Application for inclusion, change or deletion of a medicine in the WHO Model List of Essential Medicines

We are a group of authors within an external affiliated non-government organisation, the Cochrane Collaboration, called the Acute Respiratory Infections Cochrane Review Group. We are writing to propose that oseltamivir (Tamiflu) be deleted from the WHO Model Lists of Essential Medicines.

1. Summary statement of the proposal for inclusion, change or deletion

The WHO has lists of essential medicine at http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf (for adults) and http://whqlibdoc.who.int/hq/2011/a95054_eng.pdf (for children)

Both documents list oseltamivir with its indications as follows:

We propose that oseltamivir be deleted from the list forthwith because of lack of proven public health benefits including,

- for treatment, a reduction in risk of complications, hospitalisation or death and
- for prophylaxis, a reduction in transmission of influenza virus.

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

This proposal does not come from the World Health Organization (WHO).

3. Name of the organisation(s) consulted and/or supporting the application

This proposal comes from a group of Authors within an external affiliated non-government organisation, the Cochrane Collaboration, called the Acute Respiratory Infections Cochrane Review Group. We published a Cochrane (systematic) review of, first the published literature on the effectiveness of neuraminidase inhibitors (NIs)[1–3], and then the available regulatory information (unpublished Clinical Study Reports, CSRs), on the effectiveness of oseltamivir (a member of the class of NIs).[4]

Thus we are authors of the Acute Respiratory Infections Cochrane Review Group review of neuraminidase inhibitors.[4]
4. **International Nonproprietary Name (INN, generic name) of the medicine**

oseltamivir

5. **Formulation proposed for inclusion; including adult and paediatric (if appropriate)**

We are proposing the drug be deleted in any formulation.

6. **International availability - sources, if possible manufacturers and trade names**

Hoffmann-La Roche Ltd, Basel, Switzerland: “Tamiflu”

7. **Whether deletion is requested as an individual medicine or as an example of a therapeutic group**

Only oseltamivir out of the whole therapeutic group (*neuraminidase inhibitors*) is mentioned in the EML.

8. **Information on public health relevance (epidemiological information on disease burden, assessment of current use, target population)**

The EML guidelines nominate target groups as follows:

“* Oseltamivir should be used only in compliance with the WHO treatment guidelines, i.e. (1) for treatment of patients with severe or progressive clinical illness with confirmed or suspected influenza pandemic (H1N1) 2009, (2) for the treatment of patients with confirmed or suspected but uncomplicated illness due to pandemic influenza virus infection who were in higher risk groups, most notably for pregnant women and children under 2 years of age.*

(taken from the websites listed in 1. above).

In August 2010, WHO declared the influenza pandemic (H1N1) over. The H1N1 2009 influenza virus has become one of many seasonal influenza viruses. WHO’s advice on use of oseltamivir (quoted above) was specific to the pandemic scenario and is therefore no longer applicable (and perhaps never was applicable given that oseltamivir’s inclusion in the Essential Medicines List came after WHO declared the pandemic over).

The expert committee that added oseltamivir to the Essential Medicines list noted, “The majority of the randomized trials do not report clinically relevant outcomes such as the development of pneumonia, hospitalization or mortality,” but this is incorrect. The trials did report clinically relevant outcomes including pneumonia, hospitalization, and mortality. In fact, in the past, WHO and national governments have used results from clinical trials of oseltamivir in the context of seasonal
influenza to make assumptions of how oseltamivir would work in a pandemic situation.

One such instance is the WHO’s assumption that influenza antivirals could reduce the spread of a novel pandemic influenza virus, based on Roche clinical trial data conducted on seasonal influenza.[5]

Another example is the United States’ public health rationale for stockpiling oseltamivir for use in treatment: an assumed reduction in the risk of complications from influenza, e.g. pneumonia and hospitalization.[6] This assumption was based on evidence from a pooled analysis of 10 manufacturer-sponsored, randomized trials of oseltamivir for the treatment of seasonal influenza (Kaiser et al. *Arch Intern Med.* 2003;163(14):1667–72).

We have published a review of over 16,000 pages of internal company clinical study reports for randomized clinical trials of oseltamivir, including all ten studies included in the above mentioned Kaiser 2003 pooled analysis.[4]

The only benefit our review found from treatment with oseltamivir was reduction in the time to first alleviation of symptoms. Our systematic review found no substantial evidence in support of these assumed benefits.

Extract from the Cochrane review Abstract: (some parts here in bold for added emphasis)

**Main results**

We included and analysed data from 25 studies (15 oseltamivir and 10 zanamivir studies). We could not use data from a further 42 studies due to insufficient information or unresolved discrepancies in their data. The included trials were predominantly conducted in adults during influenza seasons in both hemispheres. A small number of studies were conducted in older people residing in care homes and in people with underlying respiratory diseases. The studies had adequate randomisation and blinding procedures, but imbalances in the analysis populations available (ITT influenza-infected) left many of the studies at risk of attrition bias. All the studies were sponsored by manufacturers of NIs. Time to first alleviation of symptoms in people with influenza-like illness symptoms (i.e. ITT population) was a median of 160 hours (range 125 to 192 hours) in the placebo groups and oseltamivir shortened this by around 21 hours (95% confidence interval (CI) -29.5 to -12.9 hours, P < 0.001; five studies) but there was no evidence of effect on hospitalisations based on seven studies with a median placebo group event rate of 0.84% (range 0% to 11%): odds ratio (OR) 0.95; 95% CI 0.57 to 1.61, P = 0.86). These results are based on the comprehensive ITT
population data and are unlikely to be biased. A post-protocol analysis showed that participants randomised to oseltamivir in treatment trials had a reduced odds being diagnosed with influenza (OR 0.83; 95% CI 0.73 to 0.94, P = 0.003; eight studies), probably due to an altered antibody response. Zanamivir trials showed no evidence of this. Due to limitations in the design, conduct and reporting of the trial programme, the data available to us lacked sufficient detail to credibly assess a possible effect of oseltamivir on complications and viral transmission. We postponed analysis of zanamivir evidence because of the offer of individual patient data (IPD) from its manufacturer. The authors have been unable to obtain the full set of clinical study reports or obtain verification of data from the manufacturer of oseltamivir (Roche) despite five requests between June 2010 and February 2011. No substantial comments were made by Roche on the protocol of our Cochrane Review which has been publicly available since December 2010.

Analysis 1.2 Comparison 1 Oseltamivir versus placebo, Outcome 2 Hospital admission (safety population)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oseltamivir</th>
<th>Placebo</th>
<th>Odds Ratio N,Random, 95% CI</th>
<th>Odds Ratio N,Random, 95% CI</th>
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<tbody>
<tr>
<td>W76601</td>
<td>7/953</td>
<td>4/482</td>
<td>0.87 (0.53, 1.39)</td>
<td></td>
</tr>
<tr>
<td>W15670</td>
<td>1/434</td>
<td>1/235</td>
<td>0.48 (0.22, 0.95)</td>
<td></td>
</tr>
<tr>
<td>W15671</td>
<td>5/144</td>
<td>1/204</td>
<td>2.39 (0.68, 8.11)</td>
<td></td>
</tr>
<tr>
<td>W15767</td>
<td>2/17</td>
<td>1/9</td>
<td>1.07 (0.29, 3.91)</td>
<td></td>
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<tr>
<td>W15736</td>
<td>0/31</td>
<td>0/27</td>
<td>0.0 (0.0, 0.0)</td>
<td></td>
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<tr>
<td>W15756</td>
<td>4/344</td>
<td>3/251</td>
<td>1.36 (0.80, 2.32)</td>
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<tr>
<td>W15812/15972</td>
<td>6/139</td>
<td>0/262</td>
<td>0.75 (0.25, 2.21)</td>
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<tr>
<td>W15815/15975/15978</td>
<td>5/362</td>
<td>16/373</td>
<td>0.33 (0.24, 0.43)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>28/13</strong></td>
<td><strong>1883</strong></td>
<td><strong>0.95 [0.57, 1.61]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 34 (Oseltamivir), 20 (Placebo)
Heterogeneity: Tau² = 0.0, Chi² = 1.42, df = 6 (P = 0.96); P = 0.6%
Test for overall effect: Z = 0.18 (P = 0.85)
Test for subgroup differences: Not applicable

Thus we conclude that currently there is insufficient evidence that oseltamivir reduces the risk of serious complications from influenza. This is at odds with some published data, under suspicion of have a publication bias. A detailed outline is in our Cochrane review of regulatory CSRs[4], and related publications.[7–15]

On the basis of regulatory material made available to us by the European Medicines Agency (EMA) we have concluded that the mechanism of action proposed by Roche is not supported by the evidence of the trials: oseltamivir may have a central nervous system action (centrally suppressing the immune response of the host) rather than a viral-specific action (interfering with virus replication). This hypothesis supports the
observation that oseltamivir interferes with antibody production in those infected by influenza (see Analysis 1.4, below, from the Cochrane review[4]).

**Analysis 1.4. Comparison 1 Oseltamivir versus placebo, Outcome 4 Antibody rise four-fold or greater.**

Roche state that oseltamivir does not prevent infection and does not affect antibody production.[16,17] We found no evidence that oseltamivir consumption may interrupt person to person spread or affect complications of influenza such as pneumonia (the two assumptions upon which stockpiling has taken place).

Despite an earlier promise, Roche have consistently failed to make available reports of studies which were left unpublished or distorted in the published version.

The WHO has given evasive answers to our detailed questions and dismissed two different versions of our review. The correspondence (now part of the BMJ Open Data Campaign) can be accessed at [http://www.bmj.com/tamiflu/who](http://www.bmj.com/tamiflu/who). The recent infringement procedure against Roche by EMA[18] suggests that no one, including regulators, have seen the full pre- and post-marketing oseltamivir data set. Given the uncertainty surrounding the properties of the drug and reluctance of Roche to share data we believe oseltamivir should be removed from the Essential Medicines List.

9. **History of WHO review of Oseltamivir**

Reports of the WHO Expert Committee on the Selection and Use of Essential Medicines can be found at [http://www.who.int/medicines/publications/essentialmeds_committeereports/](http://www.who.int/medicines/publications/essentialmeds_committeereports/)
The WHO Technical Report Series 958 [pdf 723 KB] incl.Children, 2009* which is listed at the above site, indicates the Committee recommended not including any of the antivirals on the Model List at the present time (year 2009). However the Committee endorsed the proposal for an emergency meeting mechanism to consider one or more of the antivirals, including for paediatric use, should a pandemic occur.

The WHO Technical Report Series 965 [pdf 1 MB] incl.Children, 2011† also listed, indicates that the Committee now recommended the use of oseltamivir for H1N1 pandemic influenza (which the WHO had declared), and based principally on observational data (and notwithstanding the reservations of the randomised studies noted by our Cochrane review[4]). This raises the question of what WHO’s current recommendations are regarding oseltamivir given that the pandemic has been declared over for over a year now.

We address this by appending an Appendix which proposes that the prominence of observational data in supporting this decision is not appropriate, Observational data should not be used alone to inform effectiveness for the inclusion of oseltamivir on the World Health Organization’s essential medicines list, P9, below.

10. Summary of comparative effectiveness in a variety of clinical settings:

We are unaware of any comparative effectiveness research in clinical settings that were undertaken or cited in support of WHO’s inclusion of oseltamivir to the Essential Medicines Lists.

11. Summary of comparative evidence on safety*:

Cited below.[4]

We have some concerns about the safety of this drug. The ways the data have been presented to the scientific world obfuscate the analysis of ‘complications’ and ‘harms’ (these terms are used in confusing and unstable manners in Roche’s clinical trials of oseltamivir). This is detailed in the Cochrane review.[4]

There are additional data collected in a manner (a proportional mortality method) not at risk from several biases, suggesting oseltamivir may have otherwise unrecognised dangers of sudden death[19] (also available at http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf) This study found (to quote from the Abstract):

* http://whqlibdoc.who.int/trs/WHO_TRS_958_eng.pdf
† http://whqlibdoc.who.int/trs/WHO_TRS_965_eng.pdf
Of 119 deaths after Tamiflu was prescribed, 38 deteriorated within 12 hours (28 within 6 hours), while of 15 deaths after Relenza, none deteriorated within 12 hours. Pooled OR for early deterioration and overall death were 5.88 (95% CI: 1.30 to 26.6, \( p = 0.014 \)) and 1.91 (\( p = 0.031 \)) respectively. Baseline characteristics including risk factors did not contribute to early deterioration after Tamiflu use.

and concluded:

These data suggest Tamiflu use could induce sudden deterioration leading to death especially within 12 hours of prescription. These findings are consistent with sudden deaths observed in a series of animal toxicity studies, several reported case series and the results of prospective cohort studies.

In addition, the manufacturer, Hoffmann-La Roche, is currently under investigation by the European Medicines Agency (EMA) for alleged non-compliance with pharmaco-vigilance obligations for its 19 centrally authorised medicines, of which one is oseltamivir. This casts further doubt on the safety profile of oseltamivir (even to the manufacturer). See [18].

We append further data in Appendix A, Observational data should not be used alone to inform effectiveness for the inclusion of oseltamivir on the World Health Organization’s essential medicines list, P9, below.

12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:

As the effects and mode of action of oseltamivir are open to question any reliable cost-effectiveness calculation is not possible.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)

Summary

<table>
<thead>
<tr>
<th>Date</th>
<th>Country</th>
<th>Approval Details</th>
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<tbody>
<tr>
<td>10/27/1999</td>
<td>USA</td>
<td>approved Tamiflu for treatment of influenza in adults</td>
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<tr>
<td>11/17/2000</td>
<td>USA</td>
<td>approved Tamiflu for prophylaxis of influenza in adults</td>
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<tr>
<td>12/14/2000</td>
<td>USA</td>
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<td>EMA</td>
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<tr>
<td>12/12/2000</td>
<td>Japan</td>
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<td>approved Tamiflu for treatment of influenza in children &gt; 40kg</td>
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<td>07/09/2004</td>
<td>Japan</td>
<td>approved Tamiflu capsules for prophylaxis of influenza in adults and adolescents</td>
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<tr>
<td>01/17/2002</td>
<td>Japan</td>
<td>approved Tamiflu oral suspension for treatment of influenza in adults, adolescents and children</td>
</tr>
</tbody>
</table>
The world’s leading regulatory body, the USA Food and Drug Administration, has put on the Tamiflu drug label a statement indicating that oseltamivir is not proven to reduce serious bacterial complications from influenza. The FDA has not approved oseltamivir for the reduction of the transmission of influenza.[4] (To assume so is a misreading of the FDA’s approval of the prophylaxis indication, which was based on a demonstrated reduction in risk of symptomatic influenza, not reduced risk of infection.) See the FDA-approved TAMIFLU label (below), Figure:

**Figure: FDA-approved label**

![FDA-approved label](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s059,021246s042lbl.pdf)


Not relevant to this application

15. Proposed (new/adapted) text for the WHO Model Formulary

Not relevant to this application
References


7. Doshi P. Neuraminidase inhibitors--the story behind the Cochrane review. BMJ. 2009 Dec 8;339(dec07_2):b5164.


9. Godlee F, Clarke M. Why don’t we have all the evidence on oseltamivir? BMJ. 2009 Dec 8;339(dec08_3):b5351.


Signed

Authors of the Acute Respiratory Infections Cochrane Review Group review of neuraminidase inhibitors.

<table>
<thead>
<tr>
<th>name</th>
<th>affiliation</th>
<th>country</th>
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<tbody>
<tr>
<td>Prof Chris Del Mar</td>
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<td>Dr Rokuro Hama</td>
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<tr>
<td>Dr Mark Jones</td>
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<tr>
<td>Dr Matthew Thompson</td>
<td>Clinical Reader, Department of Primary Care Health Sciences, University of Oxford</td>
<td>UK</td>
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</table>
Appendix A: Observational data should not be used alone to inform effectiveness for the inclusion of oseltamivir on the World Health Organization's essential medicines list

The World Health Organization approved the use of Oseltamivir on the essential medicines list in 2011 on the basis of observational data. One study—a systematic review of observational studies—dominated the decision. It was funded by the World Health Organization and McMaster University, and presented in Ghana, at the 18th Expert Committee on the selection and use of essential medicines on 21 March 2011, and subsequently published in 2012.[Hsu 2012]

The committee noted the following in the WHO report (page 190)‡

- There are no new data from randomized trials for any of the four antivirals under consideration.
- The majority of randomized trials are in the healthy adult population; there is one systematic review of trials in children (316).
- The majority of the randomized trials do not report clinically relevant outcomes such as development of pneumonia, hospitalization or mortality. The only published analysis with these data is a report of a pooled analysis from a set of data from Roche [published as Kaiser et al. (317)]. This study was excluded from the update of the Cochrane Review [published as Jefferson et al. (318)] as the data from all of the individual trials were not made available to the authors of the Cochrane Review. The exclusion of this study and the possibility of publication bias in the trials conducted by Roche has been the subject of discussion in the BMJ articles (319, 320, 321) published with the Cochrane Review.
- The observational data are summarized in the updated evidence summary for the guideline panel (322, 323, 324) and also (325, 326, 327, 328, 329, 330, 331, 332, 333, 334) and, in the population studied, including higher risk groups, suggest a significant benefit of treatment with oseltamivir in terms of reduction of hospitalization and occurrence of pneumonia. Three observational studies (322, 333, 335) suggest benefit in terms of reduction in mortality. There are fewer data for zanamivir and no current observational studies of amantadine or rimantadine that are relevant.
- Adverse effects of all four antivirals are well characterized. The only additional data from March 2009 are the observation that the neuropsychiatric effects that have been reported in relation to oseltamivir have not been reported so far in studies outside of Japan, notwithstanding extensive use in a number of countries over the last six months.

The expert committee’s statement, “The majority of the randomized trials do not report clinically relevant outcomes such as the development of pneumonia, hospitalization or mortality” is inaccurate and contradicted by the expert committee’s second statement noting a “pooled analysis” which included 10 clinical trials. These trials did report clinically relevant outcomes including pneumonia, hospitalization,

‡

http://www.who.int/entity/selection_medicines/Complete_UNEDITED_TRS_18th.pdf
and mortality. This fact is an important reason why the randomized trial evidence needs to be taken seriously.

However, as made clear in the excerpt above, the WHO’s expert committee focused on evidence from observational studies, in particular the study by Hsu et al. This systematic review and meta-analysis of observational data for antivirals for the treatment of influenza concluded, “…therapy with oral oseltamivir and inhaled zanamivir may provide a net benefit over no treatment of influenza. However the confidence in the estimates of the effects for decision making is low to very low.” [Hsu 2012]

The reported effect, in the review provided to the WHO committee suggested that oseltamivir is associated with a statistically significant reduction in mortality (OR 0.28: 95% CI 0.17 to 0.47) with similar trends seen for other outcomes, hospitalizations OR = 0.75 [CI, 0.66 to 0.89], and complications.

The review limitations, as reported [Hsu 2012] relating to the evidence itself, are as follows (emphasis added):

Many of the identified studies had a high risk for observational study bias due to the lack of control for confounders and covariates (such as the lack of adjustment for age or comorbid conditions). For example, of the entire body of evidence on inhaled zanamivir, only the estimate for the “duration of signs and symptoms” is based on study results that were adjusted for these potential confounders. Confounding by indication (a greater likelihood that sicker patients will be treated) could therefore reduce effects based on analyses that are not adjusted or are insufficiently adjusted; however, investigators or clinicians may also select healthier patients for treatment to reduce potential adverse effects of antivirals, which could bias the results in favor of treatment. Greater emphasis should be placed on data from adjusted meta-analyses. However, to provide a comprehensive view of the available evidence, we present pooled results from the adjusted and the unadjusted studies separately.

Even when adjusted analyses were available, we could not always assess whether the authors considered all pertinent variables or whether even optimal adjustment would permit valid comparisons between treated versus untreated patients in these studies. In addition, for some outcomes, such as death in the oseltamivir studies, the results may apply only to hospitalized patients because the data were derived in this patient group.

In addition, to the specific limitations outlined above, a major limitation of such observational studies is that they are merely surveillance studies which are ranked, in terms of levels of evidence, below the level of comparative observational studies (such as cohort study or case-control study).

Furthermore all of the studies (even in the studies that claim adjustment of age and comorbidities etc) are not truly adjusted for several very important factors as follows:
1) Survivor treatment selection bias (also known as survival bias, immortal time bias or time-dependent bias) [Jones et al 2012];
2) Information bias arising in the studies because of misclassification of the level of exposure to oseltamivir;
3) Confounding by the additional use of NSAIDs amongst the individuals in the studies

The review finding of a large reduction in mortality for patients treated with oseltamivir, differs substantially from the results found in systematic reviews of randomized controlled trials, which report no such effects on major complication (pneumonia), hospitalization or mortality.

Certainly, one reason for this is that the rates of mortality were much lower in the randomized trials (as they were performed in healthy individuals with influenza-like illness (ILI); whereas the observational studies were performed in hospitalised patients (see point 5 above), where mortality is higher. But, because of the potential for selection bias in this population, causality cannot be inferred. Antiviral treatment benefits on mortality are probably attributable to healthier subjects being likely to receive treatment than the less healthy. Additionally, some less healthy patients will have died before treatment could be administered.

A recent a meta-analysis of published and unpublished clinical trials reported no difference in the likelihood of hospitalization in an intention to treat analysis (33/2633 patients for oseltamivir versus 20/1694 for placebo). [Ebell 2012]

A second review was commissioned by Roche as an independent data analysis. It reported that oseltamivir reduces the risk of lower respiratory tract complications requiring antibiotic treatment by 28% overall (95% CI, 11%–42%) and by 37% among patients with confirmed influenza infections (95% CI, 18%–52%).[Hernán 2011] However, the analysis included bronchitis, for which there is limited evidence in support of antibiotic use (and in the trials many of these patients were nevertheless treated with antibiotics). But it did not include sinusitis and otitis media despite the fact that these complications were included in the definition of secondary illness in the clinical study reports (along with pneumonia and bronchitis). They also failed to report hospitalisation or death.

Our systematic review [Jefferson 2012] of neuraminidase inhibitors for preventing and treating influenza in healthy adults and children found high risks of publication and reporting biases in the trial programme of oseltamivir. By using applicable data no effect on hospitalization was identified. In addition we found strong evidence that oseltamivir is associated with reduced antibody response. This causes assignment bias (an imbalance in the assignment of patients by laboratory-confirmed infection after randomisation), a high potential for bias for estimates based on this subgroup of patients.

Finally the committee concluded the following (page 191):

Based on the available evidence of the potential benefit of oseltamivir in specific patient groups and the expected prevalence of pandemic H1N1 in the
coming seasons, the Expert Committee agreed to add this medicine to the Core List. The Committee specified that the List should include the following notes: oseltamivir should be used only in compliance with the WHO treatment guidelines, i.e. (1) for treatment of patients with severe or progressive clinical illness with confirmed or suspected influenza pandemic (H1N1) 2009, (2) for the treatment of patients with confirmed or suspected but uncomplicated illness due to pandemic influenza virus infection who were in higher risk groups, most notably for pregnant women and children under 2 years of age.

It is well documented in the literature that observational studies (especially the analysis of case series) lead to bias in epidemiological findings and have great potential for error. Bias means that a measure of association between exposure and outcome is systematically wrong. [Jepson 2004]

The large reported effect upon mortality in the Hsu review was based on the analysis of only three studies of hospitalized patients, none of which were studies of H1N1 (2009). These three studies adjusted for age and comorbid conditions; but none described the reasons for administering oseltamivir to patients.

One of these studies, undertaken in Thailand, [Hanshaoworakul 2009] was a retrospective medical record review. The investigators called for caution in interpreting their results and reported, ‘Our small, retrospective, observational study has limitations with respect to establishing causality and we lacked additional information such as functional status and severity of illness scores which may have confounded or biased our results.’ Fatal cases with laboratory confirmed influenza (n=22) and non-fatal influenza from a sample of hospitalized cases in 28 provinces were compared with regard to the use of oseltamivir. Among non-fatal cases, 310 of 423 (73%) took oseltamivir whereas 5 of 22 fatal cases (23%) took OP: Crude OR was 0.11 (p<0.0001) and age-adjusted OR was 0.13 (0.04–0.40). However only 29% of medical records for non-fatal cases were reviewed (from Figure 1) and the estimated proportion of non-fatal cases being treated with oseltamivir (74%) is very high given that in 2004 to 2006 when the study was conducted more than 95 % of world consumption of oseltamivir was in either Japan or the United States. Human influenza infections were identified in 2,075 cases (1,488 in provinces with at least one influenza death). Using these values as denominators for the non-fatal cases, the proportion of oseltamivir use in non-fatal cases was 15% or 21% respectively -- lower rates of oseltamivir use than for fatal cases.

The second study was a retrospective review of clinical data. Medical data were obtained for 67 (72%) of 93 cases diagnosed with human influenza A (H5N1) in Vietnam. [Liem 2009] Oseltamivir was administered in 55 (82%) of 67 cases. Severe cases, and expected to die, were more likely to involve symptoms and signs of multi-organ involvement at hospital admission, including diarrhoea, mucosal bleeding, raised serum transaminase levels, and depressed neutrophil and platelet counts. The effect of oseltamivir was not statistically significant after stratification by age. Nor was there adjustment for NSAIDs use, which may lead to a serious risk of bias and
may conceal harmful effects of Tamiflu. The authors reported, “…although epidemiological data derived retrospectively from medical records are not robust.” Of note, 185 children did not use antivirals and none died.

The third study, of adult patients in Toronto requiring hospitalization, a population based surveillance study funded by contract with Hoffman-La Roche Ltd was published initially as supplement. The study noted a number of limitations [Kuster 2010]. Only 63% of eligible patients were tested for influenza, data collection was by chart review which limited the number of risk factors that could have been adjusted for.

Therefore the large effects reported in the observational studies are more likely to be due to poor quality evidence and systematic biases (as acknowledged in the Hsu review).

In 1950, Bradford Hill reported confounding as the rule rather than the exception. To infer causation from non-randomized studies needs a careful examination of all possible confounding factors. Without such examination and explanations of bias, cause and effect conclusions from observational studies are unreliable.
References


