**Contributors**

**Cochrane Neuraminidase Inhibitors Review Team**, March 5, 2013  
Prof Chris Del Mar, Coordinating Editor, Acute Respiratory Infections Cochrane Review Group, Australia  
Dr Peter Doshi, Postdoctoral Fellow, Johns Hopkins University, USA  
Dr Rokuro Hama, Physician, Pharmaco-epidemiologist, Japan Institute of Pharmaco-vigilance, University of Osaka, Japan  
Dr Carl Heneghan, Clinical Reader, Department of Primary Care Health Sciences, University of Oxford, UK  
Dr Tom Jefferson, Epidemiologist, Acute Respiratory Infections Cochrane Review Group, Italy  
Dr Mark Jones, Statistician, University of Queensland, Australia  
Dr Matthew Thompson, Clinical Reader, Department of Primary Care Health Sciences, University of Oxford, UK  

**Feedback from Harri Hemilä, 6 May 2013**

**Summary**

Comment: Oseltamivir (Tamiflu) shortens the duration of influenza-like illness by 13% (95% CI: 8% to 18%)  
In studies measuring dichotomous outcomes, relative risk (RR) is a standard measure for comparing study groups. The purpose of using RR is to adjust for baseline variability in the occurrence of disease. It is easier to compare two trials on the basis of their RR estimates than on the basis of their absolute effects.  
The relative effect should also be calculated for continuous outcomes. Although the duration of disease may vary randomly in placebo groups, there are also biological reasons why diseases in different placebo groups differ in their severity and duration. For example, in Analysis 1.1 of this review, the duration of influenza-like illness in the placebo group of trial WV15671 is 35% shorter than in the placebo group of trial WV15819/WV15876/WV15978 (Z = 6.5; P = <0.00001; 125h/192h). Such very large baseline differences are not explained by chance. Differences in the study populations, influenza seasons, study protocols, etc. are plausible explanations for the baseline variation. The above-mentioned baseline difference is much greater than any of those between the oseltamivir (Tamiflu) and placebo groups in the five trials of Analysis 1.1. As for dichotomous outcomes, the baseline variability of continuous outcomes can be adjusted for by calculating the effect in percentages, i.e., the relative effect. Furthermore, the percentage effect is informative for an average reader because the reader may form an opinion on whether, for example, a 10% or 20% average decrease in the duration is worth the cost and effort of the treatment. Separate from the absolute effect in days, the percentage effect shows whether the effect is small or large.  
Therefore the effect of oseltamivir should be calculated also as a percentage effect. I calculated the relative effects for the five trials listed in Analysis 1.1, pooled them using the fixed effect inverse variance method of RevMan, and found that the average effect of oseltamivir is a 13% (95% CI: 8 to 18%) decrease in the duration of influenza-like illness.  
Furthermore, the relative effect estimate makes it possible to compare the effects of treatments for related conditions. Influenza-like illness has substantial overlap with the common cold. In our Cochrane review on vitamin C and the common cold, we calculated that ≥1 g/day of vitamin C shortens colds in adults by 8% (95% CI: 4 to 12%) and in children by 18% (95% CI: 9 to 27%) [1]. Another meta-analysis found that a high dose of zinc (>75 mg/day) as zinc acetate lozenges decreased the duration of colds by 42% (95% CI: 35 to 48%) and as zinc lozenges made with other salts by 20% (95% CI: 12 to 28%) [2]. The mechanism of the effect of vitamin C and zinc lozenges is not understood; however, there is no reason to assume that their effects are specific, for example, to the rhinovirus. If vitamin C and zinc lozenges have effects on diverse respiratory viruses, they might also have an effect on influenza viruses. In mice, influenza infection decreased vitamin C concentration in bronchoalveolar lavage fluid [3]. In mice, vitamin C deficiency increased lung pathology caused by influenza infection [4]. An early study with influenza patients reported that the occurrence of pneumonia was 80% lower (2 vs. 10 cases) in the vitamin C group, suggesting that vitamin C might also have an effect on influenza in humans [5,6]. If the effects of vitamin C and zinc lozenges on influenza-like illness are of the same magnitude as their effects on the common cold, then the effects of these treatments compare reasonably with oseltamivir. The comparison of the percentage effects of oseltamivir, vitamin C and zinc lozenges may be useful when considering how future research resources concerning the treatment of respiratory virus infections might be allocated. In this respect, the type of effect measure has a much wider importance than just its use in evaluating the effectiveness of oseltamivir as an issue of its own.  
Thus the relative effect estimate adjusts for baseline variations between trials, it is informative for most readers because people are familiar with percentages, and it makes it easier to compare different treatments for related conditions. For these reasons I would like to encourage the authors to calculate and report the relative effect estimates for oseltamivir in the next revision of the review.  

**References**

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.
Harri Hemilä
Department of Public Health, University of Helsinki

Reply

Thank you for your suggestion and comprehensive argument why you think it is important. Indeed in our 2006 and 2009 updates of A047 (the previous review on antivirals for influenza in otherwise healthy adults) we pooled hazard ratios and reported relative effects for time to alleviation of symptoms. However GSK, the manufacturer of zanamivir, made the comment that hazard ratios may not be appropriate due to non-proportional hazards. Therefore for A159 we reported absolute treatment effects for time to alleviation of symptoms but not relative effects. We agree with your argument and will report absolute and relative effects for time to alleviation of symptoms and other outcomes in the next update of 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children' due at the end of 2013.

Contributors

Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ

Review amendments, 16 May 2013

Summary

As reported in the current version of our review, we will complete the review of regulatory information which arrived after our original timelock. We will assess additional evidence from oseltamivir Modules 2, evidence on adverse events following exposure to neuraminidase inhibitors (NIs) and clinically relevant outcomes.
A rationale and description of our methods follows.

Evidence from Modules 2 (Ms2) of oseltamivir trials

1. Summary and background

This part of the document will describe our efforts to determine whether the additional information included within Modules 2 (Ms2) of clinical study reports (CSRs) would change the risk of bias assessment, identify additional useful or relevant information, and conclusions of the overall body of evidence contained within our existing review. A second aim is to construct and test a tool that could be used to extract, organise and appraise study information contained in such modules.
The items which are most commonly found in the M2 of the oseltamivir trials are Certificates of Analysis (a report on the colour, composition and content of active and control substance capsules, blank Case Report Forms (case notes for each participant), Follow up cards/Diary cards (on which each participant recorded information such as symptoms), Informed Consent text and participant contract (to be administered to and signed by each participant), Lists of Investigators in the trial, Investigation review Board, Ethics
Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children

Tom Jefferson\textsuperscript{1}, Mark A Jones\textsuperscript{2}, Peter Doshi\textsuperscript{3}, Chris B Del Mar\textsuperscript{4}, Carl J Heneghan\textsuperscript{5}, Rokuro Hama\textsuperscript{6}, Matthew J Thompson\textsuperscript{5}

\textsuperscript{1}The Cochrane Collaboration, Roma, Italy. \textsuperscript{2}Centre for Healthcare Related Infection Surveillance and Prevention, Queensland Health, Brisbane, Australia. \textsuperscript{3}Division of General Internal Medicine, Johns Hopkins University, Baltimore, Maryland, USA. \textsuperscript{4}Centre for Research in Evidence-Based Practice (CREBP), Bond University, Gold Coast, Australia. \textsuperscript{5}Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. \textsuperscript{6}Japan Institute of Pharmacovigilance, Osaka, Japan

Contact address: Tom Jefferson, The Cochrane Collaboration, Via Puglie 23, Roma, 00187, Italy. jefferson.tom@gmail.com. jefferson@assr.it.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: Edited (no change to conclusions), comment added to review, published in Issue 6, 2013.
Review content assessed as up-to-date: 12 April 2011.


Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

**Abstract**

**Background**

Planning for outbreaks of influenza is a high priority public health issue for national governments. Neuraminidase inhibitors (NIs) are thought to help reduce the symptoms of influenza with several possible mechanisms proposed. NIs have been stockpiled with a view to their widespread use in the event of a pandemic. However, the evidence base for this class of agents remains a source of debate. In a previous review we have documented substantial risks of publication bias of trials of NIs for influenza (60% of patient data from phase III treatment trials of oseltamivir have never been published) and reporting bias in the published trials. Our confidence in the conclusions of previous versions of this review has been subsequently undermined. Since we have become aware of a large number of unpublished trials of NIs in the management of influenza, this review updates and merges existing reviews in this area.

**Objectives**

To review clinical study reports of placebo-controlled randomised trials, regulatory comments and reviews (‘regulatory information’) of the effects of the NIs oseltamivir and zanamivir for influenza in all age groups and appraise trial programmes, rather than single studies. Clinical study reports are very detailed, unpublished clinical trial data containing in-depth descriptions of protocol rationale, methods analysis plans, trial results and organisational documents (such as contracts). A series of clinical studies designed and conducted by one sponsor represents a trial programme of a drug indication (for example treatment of influenza).

**Search methods**

We searched trial registries, cross-referencing published and unpublished sources and corresponded with manufacturers and regulators. We searched the archives of the US Food and Drug Administration (FDA) and European and Japanese regulators. The evidence in this review reflects searches to obtain relevant information up to 12 April 2011.

**Selection criteria**

We included regulatory information based on assessments of randomised controlled trials (RCTs) conducted in people of any age who had either confirmed or suspected influenza, or who had been exposed to influenza in the local community or place of residence. We included information which had been made available by our deadline.