonal influenza.

Clinical recommendations

Rec 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.

Rec 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 to 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.

Rec 22: If neuraminidase inhibitors are <u>not available</u> and even if the virus is known or likely to be susceptible, rimantadine should probably <u>not</u> 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.

Rec 23: In pregnant women rimantadine should <u>not</u> be administered for chemoprophylaxis of human infection with avian influenza A (H5N1) virus (strong recommendation, very low quality of evidence).

7. Co-interventions for the management of H5N1 patients

The recommendations in this section have been developed differently from those in the sections on antiviral drugs, as priority was given to the assessment of antiviral drugs. The panel did not make formal judgements about the quality of the evidence for most of the co-interventions described below. However, when there was consensus about the informal assessment of the evidence regarding benefits, harms and burdens, the panel made recommendations without quality grading. Full details are described in annex 2.

7.1 Should H5N1 patients be treated with prophylactic antibiotics? Is it possible to make general recommendations about specific antibiotics?

There are no systematic reviews that summarize the effectiveness of broad-spectrum antibiotics for prevention of secondary pneumonia in patients with primary viral pneumonia. However, many countries and specialist societies have developed standard treatment guidelines for the use of antibiotics as empirical treatment of community-acquired and hospital-acquired pneumonia and some general principles can be recommended (see annex 7).

Most hospitalized H5N1 patients have received empirical treatment with broad-spectrum antibiotics. Arguments favouring this intervention are uncertainty about the cause of infection at the time of presentation as well as the possible prevention of secondary bacterial infection. There are limited microbiological data available from H5N1 cases which suggest that the process is primarily a viral pneumonia *without* bacterial superinfection although there have been 3 cases of hospital-acquired gram-negative pneumonia in ventilated patients in Viet Nam.

Rec 24: In patients with severe community-acquired pneumonia regardless of the geographical location, clinicians should follow appropriate clinical practice guidelines (strong recommendation, the panel has not judged the quality of the evidence for this recommendation).

Remarks: The choice of antibiotics should be based on knowledge of local pathogens, other co-morbidities and resistance patterns. Hospitals should have local antimicrobial surveillance data that can be used to inform the choice. Further advice about monitoring antimicrobial resistance is available in the WHO Global Strategy for Containment of Antimicrobial Resistance, at http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf. Local standard treatment guidelines should be updated regularly.

Rec 25: In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus who do <u>not</u> need mechanical ventilation and have no other indication for antibiotics, clinicians should <u>not</u> administer prophylactic antibiotics (strong recommendation, the panel has not judged the quality of the evidence for this recommendation).

Remarks: This is a strong recommendation in part because there is no evidence that antibiotic chemoprophylaxis reduces the risk of bacterial superinfection in H5N1 or seasonal influenza, whether or not the patients require mechanical ventilation. Antibiotics are likely to select for resistant bacteria, if superinfection occurs. Thus, at present there are no known net clinical benefits from chemoprophylaxis with antibiotics.

Rec 26: In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus who need mechanical ventilation, clinicians should follow clinical practice guidelines for the prevention or treatment of ventilator associated or hospital acquired pneumonia (strong recommendation, the panel has not judged the quality of the evidence for this recommendation).

Remarks: As the risk for bacterial infection in mechanically ventilated patients is increased, this recommendation places a high value on avoiding consequences of proven or suspected bacterial infection and a low value on adverse effects of antibiotics, the development of resistance, and cost. Appropriate broad spectrum antibiotic therapy should be instituted with a commitment to tailor antibiotics as soon as possible on the basis of serial clinical and anti-microbiologic data.

Specific recommendations on antibiotics need to consider the variation in patterns of drug resistance; Annex 7 lists examples of national standard treatment guidelines for pneumonia.

7.2 Should steroids and other immunosuppressants be used in the treatment of H5N1 patients?

Corticosteroids have been used frequently in patients with H5N1 disease. Of the cases reported up to the end of 2005, 25 from a total of 55 cases were treated with varying doses. There is no clear evidence of benefits; in a very small randomized trial in Viet Nam, 4 out of 4 H5N1 patients treated with steroids died. There is currently no basis to make a recommendation for the use of corticosteroids in the management of acute H5N1 disease in humans, and there may be theoretical reasons to be cautious in using immunosuppressants in patients with viral illness. Sequelae and complications such as shock may require use of corticosteroids independent of H5N1 virus infection.

Interferon alpha has been suggested as another possible co-intervention in the management of H5N1 disease, on the theoretical basis that it has antiviral and immunomodulatory activities. However, interferon alpha can cause anaemia, hypotension and leucopenia as well as other adverse effects, and limited in vitro data suggest that H5N1 virus may be resistant to the antiviral effects of interferons. There is therefore currently no basis for use of interferon alpha in patients with H5N1 disease outside the context of a randomized controlled trial.

7.3 Should immunoglobulin be used in the treatment of H5N1 patients?

Pooled human immunoglobulin has also been considered as a possible co-intervention in patients with H5N1 disease, on the theoretical grounds that the immune response may contribute to the pathogenesis of the disease and that immunoglobulin may modify the immune response. There is no direct or in vitro evidence that this is the case in H5N1 disease and pooled human immunoglobulin is highly unlikely to contain specific antibodies against H5N1 virus. Pooled immunoglobulin can carry a risk of blood-borne infection. There is therefore currently no basis for the use of immunoglobulin in patients with H5N1 disease outside the context of a randomized controlled trial.

7.4 Should ribavirin be used in the treatment of H5N1 patients?

Ribavirin has been used as a co-intervention in the management of H5N1 patients in Hong Kong SAR and Viet Nam. In Viet Nam the use of relatively low doses of oral ribavirin was not associated with any obvious benefit. Although one in vitro study, using duck and gull H5N1 strains, has shown that ribavirin was highly effective against viral replication, its use in seasonal influenza and H5N1 infection has been not systematically reviewed. In addition, ribavirin-induced side effects, including hemolytic anaemia, have been seen in patients with SARS-associated coronarvirus (SARS-CoV) infection (Knowles 2003).

There is therefore currently no basis to make a recommendation regarding the use of ribavirin in the management of H5N1 disease in adults. In the case of pregnant women, however, there is evidence for teratogenic effects of ribavirin during pregnancy.

Rec 27: In pregnant patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians should not administer ribavirin as treatment or chemoprophylaxis (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on avoiding the high risk of teratogenic effects of ribavirin during pregnancy.

8. Antiviral drug supply

The availability of antiviral drugs, particularly oseltamivir, has been the subject of significant public discussion. Supplies, particularly of oseltamivir, have been limited but it is anticipated that this situation may change over the next year. The table below lists the current registration status (as of April 2006) of oseltamivir, zanamivir, amantadine and rimantadine in major markets, and prices of each medicine for one course of treatment in major markets. This is an indicative list only.

Any product being considered for supply or stockpiling needs to be registered/licensed in the country of supply. Registration/licensing is the only way to guarantee the adequate quality of a given product. Countries and clinicians need to be aware that the high demand for antiviral drugs has resulted in some incidents of counterfeit drugs being marketed.

If a product is not registered in the country in which it is to be used, for example in the case of emergency supply to treat patients with confirmed or suspected H5N1 infection, clinicians may have to obtain approval from the local drug regulatory authority to use the product for emergency purposes. Each country should have a legislative mechanism to allow emergency use of unregistered medicines. Consideration should also be given, where appropriate, to the possible use of flexible packaging, in order to optimize ease of dispensing and minimize potential wastage.

Table 1

Product	Manufacturer(s) examples	Generics available?	Approved indications	Drug regulatory authority	Indicative range of prices
Amantadine hydrochloride 100mg capsules	Endo Laboratories[1], Alliance[2]	yes	Chemoprophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A viruses	UK, US FDA, national authorities in Europe, Japan MHLW	US$ 6-11 for 5 capsules (US, UK)
Oseltamivir 75 mg capsules; powder for reconstitution as 60mg/5mL suspension	Roche (innovator)	Limited; licensing agreements in India	Treatment of uncomplicated acute illness due to influenza A virus infection in patients 1 year and older; and chemoprophylaxis of influenza A in patients 1 year and older (over 13 years in Japan)	US FDA, EMEA, Japan MHLW	Highly variable. For stockpiling, range currently from €12-15 per pack of 10 capsules. US$ 90.60 per pack of 10 capsules (US community pharmacy price)
Rimantadine 100mg tablets	Forest	yes	Chemoprophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A viruses	US FDA, national authorities in Europe	US$ 25 for 10 tablets (USA)
Zanamivir diskhaler (dry powder fro inhalations disks, 5mg per disk)	GlaxoWellcome	no	Treatment of uncomplicated influenza A in patients over 7 years (over 5 years in Japan); for prevention of influenza A in adults and children 5 years of age and older.[3]	US FDA, EMEA, Japan MHLW	US$ 74-87[1]; £25[2] for 5 disks

[1]USA, [2]United Kingdom, [3]Approved in the USA only on 29 March 2006.

9. Priorities for revision of the guidelines

Plans for updating the guidelines

Guidelines are living documents. To remain useful, they need to be updated regularly as new information becomes available. A revision of this document will be needed if any of the following events occur:

- major new research is published (particularly randomized controlled trials of any of the antiviral drugs or observational studies);
- new antiviral drugs becoming available;
- there is a change in the pathogenicity or transmissibility of the H5N1 virus, especially one that requires re-evaluation of the risk categories used in the document.

Independent of these three criteria, an update of the guidelines, including a complete review of new evidence, is planned no later than April 2007.

Updating or adapting recommendations locally

The methods used to develop the guidelines are transparent. It will therefore be possible to update the contents by simply re-running the search described in the annex on methods (section Search strategy, annex 3). The recommendations have been developed to be as specific and detailed as possible without losing sight of the user-friendliness of this document and the individual recommendations. The panel encourages feedback on all aspects of these guidelines including their applicability in individual countries. This feedback will be considered when revising the document. The guidelines have also been designed in a way that facilitates this process, should users need to update or adapt the recommendations before WHO has itself updated them globally.

Inclusion of additional information

As stated previously, these guidelines cover a limited number of clinical questions. Many other questions pertaining to the management of H5N1 patients have been identified as potentially important. WHO will develop a process to catalogue and prioritize additional questions to be included in subsequent revisions. Topics that were identified during the consultation as potential priorities for update and additional evidence reviews include:

- Definition of the existence (or not) of asymptomatic H5N1 virus infection (i.e. seropositive without symptoms).
- Detailed recommendations on the optimal use of personal protection equipment.
- Use of antiviral drugs during a pandemic .

- Refinement of recommendations on the use of antimicrobials in the treatment of secondary bacterial pneumonia.
- Refinement of recommendations on the use of corticosteroids.
- Review of evidence for ribavirin as a co-intervention in the management of influenza.

10. Priorities for research

General comments

These recommendations for research arise from the guideline process in which a need for more data was identified. Such needs were identified often. There is an overarching requirement for systematic high quality data collection in H5N1 patients. In addition, systems for pharmacovigilance need to be in place for all of the medications recommended for use in this document. The gaps in the evidence are summarized below as research recommendations, to facilitate those in a position to provide such information, either by routine collection of data or by the design and execution of specific research projects and programmes to answer these research questions.

Classification of a clinical recommendation as based on *low* or *very low evidence* clearly indicates an area in need of more evidence through systematic research.

Specific research questions

Neuraminidase inhibitors in the treatment of H5N1 infection

Priority research questions in relation to the use of neuraminidase inhibitors in the treatment of H5N1 infection include:

- Comparative clinical trials of neuraminidase inhibitors in H5N1 patients, or systematic prospective data collection in patients who are treated with these drugs.
- Development of additional neuraminidase inhibitors including long-acting agents.
- Studies of dose regimens including:
  - duration of treatment
  - higher dose treatment
  - use of loading doses
  - treatment of children under 1 year of age
  - treatment of pregnant women.
- Efficacy and safety of these drugs in combination with other treatments, especially the M2 inhibitors.
- Interaction of antiviral drugs with antiretroviral treatment.
- Systematic collection of data on adverse effects.

- For zanamivir specifically:
    - studies of alternate formulations
    - the pharmacokinetics of potential long-acting forms or intravenous or nebulised routes of administration
    - use of the product in patients with pneumonic disease
    - the potential development of drug resistance.

Neuraminidase inhibitors as chemoprophylaxis for H5N1 infection

- Comparative clinical trials of neuraminidase inhibitors when used as chemoprophylaxis for H5N1 infection, or systematic prospective data collection in populations in which chemoprophylaxis is used.
- Studies of dose regimens including;
    - duration of chemoprophylaxis – in particular use of long-term prophylaxis in groups with a high risk of exposure
    - higher dose chemoprophylaxis
    - prophylaxis of children under 1 year of age
    - prophylaxis of pregnant women**.**
- Systematic collection of data on adverse effects.

M2 inhibitors

Generally the same questions apply, but in addition, the following research is needed specifically for M2 inhibitors:

- Efficacy and safety in combination with other drugs (e.g. neuraminidase inhibitors), especially in areas where virus strains resistant to the neuraminidase inhibitors have been detected.
- Whether the development of resistance to amantadine is reduced by combination therapy.

Co-interventions, including antibiotics

There are no data about antibiotic co-interventions in H5N1 infections. Research is needed to guide:

- Choice of antibiotic;
- Route of administration;
- Duration of antibiotic;
- Loading dose;

- and questions of subgroups of patients using antibiotic co-interventions:
    - pregnant women;
    - treatment of children under 1 year of age;
    - severity; and
    - whether ventilated.

For other co-interventions, questions pertain to:

- the safety and efficacy of steroids and other immunosuppressants, immunoglobulin;
- the optimal dosage regimen, if effective;
- use in subgroups of patients, including pregnant women and children.

Although randomized controlled trials would provide the most reliable estimates of efficacy, they may not always be possible in the context of a relatively rare disease. However, they can be facilitated by the development of a clinical network and agreed protocols. Where randomized controlled trials are not possible, standardized collection of case data would be useful.

In addition to efficacy data, safety data are urgently needed, particularly regarding use of antiviral drugs for chemoprophylaxis in different populations. Health care professionals are encouraged to report suspected adverse reactions to their national adverse drug reaction reporting unit, and also to the manufacturer of the product concerned.

Annexes

WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus

Annex 1: Adaptation or localisation of guidelines

The ministry of health should take the lead in the process of adapting or localising these treatment guidelines if local versions are needed. Depending on when such a process takes place, the steps involved should include:

- Appointing a guideline committee comprising clinicians and methodologists
- Determining the scope of the guidelines
- Defining the clinical questions to be addressed
- Updating the evidence tables if necessary
- Reviewing the recommendations in the guidelines. The recommendations may need to be modified at a national level, depending on the local values, availability of drugs and costs
- Disseminating the guidelines , with a “use by” date
- Developing a method to obtain feedback and plans for review and update.

Annex 2: Methods used to prepare guidelines

The WHO Guidelines on the clinical management of humans infected by influenza A (H5N1) were prepared according to a modification of the WHO Guideline for Guidelines. Given the urgent need for the guidelines as a response to increasing numbers of human cases of avian influenza, the development of the document was undertaken by the WHO secretariat rather than by a full Guidelines Technical Group. The questions to be addressed by the guidelines were identified on the basis of clinical input and requests from clinicians managing patients with avian influenza. An external group was contracted to compile evidence summaries from secondary sources according to the GRADE methodology and the approach used is described below in "Preparation of Background Documentation". Search strategies used for identifying relevant systematic reviews and health technology assessments are described below.

The evidence was assessed according to the methodology described in GRADE (GRADE Working Group 2003). In this system evidence is classified as "high" , "moderate", "low" or "very low". The definition of each is listed below.

- High: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: Any estimate of effect is very uncertain.

Factors that are considered in classifying evidence are: the study design and rigour of its execution, the consistency of results and how well the evidence can be directly applied to patients, interventions, outcomes and comparator. Other important factors are whether the data are sparse or imprecise and whether there is potential for reporting bias. For human patients with avian influenza H5N1, there are currently no clinical trials in patients with the disease, which immediately raises uncertainty about whether the evidence that is available for seasonal influenza can be directly applied. It is important to note that a group of trials can be "high quality" evidence for one question, but because of uncertainty about their applicability or directness, can be "very low" quality evidence for a different question.

The recommendations were drafted according to the GRADE method for assessing quality of evidence and strength of recommendations. A guideline panel comprising international scientists and experts in clinical treatment of avian and seasonal influenza, guideline methodology, basic research, policy making, pharmacology and virology was convened in March 2006 (see annex 4 for list of members and annex 5 for conflict of interest declarations). The panel was asked to identify critical clinical outcomes for the purposes of making the recommendations. Mortality, duration of hospitalization, incidence of lower respiratory tract complications, resistance and serious adverse effects were rated as critical outcomes in the assessment of treatment interventions for human infection with avian

influenza H5N1. For chemoprophylaxis, outbreak control, drug resistance and serious adverse effects were rated as critical outcomes. All outcomes reported in the clinical trials are summarized in the evidence profiles, set out in annex 3.

The panel reviewed the evidence summaries and the draft guidelines and made recommendations. For all except one recommendation consensus was reached.

Formulation of the recommendations included explicit consideration of the quality of evidence, benefits, harms, burdens, costs and values and preferences, described in the "Remarks" for each recommendation. "Values" are the desirability or preference that individuals exhibit for a particular health state. Individuals usually assign less value to and have less preference for more impaired health states (e.g. death or dependency after a stroke) compared to other health states (e.g. full health or having a very mild stroke without serious sequelae). In this document, the term "values" refers to the relative worth or importance of a health state or consequences (benefits, harms and costs) of a decision.

Very little information about costs of treatment or chemoprophylaxis was available to the panel, so for this guideline the main cost consideration was the acquisition cost of the antiviral drugs. Estimates of current acquisition costs are in Section 8 on drug supply.

Recommendations are classified as "strong" or "weak" recommendations, as recommended in the GRADE methodology. "Strong" recommendations can be interpreted as:

- Most individuals should receive the intervention
- Most well informed individuals would want the recommended course of action and only a small proportion would not
- Could unequivocally be used for policy making

"Weak" recommendations can be interpreted as:

- The majority of well informed individuals would want the suggested course of action, but an appreciable proportion would not
- Values and preferences vary widely
- Policy making will require extensive debates and involvement of many stakeholders

After the meeting, the guidelines were revised by the WHO secretariat according to the recommendations from the panel and circulated to the panel members and other experts for peer review. Comments were reviewed by the Chair of the guidelines group and the WHO secretariat and were incorporated into the final version. A record of comments not included was kept and is available on request, with reasons for the rejections.

It is anticipated that the clinical literature will be reviewed in 6 months time (i.e. no later than October 2006) to determine whether there is any new evidence that warrants an update of the information in these guidelines. If necessary the panel will be reconvened to review and update the recommendations.

Preparation of the background documentation

Background documentation was prepared in order to assist the WHO Rapid Advice Guidelines Group on Avian Influenza in its task of updating earlier guidance on the treatment and prophylaxis of avian influenza H5N1 infection in humans.

Summaries of the best available evidence were prepared to inform six primary questions regarding the treatment and prophylaxis of H5N1:

- 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?

Additional questions included what the dose and length of treatment should be, particularly for oseltamivir, and what the mode of delivery should be, particularly for zanamivir.

Identification of important outcomes

A list of potential outcomes to be considered by the panel was initially developed by two reviewers. The team preparing the evidence summaries independently scored the relative importance of each outcome from 1-9, where 7-9 indicated the outcome was critical for a decision, 4-6 indicated it was important, and 1-3 indicated it was not important. Because the relative importance of some outcomes depended on whether a drug was being used for treatment or prophylaxis and whether there was human-to-human transmission, this was done for four scenarios. The individual scores were discussed and disagreements were resolved by consensus. Outcomes were included roughly in order of their relative importance in evidence tables; outcomes that were considered not important (a score of 3 or less) were not included.

A similar exercise was undertaken by the Guidelines Group prior to their meeting and the Cochrane Consumers network was consulted through their electronic discussion list. Both were asked to identify additional important outcomes not included in the list of potential outcomes identified by the team that prepared the background documentation.

Search strategy

The search strategy aimed to identify for systematic reviews, recent randomized trials (2005-6) for the treatment and prophylaxis of any influenza, and case series, animal studies and in vitro studies for the treatment of H5N1.

For systematic reviews, the Cochrane Library (Issue 1, 2006) was searched for records with influenza in the title, and PubMed for records with influenza in the title using the research methodology filter for systematic reviews: (influenza) AND systematic [sb] Field: Title.

For randomized controlled trials PubMed was searched using the following search strategy: influenza Field: Title, Limits: Publication Date from 2005 to 2006, Randomized Controlled Trial (publication type).

In vitro and animal studies of the effectiveness of compounds against H5N1 virus were identified using PubMed searches. The terms "zanamivir or oseltamivir or amantadine or rimantadine or interferon or ribavirin" and "H5N1 or avian influenza" were used in each search. The term "*in vitro*" was added to the first search to identify *in vitro* studies and the limit "animal" was applied to the first search to identify studies of these treatments in animals. Published case-series of H5N1 infection in humans were identified with a search of PubMed using the terms "H5N1" and limited to case series and human studies. For case-series data, articles with the most complete data were selected and no patients were duplicated. References of all papers were scanned for additional relevant studies. All searches were conducted between 17 and 21 February 2006.

Draft summaries of the evidence were sent to the members of the Guidelines Group prior to the meeting and they were asked to identify any important evidence that had not been included. Drafts were also sent to four clinical experts for review and to identify any important evidence that was missing.

Selection criteria, data collection and judgments

Systematic reviews were used to summarize the evidence from randomized trials for any influenza. Titles identified from the searches for reviews were assessed and the quality of relevant reviews was screened by two reviewers using a checklist. For each question data were extracted for all of the outcomes that were judged to be important, beginning with the most recent review of good quality, and supplementing that with additional data from other good quality reviews that addressed the same question.

Evidence profiles were created using the GRADE approach, using the GRADE profiler software (v1.12). Using this approach, assessments of the quality of evidence for each important outcome take 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. A liberal approach to assessment of study limitations was taken and the quality of evidence was not lowered because of reporting limitations, such as not clearly reporting whether there was concealment of allocation in trials. Three main criteria were used for assessing trial limitations: concealment of allocation, blinding and follow-up. If most of the evidence for an outcome (based on the weight given to each study in the meta-analysis) came from trials that did not have serious limitations, the overall assessment for that outcome was that there were no important limitations.

Because all of the evidence from trials was indirect for H5N1, that is, it was for other influenza, there was major uncertainty about its applicability for H5N1, and this lowered the confidence in the estimates of effect for H5N1 for all of the important outcomes other than side effects, which could be expected to be the same. This does not mean that the trials were of low quality, but the quality of the evidence from (non-H5N1 influenza) clinical trials is low for addressing questions about the management of H5N1 influenza.

For minor adverse effects occurring in the context of treatment there was also some uncertainty about the directness of the evidence because it was uncertain whether the outcomes reported were adverse effects or symptoms of influenza.

If data were available estimates of the relative effect for continuous outcomes, such as duration of disease, were calculated by dividing the weighted mean difference (WMD) by the weighted average of the mean for the control group; using the percent of information that each mean difference contributed to the WMD as the weight. All estimates of effect size were expressed as relative risk if it is possible to calculate it from the data provided, with absolute risk estimates included where appropriate.

One reviewer extracted data from the reviews and prepared drafts of the evidence profiles with detailed footnotes explaining the judgments that were made. These were checked by at least one other member of the team and discussed with the team that prepared the background documentation.

The quality of outcomes measured in each animal study was judged based on the whether or not 1) pathogenicity of the virus was tested in the model, 2) statistical methods were adequate, and 3) a significant effect was demonstrated. The quality of measures used to determine inhibition of virus replication for each *in vitro* study was not evaluated.

Information on virus strain, compound, assay, comparisons, outcome of viral replication inhibition, outcome of neuraminidase inhibition and conclusions were extracted from each in vitro study. Information on virus strain, animal model, treatment, regimen, numbers in experimental and control group, outcome of survival, outcome of viral titer, outcome of resistance measurements and conclusion were extracted from each animal study. Information on treatment, dose, regimen, number treated and not treated, outcomes, place and year of case series, authors' remarks and conclusion was extracted from the human case series. A description of illness for each case-series was obtained from the review article by the Writing Committee of the WHO Consultation on Human Influenza A/H5. One person extracted these data and a second person verified the extracted data. Any inconsistencies were discussed and resolved by consensus. This information was used to supplement data from non-H5N1 clinical trials.

All of the evidence profiles and additional tables were sent to four external clinical experts and all of the members of the Guidelines Group for review prior to the meeting of the Guidelines Group.

Summary of findings tables

The key findings for each question for which non-H5N1 clinical trial evidence was available were summarized in tables with the most important findings from the systematic reviews together with additional information specific to H5N1 from case reports, animal studies and in-vitro studies.

Annex 3: Evidence summaries and summaries of findings tables

TREATMENT

ORAL OSELTAMIVIR

INHALED ZANAMIVIR

ORAL AMANTADINE

RIMANTADINE

ORAL AMANTADINE VERSUS ORAL RIMANTADINE

CHEMOPROPHYLAXIS

ORAL OSELTAMIVIR

INHALED ZANAMIVIR

ORAL AMANTIDINE

ORAL RIMANTADINE

ORAL AMANTADINE VERSUS ORAL RIMANTADINE

GRADE evidence profile 1

Author(s): Meetali Kakad
Date: 28.02.2006

QUESTION: Should oral oseltamivir (5 day course, variable dosages 75mg od or bd or 150mg bd) be used for treatment of avian influenza (H5N1) in healthy individuals?

Patient or population: Clinically and laboratory confirmed avian influenza infection in healthy adults (18-65 yrs of age).
Settings: Studies undertaken in Japan, China, Europe and the USA.
Systematic reviews:

a. (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13.
b. (DH 01) Husereau DR, Brady B, McGeer A. Oseltamivir for the treatment of suspected influenza: a clinical and economic assessment. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2001. Technology Report no 21.
c. (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).

QUESTION: Should oral oseltamivir (5 day course: 75 mg bd) be used for treatment of avian influenza (H5N1) in high risk adult groups?

Patient or population: Clinically and laboratory confirmed avian influenza infection in high-risk patients (≥65 yrs of age or with chronic lung disease)
Settings: Studies undertaken in multiple sites in the northern hemisphere and the USA.
Systematic reviews:

a. (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).
b. (DH 01) Husereau DR, Brady B, McGeer A. Oseltamivir for the treatment of suspected influenza: a clinical and economic assessment. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2001. Technology Report no 21.

QUESTION: Should oral oseltamivir (5 day course: 2mg/kg, max dose 100mg) be used for treatment of avian influenza (H5N1) in children?

Patient or population: Clinically and laboratory confirmed avian influenza infection in children (1 to 12 yrs of age)
Settings: Studies undertaken in US, Canada and multiple sites in the northern and southern hemisphere
Systematic reviews:

a. (NM 03) Matheson NJ, Symmonds-Abrahams M, Sheikh A, Shepperd S, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children. The Cochrane Database of Systematic Reviews 2003. Issue 3. Art No: CD002744. DOI: 10.1002/14651858.CD002744.
b. (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No of studies (Ref)	Design	Limitations	Consistency	Directness	Other considerations	Oseltamivir	Placebo	Relative (95% CI)	Absolute (95% CI)		
Healthy adults:											
Mortality											
0	-	-	-	-	-	-	-	-	-		**9**
Hospitalisation (Hospitalisations from influenza – influenza cases only)											
5 (TJ 06)	Randomised trial	No limitations	One trial only	Major uncertainty (-2)[1]	Imprecise or sparse data (-1)	-	-	OR 0.22 (0.02 to 2.16)	-	⊕○○○ Very low	**6**
Duration of hospitalization											
0	-	-	-	-	-	-	-	-	-	-	**7**
LRTI (Pneumonia - influenza cases only)											
5 (TJ 06)	Randomised trial	No limitations	One trial only	Major uncertainty (-2)[1]	Imprecise or sparse data (-1)[2]	2/982 (0.2%)	9/662 (1.4%)	RR 0.149 (0.03 to 0.69)	-	⊕○○○ Very low	**8**
Duration of disease (Time to alleviation of symptoms/median time to resolution of symptoms – influenza cases only)											
5[3] (TJ 06) (DT 03)	Randomised trials	No limitations[4]	Important inconsistency (-1)[5]	Major uncertainty (-2)[1]	-	-	-	HR 1.30[3] (1.13 to 1.50)	-	⊕○○○ Very low	**5**
Viral shedding (Mean nasal titre of excreted virus at 24h)											
2[6] (TJ 06)	Randomised trials	No limitations	-[7]	Major uncertainty (-2)[1]	None	-	-	-	WMD -0.73[8] (-0.99 to -0.47)	⊕⊕○○ Low	**4**
Outbreak control											
0	-	-	-	-	-	-	-	-	-	-	**4**
Resistance											
0	-	-	-	-	-	-	-	-	-	-	**7**
Serious adverse effects (Mention of significant or serious adverse effects)											
0[9]	-	-	-	-	-	-	-	-	-	-	**7**
Minor adverse effects [10] (number and seriousness of adverse effects)											
3[11] (TJ 06)	Randomised trials	No limitations	-[12]	Some uncertainty (-1)[13]	Imprecise or sparse data (-1)[14]	-	-	OR range[15] (0.56 to 1.80)	-	⊕⊕○○ Low	
Cost of drugs											
0	-	-	-	-	-	-	-	-	-	-	**4**

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No of studies (Ref)	Design	Limitations	Consistency	Directness	Other considerations	Oseltamivir	Placebo	Relative (95% CI)	Absolute (95% CI)		
All other adults:											
Mortality (Number of deaths – all causes)											
1 (Elderly ≥ 65 yrs) (DH01)	Randomised trial	No limitations	Only one trial	Major uncertainty (-2)[1]	Imprecise or sparse data (-1)[16]	0/77	1/91 (1%)	-	-	⊕○○○ Very low	**9**
Hospitalisation (Hospitalisations due to complications – influenza cases only)											
2 High risk (DH 01)	Randomised trials	No limitations	-[17]	Major uncertainty (-2)[1]	Imprecise or sparse data (-1)[16]	1/149	3/173	RR 0.73 (0.04 to 11.81)	-	⊕○○○ Very low	**6**
Duration of disease (Time to alleviation of symptoms/median time to resolution of symptoms – influenza cases only)											
5 (all unpublished) High risk (DT 03)	Randomised trials	No limitations	-[18]	Major uncertainty (-2)[1]	Imprecise or sparse data (-1) [16]	341	387[8]	-	WMD -10.9. (hours) (-45.0 to 23.2)	⊕○○○ Very low	**5**
All children:											
Duration of disease (Time to alleviation of symptoms/median time to resolution of symptoms – influenza cases only)											
2 (Includes 1 study of asthmatic children) (NM03)	Randomised trials	No limitations	-[17]	Major uncertainty (-2)[1]	-	514	515[19]	-	WMD -10.3 to -36 (hours)[20]	⊕⊕○○ Low	**5**
Serious adverse effects (Mention of significant or serious adverse effects)											
2 (Includes 1 study of asthmatic children) (NM03)	Randomised trials	No limitations	-[17]	No uncertainty	Imprecise or sparse data (-1) [16]	8/ 514	4 / 515	RR 2.00 (0.60 to 6.69)	-	⊕⊕⊕○ Moderate	**7**
Minor adverse effects [14] (number and seriousness of adverse effects)											
2 (Includes 1 study of asthmatic children) (NM03)	Randomised trials	No limitations	-[17]	Some uncertainty (-1)[17]	Imprecise or sparse data (-1) [3]	-	-	OR range[21] (0.77 to 1.68)	-	⊕⊕○○ Low	

Footnotes:

1. There is major uncertainty regarding the applicability of the evidence with regards to avian influenza.
2. The confidence intervals are relatively wide and the event rate is very low. The data were from a single large trial (1644 observations).
3. An additional unpublished trial (WV15730a) from the Turner HTA was included here. The Turner HTA reported the median number of hours to alleviation of symptoms: the pooled result for the three trials of 75mg oseltamivir bd vs placebo included, was a median difference reported of -33.1 (-47.1 to -19.1) (Treanor 2000, Nicholson 2000, WV15730 (unpublished).
4. The Jefferson Lancet review mentioned that quality assessment of one review was difficult due to lack of translation of parts of the text (Kashiwagi 2000a). Another study (Li 2000) was described as badly reported. The HTA carried out JAHAD scoring but did not exclude on the grounds of low scoring – only randomized, double blinded trials were included and thus it was felt that a quality threshold was maintained. Assessment of limitations was therefore relatively difficult.
5. The UK HTA utilized 4 of the 5 studies included here and the results presented in terms of median time to alleviation of symptoms show significant heterogeneity.
6. The two studies included here had their data converted with respect to nasal viral titres into means and standard deviations to be consistent with other studies and to allow meta-analysis. The effect of this conversion was assessed with a sensitivity analysis.
7. It was not possible to assess the consistency of these two trials as the individual results were not reported in the review – nor was an analysis of heterogeneity reported. Both studies recruited from a population of healthy adults using similar symptoms as entry criteria - though not identical (as reported in the review). The WMD reported is significant in comparison with placebo and both studies were of similar sizes but it is not possible to comment on any weighting they were given in the meta-analysis.
8. The review showed that whilst treatment significantly diminished viral titres, it did not suppress viral excretion, irrespective of dose – though there were insufficient data to comment on the effects on nasal excretion of viruses of higher doses of medication. The two studies included here both assessed Oseltamivir at different dosages vs placebo (75 mg od or bd (Nicholson 2000) and 75mg bd or 150 mg bd (Treanor 2000).
9. There was no distinction made between mild and serious adverse effects by the reviewers and there was no mention in the review of the presence or absence of any serious adverse effects being reported by any of the studies.
10. The adverse effects were defined as cough, headache, diarrhoea, nasal symptoms, nausea and "all types".
11. The 3 studies included to assess the adverse effects of oseltamivir treatment, used a treatment dose of 150mg of oseltamivir. For the assessment of other outcomes, studies using both 75mg and 150mg treatment doses were included.
12. It was difficult to comment on the consistency of the results, as the results from the individual trials were not reported in this review. An odds ratio was reported for each outcome. In addition, several of the adverse effects outcomes only include 1 study in the analysis.
13. There is some uncertainty of directness here, due to the overlapping nature of the side effects of oseltamivir and the actual symptoms of influenza, making it difficult to accurately differentiate them from each other.
14. There were relatively small denominators and few studies included to assess each outcome. The numbers involved in the studies are potentially too small to adequately demonstrate their frequency. The CIs reported were wide and all crossed 1, expect nausea.
15. The only significant adverse effect reported was for nausea 1.80 (0.73 to 4.41). 1 study reported an "all types" category of adverse events, with a non-significant OR 0.67 (0.43 to 1.05).
16. The confidence intervals are wide and include both important benefits and important harms.
17. Due to the very small number of trials included it was very difficult to comment on consistency of results.
18. There is reasonable heterogeneity between the study populations. Some of the trials include healthy elderly over 65 years, whilst the others include those with chronic respiratory disease over the age of 13 years. However it was not possible to comment on the consistency of the results because individual results were not published in the Turner HTA.
19. The numbers and the WMD are from table 4 in the Matheson Review.
20. The patient numbers and WMD (the overall reduction in median time to resolution of symptoms in confirmed influenza) are from the Matheson Cochrane Review. This review includes a study of oseltamivir treatment in "at risk" children (with asthma) for whom the reduction in time to resolution of symptoms was not statistically significant. It should be noted that a much higher proportion of children (19%) were vaccinated in this study in comparison with the other (3%).
21. The only significant adverse effect reported amongst children was for vomiting OR 1.68 (1.15 to 2.47).

Summary of findings 1

SCENARIO: Should oseltamivir be used for treatment of patients hospitalised with avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Hospitalised, clinical and serologically confirmed cases of avian influenza
Information sources:
Avian influenza data: Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: Le 2005, de Jong 2005, McKimm-Breschin 2003 and Hurt 2004.
Clinical trial data: trials for non-H5N1 influenza undertaken in the USA, China, Canada, Europe and Japan under pandemic conditions or seasonal outbreaks.

Outcome	Avian Influenza H5N1 Evidence			Seasonal Influenza Evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No of participants (No of trials)	Risk without treatment (Range)	Relative effect (95% CI)	Quality	Comments
Mortality		0.64 (33 to 100%)		0	-	-	-	No deaths reported in trials amongst healthy adults[1]
Duration of hospitalization (days)[2]	0	-	-	0	-	-	-	
Duration of disease (fever)[2]	0	-	-	2207[3] (5)	Median (3.89 to 6.0 days)[4]	-	⊕○○○[5] Very low	
Resistance	2	-	H5N1 was isolated from 2 patients in Viet Nam who died, who had been treated with oseltamivir. Viral isolates had an H274 neuraminidase base substitution which was associated with high level oseltamivir resistance in vitro. H274Y has also been shown to confer oseltamivir resistance in an animal model.	(2)		-	-	No evidence of widespread naturally-occurring resistance reported for non-H5N1 viruses.
Serious adverse effects[2]	0	-	-	0	-	-	-	
Cost of drugs per patient	0	-	-	0	-	-	-	

Footnotes:

1. In a single trial of healthy elderly participants, there was one death recorded in the placebo arm (n=91) with no deaths occurring in the treatment arm (n=77). No cause of death was given.
2. These data are indirect (i.e. for non-avian influenza) and thus only a proxy measure for what might be expected for avian influenza (H5N1).
3. This is the total number of participants for these 5 trials, confirmed from 3 sources, the ITT population was 1720. The ITTI population was 1404.
4. These data are based on 4 studies and the median time to resolution of symptoms.
5. Major uncertainty about the directness of the evidence, in addition there was significant inconsistency between the results of the studies.

GRADE evidence profile 2

Author(s): Gunn E Vist
Date: 2006 02 28

QUESTION: Should inhaled zanamivir be used for treatment (5 day treatment) of avian influenza (H5N1) in otherwise healthy adults?

Patient or population: Otherwise healthy adults with confirmed influenza[1].
Settings: America and Europe (A/H3N2 (56%), and B virus (44%), 417 patients), Europe (A/H3N2, 356 patients), Japan (A/H3N2, 116 patients), North America and Europe (A/H3N2 and A/H1N1, 1256 patients), Finland (A/H3N2 and A/H1N1, 588 patients), Australia, New Zealand and South Africa (A/H3N2, 455 patients), Canada (A/H3, 35 patients).
Systematic reviews:

a) (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13.
b) (TJ 99) Jefferson T, Demicheli V, Deeks J, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. The Cochrane Database of systematic reviews. 1999, Issue 2. Art. No.;CD001265.DOI:10.1002/14651858.CD001265.
c) (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).

QUESTION: Should inhaled zanamivir be used for treatment (5 day treatment) of avian influenza (H5N1) in elderly people and adults at risk?

Patient or population: People over the age of 65 years and adults with chromic conditions with confirmed influenza (results similar in ITT group)
Setting: (Australia, New Zealand and America (39 persons), Canada, USA and 11 European countries (70 patients), 17 countries including from all 5 continents (276 elderly with asthma or COPD), Canada, Finland, UK, USA (10 patients).
Systematic review:

a) (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).

QUESTION: Should inhaled zanamivir be used for treatment (5 day treatment) of avian influenza (H5N1) in children?

Patient or population: Children with confirmed influenza (results similar in ITT groups)
Setting: 67 sites in US, Canada, Europe/Israel (471 children 5 to 12 years)
Systematic review:

a) (NJM 03) Matheson NJ, Symmonds-Abrahams M, Sheikh A, Shepperd S, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children. The Cochrane Database of Systematic Reviews 2003. Issue 3. Art No: CD002744. DOI: 10.1002/14651858.CD002744.
b) (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

Quality assessment						Summary of findings					
						No of patients		Effect			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Inhaled zanamivir	Control	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Inhaled treatment in otherwise healthy adults:											
Mortality rates											
0	-	-	-	-	-	-	-	-	-	-	**9**
Duration of hospitalisation											
0	-	-	-	-	-	-	-	-	-	-	**7**
Lower respiratory tract disease (Bronchitis and pneumonia) (Follow up: 28 days)											
3 (TJ 06)	Randomised trials	No limitations	No important inconsistency	Major uncertainty (-2)[2]	Sparse or imprecise data (-1)[3]	-	-	OR 0.73 (0.24 to 2.26)	-	⊕○○○ Very low	
Time to alleviation of symptoms (Follow up: 28 days)											
7 (TJ 06)	Randomised trials	No limitations	No important inconsistency	Major uncertainty (-2)[2]	None	-	Median 2.3 days	HR 1.33 (1.29 to 1.37)	-	⊕⊕○○ Low	
Viral shedding (Mean nasal viral titre at 24 h (concentration). Better indicated by: lower scores)											
2 (TJ 06)	Randomised trials	No limitations	No important inconsistency	Major uncertainty (-2)[2]	None	-	-	-	WMD -0.40 (-0.75 to -0.06)	⊕⊕○○ Low	**4**
Outbreak control											
0	-	-	-	-	-	-	-	-	-	-	**4**
Resistance											
0	-	-	-	-	-	-	-	-	-		**7**
Serious adverse events											
0	-	-	-	-	-	-	-	-	-	-	**7**
Minor adverse effects (Cough, headache, diarrhoea, nasal symptoms, nausea) (Follow up: 28 days)											
4 (TJ 06)	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[4]	Sparse or imprecise data (-1)[3]	-	-	OR range[5] (0.63 to 1.40) All CIs cross 1	-	⊕⊕○○ Low	
Cost of drugs											
0	-	-	-	-	-	-	-	-	-	-	**4**
Inhaled treatment in elderly and at risk adults:											
Lower respiratory tract disease (Bronchitis and pneumonia) (Follow up: 28 days)											
6 (DT 03)	Randomised trial	No limitations	No important inconsistency	Major uncertainty (-2)[2]	Sparse or imprecise data (-1)[8]	3/105 (3%)	5/122 (4%)	OR 0.69 (0.10 to 3.64)	-	⊕○○○ Very low	
Time to alleviation of symptoms (Follow up: 28 days)											
5 (DT 03)	Randomised trial	No limitations	No important inconsistency	Major uncertainty (-2)[2]	None	-	Range 6.5 to 11.5 days	-	Median difference -1.99 days (-3.08 to -0.90)	⊕⊕○○ Low	

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Inhaled zanamivir	Control	Relative (95% CI)	Absolute (95% CI)		
Inhaled treatment in children:											
Lower respiratory tract disease (Bronchitis and pneumonia) (Follow up: 28 days)											
1 (DT 03)	Randomised trial	No limitations	No important inconsistency	Major uncertainty (-2)[2]	Sparse or imprecise data (-1)[3]	1/164 (<1%)	2/182 (<1%)	OR 0.55 (0.01 to 10.72)	-	⊕○○○ Very low	
Time to alleviation of symptoms (Follow up: 28 days)											
1 (NJM03)	Randomised trial	No limitation	Only one trial	Major uncertainty (-2)[2]	Sparse or imprecise data (-1)[3]	Median 4 days	Median 5 days	-	Median difference -1.25 days (-0.5 to -2.0)	⊕○○○ Very low	
Serious adverse events (Follow up: 28 days, for children there were no withdrawal in either group)											
1 (NJM 03)	Randomised trial	No serious limitations	Only one study	Direct	Sparse or imprecise data (-1)[3]	1/224	0/247	OR 3.32 (0.13 to 81.97)	-	⊕⊕⊕○ Moderate	**7**
Minor adverse effects (Any adverse events) (Follow up: 28 days)											
1 (NJM 03)	Randomised trial	No serious limitations	Only one study	Some uncertainty (-1)[4]	Sparse or imprecise data (-1)[3]	48/224 (21%)	65/247 (26%)	OR 0.76 (0.50 to 1.17)	-	⊕⊕○○ Low	

Footnotes:

1. Otherwise healthy patients with influenza symptoms have similar results (Time to alleviation of symptoms HR 1,24 (95% confidence interval: 1,13 to 1,36).
2. Major uncertainty surrounding the applicability of this evidence to avian influenza.
3. The confidence intervals include both important benefits and important harms.
4. Some uncertainty regarding the outcome measure which overlaps with some of the symptoms of influenza.
5. The range of OR are presented, the list of mild adverse events are from the same studies and collating them would be double counting.

Summary of findings 2

SCENARIO: Should zanamivir be used for treatment of patients hospitalised with avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Hospitalised, clinical and serologically confirmed cases of avian influenza
Information sources:

Avian influenza data: : Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: McKimm-Breschin 2003 and Hurt 2004.
Clinical trial data: Randomised trials for non-H5N1 influenza undertaken in Australia, Europe, Japan, New Zealand, USA, and South Africa under pandemic conditions or seasonal outbreaks.

Outcome	Avian influenza H5N1 evidence			Seasonal influenza evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No. participants (No of trials)	Risk without treatment	Relative effect (95% CI)	Quality	Comments
Mortality	0	64% (33 to 100%)	Control group risk based on total mortality rate, although 10 (56%) of patients in Hong Kong were treated with amantadine and others received a range of treatments.	0	-	-	-	No deaths reported in trials.
Duration of hospitalisation (days)	0	-		0	-	-	-	
Time to alleviation of symptoms (days)	0	-		2117 (7)	Median 2.3 days	HR 1.33 (1.29 to 1.37)	⊕⊕◯◯ Low[1]	
Resistance	1	-	No evidence of resistance reported for H5N1. Viral isolates with the H274 neuraminidase base substitution which confers high level oseltamivir resistance are zanamivir sensitive in vitro.	0	-	-	-	No evidence of resistance reported for non-H5N1 viruses.
Serious adverse effects	0	-		0	-	-		

Footnotes:

1. These data are indirect and only a proxy measure for what might be expected for avian influenza (H5N1).

GRADE evidence profile 3

Author(s): Meetali Kakad
Date: 27.02.2006

QUESTION: Should oral amantadine be used for treatment of avian influenza (H5N1) in otherwise healthy adults[1]?

Patient or population: Clinical and serologically confirmed cases of avian influenza in healthy adults (16-65 yrs) [1].
Settings: Studies undertaken in UK, US, Hungary and Japan - some of which were under pandemic conditions or seasonal outbreaks.
Systematic reviews:

a) (TJ 04) Jefferson T, Deeks JJ, Demicheli V, Rivetti D, Rudin M. Amantadine and rimantadine for preventing and treating influenza A in adults. The Cochrane Database of Systematic Reviews 2004, Issue 3.
b) (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13.
c) (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No of studies (Ref)	**Design**	**Limitations**	**Consistency**	**Directness**	**Other considerations**	**Amantadine**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality											
0	-	-	-	-	-	-	-	-	-	-	**9**
Duration of hospitalization (Number of days)											
1 (TJ 04) (TJ 06)	Randomised trials	No limitations[2]	Only one trial[3]	Major uncertainty (-2)[7]	Imprecise or sparse data (-1)[5]	20	16	-	WMD - 0.90 (-2.20 to 0.40)	⊕○○○ Very low	**7**
Duration of fever (Number of days with a fever of 37 C or more)											
10 (TJ 04) (TJ 06)	Randomised trials	No limitations[6]	No important inconsistency	Major uncertainty (-2)[7]	None	250	292	-	WMD -0.99 (-1.26 to -0.71)	⊕⊕○○ Low	
Viral shedding (Laboratory based assessment of viral shedding at 5 days)											
3[8] (TJ 06) (TJ 04)	Randomised trials	No limitations	-	Major uncertainty (-2)[7]	Imprecise or sparse data (-1) [9]	-	-	RR 0.96 (0.72 to 1.27)	-	⊕○○○ Very low	**4**
Outbreak control											
0	-	-	-	-	-	-	-	-	-	-	**4**
Resistance											
0[10]	-	-	-	-	-	-	-	-	-	-	**7**
Serious adverse effects (Mention of significant or serious adverse effects)											
8[11] (TJ 04)	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1)[12]	0/253 (0%)	0/299 (0%)	-	No difference	⊕⊕⊕○ Moderate	**7**
Minor adverse effects (grouped into gastrointestinal, increased CNS activity, decreased CNS activity, dermatological cases)[13] (number and seriousness of adverse effects)											
4 (TJ 06) (TJ 04)	Randomised trials	Serious limitations (-1)[14]	Important inconsistency (-1)[15]	Some uncertainty (-1)[16]	Imprecise or sparse data (-1)[17]	-	-	RR range 0.77 to 1.34	-	⊕○○○ Very low	
Cost of drugs											
0	-	-	-	-	-	-	-	-	-	-	**4**
TJ 06 states there are 10 different datasets from the 7 references cited											

Footnotes

1. The Turner HTA searched for studies assessing amantadine treatment in the elderly (>65 years) and children (<18 years). They identified 2 studies that included treatment of the elderly but neither of these met the inclusion criteria (no subgroup data was presented). They identified 4 studies for treatment in children but 2 were excluded as no subgroup data were presented. The 2 studies included were Japanese trials (Kitamoto 1968 (n=54) , Kitamoto 1970 (n=50)) which were assessed as being of low methodological quality and no further data was presented in the HTA.
2. This study was really a cluster-randomised trial, but had to be treated as though individually randomised by the reviewers because of a lack of information on the clusters.
3. There are so few studies included that it was not possible to comment on the consistency between studies. No heterogeneity calculations were possible.
4. 1 study 1969 Hong Kong influenza in seven military units in Hungary. Major uncertainty about the applicability of this evidence to outbreaks of avian influenza.
5. One large study of prevention and treatment (4740 participants) with just 36 hospitalised participants. Confidence interval crosses 0.
6. Several of the trials did not use intention to treat analysis where individuals dropped out of studies and did not justify the reason for this. Only one of the trials gave a detailed description of how allocation concealment was achieved.
7. Major uncertainty regarding the applicability of the evidence to outbreaks of avian influenza.
8. Viral shedding was not an outcome formally reported in the 2004 Cochrane review but was added in the Jefferson Lancet review.
9. The size of the included studies is small and the confidence intervals include 1.
10. No studies included in the review looked at resistance. In the text a reference to Aoki 1998 is mentioned, which was subsequently excluded. In addition a preventative trial excluded from the review (Hayden 1989) looked at rimantidine resistance.
11. Out of the 10 treatment trials included pertaining to amantadine: 8 mentioned no serious/significant adverse effect or stated that no adverse effects were reported with amantadine use. Younkin 1983 lacked clarity over which type of adverse events occurred. Mate 1970 only used a pre-trial study of 50 soldiers to look at adverse events, not the main study.
12. As some serious adverse events occur infrequently, the numbers involved in these studies may be too small to detect these.
13. Four categories were used in the review: (i) gastrointestinal symptoms (nausea, vomiting, dyspepsia, diarrhoea and constipation); (ii) increased central nervous system (CNS) activity (insomnia, restlessness, light headedness, nervousness and concentration problems); (iii) decreased CNS activity (malaise, depression, fatigue, vertigo and feeling drunk); (iv) dermatological changes (urticaria and rash).
14. Several of the trials gave no description of allocation and concealment methods. One of the trials had unclear follow-up for 353 participants.
15. For gastrointestinal side effects there was significant heterogeneity between the 3 studies included. Two Japanese studies by the same PI had results in opposite directions (one showing increased GI side effects and the other showing decreased) ($p=0.02$ for heterogeneity, $I^2=81\%$).
16. There is substantial overlap between the symptoms of influenza and the adverse effects of amantadine.
17. There are wide confidence intervals for GI, increased CNS and dermatologic side effects with results from the same two studies (Kitamoto 1968 and 1970) having results in opposite directions for each of these.

Summary of findings 3

SCENARIO: Should amantadine be used for treatment of patients hospitalised with avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Hospitalised, clinical and serologically confirmed cases of avian influenza
Information sources:
Avian influenza data: Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: Ilyushina 2005 and Puthavathana 2005.
Clinical trial data: Randomised trials for non-H5N1 influenza undertaken in UK US, Hungary and Japan under pandemic conditions or seasonal outbreaks.

Outcome	Avian influenza H5N1 evidence			Seasonal influenza evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No of participants (No of trials)	Risk without treatment (Range)	Relative effect (95% CI)	Quality	Comments
Mortality		64% (33 to 100%)	Control group risk based on total mortality rate, although 10 (56%) of patients in Hong Kong were treated with amantadine and others received a range of treatments.	-	-	-	-	No deaths reported in trials.
Duration of hospitalization (days)[1]	-	-	-	36[2] (1)	6.6 days (SD 2.1)	14% reduction	⊕○○○ Very low[3, 4]	Cluster randomised trial during 1969 Hong Kong influenza epidemic in 7 military units in Hungary. Results are for subgroup of hospitalised soldiers. Data not available for length of hospitalisation for avian influenza.
Duration of disease (fever)[1]	-	-	-	542 (7)	(1.9 to 3.9 days)	33% reduction	⊕⊕○○ Low[3]	
Resistance	2		H5N1 isolated from humans in Thailand and from birds in South-East Asia carries M2 ion channel resistance mutations.	-	-	-	-	
Serious adverse effects[1]	-	-	-	2009 (6)	0%	-	⊕⊕⊕○ Moderate[4]	
Cost of drugs per patient	-	-	-	0	-	-		

Footnotes:

1. These data are indirect (i.e. for non-avian influenza) and thus only a proxy measure for what might be expected for avian influenza (H5N1).
2. Hospitalised patients out of a total of 4740 participants in the trial.
3. Major uncertainty about the directness of the evidence.
4. Imprecise or sparse data.

GRADE evidence profile 4

Author(s): Meetali Kakad
Date: 15.02.2006

QUESTION: Should rimantadine be used for the treatment of avian influenza in healthy adults (H5N1)?

Patient or population: Clinical and serologically confirmed cases of avian influenza in healthy adults.
Settings: Various locations in the USA
Systematic reviews:

a. (TJ06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13.
b. (TJ04) Jefferson T, Deeks JJ, Demicheli V, Rivetti D, Rudin M. Amantadine and rimantadine for preventing and treating influenza A in adults. The Cochrane Database of Systematic Reviews 2004, Issue 3.

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Rimantadine	Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality rates											
0	-	-	-	-	-	-	-	-	-	-	**9**
Duration of hospitalisation											
0	-	-	-	-	-	-	-	-	-	-	**7**
Duration of fever (Number of days with a fever of 37 C or more)											
3 (TJ 04) (TJ 06)	Randomised trials	No limitations[1]	No important inconsistency	Major uncertainty (-2)[2]	Imprecise or sparse data (-1) [3]	27	37	-	WMD -1.27 (-1.71 to -0.76)	⊕○○○ Very low	
Viral shedding (Laboratory based assessment of viral shedding)											
3[4] (TJ 06) (TJ 04)	Randomised trial	No limitations	- [5]	Major uncertainty (-2)[6]	Imprecise or sparse data (-1) [7]	-	-	RR 0.67 (0.22 to 2.07)	-	⊕○○○ Very low	**4**
Outbreak control											
0	-	-	-	-	-	-	-	-	-	-	**4**
Resistance											
0	-	-	-	-	-	-	-	-	-	-	**7**
Serious adverse effects (Mention of significant or serious adverse effects)											
3 (TJ 04)	Randomised trials	No limitations	No important inconsistency	No uncertainty	Imprecise or sparse data (-1) [8]	0/46 (0%)	0/58 (0%)		no difference	⊕⊕⊕○ Moderate	**7**
Minor adverse effects (grouped into gastrointestinal, increased CNS activity, decreased CNS activity, dermatological cases)[9]											
2 (TJ 04)	Randomised trials	No limitations	-[10]	Some uncertainty (-1)[11]	Imprecise or sparse data (-1)[12]	-	-	OR Range 0.22 to 1.00	-	⊕⊕○○ Low	
Cost of drugs											
0	-	-	-	-	-	-	-	-	-	-	**4**

Footnotes:

1. Hayden 1986 gave no description of treatment allocation or allocation concealment.
2. Studies carried out in US in various settings. Major uncertainty regarding the applicability of the evidence to outbreaks of avian influenza.
3. Only small one study carried out in the US.
4. Viral shedding was not an outcome formally presented in the 2004 Cochrane review (but noted in review text as being an outcome measure in one of the preventative trials included in the review - Hayden 1986) but was included in the 2006 Lancet review.
5. Three small studies were included but the individual results were not formally presented in review and thus it is not possible to comment on consistency.
6. Major uncertainty surrounding the applicability of this evidence to outbreaks of avian influenza.
7. The numbers in the studies included were very small and the confidence interval reported includes both benefits and harms.
8. Given that serious adverse effects may occur infrequently the size of the included trials are not large enough to adequately assess the risk.
9. Four categories were used in the review: (i) gastrointestinal symptoms (nausea, vomiting, dyspepsia, diarrhoea and constipation); (ii) increased central nervous system (CNS) activity (insomnia, restlessness, lightheadedness, nervousness and concentration problems); (iii) decreased CNS activity (malaise, depression, fatigue, vertigo and feeling drunk); (iv) dermatological changes (urticaria and rash).
10. There are so few studies included that it was not possible to comment on the consistency between studies. No heterogeneity calculations were possible.
11. There is substantial overlap between the adverse effects of rimantadine and the symptoms of influenza, leading to potential difficulties in assessment of adverse effects.
12. Only 2 studies with 45 participants (26 of whom received rimantadine, according to the analysis 05.03 in the review) reported any adverse effects - of which there were only 5 reported in total.

Summary of findings 4

SCENARIO: Should rimantadine be used for treatment of patients hospitalised with avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Hospitalised, clinical and serologically confirmed cases of avian influenza
Information sources:
Avian influenza data: : Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: Puthavathana 2005.
Clinical trial data: Randomised trials for non-H5N1 influenza undertaken in US under pandemic conditions or seasonal outbreaks.

Outcome	Avian influenza H5N1 evidence			Seasonal influenza evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No of participants (No of trials)	Risk without treatment (Range)	Relative effect (95% CI)	Quality	Comments
Mortality		64% (33 to 100%)	No deaths reported in trials. Control group risk based on total mortality rate.	-	-	-	-	No deaths reported in trials.
Duration of hospitalization (days)[1]	0	-	-	0	-	-	-	Data not available for length of hospitalisation for avian influenza or other non-avian influenzae.
Duration of disease (fever)[1]	0	-	-	131 (3)	(1.9 to 2.8 days)[2]	-	⊕○○○ Very low[3, 4]	
Resistance	2	-	H5N1 isolated from humans in Thailand and from birds in Southeast Asia carries M2 ion channel resistance mutations.	-	-	-	-	
Serious adverse effects[1]	0	-	-	104 (3)	0%	-	⊕⊕⊕○ Moderate[3]	
Cost of drugs per patient	0	-	-	0	-	-	-	

Footnotes:

1. These data are indirect (i.e. for non-avian influenza) and thus only a proxy measure for what might be expected for avian influenza (H5N1).
2. These values were only available from two studies included in the 2004 Cochrane review which does not include Rabinovich 1969.
3. Major uncertainty about the directness of the evidence.
4. Imprecise or sparse data.

GRADE evidence profile 5

Author(s): Meetali Kakad
Date: 27.02.2006

QUESTION: Should oral amantadine versus oral rimantadine be used for the treatment of avian influenza (H5N1) in otherwise healthy adults?

Patient or population: Clinically and serologically confirmed avian influenza in healthy adults (16-65 years)[1].
Settings: Various study settings in the US
Systematic reviews:

d) (TJ 04) Jefferson T, Deeks JJ, Demicheli V, Rivetti D, Rudin M. Amantadine and rimantadine for preventing and treating influenza A in adults. The Cochrane Database of Systematic Reviews 2004, Issue 3.
e) (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13.

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

Quality assessment						Summary of findings					
						No of patients		Effect			
No of studies	**Design**	**Limitations**	**Consistency**	**Directness**	**Other considerations**	**Amantadine**	**Rimantadine**	**Relative (95% CI)**	**Absolute (95% CI)**	**Quality**	**Importance**
Mortality											
0	-	-	-	-	-	-	-	-	-	-	**9**
Duration of hospitalisation											
0	-	-	-	-	-	-	-	-	-	-	**7**
Duration of disease (Number of days with a fever of 37 C or more)											
1 (TJ 06) (TJ 04)	Randomised trial	No limitations	One one trial	Major uncertainty (-2)[2]	Imprecise or sparse data (-1)[3]	20	20	-	WMD 0.2[4] (-0.56 to 0.96)	⊕○○○ Very low	**5**
Viral shedding											
0	-	-	-	-	-	-	-	-	-	-	**4**
Outbreak control)											
0	-	-	-	-	-	-	-	-	-	-	**4**
Resistance											
0	-	-	-	-	-	-	-	-	-	-	**7**
Serious adverse effects (Mention of significant or serious adverse effects)											
2 (TJ 06) (TJ 04)	Randomised trials	No limitations	-[5]	No uncertainty)	Imprecise or sparse data (-1)[6]	0/34 (0%)	0/39 (0%)	-	No difference	⊕⊕⊕○ Moderate	**7**
Minor adverse effects (grouped into gastrointestinal, increased CNS activity, decreased CNS activity, dermatological cases)[7] (number and seriousness of adverse effects Follow up:)											
1 (TJ 06) (TJ 04)	Randomised trial	No limitations	Only one trial	Some uncertainty (-1)[8]	Imprecise or sparse data (-1)[9]	-	-	RR 14.67 (0.88 to 245.22)[10]	-	⊕⊕○○ Low	

Footnotes

1. No studies were found comparing amantadine vs rimantadine treatment in subgroups such as the elderly, individuals with chronic disease or children.
2. Studies carried out in US in various settings. Major uncertainty regarding the applicability of the evidence to outbreaks of avian influenza.
3. Only one relatively small study included and the confidence interval for weighted mean difference spans 0.
4. The total WMD for duration of fever for rimantadine vs placebo is -1.27 (-1.77, -0.77) and for amantadine vs placebo is -0.99 (-1.26, -0.71). The confidence incidence intervals for these two results overlap implying there is no significant difference on the effect on duration of fever, between the two drugs. This is confirmed by the data comparing amantadine vs rimantadine, which also shows no significant difference.
5. Due to the very small number of studies included and the small number of participants, it was not possibly to comment on consistency of results.
6. There were only 2 small studies where amantadine and rimantadine were directly compared. As serious adverse events occur infrequently, the numbers involved in these studies may be too small to adequately demonstrate their frequency.
7. Four categories were used in the review: (i) gastrointestinal symptoms (nausea, vomiting, dyspepsia, diarrhoea and constipation); (ii) increased central nervous system (CNS) activity (insomnia, restlessness, lightheadedness, nervousness and concentration problems); (iii) decreased CNS activity (malaise, depression, fatigue, vertigo and feeling drunk); (iv) dermatological changes (urticaria and rash).
8. There is substantial overlap between the adverse effects of the drugs used and the symptoms of influenza and therefore some uncertainty in differentiating accurately between the two.
9. Only 1 study (Van Voris) with a small number of participants - 14 of whom received amantadine and 19 of whom received rimantadine - reported minor adverse effects in 5 individuals.
10. This is based on one study of 33 individuals (n=14 in the amantadine group, n=19 in the rimantadine group). 5 individuals in the amantadine group experienced decreased CNS activity related adverse effects. No gastrointestinal, dermatological or increased CNS activity adverse effects were noted.

Summary of findings 5

SCENARIO: Should oral amantadine versus oral rimantadine be used for treatment of patients hospitalised with avian influenza (H5N1)?

Transmission: No human to human transmission.
Patient or population: Hospitalised, clinical and serologically confirmed cases of avian influenza.
Information sources:

Avian influenza data: : Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: Ilyushina 2005 and Puthavathana 2005.
Clinical trial data: Randomised trials for non-H5N1 influenza undertaken in US under pandemic conditions or seasonal outbreaks.

Outcome	Avian influenza H5N1 evidence			Seasonal influenza evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No of participants (No of trials)	Risk in comparator group	Relative effect (95% CI)	Quality	Comments
Mortality		64% (33 to 100%)	Control group risk based on total mortality rate.	-	-	-	-	No deaths reported in trials.
Duration of hospitalization (days)[1]	0	-	-	0	-	-	-	Data not available for length of hospitalisation for avian influenza or other non-avian influenzae.
Duration of disease (fever)[1]	0	-	-	40 (1)	0.85 days (SD 1.22)	-	⊕○○○ Very low[2, 3]	
Resistance	2	-	H5N1 isolated from humans in Thailand and from birds in Southeast Asia carries M2 ion channel resistance mutations	-	-	-	-	
Serious adverse effects[1]	0	-	-	73 (2)	0%	-	⊕⊕⊕○ Moderate[3]	
Cost of drugs per patient	0	-	-	0	-	-	-	

Footnotes:

1. These data are indirect (i.e. for non-avian influenza) and thus only a proxy measure for what might be expected for avian influenza (H5N1).
2. Major uncertainty about the directness of the evidence.
3. Imprecise or sparse data.

GRADE evidence profile 6

Author(s): Meetali Kakad
Date: 27.02.2006

QUESTION: Should oral oseltamivir be used for post exposure prophylaxis of avian influenza (H5N1)?

Patient or population: household contacts of avian flu index case, ≥1 year old [1,2]
Settings: Studies undertaken in the US (A/H3N2) and Japan (H3N2 & H3N1)
Systematic reviews:

a. (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13.
b. (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).

QUESTION: Should oseltamivir (75mg) be used for prevention of avian influenza (H5N1)?

Patient or population: Healthy unvaccinated adults (18-65) and elderly predominantly vaccinated individuals in a residential home setting.
Settings: Studies undertaken in the US (A/H3N2) and Japan (H3N2 & H3N1)
Systematic reviews:

a. (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13.
b. (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).

QUESTION: Should oseltamivir (150mg) be used for prevention of avian influenza (H5N1)?

Patient or population: Healthy unvaccinated adults.
Settings: Studies undertaken in the US (A/H3N2) and Europe
Systematic reviews:.

a. (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13.
b. (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35).

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

Quality assessment						Summary of findings					
						No of patients		Effect			
No of studies	**Design**	**Limitations**	**Consistency**	**Directness**	**Other considerations**	**Oseltamivir**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	**Quality**	**Importance**
All populations (PEP):											
Influenza cases (Laboratory confirmed clinical influenza Follow up: 25 and 30 days)											
2[2] (TJ 06)	Randomised trial	No limitations	[3]	Major uncertainty (-2)[4]	None			RR range (0.11 to 0.32)[5]		⊕⊕◯◯ Low	**8**
Mortality											
0	-	-	-	-	-	-	-	-	-	-	**6**
Duration of hospitalisation											
0	-	-	-	-	-	-	-	-	-	-	**5**
Duration of disease											
0	-	-	-	-	-	-	-	-	-	-	**6**
Viral shedding											
0	-	-	-	-	-	-	-	-	-	-	**6**
Outbreak control											
0	-	-	-	-	-	-	-	-	-	-	**7**
Resistance (Follow up: 5 and 7 days)											
2 (TJ 06)	Randomised trials	No limitations	[-3]	Major uncertainty (-2)[4]	None	[-6]	[-6]	-	-	⊕⊕◯◯ Low	**7**
Serious adverse effects											
0	-	-	-	-	-	-	-	-	-	-	**7**
Withdrawals from the trial											
1 (DT 03)	Randomised trial	No limitations	Only one trial	No uncertainty[7]	Imprecise or sparse data (-1)[8]	5/494 (1%)	2/461 (< 1%)	-	-	⊕⊕⊕◯ Moderate	**6**

Quality assessment						Summary of findings					
						No of patients		Effect			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Oseltamivir	Placebo	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
All populations (Prophylaxis 75mg):											
Influenza like illness cases (Follow up: 6 to 8 weeks)											
2 (TJ 06)	Randomised trials	No limitations	No important inconsistency	Major uncertainty (-2)[4]	Imprecise or sparse data (-1)[9]	-	-	RR 1.28[10] (0.45 to 3.66)		⊕○○○ Very low	**8**
Influenza cases (Laboratory confirmed clinical influenza Follow up: 6 to 8 weeks)											
2 (TJ 06)	Randomised trials	No limitations	No important inconsistency	Major uncertainty (-2)[4]	None			RR 0.39 (0.18 to 0.85)		⊕⊕○○ Low	**6**
1 Elderly (80% vaccinated) (DT 03)	Randomised	No limitations	Only one trial	Major uncertainty (-2)[4]	None	1/276 (0.4%)	12/272 (4.4%)	OR 0.08[11] (0.01 to 0.61)	-	⊕⊕○○ Low	
Serious adverse effects											
0[12]	-	-	-	-	-	-	-	-	-	-	**7**
Minor adverse effects [13]											
2 (TJ06)	Randomised trials	No limitations	No important inconsistency	Some uncertainty (-1)[14]	Imprecise or sparse data (-1)[9]			OR range[15] (0.58 to 2.28)		⊕⊕○○ Low	
All populations (Prophylaxis 150mg):											
Influenza like illness cases (Follow up: 6 weeks)											
1 (TJ 06)	Randomised trial	No limitations	Only one trial	Major uncertainty (-2)[4]	Imprecise or sparse data (-1)[9]	-	-	RR 1.00 (0.25 to 3.95)	-	⊕○○○ Very low	**8**
Influenza cases (Laboratory confirmed clinical influenza Follow up: 6 weeks)											
1 (TJ 06) (DT 03)	Randomised trial	No limitations	Only one trial	Major uncertainty (-2)[1]	None	7/520 (1.3%)	25/519[16] (4.8%)	RR 0.27[17] (0.11 to 0.67)	-	⊕⊕○○ Low	**6**
Serious adverse effects											
0[12]	-	-	-	-	-	-	-	-	-	-	**7**
Withdrawals from trial (Follow up: 8 weeks)[18]											
1 (DT 03)	Randomised trial	No limitations	Only one trial	No uncertainty	Imprecise or sparse data (-1)[19]	7/520 (1.3%)	10/519 (1.9%)	-	-	⊕⊕⊕○ Moderate	**6**

Footnotes:

1. The dosages used varied: 75mg od for 7 days or 75mg bd for 10 days in adults. Dosages for children were adjusted according to age-group.
2. Hayden et al 2004 gave post-exposure prophylaxis to household contacts aged > 1 year. The other study was a cluster RCT assessing post-exposure prophylaxis in households where there had been an influenza index case. The age range of the population was from 12 to 85 years, with 13% having previously been vaccinated. In addition around 40% of the contacts had pre-existing chronic diseases (Welliver 2001).
3. Due to the small number of trials it is difficult to comment on the consistency of the results.
4. There is major uncertainty surrounding the applicability of this evidence to avian influenza.
5. The RR range quoted is based on protective efficacy for individual contacts as reported in the text of the individual studies. Hayden et al report that viral circulation was present during the study period (both influenza A and B) which meant that effectiveness was high. Neither study reported the background rate of infection in the community, nor the viral strains, though both influenza A and B were co-circulating.
6. In the text of the Lancet review it is stated that neither trial reported the onset of viral resistance after 5 days (Hayden 2004) and 7 days (Welliver 2001), at doses of 75mg bd and od respectively.
7. It was not explicitly stated in the Turner HTA, the reasons for withdrawal from the study. Thus it is difficult to comment on the directness.
8. It is possible that one trial is inadequate to demonstrate the potential withdrawal rate due to adverse effects, due to insufficient numbers.
9. The confidence intervals include both substantial harms and benefits.
10. This is reported as efficacy in the Lancet review. The RR reported here is for influenza cases. The Lancet review reports an additional category - influenza cases (asymptomatic) for which the RR was 0.73 (0.43 to 1.26).
11. The numbers in the table are for the entire study population. 80% of the study population were vaccinated and the OR for the vaccinated subgroup was 0.09 (0.001 to 0.67).
12. Serious adverse effects are not mentioned in the Lancet review explicitly for oseltamivir 75mg used as prophylaxis. The HTA records adverse effects solely for zanamivir but suggests the data for oseltamivir were insufficient for their analyses. The number of trial withdrawals for Hayden 1999 is included but the reasons for withdrawal are not stated, with the withdrawals being higher in the placebo group (4%) than the prophylaxis group (3%). The withdrawals in the treatment arm were not split by dosage.
13. These included nausea, vomiting, diarrhoea, abdominal pain, others, withdrawals due to gastrointestinal side effects.
14. There is considerable variation in definition and measurement of mild adverse effects between trials.
15. Most of the CIs for the ORs reported on adverse effects are wide and also span 1. Nausea is the only statistically significant result OR 1.79 (1.10-2.93), though the confidence interval is also rather wide.
16. The number of patients comes from the HTA report and is derived from one trial (Hayden 1999).
17. This is reported as efficacy in the Lancet review. The RR reported here is for influenza cases. The Lancet review reports an additional category, influenza cases (asymptomatic) for which the RR was 0.67 (0.35 to 1.28). The HTA report gives odds ratios for lab confirmed influenza cases, with a pooled OR of 0.26 (0.08 to 0.51).
18. The data reported here is from the Turner HTA. The data from the original study (Hayden 1999) reported withdrawals due to intercurrent illness and adverse effects. The number of withdrawals was 7 out of 520 in the treatment arm and 10 out of 519 in the placebo arm.
19. This is potentially debatable - as whilst there was only one study, it was a large one (n=1599, though 520 participants were given 75mg od). It is not possible to comment on imprecision from the data given but it appears that withdrawal rates were similar in all three groups.

Summary of findings 6

SCENARIO: Should oseltamivir be used for prevention or post-exposure prophylaxis of avian influenza (H5N1)[1]?

Transmission: No human to human transmission.

Patient or population: Household contacts of cases with presenting with symptoms of avian influenza[2]

Information sources:

Avian influenza data: Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.

Resistance data: Le 2005, de Jong 2005, McKimm-Breschin 2003 and Hurt 2004.

Clinical trial data: Randomised trials for non-H5N1 influenza undertaken in Europe, North America and Japan under pandemic conditions or seasonal outbreaks.

Outcome	Avian influenza H5N1 evidence			Seasonal influenza evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No of participants (No of trials)	Risk without treatment (Range)	Relative effect (95% CI)	Quality	Comments
Mortality		64% (33 to 100%)		0	-	-	-	
Prevention of influenza cases	0	-		1774[3] (2)	-	RR range (0.11 to 0.32)	⊕⊕◯◯[4] Low	Data shown refer to post-exposure prophylaxis within a household setting.
Duration of hospitalisation (days)[3]	0	-	-	0	-	-		
Duration of disease (time to alleviation of symptoms)[5]	0	-	-	0	-	-		
Resistance	2	-	H5N1 was isolated from 2 patients in Viet Nam who died, who had been treated with oseltamivir. Viral isolates had an H274 neuraminidase base substitution, which was associated with high-level oseltamivir resistance in vitro. H274Y has also been shown to confer oseltamivir resistance in an animal model.	(2)	-	-		No evidence of widespread naturally occurring resistance reported for non-H5N1 viruses.
# trial withdrawals	0	-	-	962[3] (1)	2/461 (< 1%)	-	⊕⊕⊕◯[6] Moderate	
Cost of drugs per patient	0	-	-	0	-	-	-	

Footnotes:

1. The dosages used for PEP were 75mg od for 7 days and 75mg bd for 10 days in adults. The dosages varied according to age-group for children.
2. Index cases were classified as those presenting with influenza-like illness during a documented community outbreak in one instance and presenting within 48 hours of cough and coryza.
3. This number refers to the total original number of participants in the PEP trial(s) included here.
4. Major uncertainty about the directness of the evidence, in addition there was significant inconsistency between the results of the studies.
5. These data are indirect (i.e. for non-avian influenza) and thus only a proxy measure for what might be expected for avian influenza (H5N1).
6. It is possible that the numbers included in the study were too small to adequately demonstrate the true withdrawal rate.

GRADE evidence profile 7

Author(s): Gunn E Vist
Date: 2006 02 28

QUESTION: Should inhaled zanamivir (preventive treatment given for 5 days) be used for post exposure prevention of avian influenza (H5N1)?

Patient or population: Household setting
Settings: Canada and USA (575 persons), Canada, Finland, UK, USA (837 persons).
Systematic review: Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35). [E3]

QUESTION: Should inhaled zanamivir (preventive treatment given for 5 days or 6 days) be used for prevention of avian influenza (H5N1) in otherwise healthy adults?

Patient or population: Healthy adults
Settings: Europe and North America (A/H3N2, 573 persons), USA (A/H3N2, 1107 persons)
Systematic review:

a) (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13. [E1]
b) (TJ 99) Jefferson T, Demicheli V, Deeks J, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. The Cochrane Database of systematic reviews. 1999, Issue 2. Art. No.;CD001265.DOI:10.1002/14651858.CD001265. [E5]
c) (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35). [E3]

QUESTION: Should inhaled zanamivir (preventive treatment given for 5 days or 6 days) be used for prevention of avian influenza (H5N1) in elderly and at risk adults?

No additional information available

QUESTION: Should inhaled zanamivir (preventive treatment given for 5 days or 6 days) be used for prevention of avian influenza (H5N1) in children?

No additional information available

QUESTION: Should intranasal zanamivir (0.32 mg, preventive treatment given for 5 days) be used for prevention of avian influenza (H5N1) in otherwise healthy adults?

Patient or population: Healthy adults
Settings: Europe and North America (A/H3N2, 573 persons)
Systematic review:

a) (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13. [E1]
b) (TJ 99) Jefferson T, Demicheli V, Deeks J, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. The Cochrane Database of systematic reviews. 1999, Issue 2. Art. No.;CD001265.DOI:10.1002/14651858.CD001265. [E5]
c) (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35). [E3]

QUESTION: Should intranasal zanamivir (0.32 mg, preventive treatment given for 5 days) be used for prevention of avian influenza (H5N1) in elderly and at risk adults?

No additional information available

QUESTION: Should intranasal zanamivir be used for prevention of avian influenza (H5N1) in children?

No additional information available

QUESTION: Should intranasal zanamivir (0.32 mg) combined with inhaled zanamivir (10 mg) (treatment given for 5 days) be used for prevention of avian influenza (H5N1) in otherwise healthy adults?

Patient or population: Healthy adults
Settings: Europe and North America (A/H3N2, 573 persons)
Systematic review:

a) (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13. [E1]
b) (TJ 99) Jefferson T, Demicheli V, Deeks J, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. The Cochrane Database of systematic reviews. 1999, Issue 2. Art. No.; CD001265.DOI:10.1002/14651858.CD001265. [E5]
c) (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35). [E3]

QUESTION: Should intranasal zanamivir (0.32 mg) combined with inhaled zanamivir (10 mg) (treatment given for 5 days) be used for prevention of avian influenza (H5N1) in elderly and at risk adults?

Patient or population: Elderly at residential home
Settings: USA (52 persons)
Systematic review:

a) (DT 03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35). [E3]

QUESTION: Should intranasal zanamivir (0.32 mg) combined with inhaled zanamivir (10 mg) (treatment given for 5 days) be used for prevention of avian influenza (H5N1) in children?

No additional information available

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

NOTE: This first table may be confusing because the systematic reviews have grouped trials in different ways. Therefore one study by Kaiser et al, 2000, is also included in the second table.

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Inhaled zanamivir	Control	Relative (95% CI)	Absolute (95% CI)		
All (post exposure households)											
Post-exposure prophylaxis on chances of laboratory confirmed influenza											
2 (DT 03)	Randomised trial	No serious limitations	No important inconsistency	Major uncertainty (-2)[1]	None	10/558 (2%)	49/567 (9%)	RR 0.21 (0.11 to 0.42)	-	⊕⊕○○ Low	
Inhaled prevention in healthy adults											
Influenza cases (Follow up: 21 days)											
2 (TJ 06)	Randomised controlled trials	No serious limitations	No important consistency	Major uncertainty (-2)[1]	None	-	6%[2]	RR 0.38 (0.17 to 0.85)	-	⊕⊕○○ Low	**8**
Influenza like illness cases (Follow up: 21 days)											
2 (TJ 06)	Randomised controlled trials	No serious limitations	No important consistency	Major uncertainty (-2)[1]	Sparse or imprecise data (-1)[3]	-	-	RR 1.51 (0.77 to 2.95)		⊕○○○ Very low	
Asymptomatic influenza cases (Follow up: 28 days)											
1 (TJ 06)	Randomised controlled trials	No serious limitations	Only one study	Major uncertainty (-2)[1]	None	-	-	RR 1.63 (0.99 to 2.67)		⊕⊕○○ Low	**6**
Mortality rates											
0	-	-	-	-	-	-	-	-	-		**6**
Duration of hospitalisation											
0	-	-	-	-	-	-	-	-	-		**5**
Duration of fever											
0	-	-	-	-	-	-	-	-	-		**6**
Viral shedding											
0	-	-	-	-	-	-	-	-	-		**6**
Outbreak control											
0	-	-	-	-	-	-	-	-	-		**7**
Resistance											
0	-	-	-	-	-	-	-	-	-		**7**
# trial withdrawals											
2 (DT 03)	Randomised trials	Serious limitation (-1)[4]	No important inconsistency	No uncertainty	None	16/1130 (2%)	24/1135 (2%)	RR 0.67 (0.36 to 1.25)	-	⊕⊕⊕○ Moderate	**6**
# individuals with adverse events to treatment											
2 (DT 03)	Randomised trials	Serious limitation (-1)[4]	No important inconsistency	No uncertainty	None	60/1130 (5%)	54/1135 (5%)	-	-	⊕⊕⊕○ Moderate	
Cost of drugs											
0	-	-	-	-	-	-	-	-	-		**5**

Quality assessment						Summary of findings					
						No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Inhaled zanamivir	Control	Relative (95% CI)	Absolute (95% CI)		
Intranasal combined with inhaled prevention in healthy adults											
Influenza cases (Follow up: 21 days)											
1 (TJ 06)	Randomised controlled trials	No serious limitations	Only one trial	Major uncertainty (-2)[1]	Sparse or imprecise data (-1)[6]	-	6%	RR 0.22 (0.08 to 0.58)	-	⊕○○○ Very low	**8**
Influenza like illness cases											
0	-	-	-	-	-	-	-	-	-		
Mortality rates											
0	-	-	-	-	-	-	-	-	-		**6**
Duration of hospitalisation											
0	-	-	-	-	-	-	-	-	-		**5**
Viral shedding											
0	-	-	-	-	-	-	-	-	-		**6**
Outbreak control											
0	-	-	-	-	-	-	-	-	-		**7**
Resistance											
0	-	-	-	-	-	-	-	-	-		**7**
Serious adverse effects											
0	-	-	-	-	-	-	-	-	-		**7**
Minor adverse effects											
0	-	-	-	-	-	-	-	-	-		
Cost of drugs											
0	-	-	-	-	-	-	-	-	-		**5**
Intranasal combined with inhaled prevention in elderly and at risk adults											
Influenza cases (Follow up: 14 days)											
1 (DT 03)	Randomised controlled trials	Serious limitation (-1)[4]	Only one study	Major uncertainty (-2)[1]	Sparse or imprecise data (-1)[3]	0/35	1/17	OR 0.15 (0.006 to 4.01)	-	⊕○○○ Very low	**8**
Influenza like illness cases (Follow up: 14 days)											
1 (DT 03)	Randomised controlled trials	Serious limitation (-1)[4]	Only one study	Major uncertainty (-2)[1]	Sparse or imprecise data (-1)[3]	0/35	1/17	OR 0.15 (0.006 to 4.01)	-	⊕○○○ Very low	
# patients with adverse events to treatment											
0	-	-	-	-	-	-	-	-	-		

Footnotes:

1. Major uncertainty surrounding the applicability of this evidence to avian influenza.
2. Only one of the trial reported influenza cases in the control group, this study included 1/3 of people and reported the control group influenza to be 6%.
3. The confidence intervals include both important benefits and important harms.
4. Jadad score 4/5.
5. Sparse or imprecise data, only one study and confidence interval includes both large benefits and large harms.
6. Sparse or imprecise data, only one study.

Summary of findings 7

SCENARIO: Should zanamivir be used for prevention or post exposure prophylaxis of avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Healthy adults
Information sources:

Avian influenza data: : Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: McKimm-Breschin 2003 and Hurt 2004.
Clinical trial data: Randomised trials for non-H5N1 influenza undertaken in Australia, Europe, Japan, New Zealand, USA, and South Africa under pandemic conditions or seasonal outbreaks. Resistance data taken from in vitro studies.

Outcome	Avian influenza H5N1 evidence			Seasonal influenza evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No. participants (No of trials)	Risk without treatment	Relative effect (95% CI)	Quality	Comments
Mortality	0	64% (33 to 100%)	Control group risk based on total mortality rate, although 10 (56%) of patients in Hong Kong were treated with amantadine and others received a range of treatments.	0	-	-	-	No deaths reported in trials.
Prevention of Influenza cases	0	-		2 (1125)	6%	RR 0.38 (0.17 to 0.85)	⊕⊕◯◯ Low[1]	The data shown refer to a mixture of post-exposure prophylaxis in a household setting and prevention in closed communities.
Duration of hospitalization	0	-		0	-	-	-	
Duration of disease	0	-		0	-	-	-	
Resistance	1	-	No evidence of resistance reported for H5N1. Viral isolates with the H274 neuraminidase base substitution which confers high level oseltamivir resistance are zanamivir sensitive in vitro.	2	-	-	-	No evidence of resistance reported for non-H5N1 viruses.
# trial withdrawals	0	-		3 (2265)	2%	No difference	⊕⊕⊕◯ Moderate[2]	
Cost of drugs per patient	0	-	-	-	-	-	-	

Footnotes:

1. These data are indirect and only a proxy measure for what might be expected for avian influenza (H5N1).
2. Serious limitations, reported Jadad score was 4/5.

GRADE evidence profile 8

Author(s): Gunn E Vist
Date: 2006 02 28

QUESTION: Should oral amantidine be used for prevention of avian influenza (H5N1) in otherwise healthy adults?

Patient or population: Healthy adults
Settings: USA (H3N2 and H1N1, 450 participants), USA (A/USSR/77, 139 paramedic recruits), USA (H1N1, 286 students), Hungary (Hong Kong influenza 1969, 4760 soldiers), Romania (Hong Kong influenza 1969, 215 individuals), Finland (Hong kong influenza 1969, 391 students), Finland (H1N1, 192 military recruits), USA (A/USSR/90/77, 444 students), USA (H1N1, H3N2, B/USSR/100/83, 476 hospital personnel), UK (H1N1, 536 young males), Sweden (Leningrad 65, 96 volunteers), USA (4183 military personnel), USA (2650 military recruits), Czechoslovakia (H3N2, 1133 students), England ((Hong Kong/1'768, 297 volunteers), Soviet Union (Hong Kong/68, 8267students), USA (A2/Japan305/57, 794 inmates)
Systematic review:

a) (TJ 06) Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13. [E1]
b) (TJ 04) Jefferson T, Deeks JJ, Demicheli V, Rivetti D, Rudin M. Amantadine and rimantadine for preventing and treating influenza A in adults. The Cochrane Database of Systematic Reviews. 2004, Issue 3. Art. No.;CD001169.pub2.DOI:10.1002/14651858.CD001169. [E]
c) (DT03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35). [E3]

QUESTION: Should oral amantidine be used for prevention of avian influenza (H5N1) in elderly?

Patient or population: Elderly people
Settings: Finland (H1N1, 188 institutionalised elderly people, 100 mg/ day), UK (54 elderly at hospital, 200 mg/ day)
Systematic review:

a) (DT03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35). [E3]

QUESTION: Should oral amantidine be used for prevention of avian influenza (H5N1) in children?

Patient or population: Children
Settings: USA (A2, 159 institutionalised children with learning difficulties, doses 70 mg/day, or 105 mg/ day or 35 followed by 140 mg/ day), USA (293 children with learning difficulties who lived in a home for children, 60 or 100 mg/ day), USA (40 residential asthmatic children, 200 mg/day)
Systematic review:

a) (DT03) Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003;7(35). [E3]

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

Quality assessment						Summary of findings					
						No of patients		Effect			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Oral amantidine	Control	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Healthy adults:											
Influenza cases (Follow up: 3 to 7 weeks)											
11[1] (TJ06, TJ04)	Randomised trials	No serious limitations[2]	Important inconsistency (-1)[3]	Major uncertainty (-2)[4]	None	146/2396 (6%)	280/2249 (12%)	RR 0.39 (0.24 to 0.65)	-	⊕OOO Very low	**8**
Influenza like illness cases (Follow up: 10 days to 9 weeks)											
15[5] (TJ06, TJ04)	Randomised trials	Serious limitations (-1)[6]	Important inconsistency (-1)[7]	Major uncertainty (-2)[4]	None	2489/9481 (26%)	2651/8015 (33%)	RR 0.75 (0.64 to 0.87)	-	⊕OOO Very low	**6**
Mortality rates											
0	-	-	-	-	-	-	-	-	-		**6**
Duration of hospitalisation											
0	-	-	-	-	-	-	-	-	-		**5**
Duration of fever											
0	-	-	-	-	-	-	-	-	-		**6**
Viral shedding (Viral assays from nasal washouts) (Follow up: 6 weeks)											
1 (TJ06)	Randomised trial	No serious limitations	Only one study	Major uncertainty (-2)[4]	Sparse or imprecise data (-1)[8]	-	-	RR 0.68 (0.53 to 0.87)	-	⊕OOO Very low	**6**
Outbreak control											
0	-	-	-	-	-	-	-	-	-		**7**
Resistance											
0	-	-	-	-	-	-	-	-	-		**7**
Serious adverse effects											
0	-	-	-	-	-	-	-	-	-		**7**
Withdrawals due to adverse effects (Follow up: 4.5 days to 7 weeks)[9]											
6 (TJ04)	Randomised trial	No serious limitations[10]	No important inconsistency	Direct	None	68/1154 (6%)	27/1122 (2%)	RR 2.39 (1.54 to 3.71)[9]	-	⊕⊕⊕⊕ High	**6**
Cost of drug											
0	-	-	-	-	-	-	-	-	-		**5**
Elderly people:											
Influenza cases (Follow up: 25 days)											
1 (DT03)	Randomised trial	Serious limitations (-1)[11]	Only one study	Major uncertainty (-2)[4]	None	6/25 (24%)	11/29 (38%)	-	-	⊕OOO Very low	**8**
Withdrawals due to treatment (Follow up: 9 weeks)											
1 (DT03)	Randomised trials	No serious limitations	Only one study	Direct	Sparse or imprecise data (-1)	5/94 (5%)	2/101 (2%)	-	-	⊕⊕⊕O Moderate	**6**
Children with learning difficulties:											
Influenza cases (Follow up: 4 weeks to 5 months)											
2 (DT03)	Randomised trials	Serious limitations (-1)[12]	No important inconsistency	Major uncertainty (-2)[4]	Sparse or imprecise data (-1)[13]	(2% and 3%)	(12% and 9%)	-	-	⊕OOO Very low	**8**
Minor adverse events (Follow up: 5 months)											
1 (DT03)	Randomised trial	Serious limitations (-1)[14]	Only one study	Direct	Sparse or imprecise data (-1)[13]	7/154	7/139	-	-	⊕OOO Very low	
Children at risk:											
Influenza cases (Follow up: 4 weeks)											
1 (DT03)	Randomised trial	Serious limitations (-1)[15]	Only one study	Major uncertainty (-2)[4]	Sparse or imprecise data (-1)[13]	7/20	8/20	-	-	⊕OOO Very low	**8**

Footnotes:

1. Oral amantadine was given in 200 mg per day (100 mg twice daily) in all but two studies, one where one additional arm was given 100 mg and one where all participants were given 100 mg.
2. Eight of the 11 trials were well designed and conducted (71% weight) so the overall judgement is No serious limitations. We note, however, that two of the trials (Dolin 1982 and Quarles 1981) had serious limitations because of large number of drop outs and losses to follow up, and one trial had very serious limitations (Kantor 1980) because of poor compliance with study protocol and reported numbers inconsistent and data for 29 participants were not presented.
3. Unexplained heterogeneity (I^2=80%).
4. Major uncertainty surrounding the applicability of this evidence to avian influenza.
5. Oral amantadine was given in 200 mg per day (100 mg twice daily) in all but three studies, one where one additional arm was given 100 mg and two where all participants were given 100 mg.
6. Six of the 15 trials (50% weight, 78% of the participants) had serious limitations to the internal validity of the studies. Three of the trials (Dolin 1982, Quarles 1981, Smorodintsev 1970) had large drop out rates or losses to follow up, three studies (Peckinpaugh/1 (two studies) and Peckinpaugh/2) only presented results in histograms so those results are estimates, and two trials (Peckinpaugh/2 and Smorodintsev 1970) had contradictions in the text.
7. Unexplained heterogeneity (I^2= 90%).
8. Sparse or imprecise data, only one study reported with maximum 479 participants included. Additionally, the Table 1 in (Jefferson 2006) presenting results of viral shedding only lists 79 observations. Unsure if this outcome only measured in 79 of the participants or if a typo has occurred.
9. Serious adverse effects are not mentioned in Jefferson 2006 explicitly, however Jefferson 2004 reported significantly more gastrointestinal adverse events (5 RCTs, I^2=47%, RR 2.39 (1.32 to 4.32) with amantadine than with placebo. And a significant increased CNS activity (9 RCTs, I^2=67%, RR 2.25 (1,39 to 3,64).
10. Three of the 6 trials were well designed and conducted (56% weight) so the overall judgement is No serious limitations. We note, however, that two of the trials (Dolin 1982 and Quarles 1981) had serious limitations because of large number of drop outs and losses to follow up, and one trial had limitations (Hayden 1981) because there were inconsistencies between text and tables.
11. The Jadad score reported by DT 03 was 2/5.
12. The Jadad scores reported by DT 03 were 0 and 3.
13. Only small studies with few events.
14. Reported (DT 03) Jadad score 3/5.
15. Reported (DT 03) Jadad score 2/5.

Summary of findings 8

SCENARIO: Should amantadine be used for prevention of avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Healthy adults
Information sources:

Avian influenza data: : Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: Ilyushina 2005 and Puthavathana 2005.
Clinical trial data: Randomised trials for non-H5N1 influenza undertaken in Australia, Europe, Japan, New Zealand, USA, and South Africa under pandemic conditions or seasonal outbreaks. Resistance data taken from in vitro studies.

Outcome	Avian influenza H5N1 evidence			Seasonal influenza evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No. participants (No of trials)	Risk without treatment	Relative effect (95% CI)	Quality	Comments
Mortality	0	64% (33 to 100%)	Control group risk based on total mortality rate, although 10 (56%) of patients in Hong Kong were treated with amantadine and others received a range of treatments.	0	-	-	-	No deaths reported in trials.
Influenza cases	0	-		4645 (11)	12%	RR 0.39 (0.24 to 0.65)	⊕○○○ Very low[1]	
Duration of hospitalization	0	-		0	-	-	-	
Duration of disease	0	-		0	-	-	-	
Resistance	2	-	H5N1 isolated from humans in Thailand and from birds in Southeast Asia carries M2 ion channel resistance mutations.	0	-	-	-	
# trial withdrawals	0	-		2276 (6)	2%	RR 2,39 (1.54 to 3.71)	⊕⊕⊕⊕ High	

Footnotes:

1. Major uncertainty surrounding the applicability of this evidence to avian influenza and unexplained heterogeneity.

GRADE evidence profile 9

Author(s): Gunn E Vist
Date: 2006 02 28

QUESTION: Should oral rimantadine be used for prevention of avian influenza (H5N1) in otherwise healthy adults?

Patient or population: Healthy adults.
Settings: USA (H3N2, 228 volunteers), USA (H3N2 and H1N1, 450 participants), USA (A/USSR/90/77, 444 students).
Systematic review:

a) **(TJ 06)** Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13. [E1]
b) **(TJ 04)** Jefferson T, Deeks JJ, Demicheli V, Rivetti D, Rudin M. Amantadine and rimantadine for preventing and treating influenza A in adults. The Cochrane Database of Systematic Reviews. 2004, Issue 3. Art. No.; CD001169.pub2.DOI:10.1002/14651858.CD001169.

QUESTION: Should oral rimantadine be used for prevention of avian influenza (H5N1) in elderly people and at risk adults?

No additional information available.

QUESTION: Should oral rimantadine be used for prevention of avian influenza (H5N1) in children?

No additional information available.

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

Quality assessment						Summary of findings					
						No of patients		Effect			
No of studies	Design	Limitations	Consistency	Directness	Other considerations	Oral rimantidine	Control	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Influenza cases (Follow up: 6 weeks)											**8**
3[1] (TJ06, TJ04)	Randomised trials	No serious limitations[2]	Important inconsistency (-1)[3]	Major uncertainty (-2)[4]	None	20/347 (6%)	54/341 (16%)	RR 0.28 (0.08 to 1.08)	-	⊕○○○ Very low	
Influenza like illness cases (Follow up: 6 weeks)											
31 (TJ06, TJ04)	Randomised trials	No serious limitations[2]	Important inconsistency (-1)[5]	Major uncertainty (-2)[4]	None	78/347 (22%)	119/341 (35%)	RR 0.65 (0.35 to 1.20)	-	⊕○○○ Very low	
Asymptomatic influenza cases (Follow up: 6 weeks)											
1 (TJ06)	Randomised trial	No serious limitations	Only one trial	Major uncertainty (-2)[4]	Sparse or imprecise data (-1)[6]	-	-	RR 1.39 (0.45 to 4.27)	-	⊕○○○ Very low	**6**
Mortality rates											
0	-	-	-	-	-	-	-	-	-		**6**
Duration of hospitalisation											
0	-	-	-	-	-	-	-	-	-		**5**
Duration of fever											
0	-	-	-	-	-	-	-	-	-		**6**
Viral shedding											
0	-	-	-	-	-	-	-	-	-		**7**
Outbreak control											
0	-	-	-	-	-	-	-	-	-		**7**
Resistance											
0	-	-	-	-	-	-	-	-	-		**7**
Serious adverse effects											
0	-	-	-	-	-	-	-	-	-		**7**
Withdrawals due to adverse effects (Follow up: 6 weeks)[6]											
3 (TJ06, TJ04)	Randomised trial	No serious limitations[2]	No important inconsistency	Direct	None	13/312 (4%)	12/313 (4%)	RR 1.10 (0.50 to 2.42)	-	⊕⊕⊕⊕ High	**6**
Cost of drug											
0	-	-	-	-	-	-	-	-	-		

Footnotes:

1. Oral rimantadine was given in 200 mg per day (100 mg twice daily) in two studies, and 100 mg per day in one study.
2. Two of the three trials were well designed and conducted (68 % weight) so the overall judgement is No serious limitations. We note, however, that one of the trials (Quarles 1981) had serious limitations because of large number of losses to follow up.
3. Unexplained heterogeneity (I^2=77%).
4. Major uncertainty surrounding the applicability of this evidence to avian influenza.
5. Unexplained heterogeneity (I^2= 83%).
6. Only one trial with confidence intervals including both important benefits and important harms.
7. Serious adverse effects are not mentioned in Jefferson 2006 explicitly, however Jefferson 2004 reported significantly more gastrointestinal adverse events (2 RCTs, I^2=0%, RR 4.04 (1.37 to 11.88)) with rimantadine than with placebo. And all adverse events (2 RCTs, I^2=0%, RR 1.72 (1.14 to 2.59).

Summary of findings 9

SCENARIO: Should rimantadine be used for prevention of avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Healthy adults
Information sources:

Avian influenza data: : Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: Puthavathana 2005.
Clinical trial data: Randomised trials for non-H5N1 influenza undertaken in Australia, Europe, Japan, New Zealand, USA and South Africa under pandemic conditions or seasonal outbreaks. Resistance data taken from in vitro studies.

Outcome	Avian influenza H5N1 evidence			Seasonal influenza evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No. participants (No of trials)	Risk without treatment	Relative effect (95% CI)	Quality	Comments
Mortality	0	64% (33 to 100%)	Control group risk based on total mortality rate, although 10 (56%) of patients in Hong Kong were treated with amantadine and others received a range of treatments.	0	-	-	-	No deaths reported in trials.
Influenza cases	0	-		688 (3)	16%	RR 0.28 (0.08 to 1.08)	⊕○○○ Very low[1]	
Duration of hospitalization	0	-		0	-	-	-	
Duration of disease	0	-		0	-	-	-	
Resistance	2	-	H5N1 isolated from humans in Thailand and from birds in Southeast Asia carries M2 ion channel resistance mutations.	0	-	-	-	
# trial withdrawals	0	-		3 (625)	4%	RR 1.10 (0.50 to 2.42)	⊕⊕⊕⊕ High	

Footnotes:

1. Major uncertainty surrounding the applicability of this evidence to avian influenza.

GRADE evidence profile 10

Author(s): Gunn E Vist
Date: 2006 02 28

QUESTION: Should oral amantadine versus oral rimantadine be used for prevention of avian influenza (H5N1) in otherwise healthy adults?

Patient or population: Healthy adults
Settings: USA (H3N2, 228 volunteers), USA (A/USSR/90/77, 444 students), USA (251 volunteers)
Systematic review:

a) **(TJ 06)** Jefferson T, Demicheli V, Rivetti D, Jones M, DiPietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367:303-13.
b) **(TJ 04)** Jefferson T, Deeks JJ, Demicheli V, Rivetti D, Rudin M. Amantadine and rimantadine for preventing and treating influenza A in adults. The Cochrane Database of Systematic Reviews. 2004, Issue 3. Art. No.;CD001169.pub2.DOI:10.1002/14651858.CD001169, (Jefferson 2004).

QUESTION: Should oral amantadine versus oral rimantadine be used for prevention of avian influenza (H5N1) in elderly people and at risk adults?

No additional information available

QUESTION: Should oral amantadine versus oral rimantadine be used for prevention of avian influenza (H5N1) in children?

No additional information available

NOTE: These GRADE Evidence Profiles have been completed from multiple sources. The source of the information (referring to one of the systematic reviews listed above) is indicated in the first column of the table under the number of studies. The quality of evidence indicates the overall quality of the evidence for the questions specified above, not the quality of the included studies or the systematic reviews. The reasons for the judgments that were made are provided in the footnotes.

Quality assessment						Summary of findings					
						No of patients		Effect			
No of studies	**Design**	**Limitations**	**Consistency**	**Directness**	**Other considerations**	**Oral amantidine**	**Oral rimantadine**	**Relative (95% CI)**	**Absolute (95% CI)**	**Quality**	**Importance**
Influenza cases (Follow up: 6 weeks)											
2[1] (TJ 06, TJ 04)	Randomised trials	Serious limitations (-1)[2]	No important inconsistency	Major uncertainty (-2)[3]	None	17/220 (8%)	19/235 (8%)	RR 0.89 (0.48 to 1.65)	-	⊕○○○ Very low	**8**
Influenza like illness cases (Follow up: 6 weeks)											
2[1] (TJ 06, TJ 04)	Randomised trials	Serious limitations (-1)[2]	No important inconsistency	Major uncertainty (-2)[3]	None	52/220 (24%)	59/235 (25%)	RR 0.88 (0.57 to 1.35)	-	⊕○○○ Very low	
Mortality											
0	-	-	-	-	-	-	-	-	-		**6**
Duration of hospitalisation											
0	-	-	-	-	-	-	-	-	-		**5**
Duration of fever											
0	-	-	-	-	-	-	-	-	-		**6**
Viral shedding											
0	-	-	-	-	-	-	-	-	-		**6**
Outbreak control											
0	-	-	-	-	-	-	-	-	-		**7**
Resistance											
0	-	-	-	-	-	-	-	-	-		**7**
Serious adverse effects											
0	-	-	-	-	-	-	-	-	-		**7**
Withdrawals due to adverse effects (Follow up: 6 weeks)[4]											
3 (TJ 06, TJ 04)	Randomised trial	Serious limitations (-1)[5]	No important inconsistency	Direct	None	30/319 (9%)	13/312 (4%)	RR 2.30 (1.23 to 4.30)	-	⊕⊕⊕○ Moderate	**6**
Cost of drug											
0	-	-	-	-	-	-	-	-	-		**5**

Footnotes:

1. Oral amantadine or oral rimantadine was given in 200 mg per day (100 mg twice daily).
2. Serious limitations because of large drop outs and number of losses to follow up in both studies.
3. Major uncertainty surrounding the applicability of this evidence to avian influenza.
4. Serious adverse effects are not mentioned in Jefferson 2006 explicitly, however Jefferson 2004 reported significantly increased CNS activity (2 RCTs, I^2=0%, RR 2.59 (1.54 to 4.35) with amantadine than with rimantadine.
5. Serious limitations because two of the trials (Dolin 1982 and Quarles 1981) had large drop outs and number of losses to follow up and the third trial contained inconsistencies between text and table.

Summary of findings 10

SCENARIO: Should amantadine versus rimantadine be used for prevention of avian influenza (H5N1)?

Transmission: No human to human transmission
Patient or population: Healthy adults
Information sources:

Avian influenza data: : Yuen 1998, Chotpitayasunondh 2005, Hien 2004, WHO Writing Committee 2005.
Resistance data: Ilyushina 2005 and Puthavathana 2005.
Clinical trial data: Randomised trials for non-H5N1 influenza undertaken in Australia, Europe, Japan, New Zealand, USA and South Africa under pandemic conditions or seasonal outbreaks. Resistance data taken from in vitro studies.

Outcome	Avian influenza H5N1 evidence			Seasonal influenza evidence (may provide indirect evidence of potential benefit in avian influenza)				
	Number of studies	Risk without treatment	Comments	No. participants (No of trials)	Risk without treatment	Relative effect (95% CI)	Quality	Comments
Mortality	0	64% (33 to 100%)	Control group risk based on total mortality rate, although 10 (56%) of patients in Hong Kong were treated with amantadine and others received a range of treatments.	0	-	-	-	No deaths reported in trials.
Influenza cases	0	-		455 (2)	-	RR 0.89 (0.48 to 1.65)	⊕○○○ Very low[1]	
Duration of hospitalization	0	-		0	-	-	-	
Duration of disease	0	-		0	-	-	-	
Resistance	2	-	H5N1 isolated from humans in Thailand and from birds in Southeast Asia carries M2 ion channel resistance mutations.	0	-	-	-	
# trial withdrawals	0	-		631 (3)	-	RR 2,30 (1.23 to 4.30)	⊕⊕⊕○ Moderate[2]	

Footnotes:

1. Major uncertainty surrounding the applicability of this evidence to avian influenza and serious limitations because of losses to follow up.
2. Serious limitations because of losses to follow up and inconsistencies between tables and text.

Summary of *in vitro* evidence of treatment for H5N1 human and H5N1 avian influenza

Reviewer: Lauren Stockman, Richard Bellamy

Search: PubMed searched on 2/17/06 of zanamivir or oseltamivir or amantadine or rimantadine or interferon or ribavirin treatment plus H5N1 or avian influenza AND in vitro, screened abstracts 33 of articles. Included H1N1 and H3N2 papers as referenced by articles or referred by colleague.

All studies measured effects in Madin-Darby canine kidney (MDCK) cell line, unless noted. Data for human strains H1N1 and H3N2 were included when relevant for comparison. Quality of each study has not yet been evaluated.

Zanamivir

Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Conclusions	Study ID
1. A/HK/156/97 (H5N1)	1. ELISA 2. Plaque assay 3. NA inhibition	1. H5N1 with avian strains	Inhibited viral replication in all viruses. Concentrations required in each virus were similar.	NA was inhibited for all viruses and concentrations required were similar for all viruses	Zanamivir inhibited both NA activity and virus replication of H5N1 and avian viruses.	Leneva 2001
1. A/Duck/MN/1525/81 (H5N1) 2. A/Gull/PA/4175/83 (H5N1) 3. H1N1 (5 strains) 4. H3N2 (12 strains)	1. Inhibition of cytopathic effect 2. Virus yield reduction 3. Time-of addition studies	1. Viruses 2. zanamivir vs. oseltamivir	Inhibited viral replication in all viruses. Required concentrations of zanamivir and oseltamivir were similar.	Not studied	Zanamivir and oseltamivir inhibited virus replication of all viruses.	Smee 2001
1. A/HK/156/97 (H5N1)	1. Plaque assay 2. NA inhibition	None studied	Inhibited viral replication	NA was inhibited	Zanamivir inhibited both NA activity and virus replication	Gubareva 1998

Oseltamivir

Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Conclusions	Study ID
1. A/HK/156/97 (H5N1)	1. ELISA 2. NA inhibition	1. H5N1 vs. H9N2 (A/HK/1974/99)	Inhibited viral replication of both viruses. Concentrations required in each virus were similar.	NA was inhibited for both viruses. Sensitivity of viruses were similar	Oseltamivir inhibits replication and NA activity of both viruses. Viruses did not differ in sensitivity to drug.	Leneva 2000

Amantadine

Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Conclusions	Study ID
1. A/Thailand/1(KAN-1) (H5N1) 2. A/Thailand/2(SP-33) (H5N1) 3. A/Thailand/3(KK-494) (H5N1) 4. A/New Caledonia/20/99 (H1N1-like) 5. A/Sydney/05/97(H3N2-like)	1. Measurement of viral nucleoprotein by ELISA	1. Viruses	High concentrations could not inhibit H5N1. H1N1-like virus could be inhibited completely with low concentrations, H3N2-like virus was inhibited 50% by low concentration	Not studied	Thailand H5N1 isolates contained asparagine instead of serine at aa31, indicating resistance to amantadine and rimantadine. Confirmed in vitro.	Puthavathana 2005

Ribavirin

Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Conclusions	Study ID
1. A/HWS/33 (H1N1) 2. A/PR/8/34 (H1N1) 3. A/Victoria/3/75 (H3N2) 4. A/New Caldonia/20/99 (H1N1) 4. A/Sydney/05/97 (H3N2) 5. A/Panama/2007/99 (H3N2) 6. A/Duck/MN/1525/81 (H5N1) 7. A/Gull/PA/4175/83 (H5N1)	1. Inhibition of viral cytopathic effect 2. NR uptake (for cytotoxicity) 3. Virus yield reduction	1. Viruses 2. Ribavirin vs. Viramidine (an analog of ribavirin)	Ribavirin and Viramidine are highly effective against replication of influenza virus. Effect against each virus is similar. Activity is similar in both drugs but viramidine is less antivirally potent than ribavirin	Not studied	Both compounds were inhibitory to all the influenza viruses evaluated.	Sidwell 2005

Interferon

Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Conclusions	Study ID
1. A/HK/156/97 (H5N1) 2. A/HK/483/97 (H5N1) 3. A/HK/486/97 (H5N1) 4. A/CK/HK/W374/97 (H5N1) 5. A/Goose/HK/W374/97 (H5N1) 6. A/HK/1/68 (H3N2) 7. A/New Caledonia/20/99 (H1N1)	1. SJPL cells cultured, pretreated with IFNs and infected with virus. Virus titer was measured in SJPL cells grown in 96-well plates. *	1. Viruses	Replication of H5N1/97 viruses was not affected by pre-treatment of IFN-a, IFN-gamma, or TNF-a. Replication in human H3N2, swine and avian influenza viruses was effectively blocked.	Not studied	All the H5N1/97 Isolates tested escaped the anti-viral activity of IFN's and TNF-a.	Seo 2004

*This study used St. Jude porcine lung (SJPL) epithelial cells for antiviral assay. Uncertain if IFN was present in cells at time of infection, therefore uncertain if this is a valid measure of viral inhibition.

Combinations of NA inhibitor plus rimantadine (data from H1N1 and H3N2)

Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Conclusions	Study ID
1. A/New Caledonia/20/99 (H1N1) 2. A/Panama/2007/99 (H3N2)	1. Extra-cellular virus yield reduction assay 3. ELISA to determine the cell-associated virus reduction	1. zanamivir + rimantadine vs. single drug 2. oseltamivir + rimantadine vs. single drug	Combination of rimantadine and zanamivir or rimantadine and oseltamivir resulted in complete reduction in H1N2 and H3N2 extracellular viral yield. Interactions were mainly syngergistic or additive.	Not studied	Combination treatment with zanamivir or oseltamivir with rimantadine markedly reduces the extracellular H1N1 and H3N2 virus yield. Synergism or additive effects seen at a range of concentrations.	Govorkova 2004

Resistance evaluations by *in vitro* study and/or sequence data

Rimantadine

Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Outcome: Change in sensitivity	Conclusions	Study ID
1. A/H3N2 (human, 22 strains with substitution in M2 gene associated with adamantane resistance)	1. Biological assay, virus replication measured by haemagglutinin titers of supernatant. Susceptibllity determined by a 4-fold reduction in haemagglutination titer.	1. A subset of 22 viruses with substitution in M2 gene vs. viruses with known M2 gene sequences	Results from screening a subset of viruses for sensitivity confirmed that resistance phenotype correlated 100% with the mutations identified by sequencing.	Not studied	Not studied	Amantadine and rimantadine resistance was 0.4% in 1994-1995 to 12.3% in 2003-2004. Increase mostly due to resistance in Asia with 61% of resistant viruses isolated since 2003 were from people in Asia.	Bright 2005

Zanamivir

Virus	Assay	Comparisons	Outcome: Viral replication inhibition	Outcome: Neuraminidase (NA) inhibition	Outcome: Change in sensitivity	Conclusions	Study ID
1. A/N1 (human, 139 strains) 2. A/N2 (human, 767 strains)	1. NA inhibition by fluorescence 2. NA inhibition by chemiluminescent	1. Viruses 2. zanamivir vs. oseltamivir	Not studied	N2 viruses were generally more sensitive to oseltamivir than zanamivir. Slight differences seen between assay types. N1 viruses were slightly more sensitive to zanamivir than oseltamivir. Slight differences seen between assay types.	No altered sensitivity in viruses that had variations in sequence residues	H1N1 and H3N2 viruses circulating 1996-1999 were susceptible to zanamivir and oseltamivir. This is before the drugs were introduced for use in the area. Some variants were seen but no evidence of naturally occurring resistance to these two drugs.	McKimm-Breschin 2003
1. A/H1N1 (human, 235 strains) 2. A/H3N2 (human, 160 strains) 3. A/H1N2 (human, 9 strains)	1. NA inhibition by fluorescence	1. N1 vs. N2 2. year of isolation 3. Australasia vs. South East Asia	Not studied	N1 viruses were more sensitive to zanamivir than oseltamivir. N2 strains were more sensitive to oseltamivir. Similar susceptibility of Australasia and South East Asia strains.	No significant decline in sensitivity in Australasia strains by year of isolation.	After NA inhibitors were in use in the region, no significant impact on susceptibility of viruses to zanamivir or oseltamivir	Hurt 2004

Oseltamivir							
Virus	**Assay**	**Comparisons**	**Outcome: Viral replication inhibition**	**Outcome: Neuraminidase (NA) inhibition**	**Outcome: Change in sensitivity**	**Conclusions**	**Study ID**
1. H5N1 variant in Viet Nam patients (H274Y substitution in neuraminidase gene)	1. isolation by RT-PCR, then sequence	N/A	N/A	N/A	Virus with mutations that confir high-resistance to oseltamivir were isolated from two patients after treatment with oseltamivir.	In some patients treatment with oseltamivir incompletely suppresses viral replication. Higher doses, longer duration or other antiviral agents may be necessary.	de Jong 2005

Amantadine							
Virus	**Assay**	**Comparisons**	**Outcome: Viral replication inhibition**	**Outcome: Neuraminidase (NA) inhibition**	**Outcome: Change in sensitivity**	**Conclusions**	**Study ID**
1. H5N1 (Avian, 8 strains)	1. Plaque reduction assay	1. Amantadine sensitive viruses vs. M2 variants	Concentrations as high as 100uM failed to inhibit replication of M2 variant strains	Not studied	A large sample of viruses was screened for gene sequence. No M2 mutant strains among sample of viruses from 1979-83. But at least some resistance among avian H5, H6, h7 strains from 2000-04	31% of H5 and 10.6% of H9 avian strains from southeast Asia isolated in 2000-04 carried M2 mutations. Raises concern about the prevalence of amantadine-resistant strains for pandemic virus	Ilyushina 2005

Annex 4: Panel members

Dr Richard Bellamy, Department of Infection and Travel Medicine, James Cook University Hospital, Marton Road, Middlesborough TS 4 3BW, United Kingdom

Dr John Beigel, National Institute of Health Clinical Center, 6700B Rockledge, MSC 7609, Bethesda, MD, USA

Dr Tawee Chotpitayasunondh, Queen Sirikit National Institute of Child Health, MOPH, 420/8 Rajavithi Road, Payathai, Rajatevi, Bangkok 10400, Thailand

Professor Chris Del Mar, Dean, Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Queensland 4229 , Australia

Professor Jeremy Farrar, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam

Professor Frederick G. Hayden, Internal Medicine & Pathology, Health Sciences Center University of Virginia, P.O. Box 800473, 22908, Charlottesville, USA

Dr Azim Nagjdaliyev, Children Clinical Hospital N2 'Kayayev' Samad Vurgus str. Baloc 956 AZ 1022 Baku, Azerbaijan

Dr Bülent Özbay, Head of Pulmonary Department, Yuzuncu Yil University Van, YYU Typ Fakültesi, Göoüs Hastalyklary Anabilim Daly, 65300 Van, Turkey

Associate Professor Holger Schünemann, Italian National Cancer Institute Regina Elena, Rome, Italy & University at Buffalo, 00144 Rome, Italy (Chair of Rapid Advice Guidelines Meeting)

Dr Norio Sugaya, Department of Pediatrics, Keio University Faculty of Medicine, Keiyu Hospital, Minato-mirai, 3-7-3 , Nishi-ku, Yokohama-shi, Kanagawa 220-0012, Japan

Dr Tim Uyeki, Medical Epidemiologist, Influenza Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, MS A-32, Centers for Disease Control and Prevention, 1600 Cliffton Road, N.E., Atlanta, GA 30333, USA

Dr Tran Tinh Hien, Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam

Dr Yazdan Yazdanpanah, Infectious Diseases Physician, Department of Infectious Disease, Tourcoing Hospital, Lille Schoole of Medicine, Pavillon Trousseau 135 rue de Président Coty F-59200 Tourcoing, France

REVIEWERS

Dr Richard Bellamy, Department of Infection and Travel Medicine, James Cook University Hospital, Marton Road, Middlesborough TS 4 3BW, United Kingdom

Dr Meetali Kakad, Norwegian Knowledge Centre for the Health Services, P.O. Box 7004, St. Olavs plass N-0130 Oslo, Norway

Dr Andy Oxman, Norwegian Knowledge Centre for the Health Services, P.O. Box 7004, St. Olavs plass N-0130 Oslo, Norway

Dr Gunn Vist, Norwegian Knowledge Centre for the Health Services, P.O. Box 7004, St. Olavs plass N-0130 Oslo, Norway

Ms. Lauren J. Stockman, Respiratory and Enteric Viruses Branch, MS A-34, Centers for Disease Control and Prevention , Atlanta, GA 30333, USA

UNICEF

Mrs Hanne Bak Pedersen, Technical Services Centre, UNICEF Supply Division, UNICEF Plads, Freeport DK-2100, Copenhagen 0, Denmark

WHO SECRETARIAT

Communicable Diseases (CDS)
Dr Michael J. Ryan
Epidemic and Pandemic Alert and Response (EPR)

Dr Keiji Fukuda
Dr Alice Croiser
Global Influenza Programme (GIP)

Dr Cathy Roth	Medical Officer
Dr Nikki Shindo	Medical Officer
Dr Gail Thomson	Medical Officer

CSR Office for Alert and Response (ARO)
Emerging and Dangerous Pathogens (EDP)

Health Technology and Pharmaceuticals (HTP)
Dr Howard A. Zucker, Assistant Director-General, HTP

Dr Hans V. Hogerzeil
Medicines Policy and Standards (PSM)

Dr Suzanne Hill
Policy, Access and Rational Use (PAR)

Annex 5: Conflicts of interest

Potential conflicts of interest of contributors (refers to the period 2002 - 2006)

In the absence of clear guidance in the WHO *Guidelines for Guidelines* the group discussed the potential conflicts of interest and took the following decisions:

1. The declared interests were professional, rather than personal and/or specific (i.e. no shares or personal funding from the companies).
2. The members' professional expertise generally outweighed the potential conflict of interest.
3. The interest was declared to the group and reported in the report.

No panel members were asked to withdraw from either voting or recommendation formulation. All other interests declared do not represent a personal specific interest in the medicines under review.

Beigel - investigator (through NIH) on trials with Roche and Biocrest, no personal funding; Del Mar - funding for trials in unrelated therapeutic area from other companies, not in the last 4 years ; Hayden - received multiple research grants for trials of antivirals, vaccines from Roche, Abbots, Biocrest and Merck over the past 4 years - the last of these was in July 2005; Schünemann - received research grants and honoraria from Pfizer, Amgen, Roche and AstraZeneca for development or consulting regarding of quality of life instruments for chronic respiratory diseases, no personal funding (all funds were deposited into research accounts or received by research group); Sugaya - has received travel grant from Roche to attend meeting on avian influenza; Yazdanpanah - investigator on trials with Tibotec Pharmaceutical, no personal funding, has received travel grants from GSK, Roche, Boehringer, BMS, Pfizer, Abbot, Gilead to attend scientific meetings. The remaining members of the panel have no conflict of interest relevant to declare.

Annex 6: Data collection forms

Example of a post-marketing surveillance form

(adapted from the standard CIOMS form and the suspected adverse drug reactions form produced by the Malaysian National Centre for Adverse Drug Reactions Monitoring)

Suspected adverse reaction form	Date of this report	
	REPORT number	

1. PATIENT INFORMATION

PATIENT INITIALS (First, last)	COUNTRY	Date of birth Day	Month	Year	Age (Years)	SEX	Wt (kg)	Ethnic group	Additional information

ADVERSE REACTION DESCRIPTION (including relevant test / laboratory data)

Time to onset of reaction			
Date of reaction			
Reaction subsided after drug discontinued or reduced	Yes ☐	No ☐	Not applicable ☐
Reaction appeared after reintroduction of the drug	Yes ☐	No ☐	Not applicable ☐
Outcome	Fatal ☐	Recovered completely ☐	Long term or permanent incapacity/disability ☐

SUSPECTED DRUG(S)*	DAILY DOSAGES	ROUTE OF ADMINSTRATION	MANUFACTURER (REG NO & BATCH NO)	THERAPY DATES Start	Stop	INDICATION

* including generic name

CONCOMITANT DRUG(S) USED*	DAILY DOSAGES	ROUTE OF ADMINSTRATION	MANUFACTURER (REG NO & BATCH NO)	THERAPY DATES Start	Stop	INDICATION

* Excluding those used to treat the reaction

OTHER RELEVANT HISTORY (include diagnostics, allergies, hepatorenal disfunction, pregancy with date of LMP

Annex 7: List of examples of national guidelines

Organization/Country	Weblink	Reference
American Thoracic Society/Infectious Diseases Society of America	http://ajrccm.atsjournals.org/cgi/reprint/163/7/1730	American Thoracic Society. Guidelines for the management of adults with community acquired pneumonia. Am J Respir Crit Care Med 2001; 163: 1730–1754.
American Thoracic Society.	http://ajrccm.atsjournals.org/cgi/reprint/171/4/388	Guidelines for the management of adults with hospital acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005 Feb 15;171(4):388-416
British Thoracic Society	http://www.brit-thoracic.org.uk/c2/uploads/MACAP2001gline.pdf	Guidelines for the Management of Community Acquired Pneumonia in Adults. 2001 GUIDELINES (pdf) Thorax 2001; 56: (suppl IV)
British Thoracic Society	http://www.brit-thoracic.org.uk/c2/uploads/MACAPrevisedApr04.pdf	Guidelines for the Management of Community Acquired Pneumonia in Adults 2004 Update
British Thoracic Society	http://www.brit-thoracic.org.uk/c2/uploads/paediatriccap.pdf	Guidelines for the Management of Community acquired Pneumonia in Childhood. British Thoracic Society Standards of Care Committee - Thorax 2002; 57: (Suppl I)
Australia	http://www.tg.com.au/?sectionid=41	Therapeutic Guidelines: Antibiotic Version 12. North Melbourne: Therapeutic Guidelines Ltd; 2003
France	http://www.infectiologie.com/site/_congres_conf_recommandations.php	Agence Française de Sécurité Sanitaire des Produits de Santé (New update due April 2006 with English language versions to follow)
Japan	http://www.jrs.or.jp/quicklink/glsm/guideline/seijinsichu_guide/	The Japanese Respiratory Guidelines for the Management of Community-Acquired Pneumonia in Adults
Japan	http://www.jrs.or.jp/quicklink/glsm/guideline/seijininnai/	The Japanese Respiratory Society guidelines for management of hospital-acquired pneumonia (English language versions of these documents will be published at the end of 2006.)
Turkey	http://www.toraks.org.tr/pnomoni.php	Arseven O, Ozlu T, Aydýn G, Baytemur M et al. Working group of respiratory system infections. Pneumonia treatment guideline (In Turkýsh). Toraks Dergisi, Vol:3, Supl:3, August 2002:1 - 35

Annex 8: Table of recommended dosages

(adapted from Table 1 in the CDC Factsheet: Antiviral Agents for Influenza: Background Information for Clinicians available at http://www.cdc.gov/flu/professionals/pdf/antiviralsbackground.pdf Last revised March 31 2006, last accessed April 6 2006)

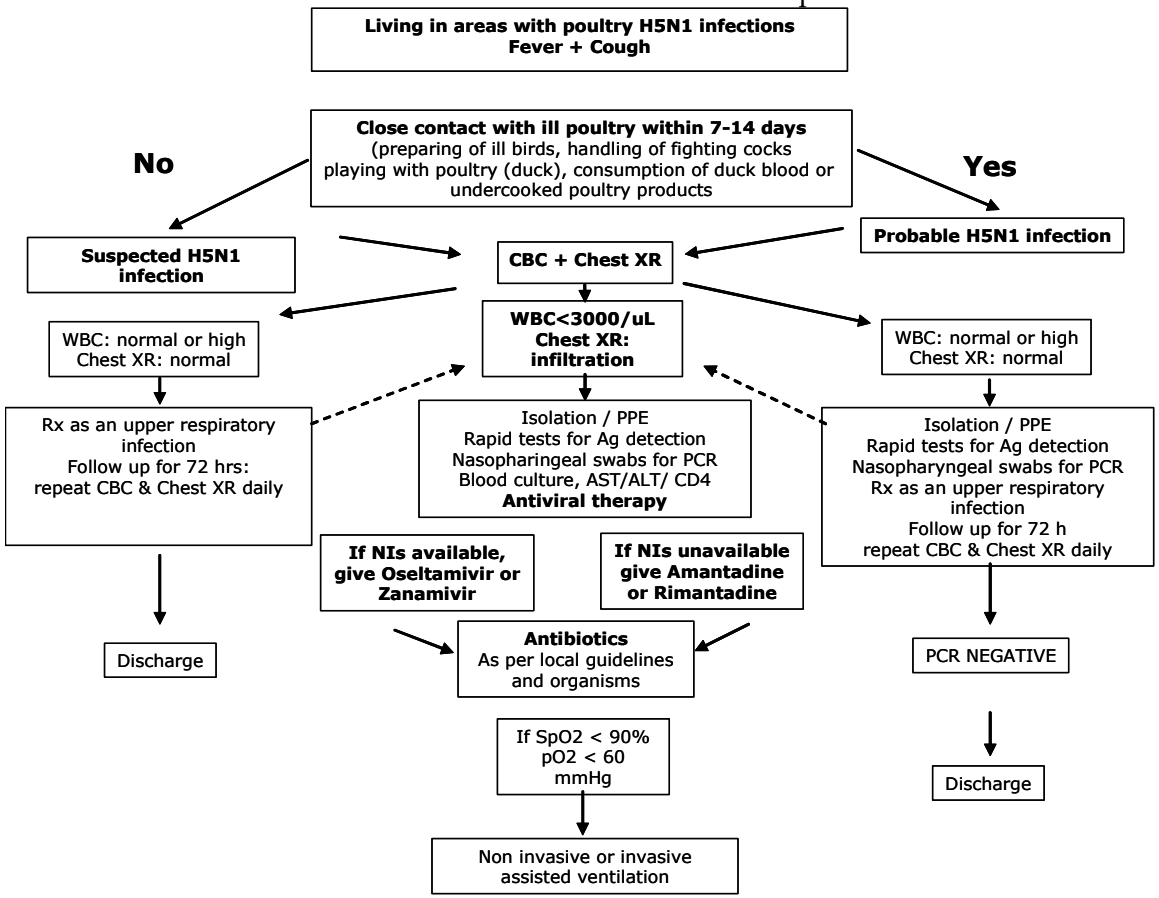
Agent	Age Groups (yrs)					
	Duration	**1-6**	**7-9**	**10-12**	**13-64**	**≥ 65**
Amantadine[22]						
Treatment	5 days	5mg/kg/day up to 150 mg in 2 divided doses	5mg/kg/day up to 150 mg in 2 divided doses	100mg twice daily for	100mg twice daily	≤ 100 mg/day
Prophylaxis	Begin as soon as exposure identified and continue for 7 to 10 days after last known exposure	5mg/kg/day up to 150 mg in two divided doses †	5mg/kg/day up to 150 mg in two divided doses	100mg twice daily	100mg twice daily	≤ 100 mg/day
Rimantadine						
Treatment,	5 days	Not licensed for use	Not licensed for use	Not licensed for use	100mg twice daily	100 mg/day
Prophylaxis	Begin as soon as exposure identified and continue for 7 days after last known exposure	5mg/kg/day up to 150 mg in two divided doses †	5mg/kg/day up to 150 mg in two divided doses †	100mg twice daily	100mg twice daily	100 mg/day
Oseltamivir						
Treatment	5 days	Weight adjusted doses: - 30mg twice daily for ≤ 15 kg - 45mg twice daily for >15 to 23 kg - 60mg twice daily for >23 to 40kg - 75mg twice daily for >40kg	Weight adjusted doses: - 30mg twice daily for ≤ 15 kg - 45mg twice daily for >15 to 23 kg - 60mg twice daily for >23 to 40kg - 75mg twice daily for >40kg	Weight adjusted doses: - 30mg twice daily for ≤ 15 kg - 45mg twice daily for >15 to 23 kg - 60mg twice daily for >23 to 40kg - 75mg twice daily for >40kg	75mg twice daily	75mg 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	75mg/day	75mg/day
Zanamivir						
Treatment	5 days	Not licensed for use	10mg (2 inhalations) twice daily	10mg (2 inhalations) twice daily	10mg (2 inhalations) twice daily	10mg (2 inhalations) twice daily
Prophylaxis	Begin as soon as exposure identified and continue for 7-10 days after last known exposure	**1-4 yrs:** NA / **5-6 yrs:** 10mg (2 inhalations) once daily	10mg (2 inhalations) once daily	10mg (2 inhalations) once daily	10mg (2 inhalations) once daily	10mg (2 inhalations) once daily

Use of antivirals in patients with renal or hepatic impairment

Agent	Duration	Renal impairment		Hepatic impairment
Amantadine				
Treatment	5 days	**Creatinine clearance (ml/min/1.73 m2)** - 30-50 - 15-29 - <15	**Dose** 200 mg 1st day and 100 mg each day thereafter 200 mg 1st day and 100 mg on alternate days 200mg every 7 days The recommended dosage for patients on haemodialysis is 200 mg every 7 days.	No formal dosage adjustment suggested but care should be exercised in these patients.
Prophylaxis	Begin as soon as exposure identified and continue for 7 days after last known exposure	See above		
Rimantadine				
Treatment	5 days	**Creatinine clearance** - Less severe renal impairment - <10	**Dose** Patients should be observed closely and dose reduced or discontinued if required 100mg/day	In patients with severe hepatic dysfunction a reduction in dosage to 100mg/day is recommended
Prophylaxis	Begin as soon as exposure identified and continue for 7 days after last known exposure	See above		See above
Oseltamivir				
Treatment	5 days	**Creatinine clearance** - 10-30	**Dose** Patients will require a dose reduction (Unpublished pharmacological data suggests that 75mg od should be used in these patients)	No dosage adjustment
Prophylaxis	Begin as soon as exposure identified and continue for 7 to 10 days after last known exposure			
Zanamivir				
Treatment	5 days	No dosage adjustment		No dosage adjustment
Prophylaxis	Begin as soon as exposure identified and continue for 7 to 10 days after last known exposure	See above		See above

Annex 9: Examples of clinical algorithms

The clinical algorithm below was adapted from one devised by Dr Tran Tinh Hien, in use at the Hospital for Tropical Diseases, Ho Chi Minh City, Viet Nam. We recommend that countries develop their own guidelines for the assessment of human patients in whom there is a suspicion of influenza A(H5N1) infection. These should include the criteria required to initiate treatment pending confirmatory laboratory testing. Such guidelines will reflect geographical location with respect to recent outbreaks of avian influenza H5N1 in birds and the locally available resources. The algorithm used by clinicians in Viet Nam is included here to assist countries with this process.



References

References cited in main document and evidence profiles

Human

Aoki F. Amantadine and rimantadine. In: Nicholson KG, Webster RG, Hay AJ, eds. Textbook of influenza. Oxford: Blackwell Science; 1998: 457–76.

Bright RA et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet 2005;366:1175-81.

Centers for Disease Control and Prevention (2006a) Factsheet: Antiviral agents for influenza: background information for clinicians. http://www.cdc.gov/flu/professionals/pdf/antiviralsbackground.pdf (Last updated 31 March 2006, accessed 11 April 2006)

Centers for Disease Control and Prevention (2006b) Guidelines and recommendations. Influenza antiviral medications: 2005-06 Chemoprophylaxis (Prevention and Treatment Guidelines. http://www.cdc.gov/flu/professionals/treatment/pdf/0506antiviralguide.pdf (Last updated 14 January 2006, accessed 11 April 2006)

Chotpitayasunondh et al. Human disease from influenza A (H5N1), Thailand, 2004. Emerging Infectious Diseases, Vol. 11, No. 2, 2005.

De Jong MD et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. N Engl J Med 2005;353:2667-72.

Dolin R, Reichman RC, Madore HP, Maynard R, Linton PN, Webber-Jones J. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. N Engl J Med 1982 Sep 2; 307(10):580–584.

Glaxo Wellcome. Relenza zanamivir. for inhalation: US Prescribing Information, 2001.

Hayden FG, Gubareva LV, Monto AS, Klein TC, Elliot MJ, Hammond JM, Sharp SJ, Ossi MJ; Zanamivir Family Study Group. Inhaled zanamivir for the prevention of influenza in families. Zanamivir Family Study Group. N Engl J Med. 2000 Nov 2;343(18):1282-9.

Hayden FG, Gwaltney JM, van de Castle RL, Adams KF, Giordani, Barreto dos Santos H. Comparative toxicity of amantadine hydrochloride and rimantadine hydrochloride in healthy adults. Antimicrobial Agents and Chemotherapy 1981;19:226-33.

Hayden FG, Monto AS. Oral rimantadine hydrochloride therapy of influenza A virus H3N2 subtype infection in adults. Antimicrob Agents Chemother 1986; 29: 339–41.

Hayden FG, Belshe RB, Clover RD, Hay AJ, Oakes MG, Soo W. Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. N Engl J Med 1989;321:1696-702.

Hayden FG. Amantadine and rimantadine – clinical aspects. In: Richman DD, ed. Antiviral drug resistance. Chichester, UK: John Wiley & Sons Ltd; 1996, pp. 59–77.

Hayden FG, Belshe R, Villanueva C et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis 2004; 189: 440–49.

Hien et al. Avian influenza A (H5N1) in 10 patients in Viet Nam. N Engl J Med, Vol. 350, No.12, 2004.

Husereau DR, Brady B, McGeer A. Oseltamivir for the treatment of suspected influenza: a clinical and economic assessment. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2001. Technology Report no. 21.

Ison M et al. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. Antiviral Ther 2003; 8:183-190.

Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006;367:303-13.

Jefferson T, Deeks JJ, Demicheli V, Rivetti D, Rudin M. Amantadine and rimantadine for preventing and treating influenza A in adults. The Cochrane Database of Systematic Reviews 2004, Issue 3. Art.No.: CD001169.pub2. DOI: 10.1002/14651858.

Jefferson T, Demicheli V, Deeks J, Rivetti D. Neuroaminidase inhibitors for preventing and treating influenza in healthy adults. The Cochrane Database of Systematic Reviews 1999, Issue 2. Art.No.: CD001265.pub2. DOI: 10.1002/14651858.

Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med 2003;163:1667–72.

Kantor RJ, Potts DW, Stevens D, Noble GR. Prevention of influenza A/USSR/77 (H1N1): an evaluation of the side effects and efficacy of amantadine in recruits at Fort Sam Houston. Military Medicine 1980;145:312-5.

Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. Clinical efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir in treating acute influenza: placebo-controlled double-blind multicenter phase III trial. Kansenshogaku Zasshi 2000;74:1044–61.

Kitamoto O. Therapeutic effectiveness of amantadine hydrochloride in influenza A2—double-lind studies. Jpn J Tuberc Chest Dis 1968;15:17–26.

Kitamoto O. Therapeutic effectiveness of amantadine hydrochloride in naturally occurring Hong Kong influenza: double-blind studies. Jpn J Tuberc Chest Dis 1971;17:1–7.

Knowles SR, Phillips EJ, Dresser L, Matukas L. Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. Clin Infect Dis 2003 Oct 15;37(8):1139-42.

Mast EE, Harmon MW, Gravenstein S, Wu SP, Arden NH, Circo R, Tyszka G, Kendal AP, Davis JP. Emergence and possible transmission of amantadine-resistant viruses during nursing home outbreaks of influenza A (H3N2). Am J Epidemiol 1991 Nov 1;134(9):988-97.

Mate J, Simon M, Juvancz I, Takatsy G, Hollos I, Farkas E. Prophylactic use of amantadine during Hong Kong influenza epidemic. Acta Microbiol Acad Sci Hung 1970;17:285–96.

Matheson NJ, Symmonds-Abrahams M, Sheikh A, Shepperd S, Harnden A. Neuroaminidase inhibitors for preventing and treating influenza in children. The Cochrane Database of Systematic Reviews 2003, Issue 3. Art.No.: CD002744.pub2. DOI: 10.1002/14651858.

Monto AS, Fleming DM, Henry D et al. Efficacy and safety of the neuraminidase inhibitor zanamivirin the treatment of influenza A and B virus infections. J Infect Dis 1999;180:254–61.

Nicholson KG, Aoki FY, Osterhaus AD et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomized controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet 2000;355:1845–50.

Peckinpaugh RO, Askin FB, Pierce WE, Edwards EA, Johnson DP, Jackson GG. Field studies with amantadine: acceptability and protection. Ann N.Y. Acad. Sci 1970; 173: 62-73.

Puhakka T, Lehti H, Vainionpaa R et al. Zanamivir: a significant reduction in viral load during treatment in military conscripts with influenza. Scand J Infect Dis 2003; 35: 52–58.

Quarles JM, Couch RB, Cate TR, Goswick CB. Comparison of amantadine and rimantadine for prevention of type A (Russian) influenza. Antiviral Research 1981;1:149-155.

Rabinovich S, Baldini JT, Bannister R. Treatment of influenza: the therapeutic efficacy of rimantadine HC1 in a naturally occurring influenza A2 outbreak. Am J Med Sci 1969;257:328–35.

Shu Y, Yu H, Li D. Lethal avian influenza A (H5N1) infection in a pregnant woman in Anhui Province, China. N Engl J Med 2006 Mar 30;354(13):1421-2.

Smorodintsev AA, Karpuhin GI, Zlydnikov DM, Malyseva AM, Svecova EG, Burov SA et al. The prophylactic effectiveness of amantadine hydrochloride in an epidemic of Hong Kong influenza in Leningrad in 1969. Bulletin of the World Health Organization 1970;42:865-72.

The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. Lancet 1998;352:1877–81.

The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. N Engl J Med 2005;353:1354-85.

Treanor JJ, Hayden FG, Vrooman PS et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial: US Oral Neuraminidase Study Group. JAMA 2000; 283:1016–24.

Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health Technol Assess 2003;7(35).

Van Voris LP, Betts RF, Hayden FG, Christmas WA, Douglas RG Jr. Successful treatment of naturally occurring influenza A/USSR/77 H1N1. JAMA 1981;245:1128–31.

Welliver R, Monto AS, Carewicz O et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA 2001;285:748.

WHO. (2006) Avian influenza ("bird flu") - Factsheet. Geneva: World Health Organization; 2006. http://www.who.int/mediacentre/factsheets/avian_influenza/en/index.html
(Last updated February 2006, accessed 11 April 2006)

WHO. WHO interim guideline on clinical management of humans infected by influenza A (H5N1). Geneva: World Health Organization; 2004.

WHO. Influenza A (H5N1): WHO interim infection control guidelines for health care facilities. Geneva. World Health Organization; 2004.

WHO. WHO global strategy for containment of antimicrobial resistance. Geneva: World Health Organization; 2001. http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf
(Last updated 2001, accessed 11 April 2006)

Wong SSY, Yuen Ky. Avian influenza virus infections in humans. Chest 2006;129:156-68.

Younkin SW, Betts RF, Roth FK, Douglas RG Jr. Reduction in fever and symptoms in young adults with influenza A/Brazil/78 H1N1 infection after treatment with aspirin or amantadine. Antimicrob Agents Chemother 1983;23:577–82.

Yuen KY et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet 1998;351:467-71.

Animal/in vitro

Abed Y, Goyette N, Boivin G. Generation and characterization of recombinant influenza A (H1N1) viruses harboring amantadine resistance mutations. Antimicrob Agents Chemother 2005;49:556–559.

Bean WJ. Unselected amantadine resistance in human influenza virus and its long-term survival in nature. American Society for Virology 11th Annual Meeting. 1992.

Govorkova EA et al. Neuraminidase inhibitor-rimantadine combinations exert additive and synergistic anti-influenza virus effects in MDCK cells. Antimicrob Agents Chemother 2004;48:4855-63.

Hay AJ. Amantadine and rimantadine – mechanisms. In: Richman DD, ed. Antiviral drug resistance. Chichester, UK: John Wiley & Sons Ltd; 1996, pp. 43–58.

Hurt AC et al. Susceptibility of human influenza viruses from Australasia and South East Asia to the neuraminidase inhibitors zanamivir and oseltamivir. Antiviral Res 2004;62:37-45.

Ilyushina NA, Govorkova EA, Webster RG. Detection of amantadine-resistant variants among avian influenza viruses isolated in North America and Asia. Virology 2005;341:102-6.

Le QM et al. Avian flu: isolation of drug-resistant H5N1 virus. Nature 2005;437:1108.

Leneva IA et al. The neuraminidase inhibitor GS4104 (oseltamivir phosphate) is efficacious against A/Hong Kong/156/97 (H5N1) and A/Hong Kong/1074/99 (H9N2) influenza viruses. Antiviral Res 2000;48:101-15.

Madren L, Shipman C, Hayden FG. In vitro inhibitory concentrations of anti-influenza agents. Antiviral Chemistry & Chemotherapy 1995;6(2):1099-113.

Houck P, Hemphill M, LaCroix S, Hirsh D, Cox N. Amantadine-resistant influenza A in nursing homes. Identification of a resistant virus prior to drug use. Arch Intern Med. 1995 Mar 13;155(5):533-7.

McKimm-Breschkin J et al. Neuraminidase sequence analysis and susceptibilities of influenza virus clinical isolates to zanamivir and oseltamivir. Antimicrob Agents Chemother 2003;47:2264-72.

Puthavathana P et al. Molecular characterization of the complete genome of human influenza H5N1 virus isolates from Thailand. J Gen Virol 2005;86:423-33.

Methodology

Grade Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.

Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. J Clin Epidemiol 1991a;44:1271-8.

WHO. WHO guidelines for guidelines. Geneva: World Health Organization; 2003.

Other references considered during the preparation of the main document and evidence profiles

Human

Adhikari N, Burns KEA, Meade MO. Pharmacologic therapies for adults with acute lung injury and acute respiratory distress syndrome. The Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD004477.pub2. DOI 10.1002/14651858.CD004477.pub2.

Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, Fry-Smith A. Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation. Health Technol Assess 2002;(9).

Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner DA, Nicholson KG. Effectiveness of neuroaminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analysis of randomised controlled trials. BMJ 2003; 326:1235.

Goodman C, Mukherjee D, Faulkner E. How effective would antiviral vaccination and antiviral drug prevention and treatment strategies be for reducing the impact of the next influenza pandemic? Copenhagen: WHO Regional Office for Europe (Health Evidence Network (HEN)) Report; 2006.

Griffin AD, Perry AS, Fleming DM. Cost-effectiveness analysis of inhaled zanamivir in the treatment of influenza A and B in high-risk patients. Pharmacoeconomics 2001;19(3):293-301.

Gross PA. Postexposure prophylaxis with oseltamivir reduced influenza transmission in households. ACP J Club 2004 Sep-Oct;141(2):40.

Hayden FG, Antiviral resistance in influenza viruses. Implications for management and pandemic response. N Engl J Med 2006;354: 8.

Husereau DR, Brady B, McGreer A. Oseltamivir for the treatment of suspected influenza: a clinical and economic assessment. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2001. Technology Report no 21.

Jefferson T, Demicheli V, Rivetti D, Deeks J. Cochrane reviews and systematic reviews of economic evaluations. Amantadine and rimantadine in the prevention and treatment of influenza. Pharmacoeconomics 1999;16 Suppl 1:85-9. Review.

Johnston SL, Ferrero F, Garcia ML, Dutkowski R. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. Pediatr Infect Dis J 2005 Mar;24(3):225-32.

Kaiser L, Keene ON, Hammond JM, Elliott M, Hayden FG. Impact of zanamivir on antibiotic use for respiratory events following acute influenza in adolescents and adults. Arch Intern Med 2000 Nov 27;160(21):3234-40.

Kaiser L, Henry D, Flack NP, Keene O, Hayden FG. Short-term treatment with zanamivir to prevent influenza: results of a placebo controlled study. Clin Infect Dis 2000; 30: 587–89.

Kiso M, Mitamura M, Sakai-Tagawa Y et al. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. Lancet 2004; 364:759–65.

Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. Arch Intern Med 2001 Jan 22;161(2):212-7.

Langley JM, Faughnan M, with the Canadian Task Force on Preventive Health Care. Prevention of influenza in the general population: systematic review and recommendations. Technical Report, 20 March 2005.

Li L, Cai B, Wang M, Zhu Y. A double-blind, randomized, placebo controlled multicenter study of oseltamivir phosphate for treatment of influenza infection in China. Chin Med J (Engl) 2003; 116:44–48.

Lynd LD, Goeree R, O'Brien BJ. Antiviral agents for influenza: a comparison of cost-effectiveness data. Pharmacoeconomics 2005;23(11):1083-106. Review.

Nathan RA, Geddes D, Woodhead M. Management of influenza in patients with asthma or chronic obstructive pulmonary disease. Ann Allergy Asthma Immunol 2001 Dec;87(6):447-54, 487.

National Institute for Clinical Excellence. Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza. London: National Institute for Clinical Excellence (NICE), 2003:30.

National Institute for Clinical Excellence. Guidance on the use of oseltamivir and amantadine for the prophylaxis of influenza. London: National Institute for Clinical Excellence (NICE), 2003:32.

Sato M, Hosoya M, Kato K, Suzuki H. Viral shedding in children with influenza virus infections treated with neuraminidase inhibitors. Pediatr Infect Dis J 2005 Oct;24(10):931-2.

Uyeki T. Influenza diagnosis and treatment in children: a review of studies on clinically useful test and antiviral treatment for influenza. Pediatr Infect Dis J 2003;22:167-77.

Animal/in vitro

Mishin P, Hayden F, Gubareva L. Susceptibility of antiviral resistant influenza viruses to novel neuraminidase inhibitors. Antimicrob Agents Chemother 2005;49:4515-4520.