HEALTH TECHNOLOGY ASSESSMENT

VOLUME 20 ISSUE 42 MAY 2016
ISSN 1366-5278

Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data

Carl J Heneghan, Igho Onakpoya, Mark A Jones, Peter Doshi, Chris B Del Mar, Rokuro Hama, Matthew J Thompson, Elizabeth A Spencer, Kamal R Mahtani, David Nunan, Jeremy Howick and Tom Jefferson

National Institute for Health Research

DOI 10.3310/hta20420

Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data

Carl J Heneghan,[1]* Igho Onakpoya,[1] Mark A Jones,[2] Peter Doshi,[3] Chris B Del Mar,[4] Rokuro Hama,[5] Matthew J Thompson,[6] Elizabeth A Spencer,[1] Kamal R Mahtani,[1] David Nunan,[1] Jeremy Howick[1] and Tom Jefferson[7]

[1]Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[2]School of Population Health, The University of Queensland, Brisbane, QLD, Australia
[3]Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, MD, USA
[4]Centre for Research in Evidence-Based Practice (CREBP), Bond University, Robina, QLD, Australia
[5]Japan Institute of Pharmacovigilance, Osaka, Japan
[6]Department of Family Medicine, University of Washington, Seattle, WA, USA
[7]The Cochrane Collaboration, Rome, Italy

*Corresponding author

Declared competing interests of authors: All review authors have applied for and received competitive research grants. Carl J Heneghan reports grants from the UK National Institute for Health Research (NIHR), the NIHR School of Primary Care, Wellcome Trust and the World Health Organization (WHO) during the conduct of the study, and has received expenses and payments for media work. In addition, he is an expert witness in an ongoing medical device legal case. He receives expenses for teaching evidence-based medicine and is paid for NHS general practitioner work in the out of hours service in Oxford. Tom Jefferson receives royalties from his books published by Blackwells and Il Pensiero Scientifico Editore, Rome. Tom Jefferson is occasionally interviewed by market research companies for anonymous interviews about Phase I or II pharmaceutical products. In 2011–13, Tom Jefferson acted as an expert witness in a labour case on influenza vaccines in health-care workers in Canada. In 1997–9, Tom Jefferson acted as a consultant for Roche, in 2001–2 for GlaxoSmithKline, and in 2003 for Sanofi-Synthelabo for pleconaril, which did not get approval from the US Food and Drug Administration (FDA). Tom Jefferson was a consultant for IMS Health in 2013, and in 2014 was retained as a scientific adviser to a legal team acting on the drug Tamiflu (oseltamivir, Roche). In 2014–15, Tom Jefferson was a member of two advisory boards for Boerhinger and is in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. Tom Jefferson has a potential financial conflict of interest in the investigation of the drug oseltamivir. Tom Jefferson is acting as an expert witness in a medicolegal negligence case involving the drug oseltamivir (Roche). Peter Doshi received €1500 (£1241; US$2052) from the European Respiratory Society in support of his travel to the society's September 2012 annual congress in Vienna, where he gave an invited talk on oseltamivir. Peter Doshi is an associate editor of the *British Medical Journal* (BMJ). Peter Doshi gratefully acknowledges the American Association of Colleges of

Pharmacy for its funding support ($10,000) for a study to analyse written medical information regarding the possible harms of statins. Peter Doshi is also an unpaid member of the IMEDS steering committee at the Reagan–Udall Foundation for the FDA, which focuses on drug safety research. CDelM is the Co-ordinating Editor of the Acute Respiratory Infections Group of the Cochrane Collaboration. CDelM reports personal fees from Key Pharmaceuticals during the conduct of the study; grants from the National Health and Medical Research Council (Australia), grants from NIHR (UK), personal fees from Elsevier and BMJ Books, from conference organisers for International Viral Infections Conference, personal fees from GlaxoSmithKline Pharmaceuticals, personal fees from Key Pharmaceutical, outside the submitted work. Rokuro Hama provided scientific opinions and expert testimony on 11 adverse reaction cases related to oseltamivir for the applications by their families for adverse reaction relief by the Pharmaceuticals and Medical Devices Agency (PMDA) and in the lawsuits for revocation of the PMDA's decision concerning with these reactions. Most of the cases were reported in the *International Journal of Research Studies in Management* (2008:**20**:5–36). Rokuro Hama was an expert witness in the lawsuit on the adverse reaction of (death from) gefitinib against AstraZeneca and Japanese Minister of Health Labour and Welfare, and provided scientific opinions and expert testimony. He argued that gefitinib's fatal toxicity was known before approval in Japan, as shown in 'Gefitinib story' (http://npojip.org/english/The-gefitinib-story.pdf) and in other articles (http://npojip.org/). Plaintiffs finally lost the case on 12 April 2013 at the Supreme Court of Japan. Rokuro Hama has received royalties from a published book.

Published May 2016
DOI: 10.3310/hta20420

This report should be referenced as follows:

Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R, *et al*. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. *Health Technol Assess* 2016;**20**(42).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.027

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 10/80/01. The contractual start date was in February 2011. The draft report began editorial review in June 2014 and was accepted for publication in October 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data

Carl J Heneghan,[1]* Igho Onakpoya,[1] Mark A Jones,[2] Peter Doshi,[3] Chris B Del Mar,[4] Rokuro Hama,[5] Matthew J Thompson,[6] Elizabeth A Spencer,[1] Kamal R Mahtani,[1] David Nunan,[1] Jeremy Howick[1] and Tom Jefferson[7]

[1]Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
[2]School of Population Health, The University of Queensland, Brisbane, QLD, Australia
[3]Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, MD, USA
[4]Centre for Research in Evidence-Based Practice (CREBP), Bond University, Robina, QLD, Australia
[5]Japan Institute of Pharmacovigilance, Osaka, Japan
[6]Department of Family Medicine, University of Washington, Seattle, WA, USA
[7]The Cochrane Collaboration, Rome, Italy

*Corresponding author carl.heneghan@phc.ox.ac.uk

Background: Neuraminidase inhibitors (NIs) are stockpiled and recommended by public health agencies for treating and preventing seasonal and pandemic influenza. They are used clinically worldwide.

Objectives: To (1) describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all clinical study reports (CSRs) of published and unpublished randomised, placebo-controlled trials and regulatory comments; and (2) determine the effect of oseltamivir (Tamiflu®, Roche) treatment on mortality in patients with 2009A/H1N1 influenza.

Methods: We searched trial registries, electronic databases and corresponded with regulators and sponsors to identify randomised trials of NIs. We requested full CSRs and accessed regulators' comments. We included only those trials for which we had CSRs. To examine the effects of oseltamivir on 2009A/H1N1 influenza mortality, we requested individual patient data (IPD) from corresponding authors of all included observational studies.

Results: *Effect of oseltamivir and zanamivir (Relenza®, GlaxoSmithKline) in the prevention and treatment of influenza*: Oseltamivir reduced the time to first alleviation of symptoms in adults by 16.8 hours [95% confidence interval (CI) 8.4 to 25.1 hours]. Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days). Oseltamivir reduced unverified pneumonia in adult treatment [risk difference (RD) 1.00%, 95% CI 0.22% to 1.49%]; similar findings were observed with zanamivir prophylaxis in adults (RD 0.32%, 95% CI 0.09% to 0.41%). Oseltamivir treatment of adults increased the risk of nausea (RD 3.66%, 95% CI 0.90% to 7.39%) and vomiting (RD 4.56%, 95% CI 2.39% to 7.58%). In the treatment of children, oseltamivir induced vomiting (RD 5.34%, 95% CI 1.75% to 10.29%). Both oseltamivir and zanamivir prophylaxis reduced the risk of symptomatic influenza in individuals (oseltamivir RD 3.05%, 95% CI 1.83% to 3.88%; zanamivir RD 1.98%, 95% CI 0.98% to 2.54%) and in households (oseltamivir RD 13.6%, 95% CI 9.52% to 15.47%; zanamivir RD 14.84%, 95% CI 12.18% to 16.55%). Oseltamivir increased psychiatric adverse events in the combined on- and

off-treatment periods (RD 1.06%, 95% CI 0.07% to 2.76%) and the risk of headaches while on treatment (RD 3.15%, 95% CI 0.88% to 5.78%). *Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza*: Analysis of summary data of 30 studies as well as IPD of four studies showed evidence of time-dependent bias. After adjusting for time-dependent bias and potential confounding variables, competing risks analysis of the IPD showed insufficient evidence that oseltamivir reduced the risk of mortality (hazard ratio 1.03, 95% CI 0.64 to 1.65).

Conclusions: Oseltamivir and zanamivir cause small reductions in the time to first alleviation of influenza symptoms in adults. The use of oseltamivir increases the risk of nausea, vomiting, psychiatric events in adults and vomiting in children. Oseltamivir has no protective effect on mortality among patients with 2009A/H1N1 influenza. Prophylaxis with either NI may reduce symptomatic influenza in individuals and in households. The balance between benefits and harms should be considered when making decisions about use of NIs for either prophylaxis or treatment of influenza.

Study registration: This study is registered as PROSPERO CRD42012002245.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of tables

List of figures

Glossary

Clinical study reports Detailed reports of a clinical trial, usually submitted to regulators, following a prescribed International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use format. Roche's reports follow a modular structure (see *Appendix 9*). Reports can be several hundred pages long and contain details of the planned design, conduct (protocol), analysis (reporting analysis plan) and results of the trial.

Compliharm Term describing events defined as either complications or harms according to ambiguous criteria that appeared to include time of analysis (with times either unspecified or inconsistent among trials) and whether or not participants were infected (by influenza). In oseltamivir treatment trials some potential harms or complications could be caused by both medication or influenza infection (e.g. vomiting), hence our classification as a compliharm.

Consolidated Standards of Reporting Trials-based extraction Extraction, synthesis and appraisal method used in this review for data from clinical study reports. Reconstructions were done by pairs of review authors and assessed in the authors' plenary session to decide whether or not included trials could proceed to stage 2 of the analysis. The structure of the reconstruction follows that of the Consolidated Standards of Reporting Trials statement.

Freedom of information Enshrined by law in the US and European Medicines Agency policy in Europe. Freedom-of-information requests in this review have been a means of access to clinical study reports and regulatory comments (regulatory information).

Individual patient data Anonymised individual data listings of characteristics and results, which form the basis for the synthetic analyses in clinical study reports.

Japanese Summary Basis for Approval (of a drug) Summary of the application dossiers included as one of the documents that is prepared and attached by the sponsoring pharmaceutical company. These are submitted to the regulatory body for approval of a new drug.

Modules Basic structure of Roche's trial reports. Today, the term 'Modules' refers to the components of a regulatory submission, as set by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (2011). Clinical study reports are just one 'module' of a regulatory submission.

Protocol Document reporting the trial's planned design and conduct, with amendments (when relevant). Confusingly, also used in submissions and regulatory documents as synonymous with study.

Public health drugs Drugs in which a considerable quantity of public money has been invested and/or are on the World Health Organization essential drugs list.

Regulatory information Term comprising clinical study reports (data) and regulatory comments and reviews.

Reporting Analysis Plan Plan of analysis that is usually linked to the trial protocol, explaining what and how the authors intend to analyse.

Table of content of regulatory reviews and comments on industry submissions Our table of content indicates which trial is cited, in which document, on which page and how many times.

Table of contents-evidence Annotated version of the table of contents. Comments and annotation are preliminary and form the basis for the weaving of the important aspects into the review narrative.

Time lock Date (12 April 2011) after which no documentation would be reviewed in the January 2012 version of the review. A cut-off was made necessary by the sheer scale of our data holdings. We were initially funded to review the full clinical study reports of the 10 treatment trials included in the Kaiser *et al.* paper (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;**63**:1667–72). We were able to access the 10 module 1s and regulatory comments (approximately 6000 pages in total). As the funder-stipulated deadline to producing our review progressively shortened, and our understanding of the issues evolved, we received notification that although the balance of the 10 study reports was unlikely to be accessible by our deadline, we would receive substantial quantities of regulatory documents from the European Medicines Agency in four tranches. When we held our second face-to-face meeting in April 2011 we had just received our first tranche of clinical study reports, consisting of just over 10,000 pages, bringing our total holdings to 16,000 pages. We decided that we did not have the resources to review any further documentation within our current funding and imposed a data time lock. Any documentation received after this date would be reviewed if and when we had more resources. The balance of documents (a further 14,000 pages) are included in this review.

Trial ID Means of identifying a trial. Usually made up of letters and numbers (WV15799). At times the ID bears a letter suffix indicating the last version of the protocol followed in the trial (e.g. WV15799H, i.e. trial carried out following amendment H).

Trial programme Series of trials designed and carried out to achieve registration or to answer specific questions. Usually, programmes of the same drug or intervention focus on the same indication or the same study population.

List of abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
BMJ	*British Medical Journal*
CDC	US Centers for Disease Control and Prevention
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSR	clinical study report
CTCAE V4.0	Common Terminology Criteria for Adverse Events Version 4.0
DARE	Database of Abstracts of Reviews of Effects
df	degrees of freedom
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FOI	freedom of information
GSK	GlaxoSmithKline
HEED	Health Economic Evaluations Database
HR	hazard ratio
ILI	influenza-like illness
IPD	individual patient data
ITT	intention to treat
ITTI	intention-to-treat-influenza-infected
ITTIINAB	intention-to-treat influenza-infected index cases who had negative virology at baseline
MD	mean difference
NCI-CTC V2.0	National Cancer Institute-Common Toxicity Criteria Version 2.0
NDA	New Drug Application
NHS EED	National Health Service Economic Evaluation Database
NI	neuraminidase inhibitor
NICE	National Institute for Health and Care Excellence
NNTB	number needed to treat to benefit
NNTH	number needed to treat to harm
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PEP	post-exposure prophylaxis
RCT	randomised controlled trial
RD	risk difference
RR	risk ratio
SAP	statistical analysis plan
SBA	Summary Basis of Approval
td-Cox	Cox regression including treatment as a time-dependent exposure
TOC	table of contents
WHO	World Health Organization

Plain English summary

Regulatory information on trials of oseltamivir (Tamiflu) and zanamivir (Relenza) for influenza in adults and children

Oseltamivir and zanamivir have been stockpiled in many countries to treat and prevent seasonal and pandemic influenza, before an influenza vaccine matched to the circulating virus becomes available.

How this review has been approached

We have updated and combined our reviews on the antiviral drugs zanamivir and oseltamivir for influenza in adults and children on the basis of the manufacturers' reports to regulators (clinical study reports) and the regulators' comments. We have called these comments and reports 'regulatory information'.

What we have found

We have used data from 46 trials (20 oseltamivir and 26 zanamivir studies) in this review. We found that both drugs shorten the duration of symptoms of influenza-like illness (unconfirmed influenza or 'the flu') by less than a day (there was no effect in asthmatic children, but in otherwise healthy children there was). Oseltamivir did not affect the number of hospitalisations. In children with asthma there was no clear effect on the time to first alleviation of symptoms.

Prophylaxis trials showed that oseltamivir and zanamivir reduced the risk of symptomatic influenza.

Oseltamivir use was associated with nausea, vomiting, headaches and psychiatric events; these last two were when it was used to prevent influenza (prophylaxis).

Low-quality data, adjusted for some likely biases, failed to show a reduction in mortality in very ill patients with H1N1 2009 and treated with oseltamivir compared with those who did not receive influenza antiviral drugs.

Scientific summary

Introduction

The World Health Organization (WHO) lists oseltamivir (Tamiflu®, Roche) as an essential influenza pandemic drug and worldwide there is considerable stockpiling for emergency use, but there is uncertainty on the reliability of the evidence base of oseltamivir and its fellow neuraminidase inhibitor (NI) zanamivir [Relenza®, GlaxoSmithKline (GSK)] and on their safety and efficacy.

In 2009 it emerged that there was substantial reporting bias in published evidence, and this led us to develop a new approach in order to update and amalgamate two pre-existing Cochrane reviews on NIs in children and adults. Over a period of 4 years we worked to obtain full, unabridged, clinical study reports for all trials in both drugs' evidence development programme. We based our current review and its 2012 predecessor uniquely on clinical study reports and other regulatory material, including regulators reports, that were available in the USA as Summary Basis of Approval and in the EU as European Public Assessment Report.

This undertaking was facilitated by the change of policy at the European Medicines Agency (EMA) in late 2010, allowing release for the first time of clinical study reports that were used during the Market Authorisation Application and its processing. Additionally, this process received the backing of the *British Medical Journal*, which launched its open data campaign on the basis of our quest for clinical study reports.

Here we present our methods and results, based on the full set of clinical study reports that fit our inclusion criteria. The reports, together with all relevant correspondence and the editors' and referees' comments, are also available. We also report our efforts to develop methods of reviewing clinical study reports and putting the trial evidence in the context of the numerous non-randomised studies that have been published since the 2009 influenza outbreak in order to present a complete picture of the topic.

Objectives

Our objective was to assess the effects of the NIs zanamivir and oseltamivir for influenza on the basis of regulatory material and within their context of use. Specifically, we aimed to:

1. describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all clinical study reports of published and unpublished randomised, placebo-controlled trials and regulatory comments
2. determine the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza.

Methods

To evaluate the effectiveness of NIs for preventing and treating influenza in adults and children:

- We searched trial registries, electronic databases (to 22 July 2013) and regulatory archives, and corresponded with manufacturers to identify all trials. We also requested clinical study reports. We focused on the primary data sources of manufacturers but we checked that there were no published randomised controlled trials (RCTs) from non-manufacturer sources by running electronic searches in the following databases: the Cochrane Central Register of Controlled Trials, MEDLINE, MEDLINE (via Ovid), EMBASE, EMBASE.com, PubMed (not MEDLINE), the Database of Abstracts of Reviews of Effects, the NHS Economic Evaluation Database and the Health Economic Evaluations Database.
- We included evidence from RCTs testing the effects of NIs for prophylaxis, post-exposure prophylaxis and treatment of influenza.
- We included only trials on people who were exposed to naturally occurring influenza, with or without symptoms.
- We analysed the effects of zanamivir and oseltamivir on time to first alleviation of symptoms, influenza outcomes, complications, hospitalisations and adverse events in the intention-to-treat population.
- The sizeable quantity of available data led us to subdivide the extraction, appraisal and analysis of the data into a two-stage exercise. In stage 1 we assessed the reliability and completeness of the identified trial data. We decided to include in stage 2 of the review (full analysis following standard Cochrane methods) only data that satisfied the following three criteria: (1) completeness, (2) internal consistency and (3) external consistency.
- We used regulatory information to assess the possible correlation between citation frequency of oseltamivir treatment trials in the US Food and Drug Administration regulatory documents and trial size.
- We used the random-effects approach of DerSimonian and Laird (DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88), based on mean differences with 95% confidence interval (CI) for analysis of time to first alleviation of symptoms. For all other outcomes we used the random-effects approach for binary data of DerSimonian and Laird, where tau-squared was estimated using the inverse variance method.

To determine the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza:

- We searched MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature, Web of Science and the Latin American and Caribbean Health Sciences Literature databases (see *Appendix 16* for details of our search strategy) for observational studies. We also hand-searched bibliographies from two relevant documents published by the WHO and two previous reviews.
- We included any study of patients with 2009A/H1N1 influenza reporting mortality outcomes and exposure to oseltamivir with at least 5% of patients untreated with influenza antiviral drugs and five or more deaths overall.
- We requested individual patient data (IPD) from the corresponding authors of all included studies and kept a record of all correspondence that ensued. IPD was provided for four studies, sent via e-mail in Excel® 2010 (Microsoft Corporation, Redmond, WA, USA) or Stata 12 files (StataCorp LP, College Station, TX, USA), checked for consistency and analysed in SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Effectiveness of neuraminidase inhibitors in the treatment of influenza

We obtained 107 clinical study reports from the EMA, GSK and Roche. We included 53 trials in stage 1 and 46 in stage 2, including 20 oseltamivir (9623 participants) and 26 zanamivir trials (14,628 participants). Most of the zanamivir studies and half of the oseltamivir studies were at high risk of selection bias as a result of inadequate reporting.

In adult treatment, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% CI 8.4 to 25.1 hours; $p < 0.0001$). There was no effect in asthmatic children, for whom symptoms increased by 5.2 hours (11.1 hours lower to 21.4 hours higher), but in otherwise healthy children there was reduction by 29 hours (95% CI 12 to 47 hours; $p = 0.001$). Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days; $p < 0.00001$) but the effect in children was not significant. In subgroup analysis there was no difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza-infected and non-influenza-infected subgroups ($p = 0.53$).

Oseltamivir significantly reduced unverified pneumonia [risk difference (RD) 1.00%, 95% CI 0.22% to 1.49%] in the treated population. The effect was not significant in the five trials that used a more detailed diagnostic form for pneumonia. There was no significant effect on pneumonia in children [risk ratio (RR) 1.06, 95% CI 0.62 to 1.83]. There was no significant effect of zanamivir treatment on pneumonia (RR 0.90, 95% CI 0.58 to 1.40). In two zanamivir adult trials, pneumonia reporting was based on a stricter definition of X-ray confirmation and there was also no significant treatment effect (RR 1.02, 95% CI 0.35 to 3.02). In prophylaxis, zanamivir significantly reduced the risk of unverified pneumonia in adults (RD 0.32%, 95% CI 0.09% to 0.41%) but not oseltamivir.

In adult treatment, oseltamivir increased the risk of nausea (RD 3.66%, 95% CI 0.90% to 7.39%) and vomiting (RD 4.56%, 95% CI 2.39% to 7.58%). The proportion of participants with fourfold increases in antibody titre was significantly lower with oseltamivir (RR 0.92, 95% CI 0.86 to 0.97). Oseltamivir significantly decreased the risk of diarrhoea (RD 2.33%, 95% CI 0.14% to 3.81%) and cardiac events (RD 0.68%, 95% CI 0.04% to 1.0%) during the on-treatment period. The rate of psychiatric adverse events increased in dose-dependent fashion based on a likelihood ratio test ($p = 0.038$) in the two 'pivotal' treatment trials that included two oseltamivir arms with doses of 150 mg and 300 mg daily. There was no indiction of a dose–response effect of treatment on psychiatric adverse events in the only prophylaxis study with multiple dose treatment groups. In the treatment of children, oseltamivir induced vomiting (RD 5.34%, 95% CI 1.75% to 10.29%). There was a significantly lower proportion of children on oseltamivir with a fourfold increase in antibodies (RR 0.90, 95% CI 0.80 to 1.00).

Effectiveness of neuraminidase inhibitors in the prevention of influenza

In prophylaxis trials, NIs reduced the risk of symptomatic influenza in individuals (oseltamivir RD 3.05%, 95% CI 1.83% to 3.88%; zanamivir RD 1.98%, 95% CI 0.98% to 2.54%) and in households (oseltamivir RD 13.6%, 95% CI 9.52% to 15.47%; zanamivir RD 14.84%, 95% CI 12.18% to 16.55%). There was no significant effect on asymptomatic influenza (oseltamivir RR 1.14 95%, CI 0.39 to 3.33; zanamivir RR 0.97, 95% CI 0.76 to 1.24). In oseltamivir prophylaxis, psychiatric adverse events were increased in the combined on- and off-treatment periods (RD 1.06%, 95% CI 0.07% to 2.76%). Oseltamivir, on treatment, increased the risk of headaches (RD 3.15%, 95% CI 0.88% to 5.78%), renal events (RD 0.67%, 95% CI –0.01% to 2.93%) and nausea (RD 4.15%, 95% CI 0.86% to 9.51%).

Comparison of core reports compared with full clinical study reports

With more detailed information, no previous assessment of 'high' risk of bias was reclassified as 'low' or 'unclear' in the main analysis, and over half (55%, 34/62) of previous assessments of 'low' risk of bias were reclassified as 'high'. Most 'unclear' risk of bias (67%, 28/42) was reclassified as 'high' risk of bias when our judgements were based on full clinical study reports.

Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza

A total of 154 full-text articles were assessed for eligibility. Of these, 30 observational studies were eligible and a total of 11,013 patients were available for qualitative synthesis. Overall, there were 1301 deaths (12%) with the percentage of deaths receiving oseltamivir similar to that of survivors (83% vs. 82%). The IPD came from four studies including 3071 patients and 242 (8%) deaths. Analysis of the IPD showed no evidence of reduced risk of mortality with oseltamivir [hazard ratio (HR) 1.03, 95% CI 0.64 to 1.65].

Discussion

Effectiveness of neuraminidase inhibitors in the prevention and treatment of influenza

The evidence that we have presented and synthesised shows that both NIs have symptom-relieving effects, especially for self-reported outcomes, shortening symptom duration and reducing the frequency of symptoms such as cough. For oseltamivir, this effect perhaps extends to cardiac symptoms, despite the short duration of treatment (5 days). We are unsure what to make of this finding but we think it deserves further investigation.

We could not decide the level of diagnostic ascertainment of diagnosis of pneumonia and other complications. In a metaregression of all 32 included studies that reported on 'pneumonia', we found evidence that treatment effects for pneumonia are statistically different depending on the method of diagnosis.

Antibody suppression seems stronger for oseltamivir than zanamivir, probably because of the difference in bioavailability. It may be that evidence of other effects, such as hyperglycaemia and renal impairment (although significance was marginal) in the prophylaxis trials may be due to inhibition of the host's endogenous neuraminidase, which impairs the cell function of various organs.

A weak dose-dependent association between oseltamivir and psychiatric harms is evident in the two pivotal treatment trials (but not in all oseltamivir treatment trials combined). It is possible that influenza-like illness and influenza symptoms masked the harms in those who were already symptomatic and therefore recruited in the treatment trials (and influenza-type symptoms were excluded as adverse events to be reported).

Comparison of core reports compared with full clinical study reports

The Cochrane risk-of-bias tool was sometimes difficult to apply to clinical study reports. This may be because the tool was constructed to assess journal publications and comprises a checklist. As information increased in the core reports, our assessment of bias became more detailed and changed some of our assessments. Our experience suggests that a more detailed extraction sheet is needed to prompt reviewers to consider additional aspects of the study design when assessing bias.

Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza

Analysis of the summary data on the 30 studies as well as the IPD showed evidence of time-dependent bias, with bias increasing with increasing odds of treatment. Analysis of the IPD using standard Cox regression on the 2056 patients with survival times gave a HR of 0.75. However, when the time-dependent nature of oseltamivir exposure, as well as the competing risk of hospital discharge were taken into account, the HR adjusting for potential confounding variables was 1.03.

Our results are substantially different from those of three other reviews, which based their primary analysis of mortality on three small studies of 681 patients, none of which had 2009A/H1N1, did not consider time-dependent treatment exposure or appeared to not take appropriate account of time-dependent treatment exposure.

Conclusions

Oseltamivir and zanamivir cause small reductions in the time to alleviation of influenza symptoms except for asthmatic children. The use of oseltamivir increases the risk of nausea, vomiting, psychiatric events in adults and vomiting in children. Observational studies do not show that oseltamivir has a protective effect on patients with 2009A/H1N1 influenza for mortality. Evidence suggests that the risk of bias has been insufficiently reported in other Cochrane reviews that are limited to published research. The balance between benefits and harms should be considered when making decisions about the use of NIs for either prophylaxis or treatment of influenza.

Research priorities

We could not reach a consensus on whether or not further trials are warranted and whether or not current trials should be discontinued. Any future trial designs should ensure that the presence of complications is ascertained using objective diagnostic criteria. Procedures for trial unblinding and dates of unblinding should be routinely reported. Registration should be made compulsory for all studies in which human beings are randomly assigned to experimental arms. There is a further need to develop the systematic review methods for the evaluation of other drugs, using full clinical study reports. Priority could perhaps be given to first drugs of a new family, drugs considered to be innovative or those that are likely to have a big market impact. Such reviews should be publicly funded, and independent from both regulators and manufacturers. To determine the risks and benefits of drugs there will be a need to move to more comprehensive reviews that incorporate more clinical study report data.

Study registration

This study is registered as PROSPERO CRD42012002245.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction and rationale

Since the mid-2000s the use of neuraminidase inhibitors (NIs) has been endorsed and billions of pounds have been spent stockpiling the two anti-influenza drugs oseltamivir (Tamiflu®, Roche) and zanamivir [Relenza®, GlaxoSmithKline (GSK)] in preparation for an influenza pandemic. When the H1N1 pandemic emerged in 2009, the drugs were rolled out worldwide for the treatment and prevention of influenza and its complications. At that time, we were asked to conduct a systematic review for Cochrane to update evidence on their efficacy, during which it emerged that the validity of a key study underpinning the evidence on efficacy was unclear. After 3.5 years of making requests to the drug manufacturers, they provided us with full clinical study reports (CSRs).

Emergence of problems

The reasons for the stockpiling of oseltamivir and zanamivir are not well known, but the decision may be based on assumptions that the drugs would reduce hospital admissions and serious complications of influenza, such as pneumonia, by half and slow down the spread of the virus.[1–3] Some of these assumptions were supported by a peer-reviewed pooled analysis of 10 randomised trials of oseltamivir published in the *Archives of Internal Medicine* in 2003 by Kaiser *et al.*[4] This analysis seemed to be of high quality and formed a powerful scientific rationale for stockpiling,[5] but during our review in 2009 it became apparent that the data underlying it were largely unpublished and inaccessible to independent scrutiny. Roche, the manufacturer of oseltamivir, funded the Kaiser review, employed some of its authors and had also sponsored the 10 trials. For 3.5 years Roche did not release the full CSRs despite a public pledge to do so made during the H1N1 'swine flu' outbreak of 2009.[6,7]

Research for our 2009 review also highlighted inconsistencies in decision-making. The US Food and Drug Administration (FDA), which had access to the full CSRs, concluded on the product label that 'Tamiflu has not been shown to prevent such complications [serious bacterial infections]'. The European Medicines Agency (EMA), which had only partial reports, and another prominent US agency, the Centers for Disease Control and Prevention (CDC), came to the exact opposite conclusion – all apparently based on the same trials.[8]

Owing to the risk of reporting bias as a result of the large amounts of unpublished data there are uncertainties about the stated benefits of oseltamivir and about the conclusions of previous Cochrane reviews of NIs in adults and children.[9,10] To address this, we worked for 4 years to obtain full CSRs of the oseltamivir trial programme. CSRs are considered to be the most exhaustive summaries of randomised controlled trials (RCTs) of drugs. They are usually composed of a main report of the trial (in introduction, methods, results and discussion style), with numerous appendices containing important supplementary data that are needed to understand and interpret the trial [e.g. protocol, protocol amendments, statistical analysis plan (SAP), blank case report forms (CRFs), certificates of analysis, randomisation list and informed consent forms].[11] In the case of oseltamivir, CSRs were of a mean length of approximately 1300 pages (median around 900 pages). As a result of increasing availability, CSRs may in the future be incorporated into systematic reviews and other forms of evidence synthesis.[12,13]

Rationale for this review

In the midst of the A/H1N1 influenza outbreak in June 2009, the Australian and UK governments commissioned an update of our long-standing Cochrane review on NIs for influenza in (otherwise) healthy adults (known as A047). At the time of publication of the 2009 update and its linked investigation by the *British Medical Journal* (BMJ), we underestimated the extent of the oseltamivir evidence development programme, expecting it to comprise around 36 trials, with only a proportion of these fitting our inclusion criteria. We were also unaware of the size and the level of detail that the CSRs contained.

Today, the obvious source of information on CSRs would be trial registries and company websites, but most trials of both NIs were carried out before inception or wide acceptance of centralised registries and company websites. In 2009–11, company websites did not, and still do not, have extensive lists of trials with downloadable CSRs. Many people had never heard of CSRs before media coverage of our work. We decided to construct our list by using multiple cross-referencing methods. We constructed a list beginning with clinical trials that were identified from previous review updates.

To ensure that the list did not include duplicate entries, we assigned to each trial a unique trial ID. 'Author' was insufficient to provide a unique trial ID, because different authors can be present across different versions of the same trial (i.e. the authors of CSRs can be different from publications arising from the same clinical trial).

Once we had as complete a list of trials as possible, we contacted manufacturers and sent them our draft list, asking them to check the accuracy and completeness of our list. Roche, GSK and BioCryst all did so, and informed us of additional trials.

We requested from Roche and GSK a series of regulatory documents under freedom of information (FOI) policies from both the FDA and the EMA. No substantial comments were made by Roche on the protocol of the Cochrane A159 review,[14] which has been publicly available since December 2010.

Soon after the publication of the review, the BMJ agreed to publish our correspondence with Roche, GSK, EMA, CDC and World Health Organization (WHO), recording our attempts at retrieving the full reports without any conditions attached, and to understand the basis for promotion of the drugs (especially oseltamivir) by public health bodies. The correspondence (which is hundreds of pages long) formed the basis for what then became the BMJ Open Data Campaign and a stimulus for the later AllTrials campaign. Public exposure of this approach and considerable media coverage led to the unconditional release of 77 reports of oseltamivir of 82 studies sponsored by Roche and the equivalent of the 30 studies we had requested from GSK. For the full correspondence, see www.bmj.com/tamiflu and www.bmj.com/relenza. The reports (amounting to over 100,000 pages) are made available with this review for the first time at: https://datadryad.org/resource/doi:10.5061/dryad.77471/2, a positive step for open science. We have described the posting of these reports in a blog posting at: http://blog.datadryad.org/2014/04/17/tamiflu-data/, and a list of neuraminidase reviews, with peer review comments and responses relevant to review A159,[14] is available at www.bmj.com/content/suppl/2014/04/09/bmj.g2545.DC1/jeft017746.ww8_default.pdf.

Before receiving the full reports, we resumed reviewing the remainder of the material that we had received in 2011. This mainly consisted of module 2s (Roche terminology for pre-study documents). Module 2s contained the information that was originally unavailable to us from Roche: study protocols with their amendments, randomisation lists, blank CRFs, certificates of analysis describing appearance and content of active and control capsules and, at times, SAPs. CRFs are containers for the rawest form of recorded data at the individual participant level.

While designing the tool to capture trial methods and assess bias, we also considered whether or not access to module 2 information (and later the full study reports) changed our perception of the trial and specifically our 'risk-of-bias' assessment. We found that access to what are supposed to be full study reports should provide clarity and remove the rationale for 'unclear' risk-of-bias judgements, and ideally remove the concept of risk leaving just 'bias', at least for certain study design elements, such as attrition bias. Either a design element introduces bias or it does not. In the case of the 15 full oseltamivir CSRs we reviewed when constructing our tool, only one report contained a protocol that predated the beginning of participant enrolment, only two reports had SAPs that clearly predated participants' enrolment and three reports had clearly dated protocol amendments. No CSR reported a clear date of unblinding.

During the latter part of 2013, we received from the manufacturers tens of thousands of pages of full CSRs for both programmes combined.

These events form the basis for this review.

Aims and objectives

The main goals of the reviews included in this report were to:

1. describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all CSRs of published and unpublished randomised, placebo-controlled trials and regulatory comments
2. determine the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza.

Research questions

The research questions addressed in this report are as follows:

- What are the potential benefits and harms of NIs for the prevention and treatment of influenza in adults and children?
- Does influenza virus-specific mechanism of action proposed by the producers fit the clinical evidence?
- Does treatment with oseltamivir confer protection against mortality in patients with 2009A/H1N1 influenza?

Chapter 2 Neuraminidase inhibitors for preventing and treating influenza in adults and children

Abstract

Background
Neuraminidase inhibitors are stockpiled and recommended by public health agencies for treating and preventing seasonal and pandemic influenza. They are used clinically worldwide.

Objective
To describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all CSRs of published and unpublished randomised, placebo-controlled trials and regulatory comments.

Search methods
We searched trial registries, electronic databases (to 22 July 2013) and regulatory archives, and corresponded with manufacturers to identify all trials. We also requested CSRs. We focused on the primary data sources of manufacturers but we checked that there were no published RCTs from non-manufacturer sources by running electronic searches in the following databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE (via Ovid), EMBASE, EMBASE.com, PubMed (not MEDLINE), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED) and Health Economic Evaluations Database (HEED).

Selection criteria
Randomised, placebo-controlled trials on adults and children with confirmed or suspected exposure to naturally occurring influenza.

Data collection and analysis
We extracted CSRs and assessed risk of bias using purpose-built instruments. We analysed the effects of zanamivir and oseltamivir on time to first alleviation of symptoms, influenza outcomes, complications, hospitalisations and adverse events in the intention-to-treat (ITT) population. All trials were sponsored by the manufacturers.

Main results
We obtained 107 CSRs from the EMA, GSK and Roche. We accessed comments by the FDA, EMA and Japanese regulator. We included 53 trials in stage 1 (a judgement of appropriate study design) and 46 in stage 2 (formal analysis), including 20 oseltamivir (9623 participants) and 26 zanamivir trials (14,628 participants). Inadequate reporting put most of the zanamivir studies and half of the oseltamivir studies at a high risk of selection bias. There were inadequate measures in place to protect 11 studies of oseltamivir from performance bias due to non-identical presentation of placebo. Attrition bias was high across the oseltamivir studies and there was also evidence of selective reporting for both the zanamivir and oseltamivir studies. The placebo interventions in both sets of trials may have contained active substances.

Time to first symptom alleviation
For the treatment of adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours [95% confidence interval (CI) 8.4 to 25.1 hours; $p < 0.0001$]. This represents a reduction in the time to first alleviation of symptoms from 7 to 6.3 days. There was no effect in asthmatic children, but in otherwise healthy children there was a reduction by a mean difference (MD) of 29 hours (95% CI 12 to 47 hours; $p = 0.001$). Zanamivir reduced the time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days; $p < 0.00001$), equating to a reduction in the mean duration of symptoms from 6.6 to

6.0 days. The effect in children was not significant. In subgroup analysis we found no evidence of a difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza-infected and non-influenza-infected subgroups ($p = 0.53$).

Hospitalisations

Treatment of adults with oseltamivir had no significant effect on hospitalisations [risk difference (RD) 0.15%, 95% CI –0.78% to 0.91%]. There was also no significant effect in children or in prophylaxis. Zanamivir hospitalisation data were unreported.

Serious influenza complications or those leading to study withdrawal

In adult treatment trials, oseltamivir did not significantly reduce those complications classified as serious or those that led to study withdrawal (RD 0.07%, 95% CI –0.78% to 0.44%), or in child treatment trials; neither did zanamivir in the treatment of adults or in prophylaxis. There were insufficient events to compare this outcome for oseltamivir in prophylaxis or zanamivir in the treatment of children.

Pneumonia

Oseltamivir significantly reduced self-reported, investigator-mediated, unverified pneumonia [RD 1.00%, 95% CI 0.22% to 1.49%, number needed to treat to benefit (NNTB) 100, 95% CI 67 to 451] in the treated population. The effect was not significant in the five trials that used a more detailed diagnostic form for pneumonia. There were no definitions of pneumonia (or other complications) in any trial. No oseltamivir treatment studies reported effects on radiologically confirmed pneumonia. There was no significant effect on unverified pneumonia in children. There was no significant effect of zanamivir on either self-reported or radiologically confirmed pneumonia. In prophylaxis, zanamivir significantly reduced the risk of self-reported, investigator-mediated, unverified pneumonia in adults (RD 0.32%, 95% CI 0.09% to 0.41%; NNTB 311, 95% CI 244 to 1086) but not oseltamivir.

Bronchitis, sinusitis and otitis media

Zanamivir significantly reduced the risk of bronchitis in adult treatment trials (RD 1.80%, 95% CI 0.65% to 2.80%; NNTB 56, 95% CI 36 to 155), but not oseltamivir. Neither NI significantly reduced the risk of otitis media and sinusitis in both adults and children.

Harms of treatment

Oseltamivir in the treatment of adults increased the risk of nausea [RD 3.66%, 95% CI 0.90% to 7.39%; number needed to treat to harm (NNTH) 28, 95% CI 14 to 112] and vomiting (RD 4.56%, 95% CI 2.39% to 7.58%; NNTH 22, 95% CI 14 to 42). The proportion of participants with fourfold increases in antibody titre was significantly lower in the treated group than in the control group (RR 0.92, 95% CI 0.86 to 0.97; I^2 statistic = 0%) (5% absolute difference between arms). Oseltamivir significantly decreased the risk of diarrhoea (RD 2.33%, 95% CI 0.14% to 3.81%; NNTB 43, 95% CI 27 to 709) and cardiac events (RD 0.68%, 95% CI 0.04% to 1.0%; NNTB 148, 95% CI 101 to 2509) compared with placebo during the on-treatment period. There was a dose–response effect on psychiatric events in the two oseltamivir 'pivotal' treatment trials: WV15670 and WV15671, at 150 mg (standard dose) and 300 mg daily (high dose) ($p = 0.038$). In the treatment of children, oseltamivir induced vomiting (RD 5.34%, 95% CI 1.75% to 10.29%; NNTH 19, 95% CI 10 to 57). There was a significantly lower proportion of children on oseltamivir with a fourfold increase in antibodies (RR 0.90, 95% CI 0.80 to 1.00; I^2 statistic = 0%).

Prophylaxis

In prophylaxis trials, oseltamivir and zanamivir reduced the risk of symptomatic influenza in individuals (oseltamivir RD 3.05%, 95% CI 1.83% to 3.88%; NNTB 33, 95% CI 26 to 55; zanamivir RD 1.98%, 95% CI 0.98% to 2.54%; NNTB 51, 95% CI 40 to 103) and in households (oseltamivir RD 13.6%, 95% CI 9.52% to 15.47%; NNTB 7, 95% CI 6 to 11; zanamivir RD 14.84%, 95% CI 12.18% to 16.55%; NNTB 7, 95% CI 7 to 9). There was no significant effect on asymptomatic influenza (oseltamivir, RR 1.14, 95% CI 0.39 to 3.33; zanamivir RR 0.97, 95% CI 0.76 to 1.24). Non-influenza, influenza-like illness (ILI) could not be assessed as a result of data not being fully reported. In oseltamivir prophylaxis studies,

psychiatric adverse events were increased in the combined on- and off-treatment periods (RD 1.06%, 95% CI 0.07% to 2.76%; NNTH 94, 95% CI 36 to 1538) in the study treatment population. While on treatment, oseltamivir increased the risk of headaches (RD 3.15%, 95% CI 0.88% to 5.78%; NNTH 32, 95% CI 18 to 115), renal events (RD 0.67%, 95% CI –0.01% to 2.93%; NNTH 150, NNTH 35 to NNTB > 1000) and nausea (RD 4.15%, 95% CI 0.86% to 9.51%; NNTH 25, 95% CI 11 to 116).

Authors' conclusions

Oseltamivir and zanamivir have small, non-specific effects on reducing the time to alleviation of influenza symptoms in adults, but not in asthmatic children. Using either drug as prophylaxis reduces the risk of developing symptomatic influenza. Treatment trials with oseltamivir or zanamivir do not settle the question of whether or not the complications of influenza (such as pneumonia) are reduced, because of a lack of diagnostic definitions. The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children. The lower bioavailability may explain the lower toxicity of zanamivir compared with oseltamivir. The balance between benefits and harms should be considered when making decisions about use of both NIs for either the prophylaxis or treatment of influenza. The influenza virus-specific mechanism of action proposed by the manufacturers does not match the observed clinical evidence.

Background

This review (known as A159) reports our work using unpublished CSRs (see *Appendix 1, Glossary*) and regulatory documents containing comments and reviews to evaluate the safety and efficacy of NIs. We have called the body of clinical studies and regulatory comments 'regulatory information'. For the history and evolution of the review, see *Appendix 1*.

Description of the condition

Influenza is mostly a mild, self-limiting infection of the upper airways with local symptoms, including sniffles, nasal discharge, dry cough and sore throat, and systemic symptoms such as fever, headache, aches and pains, malaise and tiredness.

Occasionally, patients with influenza develop complications such as pneumonia, otitis media and dehydration or encephalopathy with or without liver failure, which may be due to the effects of the influenza virus itself or associated secondary bacterial infections and/or adverse effects of drugs such as antipyretics [including salicylates and other non-steroidal anti-inflammatory drugs (NSAIDs)].[15]

Influenza is not clinically distinguishable from ILI.[16] Epidemic influenza in humans is caused by influenza A and B viruses. Currently, influenza A/H1N1, influenza A/H3N2 and influenza B cause most influenza infections worldwide.[12]

Description of the intervention

Neuraminidase inhibitors comprise inhaled zanamivir (Relenza®, GSK), oral oseltamivir (Tamiflu®, Gilead Sciences and F. Hoffman-La Roche), parenteral peramivir (Rapivab®, BioCryst Ltd), inhaled laninamivir (Inavir®, Daiichi Sankyo Co. Ltd)[17] and others still under development.[18] The use of NIs has increased dramatically since the outbreak of A/H1N1 in April 2009, partly because of the rise in amantadine (Symmetrel®, Endo Pharmaceuticals Inc.)/rimantadine (Flumadine®, Forest Pharmaceuticals Inc.) resistance and, in the early stages of the outbreak, the lack of a vaccine, which meant that NIs became a widespread public health intervention. WHO had previously encouraged member states to stockpile and gain experience of using NIs.[19–21]

How the intervention might work

Although NIs may reduce the ability of the virus to penetrate the mucus in the very early stage of infection,[6,22–24] their main mechanism of action is thought to lie in their ability to inhibit influenza viruses from exiting host cells.[23,25] The manufacturers state that oseltamivir does not prevent infection or affect antibody production,[26] but it reduces symptom duration probably by reducing viral load, spread and release of cytokines,[8,27] diminishing the chance of complications and interrupting person–person viral spread. Oseltamivir phosphate (Tamiflu) is the prodrug of oseltamivir carboxylate, the effective form. Oseltamivir phosphate dissociates in the gastrointestinal tract to form oseltamivir, which is absorbed and metabolised into oseltamivir carboxylate by hepatic carboxylesterase. Oseltamivir may have a central depressant action[15] and may also inhibit human sialidase,[28] causing abnormal behaviour. Inhaled zanamivir reaches a far lower plasma concentration than its intravenous administration.[29]

Any treatment that reduces the complications of influenza (e.g. pneumonia) and the excretion of the virus from infected people might be a useful public health measure to contain an epidemic by limiting the impact and spread of the virus. In addition to symptomatic treatment, prophylactic use for interrupting the spread of disease has informed pandemic planning over the past decade.

Why it is important to do this review

There are three major reasons for conducting this review, in addition to questions of efficacy associated with the clinical use of NIs for influenza:

1. Influenza antivirals are a commonly used and stockpiled drug against past and future pandemics on the basis of international and national recommendations. These recommendations are based on the claimed and assumed ability of the drug to reduce complications and transmission.[2,3] In theory, containing the spread of influenza allows time for an organised response with longer-term interventions (such as vaccines), which take time to produce.[3]
2. The risk of reporting bias and publication bias leads to uncertainty about the effects of NIs and the results of previous Cochrane reviews of NIs in adults[6,10,30,31] and children.[32]
3. Oseltamivir is now on the list of WHO essential drugs.[33,34]

Process

Review A159 is an amalgamation of two long-standing Cochrane reviews on the effects of NIs for influenza in healthy adults[14] (also published in the BMJ[31]) and children,[35] and it is based on the assessment of trials through their CSRs and other regulatory information; a decision we made after finding substantial reporting bias in the journal publications of the relevant trials.

For the full rationale for this process, see *Appendix 1*.

Examples of discrepancies and reporting bias

We identified that 60% (3145/5267) of patient data from randomised, placebo-controlled, Phase III treatment trials of oseltamivir have never been published. This includes M76001,[36] the biggest treatment trial ever undertaken on oseltamivir (with just over 1400 people of all ages). Exclusion of unpublished data changed our previous findings regarding the ability of oseltamivir to reduce the complications of influenza.[8,31] In some cases, mistakes in the attribution of adverse events were discovered only through matching summary tables with individual participant listings.[37–39]

A modified approach

We have modified the routine Cochrane processes to improve our previous methods, which we now consider to be inadequate. To resolve inconsistencies and under-reporting, we changed our approach by no longer including trial data as reported in papers published in biomedical journals. Instead, we treated CSRs as our basic unit of analysis. CSRs are often sent to national drug regulators, such as the FDA and the EMA (formerly the European Agency for the Evaluation of Medicinal Products), which require far more stringent standards for completeness and accuracy of reporting than biomedical journals. Journal articles

can be regarded as a very succinct synthesis of a CSR. In addition to seeking CSRs, we decided to read and review regulatory documentation. The FDA in particular (and the EMA to a far lesser extent) makes many of its scientific reviews available on its website. Unlike Cochrane review authors, regulators can have access to the whole data set and their comments can provide useful insight, helping to achieve a better understanding of trial programmes.

Clinical study reports generally remain hidden from public view and are not readily available for wider scientific scrutiny, despite the wealth of information that they contain for those willing and able to spend the time reading them and despite calls to make all relevant trial data public,[11,40] as well as the known problems with reporting biases.[41,42]

Implications

This modified approach to a Cochrane review aims to provide patients, clinicians and policy-makers with the most transparent and independent information possible about NIs for influenza. In addition, it should contribute to improving a European regulatory and pharmacovigilance legal framework, which commentators consider weak.[40,43] We believe that as NIs have become public health drugs, recommended and stockpiled globally, independent scrutiny of all of the evidence relating to harms and effects on complications is necessary to provide patients, policy-makers and physicians with a complete and unbiased view of their risks and benefits.

Implication for A/H1N1 (2009) influenza

In response to our 2010 review,[14,31] some have argued that its findings cannot be applied to the 2009 A/H1N1, suggesting that it is a new virus and that, we thus need new evidence.[44–48] Novel A/H1N1 is a new strain of a subtype that has been circulating since 1977, but it also resembles the A/H1N1 strain that has been circulating since before 1957[49] or before the 1918 pandemic.[50] Influenza subtype A/H1N1 was indeed circulating at the time when the clinical trials, included in our previous reviews, were recruiting. In addition, oseltamivir and zanamivir were approved by regulators worldwide for the treatment and prevention of influenza types A and B, not specific subtypes or strains of influenza A and B. The expectation of regulatory approval is thus that the effects of these drugs demonstrated in clinical trials will apply to future strains of influenza A and B. Use of these drugs during the pandemic was not off-label. It was approved use on the assumption that the clinical trial evidence underpinning regulatory approval applied to novel A/H1N1. We reviewed the clinical trial evidence with the expectation that our results, similar to regulators, will apply to all influenza viruses.

Wider implications

The modified approach in this Cochrane review developed from the realisation that prior methods used to review NIs were inadequate. There is little reason to think that the lessons learned are limited to these particular drugs.[40,42,51–53] On this basis, our independent scrutiny, using all possible trial information, may inform both the wider debate on the adequacy of existing regulatory frameworks in the adoption of new drugs and the question of whether or not other systematic reviews should move to this new, more rigorous, approach, which focuses on trial programmes rather than single trials[54,55] (see *Appendix 1*, *Glossary*). Although there is substantial evidence for the effects of reporting bias in estimates of effectiveness, less is known of its impact on the evidence of harms.[56] We decided to quantify the additional resources required to follow our modified methodological approach to assess the feasibility of other systematic reviews proceeding in a similar fashion.

Objective

To describe the potential benefits and harms of NIs for influenza in all age groups by reviewing all CSRs of published and unpublished randomised, placebo-controlled trials and regulatory comments.

Methods

Criteria for considering studies for this review

Types of studies

We included evidence from RCTs testing the effects of NIs for prophylaxis, post-exposure prophylaxis (PEP) and treatment of influenza. Prophylaxis is the mode of use of NIs when there is expectation of possible near-future exposure to influenza.

Post-exposure prophylaxis is the use of NIs following probable exposure to influenza but before symptoms develop. Treatment is the use of NIs in persons showing probable signs of influenza.

Owing to discrepancies between published and unpublished reports of the same trials, we included only those trials for which we had unabridged CSRs (e.g. with consecutively numbered pages), even though they may be parts of CSRs (i.e. module 1 only) and information on reports of trials that were considered 'pivotal' (i.e. first- or second-line evidence to regulators in support of the registration application).

Types of participants

We included previously healthy people (children and adults). 'Previously healthy' includes people with chronic illness (such as asthma, diabetes, hypertension), but excludes people with illnesses with more significant effects on the immune system (such as malignancy or human immunodeficiency virus infection). We included only trials on people who were exposed to naturally occurring influenza with or without symptoms. We targeted the ITT and safety populations, as our prior review discovered compelling evidence that the intention-to-treat-influenza-infected (ITTI) subpopulation – the subpopulation deemed to be influenza-infected – was not balanced between treatment groups in the Roche oseltamivir trials. In addition, estimates from the ITT population will be more generalisable to clinical practice, where routine testing for influenza is not common in many countries (and even where it is used is of variable accuracy).

Types of interventions

Neuraminidase inhibitors administered by any route compared with placebo during the period in which medication was assumed and during the follow-up (on- and off-treatment) periods.

Types of outcome measures

Primary outcomes

Primary outcome measures for treatment studies

1. Symptom relief.
2. Hospitalisation and complications.
3. Harms.

Primary outcome measures for prophylaxis studies

1. Influenza (symptomatic and asymptomatic, always with laboratory confirmation) and ILI.
2. Hospitalisation and complications.
3. Interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts).
4. Harms.

Secondary outcomes

Secondary outcome measures for treatment studies

1. Symptom relapse after finishing treatment.
2. Drug resistance.
3. Viral excretion.
4. Mortality.

Secondary outcome measures for prophylaxis studies

1. Drug resistance.
2. Viral excretion.
3. Mortality.

Although overall symptom reduction is well documented, our interest was particularly focused on complications and adverse events, as this is where evidence is currently scarce or inconclusive.[31,32] Our preliminary examination of some regulatory documents and some published versions of the studies had identified that some symptoms and sequelae of influenza (such as pneumonia) had been classified as either a 'complication of influenza' or as an 'adverse event of the treatment', or both. This is somewhat confusing and we intended to analyse 'compliharms' (see *Appendix 1*, *Glossary*) irrespective of the classification as a 'complication of influenza' or as an 'adverse event of the treatment' (see *Appendix 2*) in oseltamivir trials. Complications of particular interest included pneumonia, bronchitis, otitis media and sinusitis, as these were the secondary illnesses often collected in the Roche oseltamivir trials and we agreed that these events are clinically important. Initially, we constructed a table to illustrate the design methodology that was used for each complication by study (*Table 1*). The table included the following variables: definition of which events are termed complications; where complications are first defined in the CSR; diagnosis method; and availability of data. We then stratified our analysis by method of diagnosis with three possible criteria: (1) laboratory-confirmed diagnosis (e.g. based on radiologically or microbiologically confirmed evidence of infection); (2) clinical diagnosis without laboratory confirmation (diagnosed by a doctor after a clinical examination); and (3) other type of diagnosis, such as self-reported by patient. We conducted analysis of any complication (pneumonia, bronchitis, otitis media and sinusitis) that was classified as serious or led to study withdrawal.

In all cases of influenza complications reporting (pneumonia, bronchitis, sinusitis, otitis media) there is a variable degree of participant self-reporting, of investigator mediation (e.g. in writing down the details in the CRF) and lack of verification with investigations, such as culture or imaging. The 'self-reported, investigator-mediated, unverified' title is relevant to all complications but for brevity we use it as sparingly as possible.

For harms, we were limited by the frequency of occurrence of the adverse events collected in the trials. Consequently, we meta-analysed (1) all serious adverse events; (2) all adverse events leading to study withdrawal; (3) all withdrawals; (4) all adverse events within a CSR's defined body system; and (5) a small group of common adverse events as defined in the FDA drug label for oseltamivir. There were too few events to meta-analyse: (1) deaths; (2) serious adverse events by body system; and (3) any events that had an overall incidence of $< 0.5\%$. We did not meta-analyse outcomes with fewer than 10 events in total. We conducted analyses separately for on-treatment and off-treatment periods. However, in two cases for which (on-treatment) treatment effects were borderline statistically significant (prophylaxis with oseltamivir: renal body system on-treatment and psychiatric body system on-treatment), we conducted additional analysis combining on- and off-treatment periods to maximise statistical power. We conducted dose–response harms analysis for two treatment trials[8,58] combined and one prophylaxis study,[59] as these trials investigated the active agent at multiple doses. These studies[8,58,59] included standard-dose and

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
M76001[36]	1167	Yes/no answer to question: 'Is this event a secondary illness related to influenza?' Secondary illness is defined: sinusitis, otitis, bronchitis, pneumonia plus other chest infections that are not diagnosed as bronchitis and/or pneumonia	Investigator	In form for 'Adverse events or intercurrent illness'	No	Px
NV16871[57]	361, 389	Form states: Have there been any changes in the patient's health, including any new conditions or worsening of existing conditions since day 1 (please include secondary illnesses)? Yes/no: If 'Yes', please record the details on the 'Adverse events or secondary illness' form in the Additional Forms section of the CRF on p. 30.0. All serious adverse events must be reported within 1 working day of occurrence to Roche Page 30.0 of CRF (PDF p. 389) defines secondary illnesses as sinusitis, otitis media, bronchitis and pneumonia, and asks additional questions such as relationship to test drug and outcome, and leaves space for investigator's comments on the adverse event	Investigator	Secondary illness not listed as efficacy outcomes Recording of secondary illnesses was to occur in a form titled 'Adverse event or secondary illness'	No	Px

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15670[8]	732, 754, 791, 832	CRF (PDF p. 732) states: secondary illness reminder: has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? Yes [ ] Complete secondary illness page (not the adverse event page) No [ ] Secondary illness page CRF (PDF p. 754) requests information on date of onset, date resolved, whether or not treatment was given and, if so, what treatment or medical procedures, total daily dose, and start/end date of treatment or medical procedure In addition, participants could fill in information related to a secondary illness in their diary card in the free-text box called 'Notes', which prompts participants: 'Please can you record below any extra information about your flu which may be of interest to us, (for example: did your flu symptoms re-occur, and if so when?), and have you taken any other treatments? If so please record the treatment name and the dates you took it.' (PDF p. 791)	Participant, mediated through investigator	For investigators, on 'Secondary illness' form For participants, on 'Notes' section of diary card	No	

continued

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials (*continued*)

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15671[58]	740, 889, 1018	CRF (PDF p. 740) states: Secondary illness reminder: Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? Yes [ ] Complete secondary illness page (not the adverse event page) No [ ] Secondary illness page CRF (PDF p. 889) requests information on date of onset, date resolved, whether or not treatment was given and, if so, what treatment or medical procedures, total daily dose and start/end date of treatment or medical procedure Secondary illnesses are listed as sinusitis, otitis, bronchitis, pneumonia and other chest infections that are not diagnosed as bronchitis and/or pneumonia	Participant, mediated through investigator	Mentioned in module 1 and RAP, as tertiary outcomes not mentioned in protocol	No	Px

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
		In addition, participants could fill in information related to a secondary illness in their diary card in the free-text box called 'Notes', which prompts participants: 'Please can you record below any extra information about your flu which may be of interest to us, (for example: did your flu symptoms re-occur, and if so when?), and have you taken any other treatments? If so please record the treatment name and the dates you took it.' (PDF p. 1018)				
WV15673/ WV15697[59]	From 483	No mention of pneumonia, secondary illness, complications in the CRFs	Unclear	Secondary illnesses not listed in protocol as end points. They are listed as safety end points in the RAP, which states that 'pre-defined' secondary illnesses were 'sinusitis, otitis, bronchitis, pneumonia, and other chest infections that are not diagnosed as bronchitis and/or pneumonia, plus recurrence of symptoms from the diary card once alleviation had occurred.' (PDF p. 479)		

continued

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials (*continued*)

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15707[60]	From 98	Page 117: secondary illness reminder: Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? Yes [ ] Complete secondary illness page (not the adverse event page) No [ ] Page 131: diagnostic procedures 1. Were there any diagnostic procedures or tests carried out since day 1 as a result of influenza or secondary illness that were not scheduled as part of protocol? Yes Type of diagnostic procedure or test: 1. Chest X-rays 2. ECG 3. Bacterial culture 4. Bronchoscopy 5. Pulmonary function test	Participant, mediated through investigator	Mentioned in RAP as tertiary end points, pp. 57–8	Yes	Px

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
		6. Viral culture (other than influenza) 7. Blood tests (other than antibody sample) 8 Other specify No Secondary illness p. CRF (PDF p. 158) requests information on date of onset, date resolved, whether or not treatment was given and, if so, what treatment or medical procedures, total daily dose and start/end date of treatment or medical procedure				
WV15708[61]	From 460	Secondary illness reminder, p. 474: Has the patient reported any new episodes of sinusitis, otitis, bronchitis, other chest infection or pneumonia since screening? Yes [ ] . . . Complete adverse event page No [ ] 'Adverse events' CRF collected data on date of onset, initial intensity, test drug adjustment, whether or not treatment was given (if so, what), most extreme intensity, relationship to test drug, outcome, whether or not it led to hospitalisation and a free-text line for recording 'Comments on AE' (e.g. PDF p. 479)	Participant, mediated through investigator	Secondary illness not mentioned in protocol	No	Px

continued

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials (*continued*)

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15730[62]	From 340	Secondary illness reminder: Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline? Yes [ ] . . . Complete secondary illness page (not the adverse event page) No [ ] The secondary illness page is descriptive of dates and Px	Participant, mediated through investigator	Listed as tertiary end points in RAP, p. 297	No	Px
WV15758[63]	From 637	Has the patient reported any new adverse events or symptoms (including intercurrent illnesses and secondary illnesses)? Yes [ ] record in the adverse events/ intercurrent illness section of the case No [ ] report form Diagnostic confirmation of otitis media from p. 648 onwards	Participant, mediated through investigator	Listed as secondary illnesses in core report modules 1 and 2, p. 36	Yes	Px

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15759/ WV15871[64]	From 665	Has the subject reported any adverse events including secondary and intercurrent illnesses?	Participant, mediated through investigator	Secondary illnesses not mentioned in protocol, but secondary outcome in core report Note: worth looking at comparisons 1.49 to 1.51 in RM5. No effect but in bronchitis this study has a more conservative effect than NV16871, which has no definitions and no diagnostics	Yes	Px
WV15799[65]	From 642	Secondary illness defined as in M76001.[36] There is a generic physical examination form at p. 704, including 'lungs' normal/abnormal specify . . . . . At p. 709, has the patient reported any new AE, including intercurrent or secondary illnesses? Yes/no. If yes, record the adverse events/intercurrent illness section of the CRF (noted at p. 746 on the back of the CRF) with full history, physical examination and diagnostic work up questions for BRON ± PNUM ± LRTI ± SIN ± OM including questions about CXR, MRI, sputum, etc.	Investigator	Proportion of contacts who are classified as having a secondary illness subsequent to a confirmed episode of influenza listed as tertiary end points	Yes	Px

continued

TABLE 1 Blank CRFs' data capture for secondary illnesses in oseltamivir trials (*continued*)

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
WV15812/ WV15872[66]	From 285	Has the patient reported any new adverse events or symptoms (including intercurrent illnesses and secondary illnesses)? Yes [ ] record in the adverse events/ intercurrent illness section of the case No [ ] report form At pp. 450–74 is **diagnosis of secondary illness** page, which is very similar to the one at serial 10 Exhaustive list of diagnostic procedures	Participant mediated through investigator	Listed as secondary tertiary in protocol at p. 252	Yes	Px
WV15819/ WV15978/ WV15876[67]	From 412	Page 437 (adverse event reminder): Has the patient reported any new adverse events or symptoms (including intercurrent illnesses)? Yes [ ] record in the adverse events/ intercurrent illness section of the case No [ ] report form In CRF p. 447 and p. 443, usual secondary illness reminder	Participant, mediated through investigator	Secondary illness listed as secondary (required antibiotics) and tertiary outcomes in core report and as an addition in protocol amendment at p. 21	Yes	Px

Study	Where in CRF (PDF p. #)	Data captured	Person reporting (participant/investigator)	Where reported	Specific field for recording confirmatory assessment (e.g. CXR)	Confirmation (including Px)
		From p. 471, **diagnosis of secondary illness. This is a one-page list of diagnostics similar to that at serial 10.** The question is: 'Were there any diagnostic procedures or tests carried out since day 1 as a result of influenza or secondary illness that were not scheduled as part of protocol?' If yes, list per serial 10 From p. 486 is a list of diagnostic tests				
WV15825[68]	From 389	There is a usual note: please go to diagnosis of secondary illness at back of CRF, p. 487 Is this event a secondary illness related to influenza? **Diagnosis of secondary illness** From pp. 510–40 with exhaustive list of diagnostics as per serial 10	Participant, mediated through investigator	Secondary illness listed as secondary outcomes in protocol p. 346 Secondary illnesses recorded on 'Adverse events' CRF	Yes	Px
WV16277[69]	From 415	Not found	Not found	Secondary illness not listed as efficacy outcomes		

AE, adverse event; BRON, bronchitis; CXR, chest radiography; ECG, electrocardiography; LRTI, lower respiratory tract infection; MRI, magnetic resonance imaging; OM, otitis media; PNUM, pneumonia; Px, prognosis; RAP, reporting analysis plan; SIN, sinusitis.

high-dose oseltamivir arms. For these analyses we used logistic regression, adjusting for study effects if appropriate (i.e. for the two treatment trials[8,58]) and testing for trend using a likelihood ratio test. We tested the hypothesis that increased dose of drug leads to increased incidence of adverse effects.

Search methods for identification of studies

To identify trials in the manufacturer-funded clinical trial programmes for NIs, as well as non-manufacturer-funded clinical trials of NIs, we used a variety of methods that were applied to a variety of sources from the literature, manufacturers and regulatory bodies. These methods, as well as our methodology for identifying and obtaining relevant CSRs, are detailed in *Appendices 1, 4* and *5*.

Electronic searches

We used electronic searches to identify trials that were not identified by the methods outlined in *Appendix 1*, particularly for non-manufacturer-funded clinical trials (see *Appendix 3* for details). For the 2012 review, we updated our searches of the electronic databases of published studies that were previously carried out for the Cochrane reviews on NIs in children[35] and healthy adults,[14] and then updated the searches again on 22 July 2013.

Searching other resources

For the description of our searches for regulatory information (FDA, EMA, Roche, GSK, the Japanese Pharmaceuticals and Medical Devices Agency), see *Appendix 4*.

Data collection and analysis

Collection and inventory of the evidence base was facilitated by the tools that were specifically developed for the review (see *Appendix 5*). The overall risk of bias is presented graphically in *Figure 1* and summarised in *Figure 2*.

Selection of studies

For this 2013 review, two authors (PD and TJ) reapplied the inclusion criteria for the oseltamivir CSRs and resolved disagreements by discussion. Two review authors (ES and IO) applied the criteria for the zanamivir CSRs, whereas one review author (CH) arbitrated.

For the procedures followed in the 2012 review, see *Appendix 7*.

Data extraction and management

The sizeable quantity of available data led us to subdivide the extraction, appraisal and analysis of the data into a two-stage exercise. In stage 1 we assessed the reliability and completeness of the identified trial

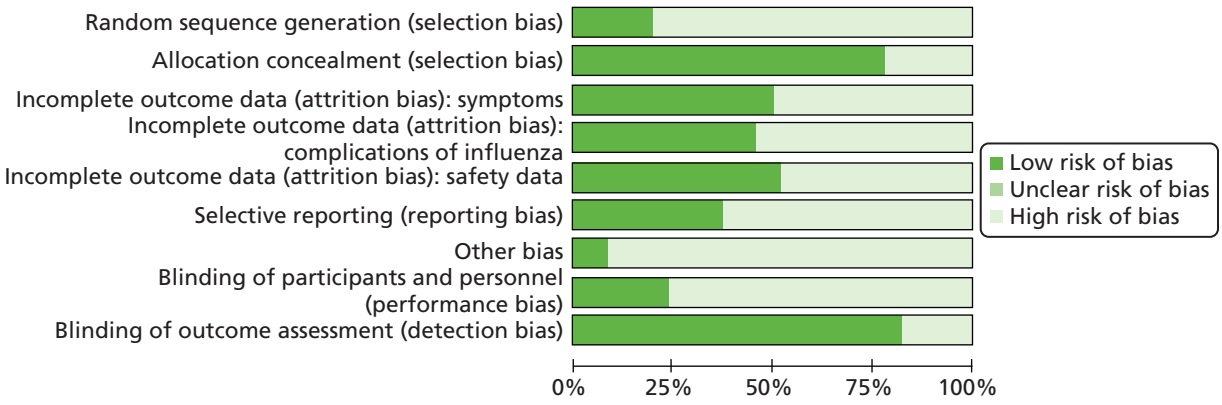


FIGURE 1 Risk-of-bias graph: review of authors' judgements about each risk-of-bias item, presented as percentages across all included studies. 'Other bias' includes potentially active placebos.

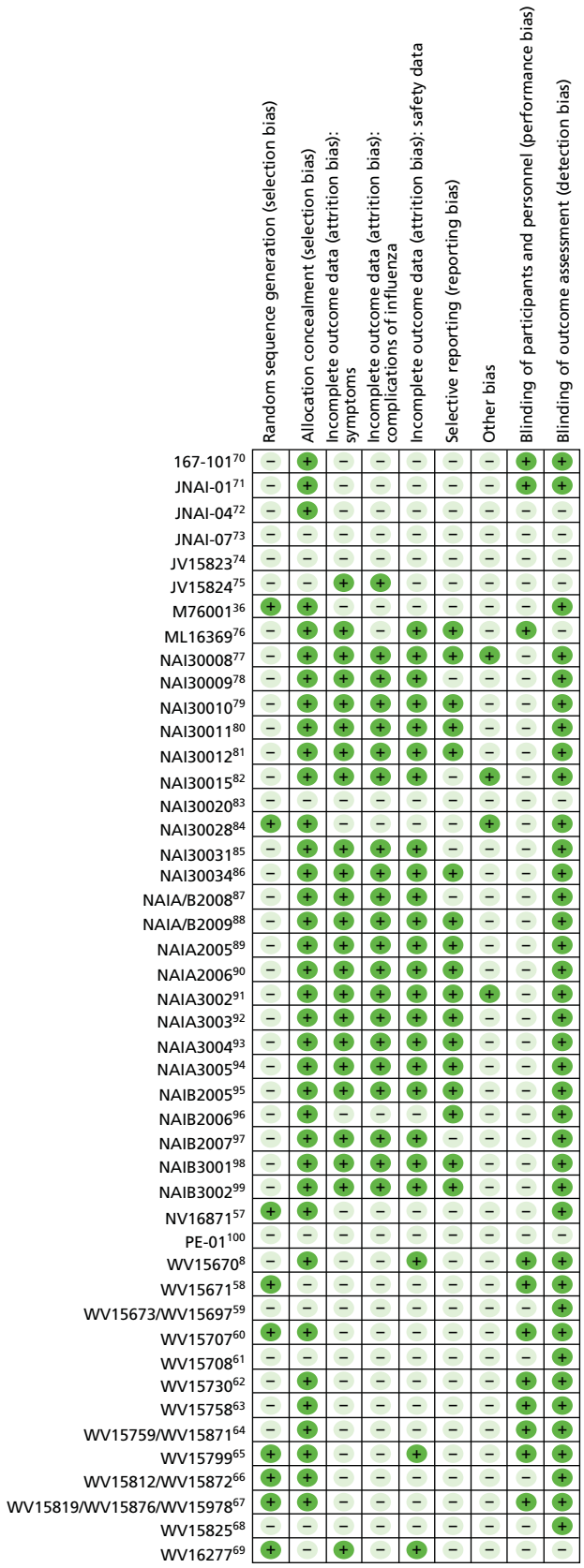


FIGURE 2 Risk-of-bias summary: review of authors' judgements about each risk-of-bias item for each included study. 'Other bias' includes potentially active placebos. +, low risk of bias; –, high risk of bias.

data. We decided to include in stage 2 of the review (full analysis following standard Cochrane methods) only data that satisfied the following three criteria:

1. *Completeness* CSRs/unpublished reports include both identifiable CONSORT (Consolidated Standards of Reporting Trials) statement-specified methods to enable replication of the study. Identifiable CONSORT statement-specified results (primary outcomes, tables, appendices) must be available.
2. *Internal consistency* All parts (e.g. denominators) of the same CSRs/unpublished report are broadly consistent.
3. *External consistency* Consistency of data as reported in regulatory documents, other versions of the same CSRs/unpublished reports and other references, to be established by cross-checking.

This was a different approach to that used in the previous version of the current review,[9] as we had only incomplete information at that time and applied only the second and third criteria.

Stage 1

For details of the use of the CONSORT-based extraction template and the assessment for stage 1 inclusion in the A159 review,[9] see *Appendix 5*. In this review, assessment for inclusion in stage 1 was part of the inclusion procedure.

Stage 2

In stage 2, one review author extracted data and a second review author checked it. We extracted data on to standard forms, checked and recorded it.

Use of regulatory information

We used regulatory information to assess the possible correlation between citation frequency of oseltamivir treatment trials in the FDA regulatory documents and trial size.

Post-protocol analyses

After publication of the A159 protocol in December 2010, but before validation of our CONSORT-based extractions in the spring of 2011, we decided to carry out analyses (which we called post-protocol analyses) to test five null hypotheses that we had formulated while reading, summarising and reconstructing the CSRs. The hypotheses originated from our observations of discrepancies and other unexpected observations in the CSRs' data, and were informed by reading regulatory information. *Appendix 8* reports the rationale, methods to formulate and test, and the results of the hypotheses.

The hypotheses reflect the uncertainty prevailing in the evidence base at a time when full CSRs were not available for all studies.

Assessment of risk of bias in included studies

Previous studies comparing regulatory with published or internal company sources of evidence have reported a variety of different biases that affect medical knowledge.[41,42,56,101] We will report in detail elsewhere our comments on using the Cochrane risk-of-bias tool[102] to appraise CSRs and for trial programmes, and our efforts to construct an instrument for assessing risk of bias in complete CSRs. A full description of the methods used to quantify biases will be published in another paper.

Measures of treatment effect

To estimate treatment effects we first calculated the risk ratios (RRs) and used the average (mean) control event rate and the pooled RRs reported in the figures to calculate the RDs. For consistency, we adopted this method for both the 'Summary of findings' tables and for the RDs reported in the text. For the analysis we chose to report the RRs, as they are more consistent across the studies, and we have reported the heterogeneity for the pooled RR. We reinterpreted the results using the RD, as this result is applicable to clinical decision-making. We calculated MDs for time to first alleviation of symptoms. For time to first alleviation of symptoms we also estimated the treatment effect as the percentage reduction in the average time to first alleviation of symptoms in the placebo group. Most zanamivir CSRs stated treatment effects only in terms of medians in each treatment

group, as well as *p*-values from a hypothesis test comparing the time-to-event distributions. These data are insufficient for conducting a meta-analysis. However, often sufficient time-to-event data were reported to allow us to estimate restricted means and standard deviations. Restricted means are based on the maximum time reported where alleviation occurred. There were some patients for whom alleviation was censored at the maximum follow-up time; therefore, restricted means are underestimates of the true means. However, the proportion of patients who were censored was generally low and similar in both treatment arms, hence this limitation is unlikely to have led to bias. The length of follow-up varied across trials and this has led to high variation in the estimated means and standard deviations across trials.

A post hoc analysis was undertaken after we discovered seven zanamivir trials that provided data on time to first alleviation of symptoms with and without relief medication. Each patient in the studies may or may not have taken relief medication [e.g. paracetamol (acetaminophen)] during the trial. Alleviation of symptoms may have occurred while the patient was taking relief medication and the 'standard' comparison was made using this scenario. However, an additional analysis used a stricter definition, for which alleviation of symptoms could be achieved only without the use of relief medication. For example, a patient may have achieved alleviation using relief medication after 5 days but took 7 days to achieve alleviation without the use of relief medication. The comparison we reported is for all patients for whom we used the stricter definition for the zanamivir group (alleviation without relief medication) and the less-strict definition for the placebo group (alleviation with relief medication).

We planned to use the tridimensional dose-relatedness, timing and patient susceptibility methodology to assess the likelihood of harms causality,[103] but the quality of the data available did not allow for this.

Unit of analysis issues

Problems with unit of analysis are described in 'Post-protocol hypotheses' (see *Appendix 8*).

Dealing with missing data

We developed a comprehensive strategy for dealing with data that we know are missing at the trial level, that is, unpublished trials (see *Search methods for identification of studies*, above, and *Appendices 1, 4* and *5*) and unreliable published records, which are a very concentrated summary of CSRs. For example, in the oseltamivir trial programme, some trials' CSRs (e.g. WP16263[104]) consist of 8545 pages. This has a 1000-fold greater length than its published version,[105] which consists of seven pages. The purpose of this review is to provide as complete a picture as possible of trial programmes, without reliance on the published literature. *Appendix 9* reports an example of the content of a typical Roche CSR.

Assessment of heterogeneity

We used tau-squared (inverse variance method) and the I^2 statistic to estimate between-study variance as measures of the level of statistical heterogeneity, and the chi-squared test to test for heterogeneity.

Assessment of reporting biases

We carried out assessment of reporting biases (comparing CSR with the relevant publication) only in the first publication of A159.[106] For this version, as we had complete CSRs for the trial programmes of the two drugs, we expected to find all of the relevant information in these documents and adopted a binary assessment (high risk, low risk or unclear bias).

Data synthesis

We used the random-effects approach of DerSimonian and Laird[107] based on MDs for analysis of time to first alleviation of symptoms. For all of the other outcomes we used the random-effects approach for binary data of DerSimonian and Laird[107] where tau-squared was estimated using the inverse variance method.

Although overall symptom reduction is well documented, our interest was particularly focused on complications and adverse events, as this is where evidence is currently scarce or inconclusive.[31,32,35] Our preliminary examination of CSRs identified that some symptoms and sequelae of influenza (such as 'pneumonia') had been classified as either a 'complication of influenza' or as an 'adverse event of the treatment', or both. We called this somewhat confusing classification 'compliharms'. We decided to deal with compliharms as follows. We identified complications of particular clinical interest as 'pneumonia', bronchitis, otitis media and sinusitis. We tabulated the type of data capture used for each complication ('secondary illness') by study, including the following variables: definition of what events are termed complications; which part of the CSR captured data on complications; who reported and captured the data; which diagnostic method was used; whether or not, and where, the diagnostic pathway was (usually a form); and whether or not prescriptions for treatment were captured. We then aimed to stratify our analysis by method of diagnosis with three possible criteria: (1) laboratory-confirmed diagnosis (e.g. based on radiologically or microbiologically confirmed evidence of infection); (2) clinical diagnosis without laboratory confirmation (diagnosed by a doctor/investigator after a clinical examination); and (3) other type of diagnosis, such as self-reported by patient. We also conducted analysis of any complication (such as 'pneumonia', bronchitis, otitis media and sinusitis) that was classified as serious or led to study withdrawal.

We tested the effects of oseltamivir in prophylaxis of influenza and ILI. However, the CSRs of prophylaxis trials do not define ILI but report eight different definitions for influenza with laboratory confirmation (see web extra influenza definitions, *Appendix 11*).

This is a complex and confusing set of definitions, in which, for example, the definition for upper respiratory tract infection with systemic disturbance is the same as one of the definitions for asymptomatic influenza. After discovering the absence of a definition for ILI, and the complex and confusing definitions for laboratory-confirmed influenza, we classified ILI as having two or more symptoms from the following: nasal congestion, headache, chills/sweats, sore throat, cough, fatigue, myalgia and fever. These were the symptoms reported in the efficacy listing of individual patients in module 3 of the prophylaxis trials CSRs.

In two oseltamivir treatment trials[8,58] and one prophylaxis study[59] there were three treatment arms comparing placebo, standard dose and high dose. For time to first alleviation of symptoms, we restricted comparison to placebo against standard dose (as this is how it was reported in the original report). However, for all other outcomes we combined the standard and high-dose treatment arms. There was little apparent difference in the incidence of outcomes between the standard- and high-dose arms, and combining the arms did not appear to cause heterogeneity. However, in two cases there was some evidence of a dose–response effect. These cases are described more fully below (see *Results*, *Analysis of harms*).

The majority of zanamivir trials compared placebo with inhaled zanamivir. However, some trials also included an intranasal zanamivir treatment arm and a combined arm of inhaled and intranasal treatment. The multiple zanamivir arms were generally combined for meta-analysis, as effects appeared similar and did not appear to cause heterogeneity.

Subgroup analysis and investigation of heterogeneity

We investigated the robustness of complications outcomes using subgroup analysis by method of diagnosis. We investigated high estimates of heterogeneity, where possible, using subgroup analysis. For example, we conducted a subgroup analysis of time to first alleviation of symptoms in studies of oseltamivir treatment in children by partitioning studies into those of otherwise healthy children and those of children with chronic illness (asthma). Based on a referee's comment, we conducted a subgroup analysis on time to first alleviation of symptoms by infection status for zanamivir. We could not do a similar analysis for oseltamivir because we did not have data on the non-influenza-infected patients, and we could not correctly identify the patients with influenza infection as a result of the effect of oseltamivir on antibodies.

In the trial programmes for both oseltamivir and zanamivir there was large variation in treatment effects for pneumonia across the populations studied (i.e. adults and children, as well as treatment and prophylaxis), hence we conducted a metaregression to investigate this heterogeneity. We included all of the studies that reported pneumonia (32 studies in total) and investigated the four binary factors: age group (adults vs. children), drug (oseltamivir vs. zanamivir): indication (treatment vs. prophylaxis) and method of diagnosis. For oseltamivir studies, the method of diagnosis was based on either data collected on non-specific adverse events or secondary/intercurrent illness forms, or data collected on specific 'diagnosis of secondary illness' forms that included objective criteria such as X-ray confirmation. For zanamivir, two trials included X-ray confirmation of pneumonia. We conducted the metaregression in Stata/SE, version 13 for Windows (StataCorp LP, College Station, TX, USA) using the *metareg* command. There were some studies where one treatment group had zero events, therefore we added 0.5 events to all treatment groups for all studies prior to analysis. The dependent variable in the regression was log-relative risk. A further post hoc analysis was undertaken after we discovered that seven trials provided data on time to first alleviation of symptoms with and without relief medication. Each patient in the studies may or may not have taken relief medication during the trial. Alleviation of symptoms may have occurred while the patient was taking relief medication, and the 'standard' comparison was made using this scenario. However, an additional analysis used a stricter definition, for which alleviation of symptoms could be achieved only without the use of relief medication. For example, a patient may have achieved alleviation using relief medication after 5 days but took 7 days to achieve alleviation without the use of relief medication. The comparison we reported is for all patients, for which we used the stricter definition for the zanamivir group (alleviation without relief medication) and the less strict definition for the placebo group (alleviation with relief medication).

Sensitivity analysis

Sensitivity analyses applicable to our post-protocol analyses have been covered above (see *Methods*). We used the fixed-effect method of Mantel and Haenszel as a sensitivity analysis to supplement our primary analyses using the random-effects method of DerSimonian and Laird.[107] Random-effects meta-analysis is known to be overly conservative with sparse data. Hence, we conducted sensitivity analysis using Peto's method on two occasions for which we had sparse data and borderline statistically significant results (prophylaxis with oseltamivir: renal body system on-treatment and psychiatric body system on-treatment).

Results

Description of studies

We searched trial registries, electronic databases and regulatory archives, and corresponded with manufacturers to identify all trials and requested CSRs. Although this review focuses on the primary data sources of manufacturers, we checked that there were no published RCTs from non-manufacturer sources by running electronic searches in the following databases: CENTRAL 2013, Issue 6, limited to year published 2010–13 (20 search results); MEDLINE (January 2011 to July week 2, 2013) (56 search results) and MEDLINE (via Ovid) from 1 January 2011 to July week 2, 2013 (56 search results); EMBASE (January 2011 to July 2013) (90 search results) and EMBASE.com from 1 January 2011 to July 2013 (90 search results); and PubMed (not MEDLINE) with no date limit (21 records). We searched PubMed to identify publisher-submitted records that will never be indexed in MEDLINE and the most recently added records not yet indexed in MEDLINE. To identify reviews that may possibly have referenced further trials we searched DARE 2013, Issue 2 of 4 April (four search results); NHS EED, Issue 2 of 4 April 2013 (two search results); both resources parts of The Cochrane Library (accessed 22 July 2013); and HEED (searched 22 July 2013) (three search results).

Results of the search

Use of regulatory information

We were able to download 2673 pages from the FDA website. The table of contents (TOC) is provided in *Tables 2–5.* We used these pages to identify all of the trials that had been conducted within a drug's trial programme. There was no correlation between citation frequency of oseltamivir treatment trials in the

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
113502			
113625			
113678			
114045			
NAI108166			
105934			
NAI106784			
107485			
108127			
112311			
112312			
113268			
GCP/95/045			
NAI10901	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	15.15	
NAI10902			
NAI30008[77]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	15	Seven documents with 14 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	13	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	19, 19, 20	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	1, 1, 3, 4, 4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/21036ltr.pdf	2	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_MEDR.pdf	33	
NAI30009[78]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	1.2	Seven documents with 110 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P1.pdf	10, 10, 12, 13, 13, 14, 14, 17, 29, 42, 61, 62, 64, 64, 65, 65, 68	

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P2.pdf	33, 34, 36, 43, 43, 43, 43, 52, 52, 52, 53, 53, 56, 57	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	5, 5, 5, 6, 6, 8, 8	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_MEDR.pdf	3, 3, 3, 3, 3, 3, 3, 4, 4, 5, 8, 9, 9, 10, 10, 11, 11, 11, 14, 14, 15, 16, 17, 19, 19, 19, 20, 20, 22, 23, 23, 23, 24, 24, 24, 25, 25, 25, 25, 25, 25, 26, 26, 26, 27, 27, 28, 28, 28, 29, 29, 31, 31, 31, 31	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_MICROBR.pdf	3, 3, 4, 4, 4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_STATR.pdf	2, 2, 2, 4, 7, 12, 18, 18, 18, 19	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P1.pdf	31.56	One document with two instances
NAI30010[79]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	1.2	Six documents with 65 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P1.pdf	10, 12, 13, 14, 14, 15, 17, 62, 62, 62, 64	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P2.pdf	34, 34, 36, 43, 53	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	5, 5, 6, 6	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_MEDR.pdf	3, 3, 3, 3, 3, 4, 5, 18, 19, 21, 21, 22, 23, 23, 23, 23, 24, 25, 25, 25, 26, 26, 26, 26, 27, 27, 27, 28, 28, 29, 29, 29, 30, 31, 31, 31, 32	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_STATR.pdf	2, 2, 13, 13, 13, 19	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	6	One document with one instance

continued

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAI30012[81]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	1	One document with one instance
NAI30015[82]			
NAI30020[83]			
NAI30028[84]			
NAI30034[86]			
NAI40012			
NAIA1009	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P1.pdf	56	Four documents with 17 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P2.pdf	1, 1, 1, 48, 49, 52	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	5, 5, 6	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_MEDR.pdf	3, 3, 6, 7, 20, 31, 31	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	18	Five documents with five instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	9	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P2.pdf	52	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	11	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_STATR.pdf	2	
NAIA3002[91]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Thirteen documents with 122 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	6, 6, 7, 7, 14, 15, 22, 22, 23	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	1, 4, 4, 12, 12, 12, 12, 17	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	4, 14, 14, 14, 14, 14, 15, 15, 15, 15, 16	

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview2.pdf	1, 2, 3, 4, 4, 5, 6, 6, 6, 8, 8, 9, 9, 9, 12, 12, 15, 16, 16, 16, 17	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview3.pdf	5, 5, 6, 6, 6, 7, 7, 7, 8, 8, 9, 9, 9, 10, 11, 12, 13, 13, 14, 15, 15, 17, 18, 18, 19, 20, 21	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	1, 1, 1, 1, 2, 6	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	4, 5, 10, 12	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	1, 1, 2, 2, 2, 2, 3, 3, 4, 4, 5, 5, 7, 8, 10, 11, 12, 14, 16, 16, 16, 16, 16, 17	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	2, 2, 6, 6, 8, 8, 9, 10	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	10	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-stats.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	15	One document with one instance
NAIA3003[92]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	17, 17, 18	Three documents with six instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	4.4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	22	
NAIA3004[93]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	14	Four documents with eight instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	7	

continued

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	18, 18, 19	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	4, 4, 4	
NAIA3005[94]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	14	Five documents with 12 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	12, 12, 12, 13, 14, 15, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	14.15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_ADMINCORRES_P2.pdf	38	
NAIB1002			
NAIB3002[99]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Fourteen documents with 99 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	14, 15, 15, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	11.12	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	4, 14, 14, 14, 14, 14, 14, 14, 14	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview2.pdf	9, 9, 9, 9, 9, 9, 10, 11, 12, 12, 12, 12, 13, 13, 13, 14, 14, 14, 15, 15, 16, 16, 16, 17	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview3.pdf	4, 5, 6, 6, 6, 7, 7, 7, 8, 8, 8, 9, 9, 11, 12, 12, 13, 13, 14, 15, 17, 18, 18, 19, 20, 21	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	1, 1, 1, 1, 2	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	4, 5, 10, 12	

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	2, 3, 3, 7, 8, 10, 11, 14, 15, 16, 16, 16	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	7, 8, 8, 8, 9, 9	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	10.2	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-stats.pdf	7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	5.5	
NAI30011[80]			
NAIB2007[97]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Seven documents with 18 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	14, 15, 15, 16, 16, 17, 17, 17, 18	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	3	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	8, 10, 10, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	2	
NAIA2006[90]			
NAIB2006[96]			
NAIB1007			
C94-009	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	17	One document with one instance

continued

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
C94-085	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	17	Two documents with two instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview9.pdf	22	
NAIB1001	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	17	One document with one instance
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/20000426_001/21–036-S001_RELENZA_BIOPHARMR.pdf	6	One document with one instance
NAIA2005[89]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Ten documents with 44 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	7, 17, 10	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin3.pdf	2.4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	4.5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	2, 2, 3, 3, 3, 3, 5, 6, 6, 6, 6, 8, 8, 8, 9, 11, 12, 12, 13, 14, 14, 14, 14, 14, 15, 18	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	3.4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	2, 5, 9, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	10	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-microbiology.pdf	21	
NAIB2005[95]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin1.pdf	15	Nine documents with 43 instances
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-admin2.pdf	17, 20, 20, 22, 23	

TABLE 2 Table of contents for studies of zanamivir described in regulatory documentation from the FDA (USA) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview1.pdf	5.5	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview4.pdf	3, 3, 3, 7, 8, 8, 8, 9, 10, 11, 11, 11, 11, 12, 12, 12, 13, 14, 14, 14, 14, 14, 14, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	7.7	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	3.4	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview7.pdf	2, 9, 15	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview8.pdf	2	
	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-microbiology.pdf	21	
NAIA/B2008[78]	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview6.pdf	4	One document with one instance
NAIA2010	Tamiflu and Relenza/Relenza/Relenza – NDA 021036/19990726_000/021036-medreview5.pdf	16	One document with one instance
NAIA/B2009[88]			
167-02			
167-03			
167-05			
167-04			
JNAI-03			
JNAI-02			
JNAI-01[71]			
JNAI-07[73]			
JNAI-04[72]			
PE-01[100]			
167-101[70]			
167T3-11			

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
NP15717	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	46.46	Six documents with 13 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	14, 15, 15	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P2.pdf	2	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_BioPharmr.pdf	5, 8, 10, 13, 31	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
NP15718	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	17	One document with one instance
NP15728	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	16.35	Three documents with six instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	11	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	45, 46, 47	
NP15757	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	92, 93, 104, 122, 126, 131, 144, 144, 145	One document with nine instances
NP15826	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	47	Nine documents with 26 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P2.pdf	2	

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_BioPharmr.pdf	4, 5, 5, 8, 8, 8, 10, 17, 29, 30, 30, 30, 30, 31, 31	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Medr.pdf	9.1	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	9.1	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
NP15827	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	10.12	Two documents with seven instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	16, 16, 17, 17, 17	
WP15525	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	21, 25, 26, 27, 27, 27, 27, 42, 42, 44	Three document with 13 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P2.pdf	2.2	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_BioPharmr.pdf	29	
WP15647	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	24, 27, 27	Two documents with four instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	44	
WP15648	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	39	Three documents with eight instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	44.44	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	94, 128, 153, 153, 154	

continued

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
WP15676	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	28.33	Three documents with four instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	11	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	45	
WV15670[8]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	2, 44, 44	Six documents with 45 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	6, 19, 37, 38, 39, 39, 39, 39, 40, 41, 41, 42, 43, 44, 48, 48, 49, 49	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	1, 25, 25, 35, 35, 39, 39, 47	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	3, 3, 4, 4, 5, 5, 5, 8, 9, 10, 17, 17, 21, 22	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	189	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
WV15671[58]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	2, 44, 44	Seven documents with 50 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	6, 16, 19, 24, 24, 25, 25, 26, 27, 27, 28, 32, 34, 35, 36, 37, 38, 39, 39, 39, 40, 41, 46, 49, 49	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	1, 25, 25, 35, 38, 47	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	3, 4, 4, 5, 5, 5, 5, 9, 10, 10, 15, 17, 21	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	189	

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
WV15673[59]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	3	Three documents with 50 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	18, 18, 18, 20, 21, 21, 21, 22, 39	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	58, 59, 71, 71, 71, 71, 71, 72, 72, 73, 73, 76, 76, 76, 76, 76, 77, 77, 79, 82, 83, 83, 84, 122, 124, 125, 126, 128, 131, 131, 132, 133, 134, 134, 145, 145, 156, 169, 177, 189	
WV15697[59]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	39	Two documents with 40 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	58, 59, 71, 71, 71, 71, 71, 72, 72, 73, 73, 76, 76, 76, 76, 76, 77, 77, 79, 82, 83, 83, 84, 122, 126, 128, 131, 131, 131, 132, 133, 134, 145, 145, 152, 153, 156, 162, 189	
WV15708[61]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	3	Three documents with 39 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	23, 35, 39, 41	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	71, 71, 71, 71, 71, 72, 72, 72, 72, 75, 75, 75, 75, 77, 77, 78, 79, 79, 82, 82, 122, 125, 125, 126, 131, 134, 134, 135, 135, 149, 151, 152, 152, 153	
WV15708D	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	3	Two documents with three instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	23.35	

continued

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
WV15730[62]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_bior.pdf	44.44	Five documents with 15 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	6, 9, 19, 49, 50, 50	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	1, 1, 25, 25, 27	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	189	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	3	
WV15731	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P2.pdf	17	Four documents with nine instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Medr.pdf	5, 30, 37	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Microbr.pdf	5.6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	5, 30, 37	
WV157588[63]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P1.pdf	12, 19, 19, 36	Nine documents with 92 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P2.pdf	2, 8, 17, 39, 39, 57, 57	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_BioPharmr.pdf	3, 4, 5, 5, 5, 8, 10, 17, 27, 30	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Corres.pdf	6.9	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Medr.pdf	5, 5, 9, 9, 10, 11, 12, 12, 16, 18, 18, 18, 19, 19, 31, 31, 31, 33, 33, 35, 36, 37, 37, 37, 37, 37, 37, 37, 40, 43	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Microbr.pdf	2, 4, 5, 6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	5, 5, 9, 9, 10, 11, 12, 12, 16, 18, 18, 18, 19, 19, 31, 31, 31, 33, 33, 35, 36, 37, 37, 37, 37, 37, 37, 37, 40, 43	

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6, 6, 8	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	2.3	
WV15759[64]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P1.pdf	12.13	Seven documents with 44 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P2.pdf	39	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Medr.pdf	5, 10, 30, 30, 30, 30, 31, 32, 32, 33, 34, 37, 37, 37, 40, 44	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Microbr.pdf	2, 4, 4, 5, 6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	5, 10, 30, 30, 30, 30, 31, 32, 32, 33, 34, 37, 37, 37, 40, 44	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6, 6, 9	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	2	
WV15799[65]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	28, 28, 28, 28, 28, 29, 29, 30, 30, 30, 30, 30, 31, 31, 31, 31, 32, 32, 32, 32, 32, 33, 33, 34, 34, 35, 35, 35, 36, 37, 37, 37, 37, 37, 38, 38, 38, 39, 39, 40, 40, 40, 40, 40, 58, 60, 71, 71, 71, 71, 71, 72, 72, 73, 76, 76, 76, 77, 78, 79, 84, 85, 122, 125, 125, 126, 126, 128, 131, 140, 140, 140, 143, 147, 149, 156, 162, 169, 175, 187, 203, 208, 208	Four documents with 89 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Medr.pdf	10.11	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	10.11	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6.7	

continued

TABLE 3 Table of contents for studies of oseltamivir described in regulatory documentation from the FDA (USA) (*continued*)

Referenced study	File name	Pages on which study is mentioned (separated by commas)	Note
WV15812[66]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	3, 6, 10, 12	Two documents with nine instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	6, 8, 10, 25, 35	
WV15819[67]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P1.pdf	6, 10, 12, 15	Two documents with eight instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/19991027_000/ 21087_Tamiflu_medr_P2.pdf	2, 6, 6, 39	
WV15825[68]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20001117_002/ 21–087SE1–002_review.pdf	41, 41, 41, 41, 42, 42, 42, 42, 42, 42, 43, 44, 58, 59, 71, 71, 71, 71, 71, 72, 72, 72, 72, 73, 73, 75, 75, 77, 77, 78, 79, 79, 79, 80, 80, 80, 81, 82, 85, 125, 125, 126, 126, 128, 131, 134, 134, 135, 135, 137, 137, 138, 145, 150, 151, 152, 152, 155, 156, 162, 169, 180, 204, 211	One document with 64 instances
WV15871[64]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P1.pdf	12.13	Seven documents with 42 instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Admindocs_P2.pdf	39	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Medr.pdf	5, 11, 30, 31, 31, 32, 32, 32, 33, 34, 37, 37, 37, 37, 37, 37, 40	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Microbr.pdf	2, 5, 6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	5, 11, 30, 31, 31, 32, 32, 32, 33, 34, 37, 37, 37, 37, 37, 37, 40	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021087/20040624_016/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_ADMINCORRES.pdf	6	
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20040624_010/ 021087_S016_TAMIFLU CAPSULES – DRY POWDER_BIOPHARMR.pdf	2	
WV15872[66]	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Medr.pdf	11.33	Two documents with four instances
	Tamiflu and Relenza/Tamiflu/Tamiflu – NDA 021246/20001214_000/ 21–246_Tamiflu_Statr.pdf	11.33	

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAI106784			
107485			
108127			
112311			
112312			
113268			
GCP/95/045			
NAI10901			
NAI10902			
NAI30008	Relenza treatment submission executive summary.pdf	4	Three documents with 10 instances
	Relenza treatment submission full document.pdf	5, 26, 26, 26, 146	
	Relenza treatment submission main text.pdf	5, 26, 26, 26	
NAI30009	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	Seven documents with 461 instances
	NAI30009 study report pdf\CSR30009.pdf		
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf		
	NAI30009 study report pdf\suptables.pdf		
	NAI30009 study report pdf\tables.pdf		
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 18, 18, 19, 27, 30, 31	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 18, 18, 19, 27, 30, 31, 76, 128, 130, 132, 134, 144	
NAI30010	NAI30010 study report\Final NAI30010 for sign-off.pdf		Seven documents with 399 instances
	NAI30010 study report pdf\NAI30010 HO final FSR.pdf		
	NAI30010 study report pdf\suptables.pdf		
	NAI30010 study report pdf\tables.pdf		
	Relenza prophylaxis submission.pdf	2, 5, 8, 11, 12, 19, 20, 21, 23, 24	
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 18, 27, 30, 31, 76, 135, 137, 139, 141, 143, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 18, 27, 30, 31	

continued

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAI30012	Relenza treatment submission executive summary.pdf	4	Three documents with eight instances
NAI30012	Relenza treatment submission full document.pdf	5, 26, 26, 146	
NAI30012	Relenza treatment submission main text.pdf	5, 26, 26	
NAI30015	Relenza treatment submission full document.pdf	146	One document with one instance
NAI30020			
NAI30028			
NAI30031			
NAI30034			
NAI40012			
NAIA1009	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	101	Two documents with three instances
	NAI30009 study report pdf\CSR30009.pdf	28.34	
NAIA3002[91]	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	Nine documents with 513 instances
	NAI30009 study report pdf\CSR30009.pdf	34.95	
	NAI30009 study report pdf\NAI30009 HO final FSR.pdf	22	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf		
	NAIA3002 study report pdf\NAIA3002 supporting tables 2.pdf		
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 47, 49	
	Relenza treatment submission full document.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31, 63, 63, 63, 76, 106, 106, 107, 107, 109, 109, 112, 112, 114, 114, 115, 115, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31	
NAIA3003	Relenza prophylaxis submission.pdf	10	One document with one instance
NAIA3004	Relenza prophylaxis submission.pdf	10	One document with one instance

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAIA3005	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	36, 94, 94, 94, 95, 96, 96, 101	Five documents with 310 instances
	NAI30010 study report pdf\NAI30010 HO FSR.pdf	6.18	
	NAIA3005 study report pdf \A3005cr01.pdf		
	NAIA3005 study report pdf\TABS.pdf		
	Relenza prophylaxis submission.pdf	2, 5, 6, 12, 13, 13, 15, 15, 16, 16, 17, 17, 18, 18	
NAIB1002			
NAIB3001	NAI30009 study report pdf\CSR30009.pdf	34, 50, 95	Eleven documents with 374 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10.22	
	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	
	NAI30010 study report pdf \NAI30010 HO FSR.pdf	17.17	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf		
	NAIB3001 study report pdf\NAIB3001 supporting tables 1.pdf		
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 18, 18, 27, 30, 31, 32, 63, 63, 63, 76, 99, 99, 101, 101, 103, 103, 105, 105, 144, 162	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 18, 18, 27, 30, 31, 32	
NAIB3002	NAI30009 study report pdf\CSR30009.pdf	34.95	Ten documents with 579 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	22	
	NAI30010 study report pdf\FINAL NAI30010 for sign-off.pdf	102	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 48, 50	
	NAIA3005 study report pdf\A3005cr01.pdf	25	

continued

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	NAIB3002 study report pdf\NAIB3002 full study report.pdf		
	NAIB3002 study report pdf \NAIB3002supporting tables 1.pdf		
	NAIB3002 study report pdf \NAIB3002supporting tables 2.pdf		
	Relenza treatment submission full document.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31, 63, 63, 63, 76, 117, 117, 117, 118, 118, 120, 120, 122, 122, 124, 124, 125, 125, 127, 127, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 17, 18, 19, 27, 30, 31	
NAI30011	Relenza treatment submission full document.pdf	146	One document with one instance
NAIB2007	NAI30009 study report pdf\CSR30009.pdf	95	10 documents with 379 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 29	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2007 study report pdf\b2007cr.pdf		
	NAIB2007 study report pdf\TABLES.pdf		
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25.26	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 29	
	Relenza treatment submission full document.pdf	16, 16, 17, 18, 18, 19, 27, 30, 31, 76, 91, 91, 92, 92, 94, 94, 96, 96, 98, 98, 144	
	Relenza treatment submission main text.pdf	16, 16, 17, 18, 18, 19, 27, 30, 31	
NAIA2006	NAIA2005 study report pdf\a2005cr.pdf	38, 73, 74	Four documents with six instances
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	
	NAIA3005 study report pdf \A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
NAIB2006	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	Three documents with three instances
	NAIA3005 study report pdf \A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
NAIB1007			
C94-009			
C94-085			
NAIB1001			
NAIB_1001			
NAIA2005	NAI30009 study report pdf\CSR30009.pdf	95	Twelve documents with 895 instances
	NAIA2005 study report pdf\a2005cr.pdf		
	NAIA2005 study report pdf\APPS_ALL.pdf		
	NAIA2005 study report pdf\TBS_ALL.pdf		
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 48, 48	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2005 study report pdf\b2005cr.pdf	7, 7, 22, 25, 26, 34, 34, 42, 71, 72, 72	
	NAIB2007 study report pdf\b2007cr.pdf	76	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 47, 47	
	Relenza treatment submission full document.pdf	16, 16, 16, 16, 17, 18, 27, 30, 76, 77, 77, 77, 79, 79, 79, 80, 80, 82, 82, 84, 84, 85, 144, 144	
	Relenza treatment submission main text.pdf	16, 16, 16, 16, 17, 18, 27, 30	
NAIB2005	NAI30009 study report pdf\CSR30009.pdf	95	Twelve documents with 838 instances
	NAIA2005 study report pdf\a2005cr.pdf	7, 8, 8, 24, 24, 25, 43, 70, 74, 74	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 48, 48	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB2005 study report pdf\APPSNEW.pdf		
	NAIB2005 study report pdf\b2005cr.pdf		
	NAIB2005 study report pdf\TBS_ALL.pdf		

continued

TABLE 4 Table of contents for studies of zanamivir described in regulatory documentation from NICE (UK) (*continued*)

Mentioned study	File name	Pages on which study is mentioned (separated by commas)	Note
	NAIB2007 study report pdf\b2007cr.pdf	76	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 47, 47	
	Relenza treatment submission full document.pdf	16, 16, 16, 16, 17, 18, 27, 30, 76, 77, 79, 79, 85, 85, 85, 86, 86, 88, 88, 90, 90, 144, 144	
	Relenza treatment submission main text.pdf	16, 16, 16, 16, 17, 18, 27, 30	
NAIA/B2008	NAI30009 study report pdf\CSR30009.pdf	95	Six documents with 16 instances
	NAI30009 study report pdf\NAI 30009 HO final FSR.pdf	10	
	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28, 28, 29, 29	
	NAIA3005 study report pdf\A3005cr01.pdf	25	
	NAIB3001 study report pdf\NAIB3001 full study report.pdf	25, 26, 26, 26, 77	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28, 28, 29, 29	
NAIA2010	NAIA3005 study report pdf\A3005cr01.pdf	25	One document with one instance
NAIA/B2009[88]	NAIA3002 study report pdf\NAIA3002 full study report.pdf	28	Three documents with three instances
	NAIA3005 study report pdf \A3005cr01.pdf	25	
	NAIB3002 study report pdf\NAIB3002 full study report.pdf	28	
167-02			
167-03			
167-05			
167-04			
JNAI-03			
JNAI-02			
JNAI-01			
JNAI-07			
JNAI-04			
PE-01[100]			
167-101[70]			
167T3–11			

NICE, National Institute for Health and Care Excellence.

TABLE 5 Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK)

Referenced study	File name volume[a]	Pages where study is mentioned (separated by commas)	Note
GS97-802			
133312			
GS-97-801			
JP15734			
JP15735			
JV15823[74]			
JV15824[75]			
JV16284			
M76001[36]	1	33, 36, 37, 37, 38, 38, 39, 67, 68, 94, 95, 224	One document with 12 instances
M76006			
ML20910			
ML22789			
ML22879			
MV21118			
MV22841			
NCT00298233			
NCT00555893			
NCT00707941			
NCT00799760			
NCT00830323			
ML25018			
NCT00867139			
NCT00873886			
NCT01002729			
NP15717	6	32, 75, 76, 77	Two documents with five instances
	8	68	
	6	73.98	One document with two instances
NP15718			
NP15728			

continued

TABLE 5 Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*continued*)

Referenced study	File name volume[a]	Pages where study is mentioned (separated by commas)	Note
NP15757	8	68	One document with one instance
NP15826	6	32, 75, 75, 75, 76, 76, 77, 78, 79, 80, 98	One document with 11 instances
NP15827	8	68	One document with one instance
NP22770			
NP25138			
NP25139			
NV16871			
NV20234			
NV20235			
NV20236			
NV20237			
NV22155			
NV25118			
NV25182			
PP16351			
WP15517	1	185.245	One document with two instances
WP15525	1	185.245	One document with two instances
WP15647			
WP15648			
WP15676			
WP15901			
WP22849			
WV144181			
WV15670[8]	1	33, 36, 37, 37, 38, 38, 39, 47, 48, 48, 49, 49, 50, 53, 54, 54, 55, 163, 171, 188, 207, 209, 224, 245, 245, 252, 253, 253	Seven documents with 1193 instances
	10	7, 36, 37, 37	
	2		
	3		
	4	90	
	6	35.98	
	8	65	
	2	20, 20, 20, 20, 20	One document with five instances

TABLE 5 Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*continued*)

Referenced study	File name volume[a]	Pages where study is mentioned (separated by commas)	Note
WV15671[58]	1	33, 36, 37, 37, 38, 38, 39, 47, 48, 49, 49, 50, 53, 54, 54, 55, 163, 171, 188, 207, 209, 224, 245, 245	Seven documents with 1222 instances
	10	7, 36, 37, 37	
	2	82	
	4		
	5		
	6	35.98	
	8	66	
WV15673[59]	8	66	One document with one instance
WV15673D	8	66	One document with one instance
WV15697[59]	8		One document with one instance
WV15697D	8		One document with one instance
WV15707[60]	1	33, 36, 37, 37, 38, 67, 68, 224, 245, 245, 245, 246	One document with 12 instances
WV15708[61]			
WV15708D			
WV15730[62]	1	33, 36, 37, 37, 38, 38, 39, 47, 53, 54, 55, 186, 207, 224, 245, 245, 246	Four documents with 22 instances
	10	7, 36, 37	
	2	82	
	4	90	
WV15731	6	98	One document with one instance
WV15758[63]	1	36, 37, 82, 83, 84, 85, 86, 92, 94, 95, 97, 106, 224, 246	Four documents with 424 instances
	6		
	7		
	8	68	
WV15759[64]	1	36, 37, 94, 95, 95, 109, 113, 114, 121, 122, 224, 246	One document with 12 instances
WV15799[65]	1	137, 139, 139, 232, 233	Three documents with 499 instances
	8		
	9		

continued

TABLE 5 Table of contents for studies of oseltamivir described in regulatory documentation from NICE (UK) (*continued*)

Referenced study	File name volume[a]	Pages where study is mentioned (separated by commas)	Note
WV15812[66]	1	36, 37, 37, 38, 38, 39, 67, 68, 68, 107, 107, 107, 108, 108, 121, 121, 122, 123, 224, 246	Two documents with 197 instances
	10		
WV15819[67]	1	33, 36, 37, 37, 38, 58, 58, 59, 59, 60, 61, 62, 62, 65, 65, 67, 68, 224, 246	Two documents with 173 instances
	10		
WV15825[68]	8	66, 66	One document with two instances
WV15871[64]	1	109, 246	One document with two instances
WV15872[66]	1	36, 37, 37, 38, 38, 39, 67, 68, 68, 107, 107, 108, 108, 121, 121, 122, 123, 224	One document with 18 instances
WV15876[67]	1	246, 246	One document with two instances
WV15978[67]	1	67, 70, 175, 246, 246	One document with five instances
WV16193			
ML16369[76]			

NICE, National Institute for Health and Care Excellence.
a Number of the volume of the Tamiflu NICE submission.
Notes
Oseltamivir trials citation by trial ID and source NICE file. Page numbers separated by commas (where applicable) indicate which trial is cited where in which file. Blank spaces indicate no citation for known trials.
All of the studies have been searched in the folder 'Roche submission'.
When there is the number of the volume but no pages are mentioned, it means that the code of the study is cited more than 100 times.

FDA regulatory documents and trial size. The biggest treatment trial[36] is cited only four times in three documents, whereas other contemporary treatment trials are cited far more.[8,58,60,62,66] One trial,[8] for example, is cited 46 times in the FDA documents. However, the combined enrolled denominator of the four treatment trials completed at the time[8,58,60,62] was 1442, smaller than 1459.[36] This suggested that the FDA's regulatory evaluation of Roche's New Drug Application (NDA) was based predominantly on what Roche had presented to them as 'pivotal', or trials that best demonstrated the properties of oseltamivir, not the complete evidence base of all oseltamivir trials. One possible alternative explanation for this observation could have been the interval between trial completion, generation of the report and NDA submission. This explanation is supported by the relatively brief interval between completion of the M76001 trial[36] (19 February 1999) and submission (on 30 April 1999) of NDA 021087 to the FDA. However, the core part of the submission (the clinical development programme) contains data from two (at the time of writing) ongoing trials.[66,67]

The basis of the selection of trials to regulators is therefore unclear but appears to be dictated by criteria other than availability and size. The importance of trials (to manufacturers and possibly to regulators) may not be based on the same criteria that systematic reviewers would use (i.e. the capability of the trial to answer questions).

Owing to the vast size of FDA documents, sometimes hundreds of pages long, it was difficult to determine important emerging themes solely by reading. To identify items of interest in the FDA comments we used word clouds.[108] Word clouds give greater prominence to words that appear more frequently in the source document. The resulting graphic representation showed words such as 'diary' and 'baseline' to be heavily mentioned in the relevant (abridged) text from the FDA's Medical Officer Review.[109] Examining the 'diary' entry in more detail, we found the following FDA comment:

> *The majority of subjects participating in the treatment trials had only used the first diary card. The second diary card was issued in 15% to 20% of participants. In response to FDA's request, the applicant provided a summary of diary card dispensing in the 8/6/99 submission. It became apparent that instructions on when to start a second diary card were not uniformly followed in three trials.[8,58,62] There were examples of patients who had alleviated symptoms yet also received a second diary card. Conversely, there were also examples of patients who did not alleviate all symptoms but did not receive a second diary card. Thus the second diary card was used inconsistently which is viewed as a flaw of these trials. The lack of consistency in collecting symptom information after alleviation precluded a complete documentation of symptom fluctuation. Also missing second diary cards in subjects who had not alleviated symptoms were responsible for the majority of censored data which may have potentially influenced the results of efficacy analysis. In order to address the impact of censoring, the applicant performed several sensitivity analyses, which will be summarized in the Integrated Summary of Efficacy.*

This comment highlights problems with the follow-up procedure of treatments trials, which may have impaired the regulator's ability to draw conclusions on the duration of effect of oseltamivir. It also provides a good example of how graphic methods can help to identify crucial comments in vast regulatory files.

Several other experiments with text from the same FDA document showed that the choice of text to be represented as a word cloud heavily influenced cloud construction, visibility of words and hence our ability to detect important comments. It is for this reason that we decided to adopt a mixed approach: mapping citations while reading FDA comments and integrating such comments in our appraisal of the evidence. Regulatory comments were all the more important because, at the time that we developed this method, we had few CSRs, and comments helped to identify the gaps in our knowledge of the trial programmes.

Once the TOC had been constructed, we postulated that, given the huge work involved in reviewing lots of regulatory files, our new instrument could also help us by indicating which parts were more important than others, thus focusing our efforts. We experimented with a variety of methods, which are reported above (see *Data collection and analysis*).

Clinical study reports

After prolonged correspondence and media pressure (see *Appendix 1*), we were able to access the trial programmes for both oseltamivir and zanamivir without clauses restricting their accessibility to third parties.

Electronic searches

Two review authors (CDM and MT) independently scanned the titles and abstracts of the electronic searches. Three identified studies[110–112] were published versions of trials that were possibly unknown to us. We wrote to the first trial author to ask for CSRs, or equivalent, on 12 November 2013, and the author confirmed that the trials had not been completed.

Included studies

The absence of documentation of trial programmes for both drugs, listing all sponsored trials completed or under way, meant that we had to rely on a variety of sources for the reconstruction of the trial programmes and identification of relevant CSRs. This complexity is reflected in the flow chart presented in *Figure 3*, illustrating the study selection process for this review. The two main pathways were the

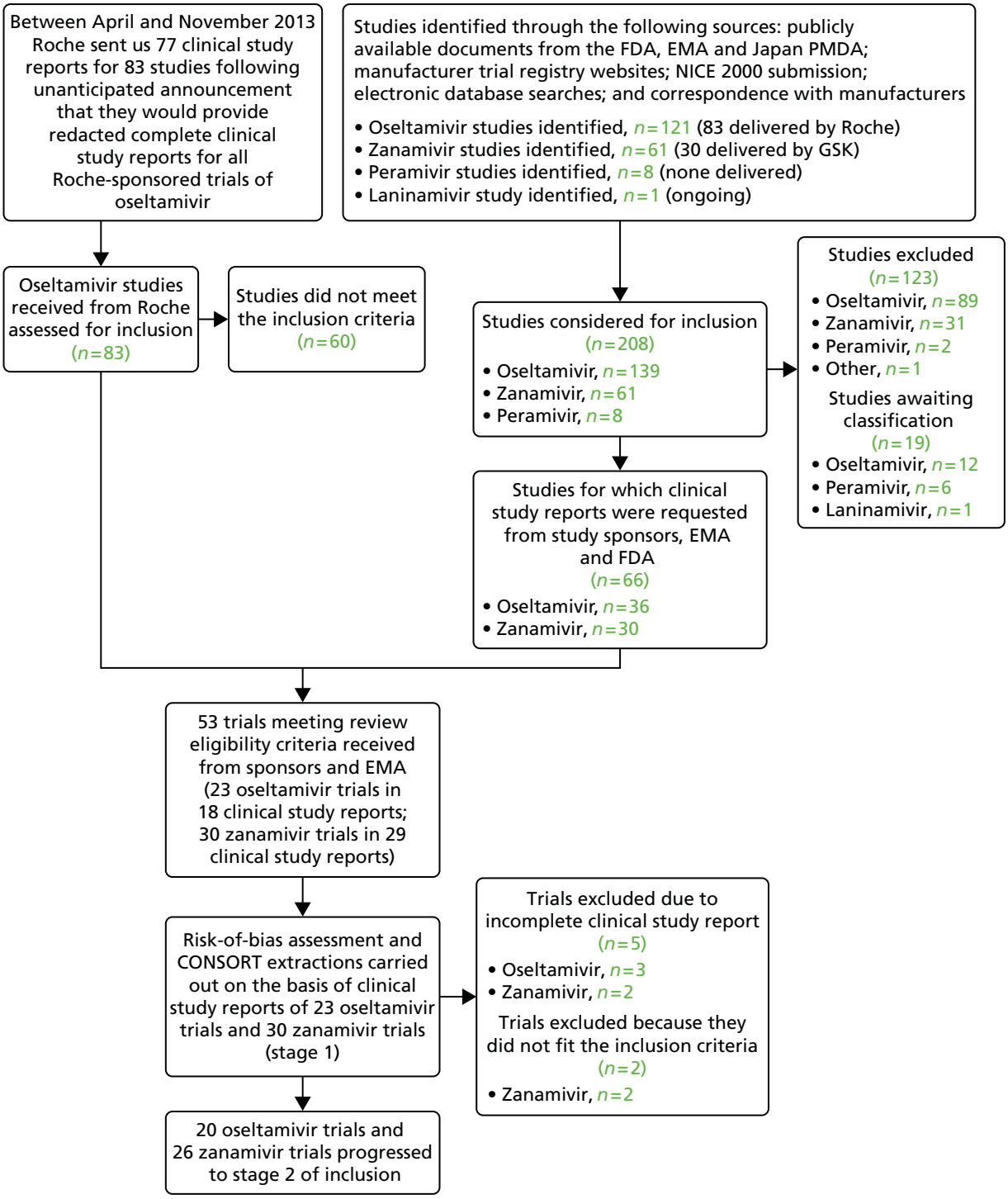


FIGURE 3 Flow diagram describing the number of studies identified, inclusion, exclusion and progression from identification to stage 1 to stage 2 of the review. PMDA, Japanese Pharmaceuticals and Medical Devices Agency.

spontaneous release of 77 full CSRs by Roche and the requests to regulatory authorities and GSK for all of the relevant reports.

We carried out the inclusion into stage 1 using the CSRs, titles, abstracts and any other relevant information. Through this process we identified 208 potentially relevant studies (139 oseltamivir trials, 61 zanamivir trials and eight peramivir trials). We excluded 123 studies (see *Appendix 10*, listed in the 'characteristics of excluded studies' table) as clearly ineligible. A further 19 studies are awaiting classification (*Table 6*). We requested 66 trials from study sponsors, the EMA and the FDA. From these

TABLE 6 Characteristics of studies awaiting assessment (ordered by study ID)

JPRN-JapicCTI-111647	
Methods	A randomised, double-blind, placebo-controlled study to confirm the efficacy in the prevention of influenza virus infection (Phase 3 study)
Duration of the study	1 October 2011 to 30 June 2012
Sponsor	Daiichi Sankyo Co., Ltd
Participants	–
Interventions	Laninamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
ML20589	
Methods	Economic and social benefits of treating and preventing influenza in aged care facilities
Sponsor	The University of Sydney, Australia anzctr.org.au number ACTRN12606000278538
Participants	–
Interventions	Oseltamivir, three different regimens
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
ML20910	
Methods	A study of Tamiflu (oseltamivir) treatment in laboratory-confirmed influenza
Sponsor	Hoffmann-La Roche, NCT00436124
Participants	–
Interventions	Oseltamivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
ML21776	
Methods	Study to evaluate nosocomial transmission of influenza
Sponsor	University Hospitals, Leicester
NCT00798421	
Participants	–
Interventions	–
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
MV21118	
Methods	Early oseltamivir treatment of influenza in children aged 1–3 years
Sponsor	Hospital District of Southwestern Finland
NCT00593502	
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study

continued

TABLE 6 Characteristics of studies awaiting assessment (ordered by study ID) (*continued*)

MV21737	
Methods	Long-term influenza prophylaxis with inhaled zanamivir or oral oseltamivir
Sponsor	University of Oxford
NCT00980109	
Participants	–
Interventions	Oseltamivir, zanamivir, placebo
Outcomes	–
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study
MV21879	
Methods	Oseltamivir randomised controlled efficacy trial
Sponsor	International Centre for Diarrhoeal Disease Research, Bangladesh
NCT00707941	
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
MV22841	
Methods	An observational clinical trial of influenza A/H1N1 2009 resistance under standard-duration oseltamivir treatment
Sponsor	Not known
Participants	–
Interventions	Oseltamivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
MV22940	
Methods	A randomised controlled trial on the effect of post-exposure oseltamivir prophylaxis on influenza transmission in nursing homes
Sponsor	National Institute for Public Health and the Environment (RIVM), The Netherlands
NCT01053377	
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00419263	
Methods	Evaluation of the efficacy and safety of peramivir in subjects with uncomplicated acute influenza
Sponsor	BioCryst Pharmaceuticals
Participants	–
Interventions	Peramivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study

TABLE 6 Characteristics of studies awaiting assessment (ordered by study ID) (*continued*)

NCT00453999	
Methods	Evaluation of the efficacy and safety of peramivir in adults with acute serious or potentially life-threatening influenza
Sponsor	BioCryst Pharmaceuticals
Participants	–
Interventions	Peramivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00486980	
Methods	Intramuscular peramivir for the treatment of uncomplicated influenza
Sponsor	BioCryst Pharmaceuticals
Participants	–
Interventions	Peramivir
Outcomes	–
Notes	Awaiting assessment as we do not yet have the clinical study reports for this study
NCT00555893	
Methods	Efficacy study of early versus late oseltamivir administration for treating and preventing influenza
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00610935	
Methods	Intramuscular peramivir in subjects with uncomplicated acute influenza
Sponsor	Marshfield Clinic Research Foundation
Participants	–
Interventions	Peramivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00705406	
Methods	A Phase II, multicentre, randomised, placebo-controlled, study to evaluate the efficacy and safety of intramuscular peramivir 600 mg in subjects with uncomplicated acute influenza
Sponsor	BioCryst Pharmaceuticals
Participants	–
Interventions	Peramivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study

continued

TABLE 6 Characteristics of studies awaiting assessment (ordered by study ID) (*continued*)

NCT00958776	
Methods	A study to evaluate the efficacy and safety of IV peramivir in addition to standard of care compared to standard of care alone in adults and adolescents who are hospitalised due to influenza
Sponsor	BioCryst Pharmaceuticals
Participants	Peramivir
Interventions	–
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT00980109	
Methods	Long-term influenza prophylaxis with inhaled zanamivir or oral oseltamivir
Sponsor	University of Oxford
Participants	–
Interventions	Oseltamivir, zanamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NCT01032837	
Methods	A study of Tamiflu (oseltamivir) for treatment of influenza with a focus on (H1N1) 2009 flu strain
Sponsor	Hoffmann-La Roche
Participants	–
Interventions	Oseltamivir, placebo
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study
NV20236	
Methods	A study of Tamiflu (oseltamivir) for seasonal prophylaxis of influenza in children
Sponsor	Hoffmann-La Roche
NCT00412555	
Participants	–
Interventions	Oseltamivir
Outcomes	–
Notes	Awaiting assessment, as we do not yet have the clinical study reports for this study

different methods, the total number of trials available for assessment for inclusion in our review at stage 1 was 53.

Twenty-three studies of oseltamivir[8,36,57–69,74–76] and 28 of zanamivir[70–73,77–100] were included in stage 1. It was not uncommon for more than one trial to be reported in the same CSRs. This was either because of the amalgamation of two or more trials due to low influenza virus circulation and difficulties in recruitment (e.g. WV15812/WV15872[66]) or because the trials bore different ID numbers when, in reality, they followed the same protocol, albeit in two different hemispheres (e.g. WV15759/WV15871[64]).

We also identified six completed or ongoing studies of peramivir in dose–response or placebo-controlled studies.[113–118]

The included trials were predominantly conducted in adults during influenza seasons in both hemispheres. A small number of studies were conducted in older people who were residing in care homes and in people with underlying respiratory diseases. All trials were sponsored by the manufacturers.

Oseltamivir

Of the 23 oseltamivir trials in stage 1, 15 were multicentre trials conducted in both the northern and southern hemispheres, whereas eight were carried out in only one country (USA, five; Japan, two; China, one). In total, 9623 participants were included (6574 in treatment trials and 3049 in prophylaxis trials). The age of the participants ranged from 1 to 82 years and the duration of follow-up varied from 6 to 42 days.

Two of the trials were conducted within nursing homes; 20 were within free-living populations; and one was performed in inpatient and outpatient departments. Three trials were conducted in children (two of the trials were among children with chronic asthma, $n = 660$; one trial was performed among otherwise healthy children, $n = 669$), whereas participants in 20 trials were adults. In some trials the eligible population included participants who were at increased risk of influenza complications, or with diagnoses of asthma or chronic obstructive pulmonary disease, but the majority included only otherwise healthy adults. In one trial,[62] participants were stratified by smoking status, whereas those in another trial were stratified by the presence or absence of otitis media.[63]

All trials compared orally administered oseltamivir (either as capsules or reconstituted powder) with placebo.

Of the 23 trials, we included 20 RCTs for the analysis examining the use of oseltamivir compared with placebo. Two RCTs were excluded from the meta-analysis because they were only synopsis reports[74,75] and another because it was not a full CSR.[76]

We finally included 20 oseltamivir trials into stage 2: 11 on treatment in adults,[8,36,57,58,60–62,66,67,69,74–76,108–112] four in children[57,63,64] and five on prophylaxis:[51,61,65,68] two in adults,[51] two in the elderly[61,68] and one in households.[65] Of the 15 included treatment trials of oseltamivir, only three[8,36,63] were successful in recruiting the a priori planned sample size.

Zanamivir

Of the 28 included zanamivir trials, 18 were multicentre trials that were conducted in both the northern and southern hemispheres and 10 were carried out in only one country (Japan, five; USA, three; Finland, one; Germany, one). In total 14,628 participants were included (7678 in treatment trials and 6950 in prophylaxis trials). Participants' age ranged from 5 to 12 years to > 65 years, and duration of follow-up varied from 5 to 35 days.

Two of the trials were performed within nursing homes; several were within free-living populations; one was performed within a university student population. In some trials the eligible population included

participants at increased risk of influenza complications, or with diagnoses of asthma or chronic obstructive pulmonary disease, but the majority included only adults who were otherwise healthy.

Zanamivir was administered as an intranasal spray, an inhalation or a combination of both, and placebos were designed to match. Administration was by the participant in the majority of trials and by nursing staff in the trials within nursing homes. Twenty-two trials compared inhaled zanamivir with placebo and six trials compared inhaled zanamivir, or intranasal zanamivir, with placebo or usual care.

Of the 28 trials,[70–73,77–100] we included 26 RCTs[70–73,77–82,84–91,93–100] for the analysis, examining the use of zanamivir compared with placebo. Two trials[83,92] were excluded from the meta-analysis because one was only a synopsis[83] and one compared zanamivir to usual care and not placebo.[92]

We finally included 26 zanamivir trials: 14 on treatment in adults,[71–73,77,80–82,87,89,91,95,97–99] two in children[78,84] and 10 trials in prophylaxis.[70,79,85,86,88,90,93,94,96,100]

Our attempt at collecting sufficient information from regulatory files to reconstruct missing CSRs also failed because the information appeared to be insufficient for a reliable reconstruction.

Excluded studies

We excluded 123 studies from entering stage 1 for various reasons. Some were pharmacokinetic studies, had an active comparator, compared higher-dose schedules with lower-dose schedules or were ongoing trials. A further 19 trials are awaiting assessment (see *Table 6*).

Risk of bias in included studies

Study-level assessments are reported in the risk-of-bias tables (see *Figure 2*). To address the problem of reporting bias, we ignored published trial reports and directed our attention to CSRs and regulatory information. Our problems in reviewing the copious material at our disposal were how to identify and analyse important details in the midst of thousands of pages of information and how to construct a coherent appraisal of large and complex trial programmes.

In addition, as we gained unrestricted access to the full CSRs (apart from personal de-identifying redactions) we took the view that all information needed to judge risk of bias should be present. Therefore, when this information was not available, we judged the corresponding risk-of-bias element as at 'high' risk of bias. For example, when details of the random sequence generation are missing from journal publications of clinical trials, it is customary to record this as 'unknown' risk of bias. This judgement usually carries the assumption that the random sequence generation details are available in more detailed reports. But when these details were still missing, even in full CSRs, we chose to rate this risk-of-bias element at 'high' risk of bias.

In the following paragraphs we report some of the salient findings using the current Cochrane format but applying the logic of reviewing regulatory data.

Allocation (selection bias)

In 10 of the 20 oseltamivir studies included in stage 2, the description of random sequence generation is missing. All of the zanamivir trials but one[84] had reporting bias due to the absence of description of random sequence generation.

Blinding (performance bias and detection bias)

The placebo and active drug capsule cap were not identical in 11 of the 20 trials of oseltamivir. This may have compromised blinding of participants. For all but one of the zanamivir trials we did not have the certificates of analysis to enable us to reconstruct the appearance, taste and texture of the two principles.

Incomplete outcome data (attrition bias)

In addition to the missing diary cards in three treatment trials (see *Results of the search,* above), we were unable to identify all of the data for all of the outcomes in all of the oseltamivir trials and in eight of the zanamivir trials. For example, hospitalisations were not reported in zanamivir trials and inconsistently reported in oseltamivir trials. The relevant data in this review come from a table of hospitalisations sent to us by Roche in late 2013. In addition, in some trials we were unable to track individual participants through tables, narratives and individual listings. The issue of compliharms impeded the ascertainment of harms in oseltamivir treatment trials (see *Appendix 1*). We had difficulty in following the logic of compliharms, even with access to full CSRs. The definition of adverse events in the RCTs of oseltamivir and zanamivir is different from the ordinary definition of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E2D guideline, which is as follows: 'An adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product' [www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Ste p4/E2D_Guideline.pdf (accessed 27 December 2013)].

As an example, the definition of adverse events in one study[58] is as follows: 'following the alleviation of influenza-like symptoms, the recurrence of a single respiratory or constitutional symptom was recorded as an adverse event, however, the reappearance of more than one symptom was recorded as influenza-like syndrome (i.e. secondary illness) and therefore do not appear as adverse events' (p. 35)[58] and: '*any adverse change from the subject's baseline (pre-treatment) condition*, which occurred during the course of the study after treatment had started, whether considered related to treatment or not'. Treatment included *all* investigational agents (including placebo and comparative agents) administered during the course of the study)' (our emphasis).[8] As a consequence, adverse events that are similar to the symptoms of influenza (such as headache and mild gastrointestinal adverse events) tend to be excluded from the treatment trials.

We identified a report of a site inspection for one adult prophylaxis trial.[59] The FDA carried out the inspection in September 2000 at various trial sites in the USA, including the West Virginia site (which was responsible for enrolling many hundreds of participants). A FDA official letter reported several violations, including failure to report serious harms to the sponsor (Roche) as the protocol required and in addition stated: '. . . we view the statement in the payment section of the consent form used in the study that subjects . . . will receive $300.00 for participating in and completing the study. No payment will be made to you if you withdraw from the study for personal reasons . . . to be an improper procedure. When subjects are to be paid for participating in a study, the payment should be prorated for the subject's actual participation in the study in order to avoid the possibility of coercion' (p. 177).[119] However, the FDA allowed the data (which had been published 1 year earlier in a prime journal) to stand in support of Roche's application for the prophylaxis indication. We do not know whether or not the participant contract was standard (i.e. whether or not the observation of possible improper procedures could be generalised to other sites and other trials) but the document cited by the FDA inspector is the subject of one of our (as yet unfulfilled) FOI requests. The possibility of financial pressure, if confirmed, could seriously confound dropout rates because of harms or any other causes in prophylaxis trials.

The significantly higher incidence of diarrhoea in placebo recipients of treatment trial WV15671[58] was identified by the FDA reviewers who remarked 'Diarrhea was reported more frequently among subjects receiving placebo than among subjects receiving Ro 64-0796 [oseltamivir]. Diarrhoea, although not specified as an inclusion criterion, has been documented to be a clinical manifestation of influenza infection. The reduction in the incidence of diarrhoea for the treatment groups compared with the placebo group could be considered as a possible treatment effect of Ro 64–0796'.[109] However, according to the Japanese Summary Basis for Approval of oseltamivir capsules for prophylaxis, diarrhoea was reported more frequently in the oseltamivir arm (49/986) than in the placebo group (38/973) in the summarised table of adverse events from three trials.[59,61,68] Our findings are inconsistent with the explanation by the FDA.

Selective reporting (reporting bias)

All of the oseltamivir trials and almost half of the zanamivir trials had selected reporting. The oseltamivir trials showed a consistent trend of missing original protocols (except for one trial[36]), changing outcome definitions while the trial was running, protocol amendments even after the trial had been completed, inconsistent approaches to outcome data collection, missing SAPs, missing date of unblinding and the use of self-reported outcomes such as pneumonia.[8,36,47,60,68,69] This represents 55% of pneumonia event data. As an example, in trial WV15670,[8] secondary illnesses were patient reported. The body of the CSR states that complications requiring antibiotic treatment were specified a priori, but, even in the final version of the protocol, for which we have the full text, there is no predefined list of secondary illnesses (i.e. no mention of pneumonia, bronchitis, sinusitis or otitis in the protocol); complications did not have anything to do with antibiotic treatment according to the protocol; and the CRF did not mention specific secondary illnesses by name. Zanamivir trials reported outcomes that were not specified in the protocol provided.

We found evidence of possible selective reporting bias when we analysed the Japanese Summary Basis for Approval data on prophylaxis. The regulatory data report tables for individual trials, as well as 10 pages of summarised tables for three trials of prophylaxis.[59,61,70] Tables for individual trials include data for high-dose arms but report few psychiatric adverse events overall. However, the summarised tables list a variety of psychiatric adverse events, including psychotic and suicidal adverse events, but not adverse events from the high-dose group. As a preliminary exploratory analysis, we combined the following suspected serious adverse events collectively: hallucination and delusion, which are classified grade 3 (serious) by the National Cancer Institute-Common Toxicity Criteria Version 2.0 (NCI-CTC V2.0); psychosis (hallucination and delusion are the two major symptoms of this disease); suicidal attempt, which is classified grade 3 (serious) by the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE V4.0); and hostility, which includes aggression, hostility, violence and murder, commonly considered as serious events although not listed in the NCI-CTC V2.0 or CTCAE V4.0. Numbers of suspected serious psychotic/suicidal adverse events (including hallucination, psychosis, schizophrenia, paranoia, aggression/hostility and attempted suicide) were five in the oseltamivir group and zero in the placebo group during the on-treatment period; when the off-treatment period data are added, the total was eight compared with one. The prophylaxis programme is crucial in understanding the harms profile of the drug, as the potential for harms witnessed to be confounded by the apparently numerous symptoms and signs of influenza infection is far less, as many participants do not become infected with influenza. This makes a causality assessment more straightforward.

Other potential sources of bias

All but three of the oseltamivir treatment trials were under-recruited. Several of the zanamivir trials were also under-recruited. We noted the use of different relief medication across different centres within the same trial, and in one zanamivir trial,[85] according to the protocol, participants receiving antibiotics for bacterial respiratory tract infection should have been excluded but in the trial this did not happen. In the zanamivir trial,[86] the definition of 'confirmed influenza' was amended after protocol closure.

We also noted several other items that were not included in all full CSRs:

- Study protocols dated prior to participant enrolment (missing for many oseltamivir trials).
- Certificates of analysis for the intervention/placebo preparations.
- Patient enrolment dates explicitly reported (only trial inception and cessation dates are given; in zanamivir trials these are partially redacted).
- Explicitly reported date of trial unblinding. We frequently noted the statement 'the database was authorised on xxxx' to identify the unblinding date but an explicit date is important to report. In some cases, the date of unblinding was reported, but the actual date within the month was redacted. This practice also applied to zanamivir protocol amendments.
- Authorship and accountability for the writing of the CSRs.

- SAPs in some cases.
- Patient consent forms (missing from most zanamivir trials).
- Patient information form (missing from most zanamivir trials).
- List of randomisation codes (variably included).
- CRF templates in zanamivir trials do not allow for determining who completes the form (patient or clinician).
- Core data sheet.

Other important documents that we did not have included:

- study manual of procedures
- minutes of safety data monitoring committee meetings.

The placebo interventions in both sets of trials may have contained active substances. The placebo for zanamivir trials contained lactose powder, which can potentially cause bronchospasm, whereas the placebo for oseltamivir trials contained dehydrocholic acid and dibasic calcium phosphate dehydrate, which can cause gastrointestinal symptoms.

Data on participants by influenza-infected status (in treatment trials) and for participants with ILI (in prophylaxis trials) were not reported in the oseltamivir CSRs.

Finally, data on the effects of rescue or relief medication (mainly paracetamol/acetaminophen) were incomplete in CSRs of oseltamivir trials and not reported separately in all of the zanamivir trials.

Effects of interventions

Analysis of time to first symptom alleviation

In adult treatment, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% CI 8.4 to 25.1 hours; I^2 statistic = 0%), representing a 10% reduction from 7 days to 6.3 days (*Figure 4*). There was no significant effect in asthmatic children: increased by 5.2 hours (95% CI 11.1 hours lower to 21.4 hours higher; I^2 statistic = 0%). But there was an effect in otherwise healthy children, based on one trial (29 hours, 95% CI 12 to 47 hours; $p = 0.001$) (see *Table 9*). Zanamivir reduced time to first alleviation of symptoms in adults by 0.60 days (95% CI 0.39 to 0.81 days; I^2 statistic = 9%), which equates to a 14.4-hour (10%) reduction in symptoms from 6.6 days to 6.0 days (*Figure 5*). There was no significant effect in children: time to first alleviation of symptoms was 1.08 days lower in the zanamivir group (95% CI 2.32 lower to 0.15 days higher; I^2 statistic = 72%).

In eight zanamivir trials that reported on use of relief medication, in all of the participants the median days to alleviation in both the placebo and the treatment arms was less than those who did not use relief medications (*Table 7*). In seven zanamivir trials, time to first alleviation of symptoms was also reported with and without rescue medication. Using these data we were able to compare zanamivir without rescue medication with placebo with rescue medication. Overall, there was a non-significant 0.41-day decrease (95% CI 0.47 days lower to 1.29 days higher; I^2 statistic = 67%) in time to first alleviation of symptoms in the placebo with rescue medication group, suggesting that zanamivir itself is no better than rescue medication, and possibly even less effective, although the varying levels of use of rescue medication in the seven trials did give rise to large heterogeneity (*Figure 6*).

In a subgroup analysis of time to first alleviation of symptoms in adults by infection status, we found no evidence of a difference in treatment effect for zanamivir on the influenza-infected subgroup compared with the non-influenza-infected subgroup ($p = 0.53$). The treatment effect was 0.67 days (95% CI 0.35 to 0.99 days; I^2 statistic = 17%) for influenza-infected patients and 0.52 days (95% CI 0.18 to 0.86 days; I^2 statistic = 0%) for non-influenza-infected patients.

Study or subgroup	Oseltamivir Mean	SD	Total	Placebo Mean	SD	Total	Weight	MD IV, random, 95% CI
M76001[36]	140.6	125.2	933	165.5	156.5	473	26.4%	−24.90 (−41.13 to −8.67)
WV15670[8]	129	114.6	240	144.5	118	235	15.9%	−15.50 (−36.42 to 5.42)
WV15671[58]	102.4	89.9	204	125.3	98.9	200	20.5%	−22.90 (−41.34 to −4.46)
WV15707[60]	154	166.5	17	93.6	134.4	9	0.5%	60.40 (−57.81 to 178.61)
WV15730[62]	107.6	104.6	31	171	177.1	27	1.2%	−63.40 (−139.68 to 12.88)
WV15812/WV15872[66]	193.7	152.3	199	203.9	146.3	202	8.1%	−10.20 (−39.44 to 19.04)
WV15819/WV15876/WV15978[67]	185	145.6	358	192.4	145.2	375	15.7%	−7.40 (−28.46 to 13.66)
WV16277[69]	138.7	138.4	226	143.7	125.4	225	11.7%	−5.00 (−29.37 to 19.37)
Total (95% CI)			**2208**			**1746**	**100.0%**	**−16.76 (−25.10 to −8.42)**

Heterogeneity: τ^2=0.00; χ^2=6.33, df=7 (p=0.50); I^2=0%
Test for overall effect: z=3.94 (p<0.0001)

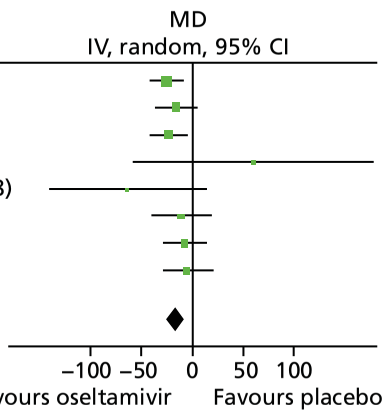


FIGURE 4 Oseltamivir vs. placebo for treatment. Time (hours) to first alleviation of symptoms in adult treatment (ITT population). df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Study or subgroup	Zanamivir Mean	SD	Total	Placebo Mean	SD	Total	Weight	MD IV, random, 95% CI
JNAI-01[71]	3.13	1.33	29	3.9	0.96	31	10.7%	−0.77 (−1.36 to −0.18)
JNAI-04[72]	3.84	2.06	32	5.68	2.75	16	1.8%	−1.84 (−3.36 to −0.32)
JNAI-07[73]	4.41	1.95	211	4.67	1.98	107	16.3%	−0.26 (−0.72 to 0.20)
NAI30008[77]	9.61	8.11	262	10.72	8.46	263	2.1%	−1.11 (−2.53 to 0.31)
NAI30010[79]	7.11	6.52	163	7.93	6.58	158	2.0%	−0.82 (−2.25 to 0.61)
NAI30012[81]	10.45	8.89	191	10.93	8.47	169	1.3%	−0.48 (−2.27 to 1.31)
NAI30015[82]	4.29	5.23	293	4.86	5.64	295	5.2%	−0.57 (−1.45 to 0.31)
NAIA/B2008[87]	5.87	2.46	834	6.34	2.25	422	33.8%	−0.47 (−0.74 to −0.20)
NAIA2005[89]	5.29	2.31	139	5.7	2.49	81	8.7%	−0.41 (−1.07 to 0.25)
NAIA3002[91]	8.34	7.4	412	8.9	7.77	365	3.6%	−0.56 (−1.63 to 0.51)
NAIB2005[95]	5.06	2.33	64	5.9	2.73	63	5.1%	−0.84 (−1.72 to 0.04)
NAIB3001[98]	6.48	3.74	227	7.35	3.83	228	8.0%	−0.87 (−1.57 to −0.17)
NAIB3002[99]	7.97	7.32	174	10.58	8.53	182	1.5%	−2.61 (−4.26 to −0.96)
Total (95% CI)			**3031**			**2380**	**100.0%**	**−0.60 (−0.81 to −0.39)**

Heterogeneity: τ^2=0.01; χ^2=13.24, df=12 (p=0.35); I^2=9%
Test for overall effect: z=5.69 (p<0.00001)

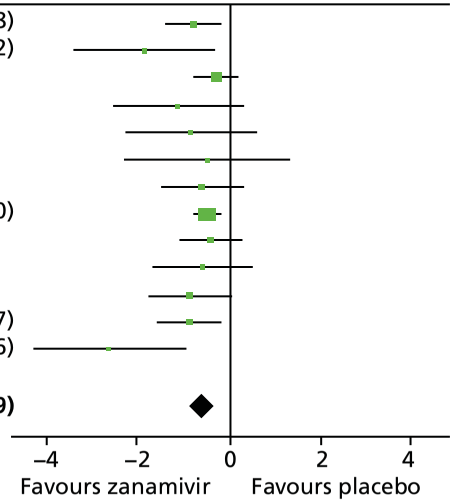


FIGURE 5 Zanamivir vs. placebo for treatment. Time (days) to first alleviation of symptoms in adult treatment. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

TABLE 7 Time to alleviation[a] of clinically significant symptoms of ILI (in all participants and participants with no use of relief medication)

Study	Sample size (*n*)		Median days to alleviation for all participants		Difference in days (*p*-value)	Median days to alleviation and no use of relief medication		Difference in days (*p*-value)
	Zanamivir	Placebo	Zanamivir	Placebo		Zanamivir	Placebo	
NAI30008[77]	262	263	6.0	7.0	1.0 (0.123)	8.0	10.0	2.0 (0.037)
NAI30009[78]	224	247	4.5	5.0	0.5 (0.011)	5.0	6.0	1.0 (0.002)
NAI30010[79]	76	81	4.5	5.5	1.0 (0.033)	5.5	6.75	1.25 (0.150)
NAI30011[80]	237	229	4.50	5.00	0.50 (0.495)	7.0	7.0	0.0 (0.623)
NAI30012[81]	191	167	6.5	7.5	1.0 (0.159)	9.0	10.0	1.0 (0.131)
NAI30015[82]	293	295	2.17	2.67	0.5 (0.166)	3.17	3.83	0.66 (0.058)
NAIA3002[91]	412	365	5.5	6.0	0.5 (0.228)	7.0	8.0	1.0 (0.054)
NAIB3002[99]	174	182	5.0	7.5	2.5 (< 0.001)	5.5	8.25	2.75 (< 0.001)

a Alleviation defined as no fever (temperature of < 37.8 °C), cough recorded as none or mild, and muscle/joint aches and pains, sore throat, feverishness/chills and headache recorded as absent/minimal.

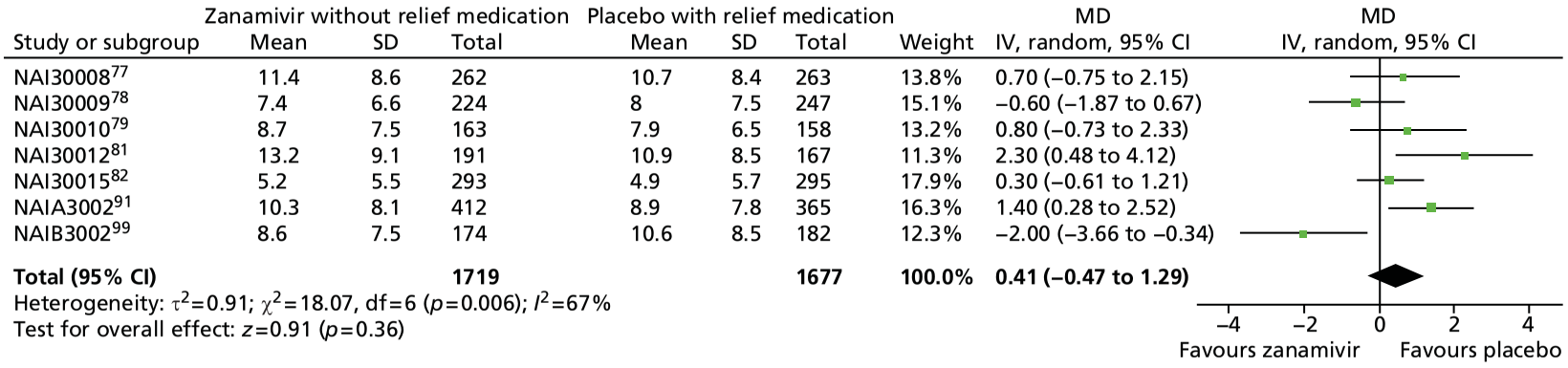


FIGURE 6 Zanamivir vs. placebo for treatment. Time (days) to first alleviation of symptoms in adults with/without relief medication. df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Analysis of hospitalisations

In oseltamivir treatment of adults, there was no significant difference in hospitalisation rate between treatment groups (RR 0.92, 95% CI 0.57 to 1.50; I^2 statistic = 0%) or in treatment of children (RR 1.92, 95% CI 0.70 to 5.23; I^2 statistic = 0%), with wide CIs; or in prophylaxis (RR 1.14, 95% CI 0.66 to 1.94; I^2 statistic = 0%). Data on hospitalisations for the zanamivir studies were not reported.

Analysis of influenza complications

Pneumonia

In adult treatment trials, oseltamivir significantly reduced self-reported, investigator-mediated, unverified pneumonia (RR 0.55, 95% CI 0.33 to 0.90; I^2 statistic = 0%; RD 1.00%, 95% CI 0.22% to 1.49%; NNTB 100, 95% CI 67 to 451) in the treated population. The effect was significant in the six trials that collected data on non-specific adverse events or secondary/intercurrent illness forms (RR 0.44, 95% CI 0.22 to 0.88; I^2 statistic = 0%; RD 0.99%, 95% CI 0.21% to 1.38%; NNTB 101, 95% CI 73 to 470). However, it was not significant in the five trials (two CSRs) that used more detailed diagnostic data collection forms, and in no studies that reported on radiological confirmation of pneumonia (*Figure 7*). There was no significant effect on pneumonia in children (RR 1.06, 95% CI 0.62 to 1.83; I^2 statistic = 0%). In two zanamivir adult trials,[81,82] pneumonia reporting was based on a stricter definition of X-ray confirmation and there was also no significant treatment effect (RR 1.02, 95% CI 0.35 to 3.02; I^2 statistic = 39%). In nine zanamivir trials,[77,79,80,87,89,91,97–99] pneumonia was a self-reported, investigator-mediated, unverified outcome (see *Figures 8* and *9*). Overall, there was no significant effect of zanamivir on mixed verified and unverified pneumonia in adult treatment (RR 0.90, 95% CI 0.58 to 1.40; I^2 statistic = 0%). In prophylaxis trials, zanamivir reduced the risk of self-reported, investigator-mediated, unverified pneumonia in adults (RR 0.30, 95% CI 0.11 to 0.80; I^2 statistic = 0%; RD 0.32%, 95% CI 0.09% to 0.41%; NNTB 311, 95% CI 244 to 1086).

In a metaregression of 'pneumonia' based on 32 studies, treatment effects were not statistically different by age group ($p = 0.22$), drug ($p = 0.89$) or indication ($p = 0.14$). However, treatment effects were statistically different by method of diagnosis ($p = 0.025$). For unclear objective diagnosis of pneumonia, the treatment effect was RR 0.51 (95% CI 0.35 to 0.75; I^2 statistic = 0%), whereas for objective diagnosis data collection of pneumonia, the treatment effect was 1.01 (95% CI 0.69 to 1.47; I^2 statistic = 0%).

Serious complications and study withdrawals

In oseltamivir trials, treatment did not significantly affect complications classified as serious or those that led to withdrawal from the trial in adults (RR 0.91, 95% CI 0.40 to 2.06; I^2 statistic = 0%) or in children (RR 1.98, 95% CI 0.58 to 6.72; I^2 statistic = 0%). This outcome could not be assessed in oseltamivir prophylaxis because of an insufficient number of events. There was no significant effect of zanamivir, in adult treatment, in reducing the risk of any complication classified as serious or which led to study withdrawal (RR 1.10, 95% CI 0.46 to 2.63; I^2 statistic = 0%) or in prophylaxis (RR 1.09, 95% CI 0.36 to 3.26; I^2 statistic = 0%). This outcome could not be assessed in children because of an insufficient number of events.

Bronchitis, sinusitis and otitis media

Neither zanamivir nor oseltamivir significantly reduced the risk of bronchitis or sinusitis in prophylaxis trials. In adults, treatment with oseltamivir did not significantly reduce the risk of bronchitis (RR 0.75, 95% CI 0.56 to 1.01; I^2 statistic = 36%), sinusitis (RR 1.03, 95% CI 0.76 to 1.40; I^2 statistic = 0%) or otitis media (RR 1.11, 95% CI 0.57 to 2.15; I^2 statistic = 0%). The result for bronchitis was sensitive to the methods used, as a fixed-effects analysis showed a significant effect ($p = 0.02$). Oseltamivir did not significantly affect complications in treatment of children, including otitis media (RR 0.80, 95% CI 0.62 to 1.02; I^2 statistic = 0%).

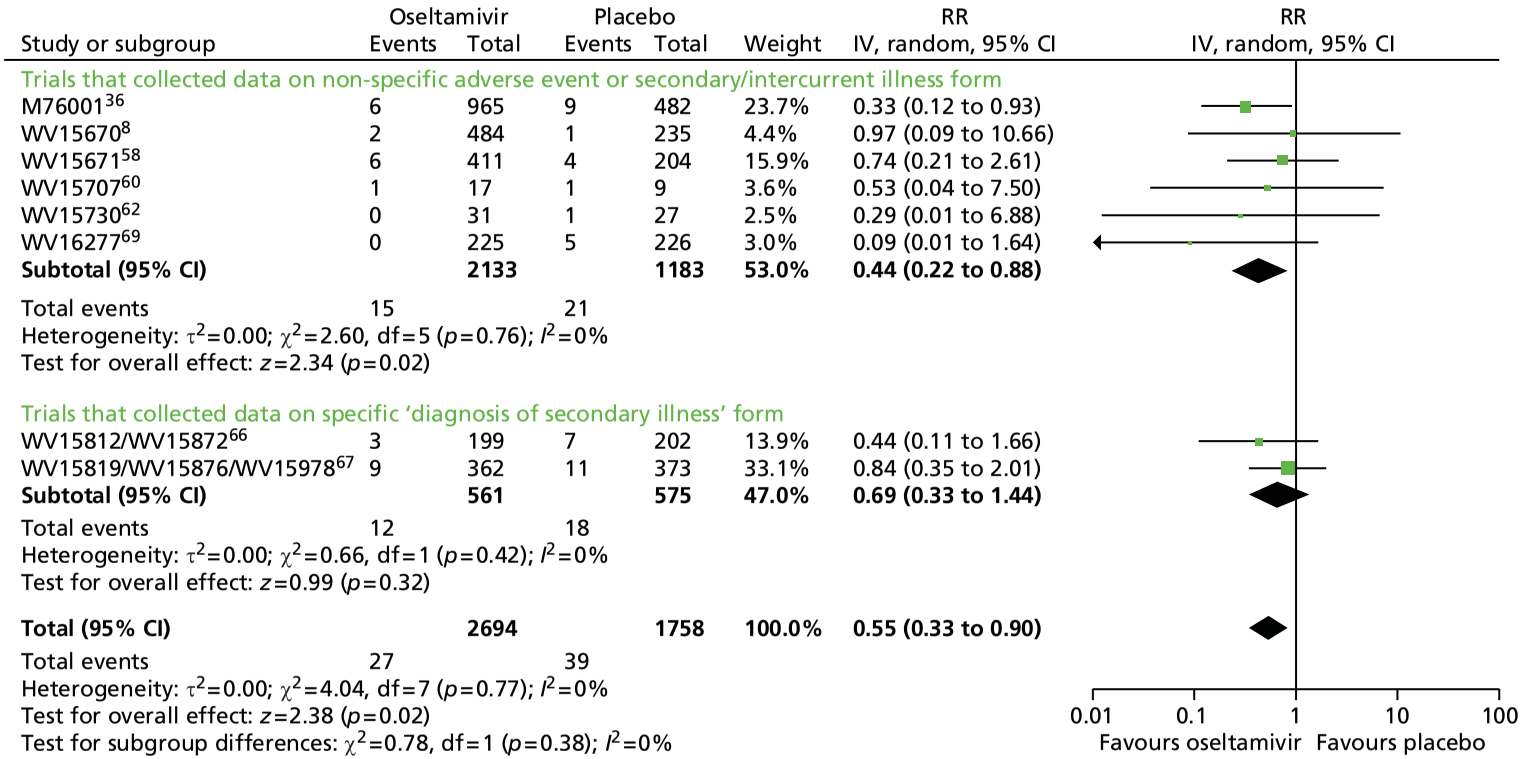


FIGURE 7 Oseltamivir vs. placebo for treatment complications: pneumonia in adult treatment. df, degrees of freedom; IV, inverse variance.

Treatment with zanamivir significantly reduced the risk of bronchitis in adults (RR 0.75, 95% CI 0.61 to 0.91; I^2 statistic = 0%; RD 1.80%, 95% CI 0.65% to 2.80%; NNTB 56, 95% CI 36 to 155), but did not reduce the risk of sinusitis or otitis media. In children, zanamivir treatment did not significantly reduce the risk of sinusitis (RR 0.87, 95% CI 0.12 to 6.45; I^2 statistic = 40%) or otitis media (RR 1.00, 95% CI 0.59 to 1.72; I^2 statistic = 0%).

See *Table 1* for a summary of the methodology used for collecting and assessing complications in oseltamivir treatment trials. For the overall results for oseltamivir in adults see *Table 8* and for children see *Table 9*. *Table 10* shows the overall results for zanamivir in adults and *Table 11* shows the results for children.

Analysis of influenza outcomes in prophylaxis studies

Symptomatic influenza was lower in the oseltamivir arms than the placebo arms in studies of prophylaxis (RR 0.45, 95% CI 0.30 to 0.67; I^2 statistic = 0%; RD 3.05%, 95% CI 1.83% to 3.88%; NNTB 33, 95% CI 26 to 55), but there were no differences for all other influenza outcomes, including overall ILI reported as an adverse event on-treatment. In household prophylaxis, one small study with missing outcome data and selective reporting, including 405 participants, showed a significant reduction of symptomatic influenza in the oseltamivir arm compared with placebo (RR 0.20, 95% CI 0.09 to 0.44; RD 13.6%, 95% CI 9.52% to 15.47%), but in the same study there was no significant reduction in asymptomatic influenza (RR 1.14, 95% CI 0.39 to 3.33). Asymptomatic influenza was not significantly reduced and there was no non-influenza ILI reported throughout the study period.

In prophylaxis trials we could not analyse effects on ILI because of a lack of definition in the CSRs. However, using our definition (see *Methods),* oseltamivir did not reduce ILI in participants (RR 0.95, 95% CI 0.86 to 1.06). See *Appendix 11* for further analysis of symptomatic ILI.

The Roche trial programme assessing the effects of oseltamivir in PEP, submitted to the FDA on 22 May 2000, consisted of two trials.[65,120] We included only one trial[65] because the other[120] was not placebo controlled. WV15799[65] was a double-blind, cluster-randomised trial in which contact clusters of index cases were randomised to oseltamivir 75 mg a day or placebo for 7 days. The manufacturer concluded that the trial proved that oseltamivir could prevent influenza in contacts by interrupting transmission from index cases. Interruption of transmission has two components: reduction of viral spread from index cases (measured by nasal shedding of influenza viruses) and prevention of onset of influenza in contacts measured with a mixture of symptoms and signs and 'laboratory confirmation' (i.e. viral culture from the upper airways and/or at least a fourfold rise in antibody titres measured between baseline and 2–3 weeks later). The design of the WV15799[65] is weak. All index cases were left untreated except for a paracetamol rescue pack, making it impossible to assess the effect of oseltamivir on nasal voidance of index cases. Nasal viral voidance was measured only in symptomatic participants thereby missing out on potential asymptomatic infected people.

TABLE 8 Oseltamivir vs. placebo for treating influenza in adults

Patient or population: healthy adults with influenza *Settings:* community, nursing homes *Intervention:* oseltamivir vs. placebo for treatment						
	Illustrative comparative risks,[a] study population (95% CI)					
	Assumed risk	Corresponding risk				
Outcomes	Placebo	Oseltamivir vs. placebo for treatment	Relative effect (95% CI)	Number of participants (studies)	RD, % (95% CI)	NNTB or NNTH (95% CI)
Time to first alleviation of symptoms in adult treatment (ITT population) (hours)		The mean time (hours) to first alleviation of symptoms adults in the intervention groups was 16.76 lower	16.8 hours (8.4 to 25.1)	3954 (8)	N/A	N/A
Adverse events: nausea in adult treatment (on-treatment)	64 per 1000	101 per 1000 (73 to 138)	RR 1.57 (1.14 to 2.15)	4452 (8)	–3.66 (–7.39 to –0.9)	NNTH 28 (14 to 112)
Adverse events: vomiting in adult treatment (on-treatment)	32 per 1000	77 per 1000 (56 to 108)	RR 2.43 (1.75 to 3.38)	4452 (8)	–4.56 (–7.58 to –2.39)	NNTH 22 (14 to 42)
Adverse events: diarrhoea in adult treatment (on-treatment)	71 per 1000	47 per 1000 (32 to 69)	RR 0.67 (0.46 to 0.98)	4452 (8)	2.33 (0.14 to 3.81)	NNTB 43 (27 to 709)
Complications: self reported, investigator-mediated, unverified pneumonia in adult treatment	22 per 1000	12 per 1000 (7 to 20)	RR 0.55 (0.33 to 0.90)	4452 (8)	1.00 (0.22 to 1.49)	NNTB 100 (67 to 451)
Adverse events: cardiac body system in adult treatment (on-treatment)	13 per 1000	7 per 1000 (3 to 13)	RR 0.49 (0.25 to 0.97)	3943 (6)	0.68 (0.04 to 1.00)	NNTB 148 (101 to 2509)
Adverse events: hospital admission in adult treatment	18 per 1000	17 per 1000 (11 to 28)	RR 0.92 (0.57 to 1.50)	4394 (7)	0.15 (–0.78 to 0.91)	NNTB 687 (NNTB 110 to ∞ to NNTH 128)

N/A, not applicable.
a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

TABLE 9 Oseltamivir vs. placebo for treating influenza in children

Patient or population: healthy children with influenza *Settings:* community *Intervention:* oseltamivir vs. placebo for treatment						
	Illustrative comparative risks,[a] study population (95% CI)					
	Assumed risk	Corresponding risk				
Outcomes	Placebo	Oseltamivir vs. placebo for treatment	Relative effect (95% CI)	Number of participants (studies)	RD, % (95% CI)	NNTB or NNTH (95% CI)
Time to first alleviation of symptoms in child treatment (hours)		The mean time (hours) to first alleviation of symptoms in children in the intervention groups was 8.04 lower (33.34 lower to 17.26 higher)		1329 (3)		Not significant
Hospital admission in child treatment (safety population)	9 per 1000	17 per 1000 (6 to 46)	RR 1.92 (0.7 to 5.23)	1359 (3)	–0.81 (–3.72 to 0.26)	NNTH 124 (NNTB 379 to ∞ to NNTH 27)
Complications: bronchitis in child treatment	31 per 1000	20 per 1000 (8 to 48)	RR 0.65 (0.27 to 1.55)	1359 (3)	1.08 (–1.69 to 2.25)	NNTB 93 (NNTB 45 to ∞ to NNTH 59)
Complications: otitis media in child treatment	163 per 1000	130 per 1000 (101 to 166)	RR 0.8 (0.62 to 1.02)	1359 (3)	3.26 (–0.33 to 6.18)	NNTB 31 (NNTB 17 to ∞ to NNTH 308)
Complications: pneumonia in child treatment	37 per 1000	39 per 1000 (23 to 68)	RR 1.06 (0.62 to 1.83)	1359 (3)	–0.22 (–3.07 to 1.41)	NNTH 450 (NNTB 71 to ∞ to NNTH 33)
Adverse events: diarrhoea in child treatment (on-treatment)	72 per 1000	63 per 1000 (42 to 92)	RR 0.87 (0.58 to 1.28)	1358 (3)	0.93 (–2.01 to 3.02)	NNTB 108 (NNTB 34 to ∞ to NNTH 50)
Adverse events: vomiting in child treatment (on-treatment)	76 per 1000	130 per 1000 (94 to 179)	RR 1.7 (1.23 to 2.35)	1358 (3)	5.34 (1.75 to 10.29)	NNTH 19 (10 to 57)

a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

TABLE 10 Zanamivir vs. placebo for treating influenza in adults

Patient or population: healthy adults with influenza *Settings:* community, nursing homes *Intervention:* zanamivir vs. placebo for treatment						
	Illustrative comparative risks,[a] study population (95% CI)					
	Assumed risk	Corresponding risk				
Outcomes	Placebo	Zanamivir vs. placebo for treatment	Relative effect (95% CI)	Number of participants (studies)	RD, % (95% CI)	NNTB or NNTH (95% CI)
Time to first alleviation of symptoms in adult treatment (days)		The mean time (days) to first alleviation of symptoms in adults in the intervention groups was 0.60 lower	0.60 days (0.39 to 0.81)	5411 (13)	N/A	N/A
Complications: pneumonia confirmed with X-ray in adult treatment	32 per 1000	33 per 1000 (11 to 98)	RR 1.02 (0.35 to 3.02)	946 (2)	–0.06 (–6.56 to 2.11)	NNTH 1540 (NNTB 48 to ∞ to NNTH 16)
Adverse events: nausea/vomiting in adult treatment (on-treatment)	41 per 1000	24 per 1000 (16 to 38)	RR 0.6 (0.39 to 0.94)	6553 (15)	1.63 (0.24 to 2.48)	NNTB 62 (41 to 411)
Adverse events: psychiatric body system in adult treatment (on-treatment)	6 per 1000	6 per 1000 (3 to 13)	RR 1.16 (0.57 to 2.38)	4732 (10)	–0.09 (–0.76 to 0.24)	NNTH 1132 (NNTB 421 to ∞ to NNTH 132)
Complications: bronchitis in adult treatment	72 per 1000	54 per 1000 (44 to 65)	RR 0.75 (0.61 to 0.91)	6072 (12)	1.80 (0.65 to 2.80)	NNTB 56 (36 to 155)

N/A, not applicable.
a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

TABLE 11 Zanamivir vs. placebo for treating influenza in children

Patient or population: **healthy children with influenza** ***Settings:*** **community** ***Intervention:*** **zanamivir vs. placebo for treatment**						
	Illustrative comparative risks,[a] study population (95% CI)					
	Assumed risk	**Corresponding risk**				
Outcomes	**Placebo**	**Zanamivir vs. placebo for treatment**	**Relative effect (95% CI)**	**Number of participants (studies)**	**RD, % (95% CI)**	**NNTB or NNTH (95% CI)**
Time to first alleviation of symptoms in children (days)		The mean time (days) to first alleviation of symptoms in children in the intervention groups was 1.08 lower (2.32 lower to 0.15 higher)		723 (2)	N/A	N/A
Complications: sinusitis in child treatment	15 per 1000	13 per 1000 (2 to 96)	RR 0.87 (0.12 to 6.45)	737 (2)	0.19 (–8.09 to 1.31)	NNTB 519 (NNTB 13 to ∞ to NNTH 77)
Complications: otitis media in child treatment	71 per 1000	71 per 1000 (42 to 122)	RR 1.0 (0.59 to 1.72)	737 (2)	0.00 (–5.13 to 2.92)	NNTB ≥ 1000 (NNTB 35 to ∞ to NNTH 20)

N/A, not applicable.
a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

Zanamivir similarly significantly reduced the risk of symptomatic influenza for individuals (RR 0.39, 95% CI 0.22 to 0.70; I^2 statistic = 45%; RD 1.98%, 95% CI 0.98% to 2.54%; NNTB 51, 95% CI 40 to 103), as well as households (RR 0.33, 95% CI 0.18 to 0.58; I^2 statistic = 40%; RD 14.84%, 95% CI 12.18% to 16.55%; NNTB 7, 95% CI 6 to 9). However, it did not reduce the risk of asymptomatic influenza in the prophylaxis of individuals (RR 0.97, 0.76 to 1.24; I^2 statistic = 0%) or asymptomatic individuals in PEP of households (RR 0.88, 95% CI 0.65 to 1.20; I^2 statistic = 0%). See *Table 10* for the overall results for zanamivir in adults and *Table 11* for results in children. See *Tables 12* and *13* for the overall results for zanamivir in adults.

Analysis of harms

Oseltamivir treatment

Nausea, vomiting and diarrhoea Oseltamivir in the treatment of adults is associated with increased risk of nausea (RR 1.57, 95% CI 1.14 to 2.15; I^2 statistic = 43%; RD 3.66%, 95% CI 0.90% to 7.39%; NNTH 28, 95% CI 14 to 112) and vomiting (RR 2.43, 95% CI 1.75 to 3.38; I^2 statistic = 12%; RD 4.56%, 95% CI 2.39% to 7.58%; NNTH 22, 95% CI 14 to 42). It is associated with a decreased risk of diarrhoea (RR 0.67, 95% CI 0.46 to 0.98; I^2 statistic = 44%; RD 2.33%, 95% CI 0.14% to 3.81%; NNTB 43, 95% CI 27 to 709) compared with placebo during on-treatment periods. Both nausea and vomiting were associated with significant heterogeneity, when treatment effects appeared larger in otherwise healthy adults than in the elderly and the chronically ill. However, one trial of otherwise healthy adults[69] also showed smaller effects. Vomiting was more common in those children on oseltamivir treatment than in those on placebo treatment (RR 1.70, 95% CI 1.23 to 2.35; I^2 statistic = 0%; RD 5.34%, 95% CI 1.75% to 10.29%; NNTH 19, 95% CI 10 to 57).

Cardiac effects The cardiac effects of oseltamivir are unclear. Exposure to oseltamivir may reduce cardiac general events compared with placebo (RR 0.49, 95% CI 0.25 to 0.97; I^2 statistic = 0%; RD 0.68%, 95% CI 0.04% to 1.00%; NNTB 148, 95% CI 101 to 2509), excluding one trial[70] in which electrocardiography was included in the safety parameters. However, exposure to oseltamivir may increase corrected QT interval prolongation (including borderline) as reported in trial WV16277[70] (RD 4.0%, 95% CI 0.71% to 7.30%; NNTH 25, 95% CI 14 to 140) compared with placebo during on-treatment periods.

Psychiatric effects In treatment trials, there was no significant increase in risk between oseltamivir and on-treatment psychiatric adverse events overall (RR 0.93, 95% CI 0.43 to 2.03; I^2 statistic = 0%). However, there was a dose–response effect in the two 'pivotal' treatment trials.[8,58] In the identically designed trials[8,58] there were two active treatment groups: 150 mg (standard dose) and 300 mg (high dose) oseltamivir per day. In the dose–response analysis there was an increased risk of psychiatric body system adverse events over the entire follow-up period ($p = 0.038$, based on likelihood ratio test). In one trial,[8] the event rates were 1 of 204, 1 of 206 and 4 of 205 in the placebo, 75-mg and 150-mg arms, respectively, whereas the second trial[58] had rates of 2 of 235, 0 of 242 and 5 of 242, respectively.

Effect on antibodies (post-protocol hypotheses) The proportion of patients being diagnosed as influenza infected in oseltamivir treatment of adults was significantly lower in the treated group than in the control group (RR 0.95, 95% CI 0.91 to 0.99; I^2 statistic = 0%). The proportion of patients with fourfold increases in antibody titre was significantly lower in the treated group than in the control group (RR 0.92, 95% CI 0.86 to 0.97; I^2 statistic = 0%). This represents an absolute difference of 5% between treatment groups. There was a lower proportion of children on oseltamivir with a fourfold increase in antibodies (RR 0.90, 95% CI 0.80 to 1.00; I^2 statistic = 0%).

TABLE 12 Zanamivir vs. placebo for preventing influenza in adults

Patient or population: healthy adults without influenza *Settings:* community, nursing homes *Intervention:* zanamivir vs. placebo for prophylaxis						
	Illustrative comparative risks,[a] study population (95% CI)					
	Assumed risk	Corresponding risk				
Outcomes	Placebo	Zanamivir vs. placebo for prophylaxis	Relative effect (95% CI)	Number of participants (studies)	RD, % (95% CI)	NNTB or NNTH (95% CI)
Symptomatic influenza in prophylaxis of individuals	33 per 1000	13 per 1000 (7 to 23)	RR 0.39 (0.22 to 0.70)	5275 (4)	1.98 (0.98 to 2.54)	NNTB 51 (40 to 103)
Asymptomatic influenza in prophylaxis of individuals	50 per 1000	48 per 1000 (38 to 60)	RR 0.97 (0.76 to 1.24)	5275 (4)	0.14 (–1.1 to 1.1)	NNTB 729 (NNTB 91 to ∞ to NNTH 91)
Symptomatic influenza in household prophylaxis	190 per 1000	42 per 1000 (25 to 68)	RR 0.22 (0.13 to 0.36)	824 (2)	14.84 (12.18 to 16.55)	NNTB 7 (6 to 9)
Asymptomatic influenza in household prophylaxis	107 per 1000	97 per 1000 (64 to 145)	RR 0.90 (0.6 to 1.35)	824 (2)	1.32 (–2.2 to 3.84)	NNTB 76 (NNTB 26 to ∞ to NNTH 46)
Complications: pneumonia in adult prophylaxis	5 per 1000	1.5 per 1000 (1 to 4)	RR 0.30 (0.11 to 0.8)	7662 (6)	0.32 (0.09 to 0.41)	NNTB 311 (244 to 1086)
Complications: bronchitis in adult prophylaxis	15 per 1000	8 per 1000 (3 to 18)	RR 0.49 (0.02 to 1.19)	7662 (6)	0.79 (–0.29 to 1.24)	NNTB 127 (to NNTB 81 to ∞ to NNTH 341)

a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

TABLE 13 Oseltamivir vs. placebo for preventing influenza in adults

Patient or population: healthy adults without influenza *Settings*: community, nursing homes *Intervention*: oseltamivir vs .placebo for prophylaxis						
	Illustrative comparative risks,[a] study population (95% CI)					
	Assumed risk	Corresponding risk				
Outcomes	Placebo	Oseltamivir vs. placebo for prophylaxis	Relative effect (95% CI)	Number of participants (studies)	RD, % (95% CI)	NNTB or NNTH (95% CI)
Symptomatic influenza in adult prophylaxis of individuals	55 per 1000	25 per 1000 (17 to 37)	RR 0.45 (0.30 to 0.67)	2479 (3)	3.05 (1.83 to 3.88)	NNTB 33 (26 to 55)
Symptomatic influenza in household prophylaxis	170 per 1000	34 per 1000 (15 to 75)	RR 0.2 (0.09 to 0.44)	405 (1)	13.6 (9.52 to 15.47)	NNTB 7 (6 to 11)
Adverse events: psychiatric body systems in adult prophylaxis (all events on- and off-treatment)	13 per 1000	23 per 1000 (14 to 40)	RR 1.80 (1.05 to 3.08)	3434 (4)	–1.06 (–2.76 to –0.07)	NNTH 94 (36 to 1538)
Adverse events: headache in adult prophylaxis (on-treatment)	175 per 1000	207 per 1000 (184 to 233)	RR 1.18 (1.05 to 1.33)	3434 (4)	–3.15 (–5.78 to –0.88)	NNTH 32 (18 to 115)
Adverse events: nausea in adult prophylaxis (on-treatment)	43 per 1000	85 per 1000 (52 to 138)	RR 1.96 (1.2 to 3.2)	3434 (4)	–4.15 (–9.51 to –0.86)	NNTH 25 (11 to 116)
Adverse events: vomiting in adult prophylaxis (on-treatment)	10 per 1000	20 per 1000 (7 to 55)	RR 1.91 (0.7 to 5.22)	3434 (4)	–0.95 (–4.41 to 0.31)	NNTH 106 (NNTB 319 to ∞ to NNTH 23)
Adverse events: headache in adult prophylaxis (off-treatment)	37 per 1000	33 per 1000 (23 to 46)	RR 0.88 (0.63 to 1.24)	3434 (4)	0.44 (–0.89 to 1.37)	NNTB 226 (NNTB 74 to ∞ to NNTH 113)

a To estimate treatment effects we first calculated risk ratios and used the average (mean) control event rate and pooled risk ratios reported in figures to calculate risk differences.

Oseltamivir prophylaxis

Headaches and nausea In oseltamivir prophylaxis, there was an increased risk of headaches on-treatment (RR 1.18, 95% CI 1.05 to 1.33; I^2 statistic = 0%; RD 3.15%, 95% CI 0.88% to 5.78%; NNTH 32, 95% CI 18 to 115) (*Figure 8*) and nausea on-treatment (RR 1.96, 95% CI 1.20 to 3.20; I^2 statistic = 49%; RD 4.15%, 95% CI 0.86% to 9.51%; NNTH 25, 95% CI 11 to 116). There was also a dose–response effect for headaches in study[52] ($p = 0.013$, based on likelihood ratio test), for which on-treatment rates were 202 of 519, 225 of 520 and 242 of 520 in the placebo, standard-dose and high-dose arms, respectively.

Psychiatric effects *Figure 9* shows that in prophylaxis trials of oseltamivir there was a significant increase in patients with psychiatric adverse events over the on- and off-treatment periods (RR 1.80, 95% CI 1.05 to 3.08; I^2 statistic = 0%; RD 1.06%, 95% CI 0.07% to 2.76%; NNTH 94, 95% CI 36 to 1538). Initial analysis of patients with psychiatric adverse events in the on-treatment period showed a borderline statistically significant result ($p = 0.06$), hence we conducted sensitivity analysis using Peto's method ($p = 0.05$) as well as the analysis reported in *Figure 9*.

Table 14 shows a summary of all of the psychiatric adverse events in oseltamivir prophylaxis trials. Of particular note was an oseltamivir patient in one study[68] who had severe confusion on day 27 and was hospitalised. On day 28 the patient was taken off medication and the event resolved. On day 29 the patient was discharged from hospital and subsequently resumed medication. However, confusion reappeared on day 32. The initial event was misclassified in the CSR as 'mental impairment' but has since been corrected in an erratum published in the same journal that published the original trial manuscript.[37,38]

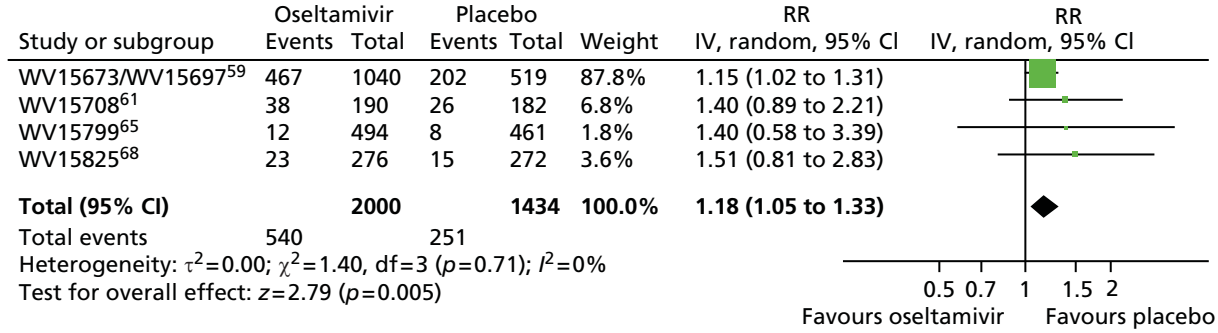


FIGURE 8 Oseltamivir vs. placebo for prophylaxis, outcome: adverse events – headache in adult prophylaxis (on-treatment). df, degree of freedom; IV, inverse variance.

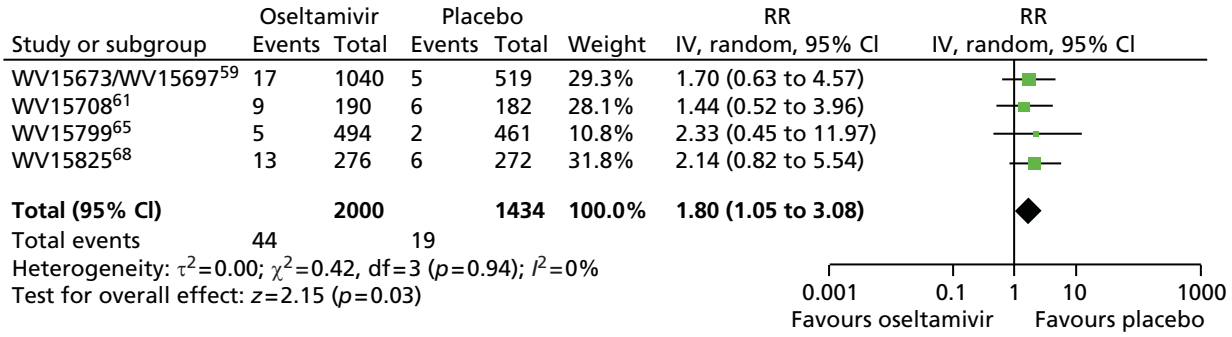


FIGURE 9 Oseltamivir vs. placebo for prophylaxis: adverse events – psychiatric body system in adult prophylaxis (on- and off-treatment). df, degree of freedom; IV, inverse variance.

TABLE 14 Psychiatric adverse events in oseltamivir prophylaxis trials

	Oseltamivir		Placebo		Total	
Event type	Number of events	%	Number of events	%	Number of events	%
Confusion	5	0.25	1	0.07	6	0.17
Depression	14	0.7	6	0.42	20	0.58
Hallucinations	2	0.1	0	0.00	2	0.06
Anxiety	7	0.35	8	0.56	15	0.44
Psychosis	2	0.1	1	0.07	3	0.09
Schizophrenia	1	0.05	0	0.00	1	0.03
Bipolar disorder	0	0	1	0.07	1	0.03
Sleeping disorder	2	0.1	0	0.00	2	0.06
Aggression	1	0.05	0	0.00	1	0.03
Stress symptoms	3	0.15	0	0.00	3	0.09
Restlessness	1	0.05	0	0.00	1	0.03
Nervousness	1	0.05	0	0.00	1	0.03
Suicide ideation	1	0.05	0	0.00	1	0.03
Paranoia	1	0.05	0	0.00	1	0.03
Alcohol related	6	0.3	2	0.14	8	0.23
Total	47	2.35	19	1.32	66	1.92

Renal effects There was a non-significant increase in renal events on-treatment (RR 3.17, 95% CI 0.96 to 10.49; I^2 statistic = 0; RD 0.67%, 95% CI –0.01% to 2.93%; NNTH 150, 95% CI NNTH 35 to ∞ to NNTB > 1000). However, in sensitivity analysis using Peto's method the result for renal events was statistically significant ($p = 0.02$).

Zanamivir

Serious adverse events There was no significant effect on serious adverse events in adult treatment trials (RR 0.86, 95% CI 0.49 to 1.50; I^2 statistic = 0%).

Nausea, vomiting and diarrhoea In treatment trials, there was no significant effect on diarrhoea in adults (RR 0.87, 95% CI 0.66 to 1.14; I^2 statistic = 5%) or headache (RR 0.84, 95% CI 0.60 to 1.18; I^2 statistic = 0). However, during the on-treatment phase, nausea and vomiting were significantly less frequent in the zanamivir arm (RR 0.60, 95% CI 0.39 to 0.94; I^2 statistic = 0%; RD 1.63%, 95% CI 0.24% to 2.48%; NNTB 62, 95% CI 41 to 411).

Renal, psychiatric and other harms There was no significant effect observed on the renal system (RR 0.84, 95% CI 0.41 to 1.72; I^2 statistic = 0%) or the psychiatric system (RR 1.16, 95% CI 0.57 to 2.38; I^2 statistic = 0%). In adult treatment trials of zanamivir, there was no significantly increased risk of any other reported adverse events, and there was no significant increase in adverse effects observed in prophylaxis trials, including psychiatric (RR 1.05, 95% CI 0.48 to 2.29; I^2 statistic = 25%) and renal effects (RR 0.67, 95% CI 0.35 to 1.26; I^2 statistic = 0%) on-treatment. There was no significant increase in harms associated with zanamivir treatment of children but data were sparse.

Effect on antibodies There was no significant effect of zanamivir treatment on influenza diagnosis (RR 1.02, 95% CI 0.98 to 1.06; I^2 statistic = 0%) or probability of a fourfold increase in antibody titre (RR 1.06, 95% CI 0.96 to 1.06; I^2 statistic = 0%).

Deaths

In oseltamivir treatment trials, there was one death overall. This event occurred as a result of acute respiratory syndrome in a placebo patient without influenza in study.[66] In prophylaxis trials, there were four deaths in total, all in elderly patients, with two in the placebo group and two in the oseltamivir group. Causes of death were reported as two cancers, one myocardial infarction and one intestinal perforation. However, for both deaths in the oseltamivir arms the participants experienced acute renal failure on-treatment prior to death.

There were eight deaths in total in the zanamivir trials. Six of the deaths were caused by neoplasias or cardiovascular events in elderly patients with multiple pathologies. However, two deaths were reported as being due to influenza A pneumonia. One participant was on inhaled rimantadine plus placebo and the other on zanamivir.

The results of post-protocol hypotheses are in *Appendix 8*.

Discussion

Oseltamivir and zanamivir have small, non-specific effects on reducing time to alleviation of ILI symptoms in adults but not in asthmatic children. Using either drug as prophylaxis reduces the risk of developing symptomatic influenza. Treatment trials with oseltamivir or zanamivir do not settle the question of whether or not complications of influenza, such as pneumonia, are reduced, because of a lack of diagnostic definitions. Use of oseltamivir increases the risk of adverse effects such as nausea, vomiting, psychiatric effects and renal events in adults, and the risk of vomiting in children. The lower bioavailability may explain the lower toxicity of zanamivir than that of oseltamivir. The influenza virus-specific mechanism of action proposed by the producers does not fit the clinical evidence, which shows no such effects.

Reconstructing trial lists and indexing regulatory comments

Calls for incorporating unpublished data to supplement published trial data in systematic reviews and meta-analyses highlight deficiencies in the current methods for obtaining the most complete understanding of a drug's effects.[121] Our methodological approach entailed comprehensive searching of unpublished sources, with a particular emphasis on obtaining unpublished and internal reports from drug manufacturers, intended for regulatory submission, and comments from national regulatory bodies. Our decision not to use published evidence as a basis for trial appraisal and data extraction meant that we had to reconcile and synthesise information from multiple unpublished sources. We had to devise a new method of searching, indexing, retrieving and reviewing trial data, and to combine this understanding with regulatory comments to produce an informative review. The first step in this process entailed the need to develop our own reconstruction of the trial programme without initial help from outside sources. The reconstructed list of trials and then programmes took a whole-time equivalent researcher 20 days to compile. Owing to the complexity of the task, we suggest that, in the future, some of the essential phases, such as checking the trial identification number across multiple documents and databases, be conducted in pairs.

One of the comments received on our protocol suggested that discrepancies between published and unpublished versions of the same data set could be due to mistakes in the non-peer reviewed, unedited CSRs (which may be corrected by the time of publication). Our experience, especially with the non-reporting of serious adverse events, points to the opposite being the case.[122] Considering the fact that unintentional errors can occur, we believe that the response should not be a resort to published papers as 'most accurate' and best unit of analysis, but rather that CSRs – as by far the most comprehensive record of a trial – remain the key unit of analysis, with the expectation that they be amended and kept as accurate as possible over

time, with complete documentation of reasons for any amendments. We believed that the results of our review would be undermined without accessing a more complete body of evidence that we knew to be outside the public domain.

In theory, trial registers would be expected to provide a comprehensive picture of a drug's trial programme. However, registers were not our primary instruments to reconstruct zanamivir and oseltamivir trial programmes. Both drugs' programmes were mainly run in the late 1990s, before trial registration became the norm. In addition, registers may suffer from some of the problems that we were trying to address. Bourgeois *et al.*[123] audited entries for 546 trials of five major classes of drugs on ClinicalTrials.gov, the biggest prospective register of clinical trials, and found evidence of risk of reporting bias and delay in reporting of results. Another review of 152 trials found that the description of 123 (or 81%) of the trials in the sample had been changed in at least one key element in the time between registration and publication. The most frequent changes regarded outcomes.[124] Despite the current limits of registers, both specifically to this review and in the way they are run and updated, we believe that registers are an obvious first choice to start reconstruction of trials programmes. Searching for unpublished material has not yet become standard practice in conducting Cochrane reviews,[125] and is currently variably reported.[126]

The indexing and review of regulatory files was also a very laborious task. It took a whole-time equivalent researcher 3 days to review the FDA regulator's comments and gain a basic understanding of the content. Four additional days were needed to read and annotate the FDA zanamivir files and 28 days for reading and annotating the oseltamivir files and building the table of contents-evidence (see *Appendix 11*). The exercise had to be repeated several times to cross-check content and expand annotations. Construction of the TOC was laborious. A first attempt at electronic mapping the TOC content took 12 and 8 hours, respectively, for the FDA and National Institute for Health and Care Excellence (NICE) regulatory documents. This was carried out using the Adobe Acrobat (Adobe Systems; https://acrobat.adobe.com/us/en/acrobat/how-to/ocr-software-convert-pdf-to-text.htm) optical character recognition search facility, which enabled mapping of citation counts by document and by trial ID. Initially, we used the trial prefix followed by the serial number ('WV15670') as ID. This procedure, however, had one major drawback linked to the nature of regulatory documents. As regulatory documents consist of notes, correspondence and reviews, the same trial is cited in a non-standardised way. For example, trial WV15670[8] is cited as 'WV15670' 15 times, as 'WV_15670' 12 times and simply as '15670' 19 times. Thorough searches must be conducted using all of the different terms. As this can be very time-consuming, we decided to compare an Acrobat search with a Boolean string strategy containing all of the possible citation formats (e.g. WV15758 OR WV 15758 OR Trial 15758 OR Trial15758 OR Trials 15758 OR Trials15758 OR 15758 OR study 15758 OR study15758) (this is logically equivalent to 'WV 15758 OR WV 15758') with a term-by-term search (i.e. separately searching for WV15758 and then for WV 15758 and so on). We reasoned that if the yield were comparable, the Boolean strategy would have been faster. The yield of citations of the two strategies was the same for six of seven 'tracker' studies, but use of a Boolean string was considerably faster (an average of 3 vs. 14 hours) than the term-by-term strategy. The NICE submission citations took 2 hours to list in a TOC using a Boolean strategy. We adopted the Boolean search strategy to construct our TOC. Ultimately, it is possible that a search with the trial numerals ('15670') may be sufficient to identify the vast majority of citations. To validate this method of searching further, our methods should be repeated on other sets of regulatory documents.

Once we had reconstructed the trial programmes, we submitted the results to GSK and Roche for their input. We received detailed feedback from both but, into 2011, Roche's list of trials was still incomplete. Despite the laboriousness of the methods, we believe that we ended up with a far more comprehensive and less biased set of evidence than that available through the current system of journal-based publications. This shift in our data synthesis paradigm was made necessary by the numerous and documented discrepancies between regulatory and published evidence and by the sizeable risk of publication bias of the oseltamivir trial programme. The importance of reconstructing the trial programme by first generating a complete trial list was further reinforced upon discovering bias and oversights in regulators' handling of the trial programme. Regulators focus on a few mutually agreed 'pivotal' trials, the data analyses of which are replicated by the FDA but not by the EMA. Both largely ignored trial M76001,[36] the largest oseltamivir

treatment trial that was conducted prior to initial registration of the drug (and still unpublished). Although the manufacturer may not have offered it as a 'pivotal' trial, far smaller and even ongoing studies were included in the evidence base to support Roche's year 1999 NDA number 021087 (treatment of uncomplicated acute illness due to influenza infections in adults who have been symptomatic for no more than 2 days). The history of the EMA scrutiny is harder to assess as we could find no reports of trial site visits or of data analysis replication, but we identified a pooled analysis of treatment trials, very similar to the Kaiser 2003 analysis,[4] which formed the basis for the EMA conclusion that oseltamivir affected complications reported, for example on EMA's 4 October 2012 Summary of Product Characteristics (www.bmj.com/tamiflu/ema). We requested modules 3–5 (individual listings, demographic data and the statistical analysis report) from the EMA. However, for most oseltamivir trials, the EMA does not have the relevant documents and neither apparently does the National Competent Authorities (e-mail from the EMA, 24 May 2011; e-mail from Dutch regulator Medicines Evaluation Board, 20 July 2011). This means that the modules do not appear to have been either submitted to or requested by regulators, raising questions as to the extent of scrutiny of the clinical trials during the regulatory review of oseltamivir in Europe.

Our new method

Reviewing large quantities of complicated data and linked comments is a very difficult and delicate process. The main problem is not so much the appraisal following standard rules and possible synthesis of data (as when we review published information), but the reconstructions and logical threading of a trial programme generating huge amounts of data needing appraisal. Also the manufacturer's full regulatory submission, which may have even more information than a full CSR, remains confidential. Most of the essential data required are available in CSRs, together with masses of less important data, but, as we have explained, even in this case there may be important omissions, such as mislaid diary cards (*Figures 10* and *11*) for follow-up. Manufacturers are under obligation to provide regulators with all of the data requested to enable them to reach a decision: in doing so they produce vast submissions. None of the authors (all experienced systematic reviewers) had any experience of reviewing regulatory information, but we could not find any workable shortcuts. We believe that providing a critical overview of a trial programme rather than minute dissection of each trial is necessary. This can be done by identifying the important topics in the trial programme (such as the effects of the drug on symptoms, infection, complications, transmission and well-being) and following them throughout the programme, putting the evidence together coherently. This includes carrying out a high-level overview of the mode of action of the drug in different populations for different indications. Understanding a drug's mode of action underpins correct reporting of its strengths and limitations. In addition, a large part of the regulatory submission is made up of chemistry, microbiological, animal model pharmacodynamic and pharmacokinetic studies, which are important for shedding light on the trial programme but which seldom feature in systematic reviews. We are unsure whether or not this information could be considered as core information, but an exhaustive review of a trial programme should include reviews dedicated to such topics.

These methods revealed possible problems in trial conduct and validity, including the lack of comparability between arms induced by subset analysis and by the randomisation analysis fork, high positivity rate of influenza, high gastrointestinal events in the placebo arms, possibly active placebo content and possible procedural breaches in several trials. The ideal option is to carry out analyses on the basis of the ITT population, in which units of randomisation and analysis are the same and many of the potential problems listed are either not present or minimised. We are continuing to develop further methods for using such data.

GlaxoWellcome Confidential

NAIB3002

DAY 6
Post-Treatment Visit

Date of assessment ___ VSDT (D7) [R]

Diary Card

Was the subject's Diary Card (Days 1-5) reviewed for accuracy and completeness? Yes ☐ No ☐

Please resolve any discrepancies in the Diary Card with the subject. DCCHK (A1) [R] [UYESNO]

Global Assessment of Symptoms SYMEVF (A1) [R]

How would you rate the subject's overall influenza-like symptoms? [VISEVF]

None ☐ Mild ☐ Moderate ☐ Severe ☐

Influenza Complications FLUCP (A1) [R] [YNALL]

Has the subject experienced any complications, since the last visit, as a result of their influenza-like illness? Yes ☐ No ☐

If YES, please ✔ ALL complications below: CPTY (A3) [R] [VCPTY]

Pulmonary		Cardiovascular	
Pneumonia	☐ PN	Congestive heart failure	☐ CHF
Exacerbation of COPD*	☐ EXA	Angina	☐ AN
Exacerbation of asthma	☐ AEX	Myocardial infarction	☐ MI
Bronchitis	☐ BR	Arrhythmia	☐ AR
Respiratory failure	☐ REF	Other	☐ OO Specify: CPTX (A66) [R]
Other	☐ PO Specify: CPTX (A66) [R]		

*COPD = Chronic Obstructive Pulmonary Disease

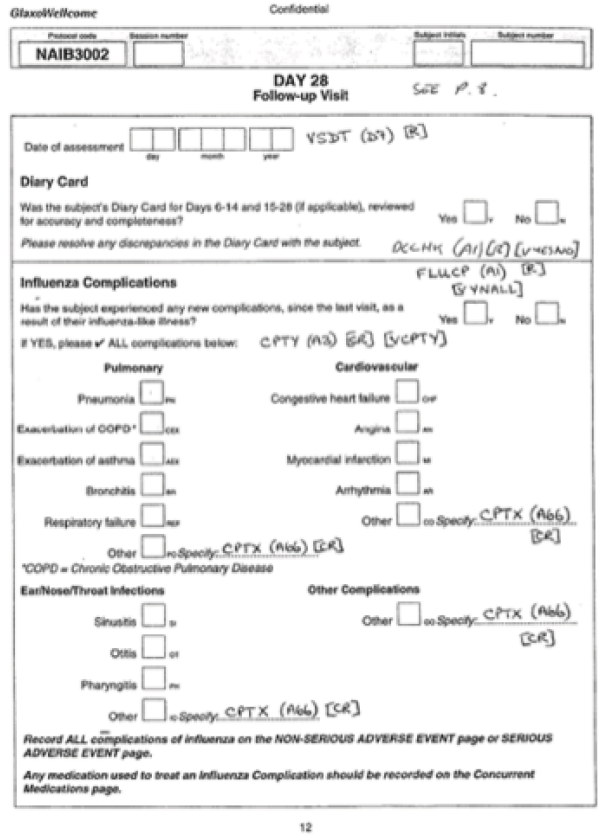
Ear/Nose/Throat Infections		Other Complications	
Sinusitis	☐ SI	Other	☐ OO Specify: CPTX (A66) [R]
Otitis	☐ OT		
Pharyngitis	☐ PH		
Other	☐ EO Specify: CPTX (A66) [R]		

Record ALL complications of influenza on the NON-SERIOUS ADVERSE EVENT page or SERIOUS ADVERSE EVENT page.

Any medication used to treat an Influenza Complication should be recorded on the Concurrent Medications page.

8

FIGURE 10 Example diary card from CRF for zanamivir trial (1).



GlaxoWellcome Confidential

NAIB3002

DAY 28
Follow-up Visit SEE P. 8.

Date of assessment ___ VSDT (D28) [R]

Diary Card

Was the subject's Diary Card for Days 6-14 and 15-28 (if applicable), reviewed for accuracy and completeness? Yes ☐ No ☐

Please resolve any discrepancies in the Diary Card with the subject. DCCHK (A1) [R] [UYESNO]

Influenza Complications FLUCP (A1) [R] [YNALL]

Has the subject experienced any new complications, since the last visit, as a result of their influenza-like illness? Yes ☐ No ☐

If YES, please ✔ ALL complications below: CPTY (A3) [R] [VCPTY]

Pulmonary		Cardiovascular	
Pneumonia	☐ PN	Congestive heart failure	☐ CHF
Exacerbation of COPD*	☐ EXA	Angina	☐ AN
Exacerbation of asthma	☐ AEX	Myocardial infarction	☐ MI
Bronchitis	☐ BR	Arrhythmia	☐ AR
Respiratory failure	☐ REF	Other	☐ OO Specify: CPTX (A66) [R]
Other	☐ PO Specify: CPTX (A66) [R]		

*COPD = Chronic Obstructive Pulmonary Disease

Ear/Nose/Throat Infections		Other Complications	
Sinusitis	☐ SI	Other	☐ OO Specify: CPTX (A66) [R]
Otitis	☐ OT		
Pharyngitis	☐ PH		
Other	☐ EO Specify: CPTX (A66) [R]		

Record ALL complications of influenza on the NON-SERIOUS ADVERSE EVENT page or SERIOUS ADVERSE EVENT page.

Any medication used to treat an Influenza Complication should be recorded on the Concurrent Medications page.

12

FIGURE 11 Example diary card from CRF for zanamivir trial (2).

Regulatory comments

Reviewing regulatory comments was essential to expand our understanding of the trial programme. We expected that detailed reading of regulatory material would allow us to understand discrepancies between US and European regulators' conclusions regarding the effects of oseltamivir, particularly (but not limited to) their putative effect on complications.[8] We were interested in what led the FDA to have far more cautious and conservative statements – as witnessed in the Tamiflu product label and FDA letters – in comparison with European regulators. Our access to huge amounts of FDA regulatory data allowed for many insights but gave us little visibility of manufacturers' responses.

Some of the statements (such as NIs reduce bacterial complications) made by the manufacturer in the CSRs, and, subsequently, in contemporaneous publications and advertisements, appeared unsupported by the evidence provided at the time. The FDA drug regulatory reviewers' comments, although laborious to summarise and contextualise (because of the non-availability of the whole pharmaceutical submission), were confirmed by our reading of the CSRs. However, we were unable to find a statement explaining how the FDA reviewed each NDA. FDA reviewing methods appeared to be a mixture of spot checks, re-run of statistical analyses and on-site inspections. A FDA methods volume or standard operational procedure may be among the documents not available from the web but accessible through a FOI request. Neither the FDA nor the EMA have inventories of held documents, making it very difficult to know what to ask for under FOI rules. We concentrated on downloading or asking for specific CSRs and related documents or reviewers' comments on a particular NDA. The quantity of information held by regulators is likely to be large. For example, NDA 21–246, regarding the use of Tamiflu in the treatment of influenza in children, submitted to the FDA on 15 June 2000, consisted of 137 volumes of study documents and possibly several electronic files. Although we do not know exactly how long a volume was, we have seen references to up to hundreds of pages in each volume.

Requesting specific documents and packages of information is especially important to allow a more efficient and timely reviewing process when confronted with a large volume of evidence, most of which could be of peripheral value. A request for a specific document is likely to be dealt with far more efficiently than a generic request for 'all documentation relating to oseltamivir'. This is one of the reasons why developing a TOC for any drug or family of drugs (no matter how time-consuming) is an absolute prerequisite for any serious attempt at reviewing regulatory evidence. This introduces another very difficult problem: how to handle huge quantities of structured information and the ethics of drawing conclusions from what is still a fragmentary (albeit sizeable) evidence base.

Overall, the FDA assessment of the performance of oseltamivir was 'modest'. This adjective appears six times in a 50-page review document.[109] For example, in the Division Director Memorandum dated 25 October 1999, under the heading 'Public health role of antiviral treatment' the FDA[109] states: 'The clinical relevance of the modest treatment benefit is a highly subjective question' (p. 3). The FDA refused to accept claims of oseltamivir's effects on influenza complications as 'false or misleading' statements in promotional materials.[122] A FDA warning letter seems to imply, for example, that oseltamivir's mode of action is 'proposed' or 'possibly' (that proposed by the manufacturers) (i.e. not certain).[127] However, FDA reviewers appear to have missed important problems in Roche's clinical trials (such as the imbalance in the numbers of individuals classified as influenza infected in oseltamivir treatment trials). Importantly, there appears to have been no investigation into the coherence of the evidence with the proposed mode of action of the drug.

Summary of main results

For the first time, a Cochrane review is based on all relevant full CSRs of a class of drugs integrated by regulatory comments. Also for the first time, all CSRs of trials in a manufacturer's programme (regardless of their relevance to the review) are available to readers without any restriction (apart from minimal redactions to protect anonymity further). The role of Roche and GSK in making this possible should be recognised, as well as that of the BMJ, which kept the issue in the public eye until it was resolved.

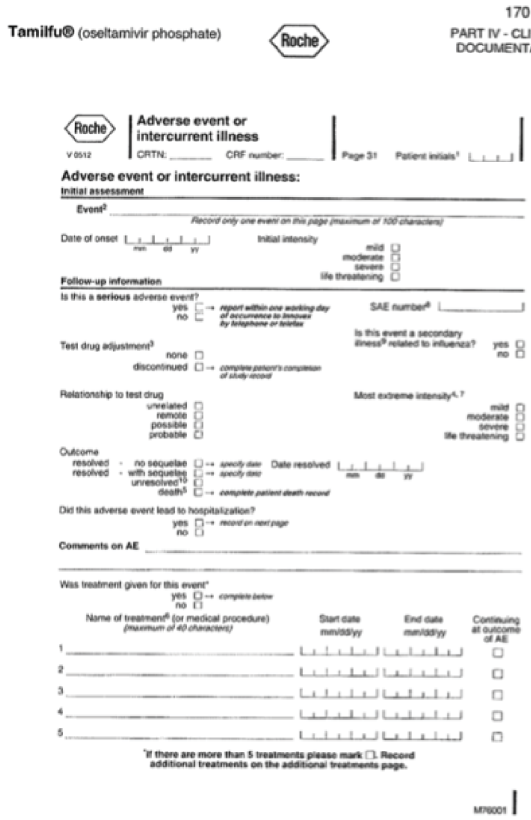
The evidence we have presented and synthesised shows that both of the NIs in this review have symptom-relieving effects, especially for self-reported outcomes. They appear to have symptom-relieving properties that make people with ILI and self-reported, investigator-mediated, unverified pneumonia feel better by shortening symptom duration and reducing the frequency of symptoms, such as cough. For oseltamivir, this effect perhaps extends to cardiac symptoms, despite the short duration of treatment (5 days). We are unsure what to make of this finding but we think it deserves further investigation.

The issue which triggered our change of evidence-seeking methods is partly resolved: no definitions of secondary illnesses were given anywhere in the CSRs [e.g. 'pneumonia' was defined as 'pneumonia' in the CRFs (see *Table 1*) and diagnostic criteria were not given]; clinical diagnosis in the absence of criteria and without X-ray has only a moderate chance of being correct.

We could not decide the level of diagnostic ascertainment of diagnosis of pneumonia and other complications, as it is unclear from the CSRs. Definitions of pneumonia were not given and the algorithm for classification of an event as pneumonia was not supplied. In oseltamivir trials, the CRF trigger for recording of adverse events and secondary illness was a question to the participant posed by the investigator. A typical phrasing is as follows: 'Secondary illness reminder: Has the patient reported any sinusitis, otitis, bronchitis, other chest infection or pneumonia since baseline?' This was followed by a yes/no box to be ticked and an additional form was to be filled out by the investigator for collecting details on the secondary illness. A record of medications outside trial allocation was elicited in addition to the participant's diary card. The original and Medical Dictionary for Regulatory Activities terms suggest diagnoses for all secondary illnesses and adverse events but there is no indication as to how the original and preferred terms were assigned. We therefore considered these outcomes to be 'self-reported, investigator-mediated, unverified' outcomes. For a subset of trials, secondary/intercurrent illness and adverse event data were collected on a single, one-page form. In our meta-analyses, we called this subanalysis 'Trials which collected data on non-specific adverse events or secondary/intercurrent illness form'. For a different subset of trials, CRFs contained space to record diagnostic tests, such as chest X-rays, tympanometry and sinus X-rays for all secondary illness but there was no reporting of such variables in the CSRs (*Figures 12–15*). In our meta-analyses, we called this subanalysis 'Trials which collected data on specific "Diagnosis of Secondary Illness" form'. None of the complications was defined as primary outcomes in any trial, which may explain the poverty of data definition.

In a metaregression of all of the 32 included studies that reported on 'pneumonia', we found evidence that treatment effects for pneumonia are statistically different depending on the method of diagnosis. Unclear objective diagnosis was associated with an apparent 46% reduction in pneumonia as a result of treatment with NIs, whereas the use of objective criteria in the data collection showed no evidence of effect, with a RR of 1.0. Age group (adults vs. children), drug (oseltamivir vs. zanamivir) and indication (treatment vs. prophylaxis) showed no evidence of association with treatment effect.

Meaningful conclusions on the effect of either NI on complications of influenza are difficult to draw based on the trial evidence. In part, this was due to the lack of standardised definitions. In addition, meta-analyses of these outcomes that lacked definitions were based on few events and therefore not robust. Caution is therefore urged in interpreting the meta-analysis result, which suggests that 100 patients (95% CI 67 to 451 patients) need to be treated with oseltamivir for one less self-reported, investigator-mediated, unverified pneumonia. The same applies to the zanamivir treatment result, which suggests a reduced risk of self-reported, investigator-mediated, unverified bronchitis in adults (NNTB 56, 95% CI 36 to 155). The evidence suggested that oseltamivir had a similar effect, although the result was non-significant.



Tamiflu® (oseltamivir phosphate) Roche 170 - 145 PART IV - CLINICAL DOCUMENTATION

Roche **Adverse event or intercurrent illness** V 0512 CRTN: _____ CRF number: _____ Page 31 Patient initials[1] [ ][ ][ ]

Adverse event or intercurrent illness:

Initial assessment

Event[2] _____

Record only one event on this page (maximum of 100 characters)

Date of onset [ ][ ] [ ][ ] [ ][ ] mm dd yy

Initial intensity: mild ☐ moderate ☐ severe ☐ life threatening ☐

Follow-up information

Is this a **serious** adverse event? yes ☐ → *report within one working day of occurrence to Innovex by telephone or telefax* no ☐

SAE number[6] [_____]

Test drug adjustment[3]: none ☐ discontinued ☐ → *complete patient's completion of study record*

Is this event a secondary illness[5] related to influenza? yes ☐ no ☐

Relationship to test drug: unrelated ☐ remote ☐ possible ☐ probable ☐

Most extreme intensity[4, 7]: mild ☐ moderate ☐ severe ☐ life threatening ☐

Outcome: resolved - no sequelae ☐ → *specify date* Date resolved [ ][ ] [ ][ ] [ ][ ] mm dd yy; resolved - with sequelae ☐ → *specify date*; unresolved[13] ☐; death[5] ☐ → *complete patient death record*

Did this adverse event lead to hospitalization? yes ☐ → *record on next page* no ☐

Comments on AE _____

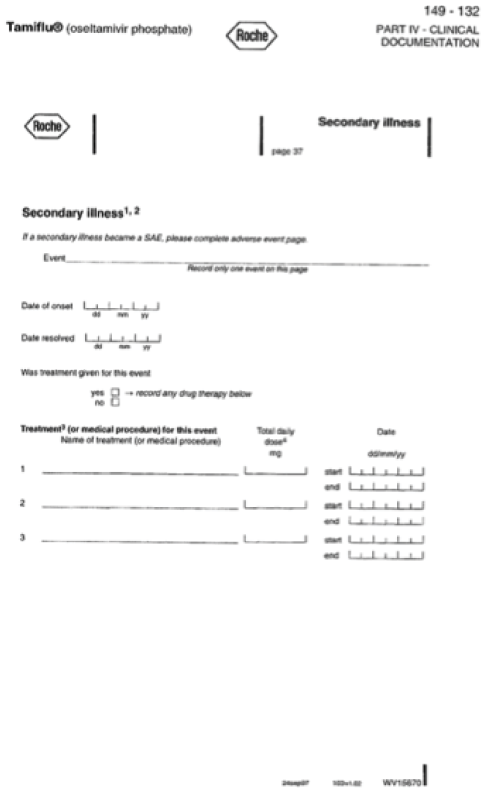
Was treatment given for this event* yes ☐ → *complete below* no ☐

	Name of treatment[8] (or medical procedure) *(maximum of 40 characters)*	Start date mm/dd/yy	End date mm/dd/yy	Continuing at outcome of AE
1	_____	[ ][ ] [ ][ ] [ ][ ]	[ ][ ] [ ][ ] [ ][ ]	☐
2	_____	[ ][ ] [ ][ ] [ ][ ]	[ ][ ] [ ][ ] [ ][ ]	☐
3	_____	[ ][ ] [ ][ ] [ ][ ]	[ ][ ] [ ][ ] [ ][ ]	☐
4	_____	[ ][ ] [ ][ ] [ ][ ]	[ ][ ] [ ][ ] [ ][ ]	☐
5	_____	[ ][ ] [ ][ ] [ ][ ]	[ ][ ] [ ][ ] [ ][ ]	☐

*If there are more than 5 treatments please mark ☐. Record additional treatments on the additional treatments page.

M76001

FIGURE 12 Sample 'Adverse event or intercurrent illness' form (oseltamivir study M76001[36]).



Tamiflu® (oseltamivir phosphate) Roche 149 - 132 PART IV - CLINICAL DOCUMENTATION

Roche **Secondary illness** page 37

Secondary illness[1, 2]

If a secondary illness became a SAE, please complete adverse event page.

Event _____

Record only one event on this page

Date of onset [ ][ ] [ ][ ] [ ][ ] dd mm yy

Date resolved [ ][ ] [ ][ ] [ ][ ] dd mm yy

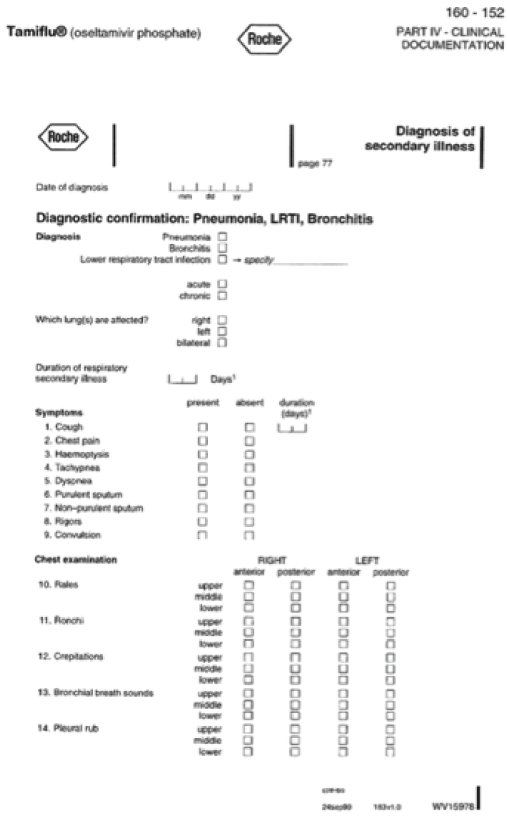
Was treatment given for this event

yes ☐ → *record any drug therapy below* no ☐

	Treatment[3] (or medical procedure) for this event Name of treatment (or medical procedure)	Total daily dose[4] mg	Date dd/mm/yy	
1	_____	[_____]	start	[ ][ ] [ ][ ] [ ][ ]
			end	[ ][ ] [ ][ ] [ ][ ]
2	_____	[_____]	start	[ ][ ] [ ][ ] [ ][ ]
			end	[ ][ ] [ ][ ] [ ][ ]
3	_____	[_____]	start	[ ][ ] [ ][ ] [ ][ ]
			end	[ ][ ] [ ][ ] [ ][ ]

WV15670

FIGURE 13 Sample 'Secondary illness' form (oseltamivir study WV15670[8]).



Tamiflu® (oseltamivir phosphate) Roche

160 - 152
PART IV - CLINICAL DOCUMENTATION

Roche | page 77 | Diagnosis of secondary illness

Date of diagnosis [ ][ ] / [ ][ ] / [ ][ ]
mm dd yy

Diagnostic confirmation: Pneumonia, LRTI, Bronchitis

Diagnosis
Pneumonia ☐
Bronchitis ☐
Lower respiratory tract infection ☐ → *specify:* _____

acute ☐
chronic ☐

Which lung(s) are affected?
right ☐
left ☐
bilateral ☐

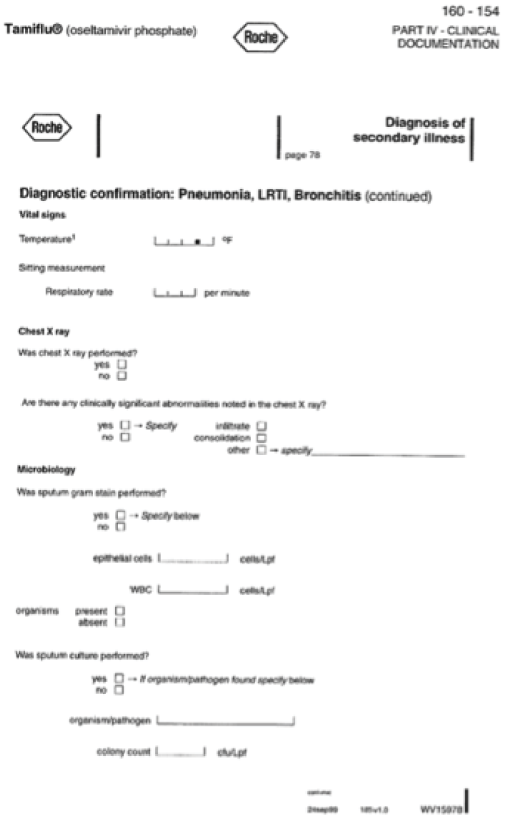
Duration of respiratory secondary illness [ ][ ] Days[1]

Symptoms	present	absent	duration (days)[1]
1. Cough	☐	☐	[ ][ ]
2. Chest pain	☐	☐	
3. Haemoptysis	☐	☐	
4. Tachypnea	☐	☐	
5. Dyspnea	☐	☐	
6. Purulent sputum	☐	☐	
7. Non–purulent sputum	☐	☐	
8. Rigors	☐	☐	
9. Convulsion	☐	☐	

Chest examination		RIGHT anterior	RIGHT posterior	LEFT anterior	LEFT posterior
10. Rales	upper	☐	☐	☐	☐
	middle	☐	☐	☐	☐
	lower	☐	☐	☐	☐
11. Ronchi	upper	☐	☐	☐	☐
	middle	☐	☐	☐	☐
	lower	☐	☐	☐	☐
12. Crepitations	upper	☐	☐	☐	☐
	middle	☐	☐	☐	☐
	lower	☐	☐	☐	☐
13. Bronchial breath sounds	upper	☐	☐	☐	☐
	middle	☐	☐	☐	☐
	lower	☐	☐	☐	☐
14. Pleural rub	upper	☐	☐	☐	☐
	middle	☐	☐	☐	☐
	lower	☐	☐	☐	☐

WV15978

FIGURE 14 Sample 'Diagnosis of secondary illness' form, page 1/2 (oseltamivir study WV15978[67]).



Tamiflu® (oseltamivir phosphate) Roche

160 - 154
PART IV - CLINICAL DOCUMENTATION

Roche | page 78 | Diagnosis of secondary illness

Diagnostic confirmation: Pneumonia, LRTI, Bronchitis (continued)

Vital signs

Temperature[1] [ ][ ].[ ] °F

Sitting measurement

Respiratory rate [ ][ ] per minute

Chest X ray

Was chest X ray performed?
yes ☐
no ☐

Are there any clinically significant abnormalities noted in the chest X ray?
yes ☐ → *Specify* infiltrate ☐
no ☐ consolidation ☐
other ☐ → *specify:* _____

Microbiology

Was sputum gram stain performed?
yes ☐ → *Specify below*
no ☐

epithelial cells [ ] cells/LPF

WBC [ ] cells/LPF

organisms present ☐
absent ☐

Was sputum culture performed?
yes ☐ → *If organism/pathogen found specify below*
no ☐

organism/pathogen [ ]

colony count [ ] cfu/LPF

WV15978

FIGURE 15 Sample 'Diagnosis of secondary illness' form, page 2/2 (oseltamivir study WV15978[67]).

As stated above, there is no evidence that definitions of complications in paediatric, elderly or adult trials were ever prepared and incorporated in the trials' design. Therefore, the reporting of cases of 'otitis media', 'pneumonia', 'sinusitis' or 'bronchitis' are of unclear significance and importance, making it impossible to attribute a cause and draw conclusions.[128] This is probably why the FDA-approved oseltamivir package insert, since 17 November 2000, has consistently stated: 'serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. TAMIFLU has not been shown to prevent such complications'. The original product label did not contain such a statement but, on 14 April 2000, after oseltamivir was approved for sale in the USA, the FDA sent Roche an untitled letter about 'Misleading Efficacy Claims', which the FDA had noted in Roche's promotional materials (p. 3[129]). One of the statements that Roche made was: 'Tamiflu reduces incidence of secondary complications (i.e. bacterial infections) by 45%'. The FDA commented: 'Further, you have claimed reductions in severity and incidence of secondary infections with Tamiflu that are misleading because they are not supported by substantial evidence' (p. 3[129]). We do not know how Roche responded to the FDA but in subsequently available Roche promotional material information, Roche's statements were consistent with the FDA's demands.[8]

There is uncertainty in the 'complications' and 'secondary illnesses' outcome definition, therefore we carried out an analysis on the data from adult treatment trials on those complications classified as serious or those which led to study withdrawal. For oseltamivir, there was no evidence that treatment affected such complications (RD 0.07%, 95% CI –0.78% to 0.44%). This outcome could not be assessed in oseltamivir prophylaxis due to an insufficient number of events. For zanamivir, there was no significant evidence of a treatment effect on such complications (RD –0.04%, 95% CI –0.64% to 0.24%). This outcome could not be assessed in children because of an insufficient number of events.

Contrary to the FDA, the EMA's oseltamivir Summary of Product Characteristics states that oseltamivir significantly reduces the incidence of 'specified lower respiratory tract complications (mainly bronchitis) treated with antibiotics' in individuals aged $\geq$ 13 years. This claim is based on 'a pooled analysis of all influenza-positive adults and adolescents ($N = 2413$) enrolled into treatment studies', of which 1063 were in the placebo group and 1350 were in the oseltamivir-treated population.[130] This statement appears in the EMA files as early as 2001.[131] These exact denominators appear in the Kaiser *et al.*[4] 2003 meta-analysis.

The design of the trials – as defined in the protocol with amendments, SAP and CRFs – does not allow any further inferences. The effect on outcomes that were originally considered of secondary or tertiary importance (such as bronchitis and pneumonia) would have been clarified with better clinical definitions and investigations, as were some of the serious adverse events. These benefited from a paragraph-length narrative, which reported most of the salient features of the event.

Our previous decision to analyse the effects of oseltamivir and zanamivir on the ITT population has been confirmed for oseltamivir, with the demonstration of the effect on antibody responses in participants in treatment trials, although no such effect is discernible for zanamivir. This effect leads to the introduction of selection bias, with a significantly reduced probability of being diagnosed with influenza and an imbalance in the two arms if the ITTI population is analysed. The effect of oseltamivir on antibodies appears to be carried over to children with ILI. Its finding contradicts statements made by the manufacturer.

The apparent incomparability between arms of the influenza-infected subpopulations in the oseltamivir trials raises the question of how an appropriate analysis should be conducted. If influenza-infected groups are comparable (as appears to be the case in zanamivir treatment trials) then an appropriate analysis strategy (based on Senn[132]) would be to first determine the effect of treatment in the ITT population. If there is evidence of a treatment effect then treatment by infected status interaction could be tested. If there was evidence of an interaction then estimates of treatment effect could be derived separately for the influenza-infected and non-influenza-infected subpopulations. However, this analysis should be conducted on the ITT population using a single appropriate statistical model, obviating the need to conduct separate analysis on the influenza-infected subpopulation. Roche used geometric mean titres indicating antibody responses in the ITTI population to support their statement that oseltamivir does not affect antibody

responses (e.g. in *Table 15* and linked text of module 1 of trial WV15799[65]). However, the use of such measures can be misleading. What are required for such an analysis are data on how many ITT population participants responded by arm, at what level of antibody response and how many were tested. Such data could not be identified with certainty. A further effect of choosing a subpopulation analysis (ITTI in treatment trials and ITTIINAB (ITT influenza-infected index cases who had negative virology at baseline) in prophylaxis trials) as the primary analysis is the restriction of the generalisability of results. This is especially so in the case of design flaws (e.g. in the case of the PEP trial WV15799,[65] in which all index cases were not treated and around 55% of participants were dropped from the ITTIINAB analysis). In this cluster trial design, households should be included as random effects in the analysis to take account of within-household correlations.

A significant but slight reduction of the proportion with serum antibody (mostly haemagglutination inhibition antibody) titre rise by fourfold or more among those who were tested was shown in this review. This was consistent with the evidence from animal tests using a subclinical dose of oseltamivir in influenza A/H1N1-infected mice.[133] Takahashi *et al.*[133] reported a non-significant slight reduction of haemagglutinin-specific secretory immunoglobulin G antibody in the serum and spleen, whereas they reported about an 80% significant reduction of haemagglutinin-specific secretory immunoglobulin A antibody in the nasal wash and bronchoalveolar fluids on day 12. From this evidence, they warned that the risk of reinfection may increase in patients showing a low mucosal immunoglobulin A antibody response following oseltamivir administration. These experiments were done because they had the unexpected finding that patients with paediatric influenza who were treated orally with oseltamivir for 5 days had significantly low levels (about 60% reduction on day five) of anti-influenza secretory-immunoglobulin A nasopharyngeal fluids compared with levels in patients who were not treated with oseltamivir.[134] Their findings are consistent with our findings that serum haemagglutinin inhibition antibody response was decreased by oseltamivir administration, although secretory immunoglobulin G antibody could not be analysed in our study because the data were not reported in the CSRs.[133,134] These findings are also consistent with the evidence on the mode of action of oseltamivir from animal models[8,58,135] and from viral challenge, randomised, placebo-controlled studies in humans.[27]

Pro-inflammatory cytokines, including interleukin 6, tumour necrosis factor alpha and interferon gamma, were completely suppressed by oseltamivir administered 28 hours after the experimental inoculation of influenza virus, whereas the reduction of viral titre in nasal lavages was partial.[27]

There is decisive evidence that administration of oseltamivir in animals challenged by respiratory syncytial virus, which lacks a neuraminidase gene, showed a symptom-relieving effect (decreased weight loss) and inhibition of viral clearance.[136] These effects were accompanied by a decreased cluster of differentiation +8 T-cell surface sialoglycosphingolipid GM1 level, which is regulated by the endogenous sialidase/neuraminidase in response to viral challenge along with suppression of cytokine expression.[136] They are consistent with those findings from the pharmaceutical company and their investigators. The findings of the study by Moore *et al.*[136] suggest a risk of infection and exacerbation of infection by pathogens other than influenza virus despite the apparent reduction of symptoms from infection.

TABLE 15 Proportions of contacts with positive serology data (WV15799[65] ITTIINAB population)

	Group		
Positive serology	Placebo, *n* (%)	Tamiflu, *n* (%)	Total
No	166 (83.0)	192 (93.7)	358
Yes	34 (17.0)	13 (6.3)	47
Total	200	205	405

Chi-squared $p = 0.001$.

Sufficient plasma concentration of oseltamivir carboxylate from orally administered oseltamivir phosphate may act directly on the host endogenous neuraminidase to reduce (or suppress) the immune response even at the dose of 20 mg twice a day for 5 days. However, the bioavailability of inhaled zanamivir seems to be very broad: about 10–70%, as estimated by the area-under-the-curve data from the inhalation and intravenous study from the Japanese Summary Basis for Approval. The difference in peak concentration (C_{max}) was much larger (sixfold to 37-fold). This means that inhaled zanamivir could reach a high enough concentration to reduce the immune response, if it is administered at a high dose or for a long period, or if the patient is very susceptible. In fact, a double-blind, placebo-controlled trial[137] using healthy volunteers to investigate the effect of zanamivir treatment (20 mg/day for 14 days) on the humoral immune response to influenza vaccine showed that the zanamivir group responded with significantly lower antibody titres to the H1N1. Pro-inflammatory cytokines, including interleukin 6, tumour necrosis factor alpha, interferon gamma and other chemokines, were almost completely suppressed in the viral challenge RCT using a very high dose (600 mg) of intravenous zanamivir before inoculation of the influenza virus in human adults.[138]

These findings all suggest that the low immune response, with a low level of pro-inflammatory cytokines, induced by the action of oseltamivir carboxylate, may reduce the symptoms of influenza irrespective of an inhibition of influenza virus replication, which is widely believed to be the main mode of action of NIs.

In addition, the potential hypothermic or antipyretic effect of oseltamivir (but not zanamivir) as a central nervous system depressant may also contribute to the apparent reduction of host symptoms.[139,140]

Zanamivir had no effect on pneumonia symptoms in treatment trials, even when the diagnosis was supported by a chest radiograph, nor did it affect antibody responses, but it did affect bronchitis. We think that this shows a symptom-relieving effect of both drugs, which also applies to more severe, if undefined, syndromes. Both drugs relieve ILI symptoms by around 0.6–0.7% day's reduction although this is first relief and not necessarily complete relief. In the case of oseltamivir, the mix-up with the follow-up cards does not allow us to draw any conclusions on a possible length of the duration of symptom relief. Also of note is the fact that this important information came to light from the FDA reports and not from the CSRs of the relevant trials.[8,58] This points to the incomplete nature of reporting in the CSRs and the important role of Summary Basis of Approval (SBA) regulatory information.

In a subgroup analysis we found no evidence of a difference in treatment effect for zanamivir on time to first alleviation of symptoms in adults in the influenza- and non-influenza-infected subgroups. Both subgroups showed strong evidence of treatment effect of 0.5–0.7% day's reduction in time to first alleviation of symptoms. This strongly supports our hypothesis that these drugs do not have an influenza-specific effect.

Oseltamivir relieves symptoms in otherwise healthy children, but no effect was noted with zanamivir, which may be because of the limited power of the two eligible trials, with just over 700 children in total. However, oseltamivir does not have any effect on asthmatic children with ILI, a population that should benefit most from its use. One explanation for this finding is in the nature of the young asthmatic population, which is well cared for and used to regular powerful medications and close follow-up. The incremental benefit of oseltamivir is thus likely to be undetectable in such a population. An alternative explanation could be the higher susceptibility of the immune system to suppression by oseltamivir carboxylate in asthmatic children compared with those in the placebo group. The finding that oseltamivir administered to asthmatic children reduces symptoms faster than in placebo recipients at the beginning of the study, but during the off-treatment period more recovered later than those administered placebo, gives some support to this explanation.

There is no evidence of an effect of oseltamivir on hospitalisations. Hospitalisations are an important but poorly defined outcome in the oseltamivir protocols, inconsistently reported in the CSRs and overlooked in the zanamivir protocols and reports.

The oseltamivir trials did not detect any influenza-related deaths, reflecting the relatively benign nature of influenza in the study populations. The zanamivir trials detected eight deaths, of which only two were likely to be caused by influenza and both occurred in the intervention arms. All of the trials were likely to be underpowered to detect differential effects on mortality, but the absence of deaths in placebo recipients again underlines the benign nature of influenza. In fact, mortality in Japan during the 2009A/H1N1 influenza outbreak was 198 among about 20 million patients with influenza (1 in 100,000 infected). Early deterioration leading to death was observed more frequently in oseltamivir recipients than in zanamivir recipients or no antiviral recipients.[141]

Overall, the two drugs have similar benefits but markedly different toxicity profiles. On average, for every 28 (95% CI 14 to 112) adults treated with oseltamivir there will be one more report of nausea and for every 22 (95% CI 14 to 42) adults and 19 (95% CI 10 to 57) children there will be one more report of vomiting. Oseltamivir seems to have an apparent protective effect on diarrhoea, contrary to the other evidence of gastrointestinal disturbance. This finding might be as an effect of a placebo containing dehydrocholic acid or it might be one of the results of the ILI symptom-relieving effects (similar to relief of tachycardia and palpitation). The other apparent gastrointestinal events, such as nausea and vomiting, may be the result of central nervous disorders indicated by 'only day 1 increase of vomiting' in treatment trials in children.

For every 62 (95% CI 41 to 411) adults exposed to zanamivir there will be one fewer case of nausea and vomiting, but no such effect was visible in children, probably because of a lack of power. Zanamivir does not appear to affect the frequency of bowel movements.

In the prophylaxis data set, 'influenza without laboratory confirmation' (i.e. ILI) was only partially reported in the oseltamivir CSRs and not reported in the zanamivir CSRs, except for one report,[86] in which no significant reduction was observed (zanamivir 9% vs. placebo 10%). As a consequence we are unable to report on that outcome. The size of the reduction in influenza symptoms in oseltamivir prophylactic trials is inferior in magnitude to that seen in hand washing to prevent severe acute respiratory syndrome, based on seven case–control studies [odds ratio (OR) 0.77, 95% CI 0.70 to 0.84; I^2 statistic = 68%; RD –0.12, –0.16 to 0.08; I^2 statistic = 26%], the NNTB being approximately '50' for prophylaxis with oseltamivir and '8' with handwashing.[142]

There is a significant reduction in the proportion of patients with symptomatic influenza with both NIs. However, these findings do not reflect the true efficacy for prevention of influenza because they conceal the positivity of laboratory testing (measured through tests of viral shedding and fourfold antibody titre rise).

We found an apparent prophylactic effect of zanamivir on pneumonia (which was not defined in CRFs) when it was used for 14–28 days. However, we found no evidence of significant effects on other complications and no evidence of an effect of oseltamivir on complications or hospitalisations.

Oseltamivir induced nausea in people who were undergoing prophylaxis but there was insufficient evidence to show an association with vomiting.

On-treatment renal adverse events were three times more common in the oseltamivir arms than in the placebo arms, with 150 treated patients leading to one additional event. The two participants who died in the oseltamivir arms both experienced acute renal failure while on-treatment, although only one of those events was listed as an adverse event. The unlisted event was in a 91-year-old female who was 'withdrawn from the study on Study Day 15 because her estimated creatinine clearance was less than 30 ml/minute (WV15708, p. 44).[61] The screening laboratory examinations, that were carried out 10 days before the start of study treatment, were normal'. Hyperglycaemic adverse events (aggravated diabetes mellitus or hyperglycaemia) were also more common in the oseltamivir arms, with eight events in total (one in WV15673/WV15697,[59] two in WV15708[61] and five in WV15825[68]) compared with none in the corresponding placebo arms. These data are only presented descriptively, as they are too few (< 10) to meta-analyse formally, as prespecified in our analysis plan.

Finally, oseltamivir caused headaches and psychiatric harms in adult prophylaxis trials. Headaches are one of the most prominent harms of oseltamivir. There is evidence of a dose–response effect in prophylaxis trials ($p = 0.013$),[59] in which headaches were observed in 202 of 519, 225 of 520 and 242 of 520 participants in the placebo, oseltamivir 75 mg once daily and twice daily arms, respectively.

In the psychiatric category, several rare and severe single events (nervousness, aggression, hallucinations, psychosis, suicide ideation and paranoia) were reported significantly more frequently in the intervention arm. Added to other more frequently reported but not significantly different events (such as depression and confusion), this gave a large effect and a relatively small NNTH of 94 (95% CI 36 to 1538). The importance of such a finding lies in the distribution of oseltamivir to large numbers of asymptomatic individuals following pandemic plans. There were no prophylaxis trials in children that met our inclusion criteria, therefore we cannot report on prophylaxis harms in this important population.

The question of why oseltamivir treatment trials failed to identify a clear association between oseltamivir and psychiatric harms, although a weak dose-dependent association was observed, is a moot point. It is possible that ILI and influenza symptoms masked the harms in those who were already symptomatic and therefore recruited in the treatment trials (and influenza-type symptoms were excluded as adverse events to be reported). The reporting issue of compliharms may have helped to mask such events. Alternatively, it could be that these events are rare in the populations studied and that there was insufficient power to detect an association. The CI was wide (0.43 to 2.03) and does not rule out a doubling in risk as a result of treatment, as was found in the prophylaxis trials. It is also possible that the risk of psychiatric harm increases with increasing dose (as the data from two trials[8,58] suggest) and increasing duration of treatment (as the prophylaxis trials suggest).

Toovey *et al.*[143] assessed the issue and failed to find an association between neurological and psychiatric adverse events and oseltamivir exposure. The outcomes studied were not based on the a priori definition of psychiatric adverse events as defined in the CSRs. The definition was constructed post hoc, based on a selected group of adverse events taken from the psychiatric, neurological and injury body systems in the reports. The issues are described fully in another report[144] and Toovey's response.[145] Toovey *et al.*[143] reviewed only retrospective observational studies and did not review three prospective cohort studies conducted in Japan.

A meta-analysis of three prospective cohort studies of neuropsychiatric adverse events (NPAEs) in Japanese children show a pooled OR for abnormal behaviours due to oseltamivir exposure of 1.55 (95% CI 1.21 to 1.98; $p = 0.0005$) without significant heterogeneity.[146] In one prospective study[147] of several thousand children with influenza, carried out to test the hypothesis of a causal relation between oseltamivir and neuropsychiatric events, abnormal behaviour was observed more frequently in oseltamivir recipient children than in control subjects (RR 1.57, 95% CI 1.34 to 1.83). Abnormal behaviour was observed in 3.4 per 100 person-days (or 13.8%) in the oseltamivir group compared with 2.2 per 100 person-days (or 8.8%) in the control group. Reanalysis of this study population, focusing on delirium and unconsciousness, also showed a significant association between oseltamivir and neuropsychiatric events, especially in the very early phase of the illness within a day of commencement of fever.[148] These indicate that prospective and intentional collection with this scale of participants may be necessary in treatment RCTs.

Animal toxicity study results firmly support the effect of oseltamivir on the central nervous system. One of these is the hypothermic effect of oseltamivir (but not zanamivir) administered orally, intraperitoneally[139,140] and intracerebroventricularly.[140] The other is that intraduodenal or intravenous administration of oseltamivir to mature rats induced respiratory arrest shortly followed by cardiac arrest. These studies clearly show central depressant effects of oseltamivir.[149] Moreover, in the post-marketing toxicology phase studies by Roche, many symptoms that the manufacturer considered 'item-related' were observed: alterations in respiration including decreased respiratory rate/gasping and altered mucous membrane/skin colour (pale) prior to death. Although the manufacturer denied the causality,[150] symptoms at 2 hours after administration that showed dose-related increase were lack of olfactory orientation, lack of cliff aversion and low/very low

arousal. Twenty-four of 52 pups that did not exhibit cliff aversion were later found dead. Fourteen of 17 animals with low or very low arousal died thereafter. These findings are consistent with the clinically observed psychiatric symptoms in the RCTs and post-marketing spontaneous reports.

Zanamivir was well tolerated. However, a potentially active placebo may have masked the occurrence of bronchospasm in zanamivir trials.

Treatment trials were mostly under-recruited and often their results pooled post hoc in two, or even three, trials, and yet they showed very high influenza positivity rates. One possible explanation for this lies in the intensive surveillance carried out in the predefined trial centre areas and the restricted time span of recruitment during high likelihood of positivity periods. This may be why many centres with low levels of recruitment are listed in the CSRs; this limits the generalisability of the results to everyday life.

In a primary or secondary prophylaxis indication the postulated central effect of oseltamivir is confined to suppressing symptoms, as infection was not prevented even when oseltamivir was administered prior to the inoculation of influenza virus both in animals[135] and in humans,[27] and the prophylaxis trials. However, the central problem remains the incompatibility of the two contrasting claims of its activity against antibody production. If, as reported in many documents, oseltamivir does not interfere with antibody production (e.g. see FDA[151] and Roche Investigators' Guide[152]), how is it possible that oseltamivir prevents cases of influenza when part of the definition of prevented cases in oseltamivir trials was based on the absence of antibody response?

The apparent ability of oseltamivir to interfere with antibody response calls into question the mode of action of the drug and puts in doubt the proposed effects of oseltamivir. One possibility in treatment trials is that oseltamivir administration, by interfering with antibody production, has the effect of selecting the strongest antibody responders in the ITTI subpopulation. These individuals are classified as influenza cases and are included in the oseltamivir arm of the ITTI population. This selected subpopulation probably represents the healthiest or those least likely to experience complications. An alternative consequence could be that interference with antibody production in the oseltamivir arm led to active arm participants being more likely to develop complications as a result of impaired immune function.

Evidence from prophylaxis and secondary prophylaxis trials suggests that in addition to the apparent similar mode of action as in the treatment studies, suppression of viral shedding in nasal swabs may be of importance. In the former, participants who become positive (i.e. who are subsequently classified as cases of influenza) in the oseltamivir arms are the few who mount a strong response despite oseltamivir interference. The remainder (who are significantly more than in the placebo arm) are classified as prevented or avoided cases. However, as prophylaxis CSRs do not report antibody responses and viral isolate results for the ITT populations either, it is impossible to tell whether or not this proposed mode of action fits all of the evidence. The effect of oseltamivir on nasal shedding is consistent with the proposed mode of action of NIs in preventing the virus from leaving the host respiratory epithelial cells, which are covered by a mucous layer. Compared with the rather small reduction of symptoms of ILI and reduction in antibody rise (up to 10%) by both oseltamivir and zanamivir, the extent of the reduction of symptomatic influenza is almost half. This may be as a result of reduction of influenza viruses in the nasal swab sample.

In prophylaxis there is no evidence that oseltamivir reduces symptomatic ILI. Oseltamivir reduces the number of prophylaxis participants testing positive (based on antibody rise and/or culture test). However, this finding is weakened by oseltamivir's interference with the viral replication on the swab and effect on antibody production. In addition oseltamivir does not affect asymptomatic influenza and there is no evidence that it interferes with person-to-person spread.

Similar to the FDA,[109,153] because of the problems with the design of study WV15799[65] we could not draw any conclusions on the ability of oseltamivir to interrupt viral transmission.

This is important as the results of the trial[65] formed part of the WHO[3] rationale for use of the drug to interrupt transmission from person to person, and allow time before the arrival of vaccines in the event of a pandemic furnishing a seemingly powerful rationale for stockpiling oseltamivir.

This shows the importance of availability of full CSRs, something the WHO did not have.

Antibody suppression seems stronger for oseltamivir than zanamivir, probably because of the difference in bioavailability. It may be that evidence of other effects, such as hyperglycaemia and renal impairment (though significance was marginal) in the prophylaxis trials may be due to inhibition of the host's endogenous neuraminidase, which impairs the cell function of various organs.[15] Overall, the significance of oseltamivir for nasal shedding is unclear but problems with sampling and culture undermine any claims as to its secondary prophylactic properties, as the FDA made clear in its response.[109]

The dose–response increase in psychiatric events in the 'pivotal' oseltamivir treatment trials and the increase in vomiting only on day 1 in treatment trials in children may be caused by the sudden onset of the central action of unchanged oseltamivir.[15] Brain concentration of unchanged oseltamivir increases during the early phase of influenza in juvenile animals[150] as a result of a reduced or low function of *p*-glycoprotein, a major transporter of oseltamivir at the blood–brain barrier.[15,149] The likely centrally mediated mode of action of oseltamivir is supported by the finding of adverse events in healthy people in prophylaxis trials. However, these effects may also be derived from a delayed action that is associated with host endogenous neuraminidase inhibition by oseltamivir,[15] because this appeared after more than 1 week's exposure to the drug and lasted for > 2 weeks. Other effects, such as pain in the limbs, hyperglycaemia or diabetic events, reduction of antibody rise and reduction of cytokine induction, may also result from the suppression of the host's endogenous neuraminidase by oseltamivir.[136] Pain in the limbs and metabolic control events (mainly hyperglycaemia) were in excess in the oseltamivir arms, but we did not carry out a formal meta-analysis, as they were not prespecified in our analysis plan and the number of events was < 10 for metabolic events.

Statements made about the capacity of oseltamivir to interrupt viral transmission and reduce complications are not supported by any data that we have been able to access.

We have not reviewed other NIs, such as laninamivir and peramivir, or other antivirals, such as the adamantanes (amantadine and rimantadine) or antipyretic/anti-inflammatory agents. Laninamivir and peramivir may be more potent as NIs because their bioavailability is far higher than zanamivir and may affect the host's endogenous neuraminidase. Adamantanes are well known centrally active agents and may be more harmful than oseltamivir and zanamivir. Anti-inflammatory antipyretics (except paracetamol) may be more toxic than NIs.[15] Hence, the other NIs, adamantanes and anti-inflammatory antipyretics may not be alternatives to oseltamivir and zanamivir.

Overall completeness and applicability of evidence

We used the Cochrane seven-domain risk-of-bias instrument to assess bias. The availability of partial or complete CSRs decreased the uncertainty and allowed definitive judgements to be made. Previous unclear risk of bias became certainty of bias or certainty of absence of bias. Certainty or low levels of uncertainty are due to our expectations regarding the complete CSRs. We were expecting to have all relevant and consistent information available for our reviews, but, when it was not, our judgements changed because we found gaps in the availability of information and inconsistent information. We are still uncertain as to whether or not the complete study reports represent an exhaustive and coherent source of trial narrative and data.

In the case of treatment trials, conclusions and generalisations are drawn from a subpopulation in which the two arms do not appear comparable as a result of the apparent ability of oseltamivir to interfere with influenza antibody production. The effect of oseltamivir on the gastrointestinal tract appears to be notable, although a definitive statement will be possible only once the mode of action and dosage of dibasic calcium phosphate dihydrate and dehydrocholic acid have been clarified. The high percentage of influenza infections appears to be in contrast with the need to pool or delay several trials and the small recruitment

size of others because of a lack of influenza circulation. In the case of PEP trials, the selection of the infected population has the effect of excluding from the analysis large percentages (in some cases > 50%) of participants. This brings the generalisability of the results of these trials into question.

Much has been made in the trial programmes of viral nasal voidance as a marker of effect. However, its measurement was unreliable in treatment trials, as this verbatim quote from the FDA review shows:

> *Duration of viral shedding was measured from treatment initiation to the time of the first negative virus culture with no subsequent positive cultures. Upon reviewing a list of viral shedding patterns provided by the applicant on 8/16/99, two problems emerged: (1) the pattern of virus shedding was fluctuating in at least 33 subjects (i.e. pos-neg-pos-neg, with or without a subsequent negative result). (2) In at least 100 subjects, the last virus shedding sample was the first negative sample in sequence, meaning there was not a subsequent negative confirmation. Given the fluctuating pattern of virus shedding, to estimate the duration of viral shedding based on the occurrence of a single first negative data poses a high level of uncertainty.*
>
> *FDA, p.14*[109]

In all of the programmes, the effect on complications was based on unclear and potentially unreliable definitions, often at the discretion of local clinicians, and confirmation (e.g. radiological confirmation of pneumonia) was not consistently reported when it did occur. In the ITT population, the correct population for analysis, there is no credible effect of oseltamivir against pneumonia as the significance of the term 'pneumonia' is not clarified.

In the case of PEP trial,[65] nasal voidance was measured only in symptomatic subjects, as an adjunct to the protocol version. However, this does not prevent the manufacturers from making claims of effect for all of these outcomes.

Other general requirements, such as presentation within 36–48 hours, raise questions about the generalisability of the research evidence. However, underlying all our doubts is the conflicting evidence on the mode of action of the drug.

Most of the trials were substantially under-recruited and so had insufficient power individually to answer the research question.

Quality of the evidence

We assessed all full CSRs of relevant trials. An example of the kind of detail available in complete CSRs and the importance of the trial timeline in assessing the presence of bias is the observation that of the CSRs for the included trials, only one contained a protocol that predated the beginning of participant enrolment, only two had SAPs that clearly predated participant enrolment and three had clearly dated protocol amendments. No oseltamivir CSR included a clear date of unblinding.

All reports in our review were sponsored by the manufacturers. It is known that published studies sponsored by the pharmaceutical industry are more likely to have outcomes favouring the sponsor than studies that have other sponsors.[154,155] As the evidence relates to published studies, we do not know whether or not the findings are applicable to CSRs.

Potential biases in the review process

The main limitation of our study is our relative inexperience in dealing with large quantities of information and our lack of familiarity with certain trial documents, such as randomisation lists. Randomisation lists appeared to be of two types. The first was a pre-randomisation list of random codes with which participants' IDs cannot be matched with the participant IDs used within other sections of the CSR. The second was a post hoc randomisation list to which individual participants can be matched but the original generated codes are not shown. In both cases the truly random generation of the sequence could not be

properly assessed because either the original codes are not provided or the original codes cannot be matched to patients.

We have created methods and procedures to address the risk of reporting bias that we identified in published trials, but remain uncertain about the success of these new methods.

Agreements and disagreements with other studies or reviews

Several reviews of NIs are now available,[156–160] including several separate versions of our previous reviews.[30–32,35] All are mainly based on published information and reach similar conclusions to our 2006 review, which sparked the reader's comment and subsequent investigation and change of methods.

Following publication of our review update in December 2009, Roche asked the Harvard-based academics Hernan and Lipsitch[161] to repeat the Kaiser analysis[4] to confirm or reject Kaiser's conclusions. They were not provided with any funding to carry out this analysis and Roche ultimately provided them with patient-level data sets and module 1 for the 10 Kaiser trials and one more treatment trial.[69] An important methodological difference between Hernan and Lipsitch's analysis[161] and that of Kaiser[4] was Hernan and Lipsitch's decision to privilege a true ITT analysis over the subpopulation analysis featured in the Kaiser analysis. Our Cochrane review also analyses the ITT population.

The Kaiser analysis[4] concluded that oseltamivir provided two statistically significant reductions: in lower respiratory tract complications and in hospitalisations.

Hernan and Lipsitch[161] evaluated lower respiratory tract complications and found a statistically significant, but smaller, reduction in the risk of these complications.

Hernan and Lipsitch[161] omitted evaluating the Kaiser paper's conclusion that oseltamivir reduced the risk of hospitalisation. They wrote, 'it was not possible to assess the potential benefit for high-risk participants who are hospitalised, because the sample size of most studies was too small to consider hospitalisation as an outcome'.

Hernan and Lipsitch[161] do not elaborate on or highlight their apparent methodological disagreement with the Kaiser 2003 analysis[4] and it is not reflected in the news article published on the Harvard website entitled 'Oseltamivir effect on complications confirmed by reanalysis' (http://ccdd.hsph.harvard.edu/NewsEvents/Oseltamivir-reanalysis). In fact, Hernan and Lipsitch[161] did not confirm one of the key conclusions of the Kaiser paper.[4]

Unfortunately, the Hernan–Lipsitch analysis[161] has been cited by influential bodies, such as the European Centre for Disease Prevention and Control, as 'confirmation of the original Kaiser meta-analysis' (http://ecdc.europa.eu/en/activities/sciadvice/_layouts/forms/Review_DispForm.aspx?ID=561&List=a3216f4c%2Df040%2D4f51%2D9f77%2Da96046dbfd72) despite the fact that Hernan and Lipsitch[161] did not confirm one of the key conclusions of the Kaiser paper.[4]

For complications, although Hernan and Lipsitch[161] clearly produced similar results to Kaiser,[4] we do not think that this means that the result is more credible. In view of our findings, we suggest that these results should be interpreted with caution. We have published our preliminary comments.[162] The approach Hernan and Lipsitch[161] took in analysing data was insufficient to provide a credible, independent check on validity, and reinforces the importance of detailed, critical assessment of entire trial programmes, with access to full-length study reports. Our analysis questions the coherence between the evidence and the proposed mode of action of oseltamivir.

The Ebell *et al*.[163] review concluded that there was 'no evidence that oseltamivir reduces the likelihood of hospitalisation, pneumonia or the combined outcome of pneumonia, otitis media and sinusitis in the ITT population'. This conclusion was based on module 1 of the 10 Kaiser trials plus WV16277.[69] These are the same 11 trials included by Hernan and Lipsitch.[161]

Conclusions

Main conclusions

These data show that oseltamivir and zanamivir cause small reductions in the time to alleviation of influenza symptoms in adults, but not in asthmatic children. The use of oseltamivir increases the risk of nausea, vomiting and psychiatric events in adults and vomiting in children and may reduce risk of diarrhoea and cardiac events in adults. Observational studies fail to show that oseltamivir has a protective effect on mortality among patients with 2009A/H1N1 influenza. Prophylaxis with either oseltamivir or zanamivir may reduce symptomatic influenza in individuals and in households but there was no reduction in all other influenza outcomes, including overall ILI reported as an adverse event on-treatment. In previous Cochrane reviews it is likely that evidence from published data was insufficient to fully assess risk of bias within the trials. Our results do not discount a potential benefit of using zanamivir and oseltamivir in individuals under particular situations, for example in immunocompromised or in compassionate cases, for which few other therapeutic options may exist. However, NIs themselves may be immunosuppressants.

The balance between benefits and harms should be considered when making decisions about use of NIs for either prophylaxis or treatment of influenza.

Implications for practice

These results show that both oseltamivir and zanamivir reduce the time to symptomatic improvement in adults (but not asthmatic children) with ILI. The size of this effect is small – approximately half a day. We have no data comparing oseltamivir or zanamivir with paracetamol and other antipyretics. We did not find convincing evidence that either oseltamivir or zanamivir reduces the risk of complications of influenza, particularly pneumonia, or reduce risk of hospitalisation or death. Even in individuals at higher risk of complications, such as children with asthma or the elderly, there was no evidence of a beneficial effect for reducing risks of complications.

The findings demonstrate a minimal effect on prevention of influenza by oseltamivir or zanamivir among individuals or families. This suggests little support for their use as prophylactic agents, for example during influenza epidemics.[164]

Implications for research

The considerable body of evidence from RCTs included in this review indicates either no effect or a relatively small absolute effect size against the complications of influenza. Such an effect, even if statistically significant, would be too small to warrant treatment with NIs in a primary care setting, especially as effective diagnosis and treatments for rare complications (such as pneumonia) are available. Lack of evidence of an effect on hospitalisations probably indicates lack of severity in the first place. Assuming an influenza incidence rate of 2% (similar to that in the control arms of oseltamivir treatment trials) to detect a 25% clinically significant reduction in pneumonia, 21,500 participants would have to be enrolled in a clinical trial.

Our findings have implications for research on the mechanism of action of NIs, with special regard to any direct central action of oseltamivir and the inhibitory effect of the host endogenous neuraminidase of various organs and systems. We could not reach a consensus on whether or not further trials are warranted and whether or not current trials should be discontinued.

Published trials are unlikely to provide the level of detail to allow the results of a drug trial to be properly evaluated and risk presenting a partial and potentially biased report of trial conduct and findings. This has implications not only for the reporting of trials but also the weight that can be applied to published studies alone.

Our calculation is likely to underestimate population size, as the 2% incidence rate was derived from trials that used enhanced ad hoc surveillance systems. Any trial design would have to ensure that the presence of complications is ascertained using objective diagnostic criteria (e.g. with confirmation using imaging or laboratory testing for pneumonia). Such trials would also have to consider the ethical implications of conducting studies for which the estimate of benefit (based on 11 RCTs) in otherwise healthy people is likely to be small, and would have to be balanced against the apparent risks of adverse effects from NIs. We think research should be aimed at more effective preventative measures and early identification of complications.

The methods used to conduct our evidence synthesis need to be repeated across further interventions and by other researchers, and may need to be refined further. Given the considerable resources involved in using these methods, a system is needed to prioritise reviews of important drugs so that such methods are reserved for drugs that meet certain conditions. Priority could perhaps be given to first drugs of a new family, drugs considered to be innovative or those that are likely to have a big market impact. Such reviews should be publicly funded and be independent of both regulators and manufacturers. Researchers who conduct these 'high-scrutiny' reviews need to be free of recent ties to either government or the pharmaceutical industry. Systematic review groups such as The Cochrane Collaboration should consider adopting these methods for other drugs and whether, perhaps, to scrutinise the published reviews of prioritised drugs.

Implications for policy

These findings suggest that the current recommendations for oseltamivir as an essential medicine for the treatment of seriously ill patients or those in higher-risk groups with influenza 2009A/H1N1 need revision.[33,34] The small benefits in symptomatic improvement and the lack of evidence for an effect on serious complications need to be balanced with the adverse effects found with these drugs in meta-analyses, especially diabetic/hyperglycaemic, renal and neuropsychiatric effects in all of those people for whom the WHO recommends its use.

Policy-makers should be cautious in interpreting and using the findings of systematic reviews including only published studies, particularly those that comprise only a portion of an entire drug trial programme or which contain only a portion of the results of trials. The current findings suggest that numerous national and international bodies may have been based on inadequate or poor-quality information.[165] This could be obviated by ensuring that documentary evidence relating to a trial on humans (including CSRs, regulatory documents, evidence syntheses) should be archived electronically with no statute of limitations.

Several steps are required to provide patients, clinicians and policy-makers with the most transparent assessment of the relative benefits and risks of new drugs.

Based on the length of time it has taken to provide a definitive answer on the efficacy of the NIs, the challenges in obtaining the full information and the methods that we needed to develop to conduct the evidence synthesis, we believe the main implication of our review is the need for reform of multiple components of the research and development, regulatory and assessment pathway of new drugs.

Pharmaceutical sponsors of drug trials should follow a data access and sharing procedure which is similar to that of the EMA, and sponsors should make all full CSRs available to be downloaded from their websites and shared freely once a regulatory decision has been made. Redactions should be kept to the minimum. Part of this process needs to include a full list of the entire drug development programme to avoid assessment of an incomplete set of trials. Researchers and industry employees who are listed in trial documents should be considered to have legal responsibility for the conduct and reporting of a trial.

Regulators should post an inventory of their documentary holdings on their websites with a brief description of the main content and size of each file. They should make all information available shortly after making a registration decision on a drug and within a reasonable time period. The information should be in electronic format and anonymised (i.e. participants' details should be removed to prevent each person being identified but no further).

Trial registries have improved the reporting of new trials. However, on their own they will not be adequate to resolve the problems we encountered. The completeness of trial registries needs to be tested with a random sampling procedure. Clear instructions for the reporting and updating of their content should be promulgated and penalties imposed on breaches of these procedures. Trial registration should include the original and final versions of a trial protocol, with a full declaration of dated amendments. Procedures for trial unblinding and dates of unblinding should be routinely reported. Registration should be made compulsory for all studies in which human beings are randomly assigned to experimental arms. Ethical and consent procedures for all trials should include obligations of the trial sponsor to ensure that results are made public. Failure to report the existence of a trial on humans and to make results available should be considered as an ethical breach of conduct and be subject to appropriate penalties.

Authors' note: In reviewing over 2 GB of data there is the possibility of mistakes. The authors would be grateful if readers could identify these. We promise that, if we concur, the record will be amended accordingly.

Chapter 3 Effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza: a systematic review and individual patient data meta-analysis of observational studies

Abstract

Objectives
To determine the effect of oseltamivir on mortality in 2009A/H1N1 influenza patients.

Design
Systematic review of observational studies.

Data sources
Summary and individual patient data (IPD) from published observational studies.

Eligibility criteria for selecting studies
Any study of 2009A/H1N1 influenza patients reporting mortality outcomes and exposure to oseltamivir with at least 5% of patients untreated with influenza antivirals and five or more deaths overall.

Main outcome measures
Mortality.

Results
A total of 1117 studies were identified and screened, with 154 full-text articles assessed for eligibility. Of these, 30 observational studies of hospitalised patients were eligible and a total of 11,013 patients were available for qualitative synthesis. Overall there were 1301 deaths (12%) with the percentage of deaths receiving oseltamivir similar to that of survivors (83% vs. 82%). We found evidence of time-dependent bias in the summary data and the IPD. The IPD came from four studies including 3071 patients and 242 (8%) deaths. After taking account of time-dependent bias, potential confounding variables, and the competing risk of hospital discharge, analysis of the IPD showed insufficient evidence that oseltamivir reduced the risk of mortality [hazard ratio (HR) 1.03, 95% CI 0.64 to 1.65].

Conclusions
We found insufficient evidence from 30 observational studies to support oseltamivir having a protective effect on 2009A/H1N1 influenza patients for mortality. However, the included studies were observational and IPD analysis was based on only four studies without adjustment for baseline severity of illness or other drug use hence the findings should be interpreted with caution. Observational studies with time-dependent treatment exposure appear to be at a high risk of time-dependent bias unless an appropriate analysis is conducted.

Introduction

Influenza is a seasonal, mostly mild and self-limiting infection of the upper airways. Occasionally, patients with influenza develop complications, including pneumonia, encephalopathy and multiorgan failure, often requiring hospitalisation and, in a small number of cases, patients die. Influenza is mainly caused by influenza A and B viruses and the predominant subtype of viruses changes from season to season. A novel strain of influenza 2009A/H1N1 was the predominant cause of influenza infections worldwide resulting in the WHO declaring a pandemic in April 2009.

Oral oseltamivir is an antiviral and a NI. It has been used primarily in Japan and the USA prior to 2009. However, its use increased dramatically in the A/H1N1 pandemic when oseltamivir became a widespread public health intervention.[166]

Mortality is a generally rare, but important, outcome of influenza and RCTs have not been powered to address this outcome. To our knowledge, there have been five deaths in comparative Phase II/III RCTs of oseltamivir;[167,168] however, none of the deaths was in a patient with confirmed influenza. Reviews of observational studies of influenza 2009A/H1N1 have shown protective effects of NIs on mortality[169–173] and oseltamivir is now listed as an essential medicine,[174] although there is insufficient evidence based on randomised studies to show that oseltamivir reduces complications of influenza[106] and case series have suggested increased mortality.[15,141]

The objective of this systematic review was to determine the effect of oseltamivir treatment on mortality in patients with 2009A/H1N1 influenza. We focused on 2009A/H1N1 influenza specifically because WHO and others have suggested that studies of antivirals for seasonal influenza may not be relevant to the current novel form of circulating influenza,[46,47] and current antiviral treatment policies have been largely influenced by the results of observational studies of 2009A/H1N1 influenza.

Methods

Ethics approval was not required for this research because it is a systematic review of published studies. Any study comparing oseltamivir with no treatment in patients with confirmed 2009A/H1N1 influenza and reporting mortality outcomes was eligible for inclusion. The definitions for mortality and treatment exposure were as used in the individual studies. We did not include studies where < 5% of patients or < 10 patients were untreated and studies in which fewer than five patients in total died. If there were multiple publications of the same or overlapping cohorts of patients we included the largest cohort in our review. Studies reported in languages other than English were potentially eligible for inclusion but only if data were clearly reported by mortality and treatment status. Studies that were reported in abstracts but not published in full were not eligible for inclusion. We searched MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, Web of Science and Latin American and Caribbean Health Sciences Literature databases (see *Appendix 12* for details of our search strategy). We also hand-searched bibliographies from two relevant documents published by WHO[169,175] and two previous reviews.[171,172]

Three reviewers separately assessed the studies identified during the search and applied inclusion criteria. Any disagreements were resolved by discussion. Data from included studies were extracted and checked by a second reviewer. Variables included in the extraction were citation; study design; study setting (country, city, institution); study population (sex, age groups, types of patients, severity of disease); time period of study; how and if influenza was confirmed; number of patients (by survival status and antiviral treatment received); and timing of hospital admission and treatment from onset of symptoms.

To address the limitations of using summary information from observational studies for meta-analysis, we requested IPD from the corresponding authors of all of the included studies and kept a record of all of the correspondence that ensued (see *Appendix 13* for a template of the letters that we sent to the corresponding authors).

Our primary analysis was to compare use or non-use of oseltamivir as a binary exposure between patients with fatal and non-fatal outcome. We planned to use Cochran's Q chi-squared statistic to test for statistical heterogeneity and the I^2 statistic to estimate heterogeneity and perform a random-effects meta-analysis of the primary outcome using the method of DerSimonian and Laird.[107] For studies with no events in one of the treatment groups we added a continuity correction of one event to all four cells of the study to enable estimation of ORs. Small study effects were intended to be formally assessed using the method of Harbord *et al.*[176] and investigated using a funnel plot. In fact we used the method of Rucker *et al.*[177] to test for small studies effect as a result of their method of moments test being the only one we could find that is appropriate when heterogeneity is substantial ($\tau^2 > 0.1$). The Meta-analysis of Observational Studies in Epidemiology guidelines were followed in the reporting of this systematic review.[178] A protocol outlining our proposed study is available from: www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002245.

In the subgroup of studies for which we obtained IPD we planned to investigate the time-dependent effect of oseltamivir on mortality (by fitting treatment as a time-dependent exposure in a Cox regression model), adjust for potential confounding variables and identify predictors of treatment using logistic regression. A detailed example of the methodology we used for fitting a time-dependent variable in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) is provided in the following web link: http://support.sas.com/documentation/cdl/en/statug/63347/HTML/default/viewer.htm#statug_phreg_sect049.htm. Analysis 1 is appropriate for our study because we had one time-dependent exposure variable and a number of baseline covariates. Potential confounding variables that were investigated included patient comorbidities (respiratory, cancer, obesity, heart disease, infection, immunosuppression, diabetes, neurological), age and time from onset of symptoms to hospital presentation. After taking account of time-dependent bias (using proper hazard-based analyses for which oseltamivir is included as a time-dependent exposure) and missing data (using multiple imputation and adjusting for potential confounding variables), we planned to report the overall estimate of treatment effect of oseltamivir on mortality, as well as the treatment effect by the timing of treatment categorised into early (≤ 2 days from onset of symptoms) or late (> 2 days from onset of symptoms). Survival analyses were stratified by study, and logistic models were adjusted for study. Multivariable analysis was conducted when all potential confounders were included in the models. Multiple imputation was implemented in a sensitivity analysis to assess the potential influence of missing data using *proc mi* and *proc mianalyze* commands in SAS. We specified multivariate imputation by a fully conditional specification method using regression models that we developed for predicting the missing data and created 20 imputed data sets. Covariates included in the regression models were mortality status, age, study, treatment group, time from onset to presentation and comorbidities (as detailed above).

On the basis of a recommendation by Wolkewitz and Schumacher,[179] we conducted competing risks survival analysis on the IPD, for which the competing risks were death and hospital discharge. Wolkewitz and Schumacher[179] suggest that a fundamental assumption in survival analysis is that the death hazard remains the same after censoring. This may be violated because discharged patients are usually in a better health condition than patients who remain in hospital. Hence, discharge from hospital should be directly modelled and treated as a competing event for dying in hospital. We performed competing risks analysis using the method of Fine and Gray[180] on the three cohorts that provided data on hospital discharge, with adjustment for all potential confounders but no imputation for missing data. Oseltamivir treatment was fitted as a time-dependent exposure because time-dependent bias may also occur for hospital discharge because, for example, patients who recover quickly may not get the opportunity for antiviral treatment.

Results

On the basis of searches conducted on 15–18 February 2013, we identified 1107 potential studies for inclusion. We identified a further 10 studies through hand-searching. After assessing the abstracts of these studies, we agreed that 154 full manuscripts were required for further assessment. Of these 154 full manuscripts, 124 were excluded for the reasons given in *Figure 16* and references are provided in *Appendix 14*. We initially excluded 18 studies because they did not present a breakdown of numbers of patients dying as a

result of oseltamivir exposure. We wrote to the corresponding authors of these studies requesting this additional summary data and received replies from 12, of which six provided data that we were able to use. In total, 30 studies[181–210] are included in the qualitative synthesis (*Table 16* and see *Figure 16*).

Quality of the included studies

We included observational studies that reported on series of cases with laboratory-confirmed 2009A/H1N1 influenza. There were no randomised or prospective cohort studies or case–control studies comparing death or severe cases with matched uncomplicated patients despite the call for this type of study.[211,212] *Table 16* shows information on the design characteristics of the included studies and *Table 17* provides details on outcomes and analysis methods used. The proportion of patients treated in the studies ranged from 35% to 94%, with a median of 82%.

Although all 30 studies classified patients by treatment exposure, only two defined it: one as 'at least one dose of oseltamivir'[181] *and* the other as 'at least one day of treatment'[182] [although it was unclear how they classified patients who received one dose only; there were 26 such patients excluded from the study [Iratxe Puebla, *PLOS ONE* journal editor, 7 August 2012, personal e-mail communication)]. It is unknown how many other studies failed to report excluded patients but we note that a number of studies had missing information on mortality status and/or treatment status (for 200 patients in one study,[183] for which missing data were more common in patients with less-severe disease), whereas other studies reported complete information. None of the included studies reported over-the-counter medication use prior to

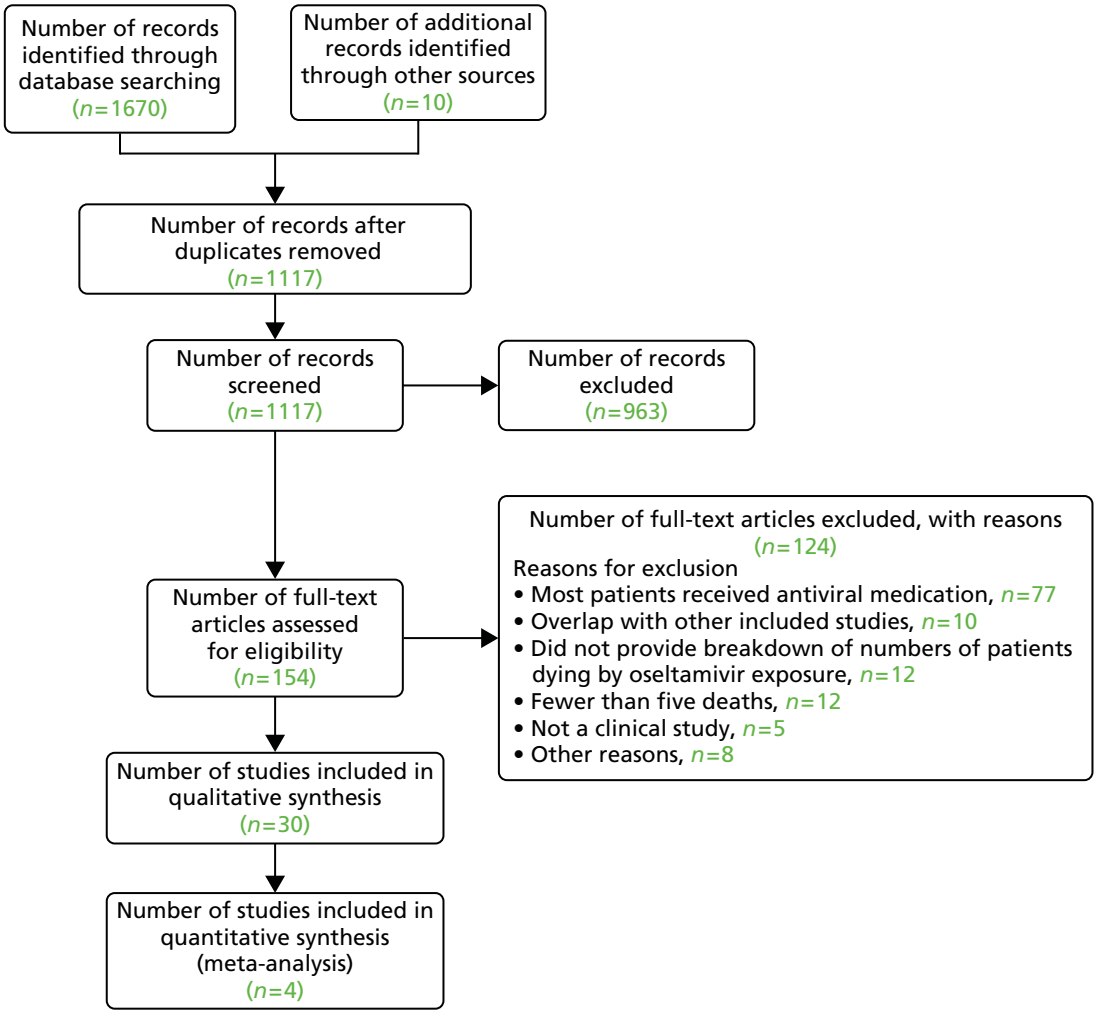


FIGURE 16 Flow diagram showing process for inclusion and analysis of observational studies examining the effect of oseltamivir on mortality in patients with 2009A/H1N1 influenza.

TABLE 16 Characteristics of the 30 included studies

Study	Setting and population	Time period	Definition for death	Description of treatment exposure	Drug use before admission
Siston *et al.*[183]	USA, pregnant women	April to December 2009	Maternal influenza deaths	Antiviral (492/496 received oseltamivir)	Not reported
Louie *et al.*[181]	California, all ages, critically ill	3 April 2009 to 10 August 2010	Died from pandemic H1N1 infection	One dose of antiviral (1671/1675 received oseltamivir)[a]	Not reported
Jain *et al.*[189]	USA, all ages, hospitalised	April to June 2009	Not reported	Antiviral (188/200 received oseltamivir)	Antiviral, antibiotic
Farias *et al.*[190]	Argentina, children, critical	15 June to 31 July 2009	Mortality at 28 days	Oseltamivir	Not reported
Yang *et al.*[191]	Beijing, all ages, hospitalised	Up to 31 December 2009	Cause of death 2009 H1N1 influenza	NI	Not reported
Altmann *et al.*[185]	Germany, children, critically ill	August 2009 to 30 April 2010	Not reported	Oseltamivir	Not reported
Enstone *et al.*[192]	UK, all ages, hospitalised	11 May 2009 to 31 January 2010	Deaths attributed to pandemic (H1N1) 2009	Received antiviral as inpatients	Patients infected in hospital
Dominguez-Cherit *et al.*[184]	Mexico, all ages, critically ill	24 March to 1 June 2009	ICU and hospital mortality at 14, 28, 60 days	NI (44/45 received oseltamivir)	Not reported
Kumar *et al.*[187]	Canada, adults, critically ill	16 April to 12 August 2009	28- and 90-day mortality	Oseltamivir	Not reported
Nguyen-Van-Tam *et al.*[186]	UK, all ages, hospitalised	27 April to 30 September 2009[b]	In-hospital death	Oseltamivir	Antiviral
Chitnis *et al.*[193]	Wisconsin, USA, all ages, hospitalised	23 April 23 to 15 August 2009	Not reported	Antiviral (99% got oseltamivir)	Not reported
ANZIC[194]	Australasia, pregnant women, intensive care	1 June to 31 August 2009	Maternal death	Oseltamivir	Not reported
Yung *et al.*[195]	Australasia	From 1 June to 31 August 2009	In-hospital death	Oseltamivir	Not reported
Javadi *et al.*[196]	Iran, all ages, hospitalised	September 2009 to February 2010	Not reported	Oseltamivir	Not reported
Miranda-Choque *et al.*[197]	Peru, children, hospitalised	June to September 2009	Death related to pandemic influenza	Oseltamivir	Antibiotics
Poeppl *et al.*[198]	Austria, all ages, hospitalised	20 September 2009 to 2 February 2010	In-hospital death	Oseltamivir	Not reported
Riquelme *et al.*[199]	International, all ages, hospitalised	April to October 2009	In-hospital all-cause mortality	Oseltamivir	Not reported
Yokota *et al.*[200]	Brazil, all ages, hospitalised	July 2009	Death caused by pandemic (H1N1) 2009	Oseltamivir	Oseltamivir
Thompson *et al.*[188]	USA, all ages, hospitalised	14 September 2009 to 13 January 2010	Influenza-related in-hospital death	Neuraminidase antiviral	Not reported

continued

TABLE 16 Characteristics of the 30 included studies (*continued*)

Study	Setting and population	Time period	Definition for death	Description of treatment exposure	Drug use before admission
Bagdure *et al.*[201]	Colorado, USA, children, hospitalised	1 May to 30 November 2009	Death in hospital or emergency room	Oseltamivir	Not reported
Blumental *et al.*[202]	Belgium, children > 2 years, hospitalised[c]	1 July 2009 to 31 January 2010	Not reported but all were due to influenza	Oseltamivir	Not reported
Chemaly *et al.*[203]	International, hospitalised cancer patients	During the 2009–10 H1N1 pandemic	Death within 60 days of onset of symptoms	Oseltamivir	Not reported
Çiftçi *et al.*[204]	Turkey, children, hospitalised	17 July 2009 to 10 February 2010	Not reported but causes described	Oseltamivir	Not reported
del Rosal *et al.*[205]	Spain, children, hospitalised	1 May to 30 November 2009	Not reported but causes described	Oseltamivir	Not reported
Kusznierz *et al.*[206]	Argentina, all ages, hospitalised	May to December 2009	Not reported	Oseltamivir	Not reported
Mickienė *et al.*[207]	Lithuania, adults, hospitalised	1 November 2009 to 15 March 2010	Not reported	Antiviral (all received oseltamivir)	Not reported
Moretti *et al.*[208]	Brazil, all ages, hospitalised	28 April to 31 December 2009	Not reported	Oseltamivir	Not reported
Brink *et al.*[209]	Sweden, all ages, critically ill	August 2009 to February 2010	Mortality at 28 and 90 days after admission	Oseltamivir	Oseltamivir, antibiotics
Rahamat-Langendoen *et al.*[210]	Netherlands, all ages, hospitalised	June 2009 to July 2010	Not reported	Oseltamivir	Not reported
Yang *et al.*[182]	China, children, hospitalised with pneumonia[d]	1 September to 31 December 2009	In-hospital and 60-day mortality	1-day oseltamivir[a]	Not reported

ICU, intensive care unit.
a Data on a larger cohort of patients were supplied by the corresponding author.
b A second wave of patients was also included in the data supplied by the corresponding author.
c Cohort of < 2 years was not included as there were no deaths.
d Adult cohort not included as > 95% received oseltamivir.

TABLE 17 Details on timing of admission and treatment, numbers and percentages of patients with oseltamivir exposure by survival status, number of patients not included in mortality breakdown and analysis methods for the 30 included studies

Study	Time from symptom onset to admission[a]	Time from symptom onset to treatment[a]	Time from admission to treatment[a]	Oseltamivir exposure for deaths, *n*/*N* (%)	Oseltamivir exposure for survivors, *n*/*N* (%)	Not included because of missing data	Statistical analysis method used
Siston *et al.*[183]	Not reported	2 (–2 to 21)[b]	Not reported	25/30 (83)	471/545 (86)	200 patients	Mantel–Haenszel test, Fisher's exact test
Louie *et al.*[181]	3 (0–42)	4 (0–52)	Not reported	416/492 (85)	1260/1367 (92)	91 patients	Chi-squared test, Fisher's exact test, Cochran–Armitage test
Jain *et al.*[189]	3 (0–18)	3 (0–29)	46% after admission	17/19 (89)	183/249 (73)	4 patients	Multivariate logistic regression
Farias *et al.*[190]	Not reported	Not reported	86% within 24 hours	52/57(91)	83/90 (92)	0 patients	Multivariate logistic regression
Yang *et al.*[191]	30% after 48 hours	71% not within 48 hours	Not reported	54/69 (78)	355/436 (81)	112 patients	Multivariate logistic regression
Altmann *et al.*[185]	2 (IQR 1–5)	4 (IQR 1–7)	Not reported	7/10 (70)	44/74 (59)	9 patients	Logistic regression
Enstone *et al.*[192]	Not applicable	Range 0–8	Not applicable	5/6 (83)	15/20 (75)	4 patients	No statistical analysis performed
Dominguez-Cherit *et al.*[184]	6 (IQR 4–8)	Not reported	Not reported	14/18 (78)	31/34 (91)	6 patients	Multiple logistic regression, Kaplan–Meier
Kumar *et al.*[187]	4 (IQR 2–7)	Not reported	Not reported	105/117 (90)	435/461 (94)	23 patients	No analysis by treatment performed
Nguyen-Van-Tam *et al.*[186]	2 (0–33)	Not reported	Not reported	60/80 (75)	1023/1440 (71)	0 patients	Multivariable logistic regression
Chitnis *et al.*[193]	50% <48 hours	38% within 48 hours	77% within 24 hours	9/11 (82)	206/239 (86)	2 patients	Chi-squared test, Fisher's exact test, Mantel–Haenszel test

continued

TABLE 17 Details on timing of admission and treatment, numbers and percentages of patients with oseltamivir exposure by survival status, number of patients not included in mortality breakdown and analysis methods for the 30 included studies (*continued*)

Study	Time from symptom onset to admission[a]	Time from symptom onset to treatment[a]	Time from admission to treatment[a]	Oseltamivir exposure for deaths, *n*/*N* (%)	Oseltamivir exposure for survivors, *n*/*N* (%)	Not included because of missing data	Statistical analysis method used
ANZIC[194]	6 (0–35)	6 (0–37)	Not reported	7/7 (100)	45/57 (79)	0 patients	Descriptive analysis
Yung *et al.*[195]	5 (IQR 2–8)	Not reported	Not reported	5/6 (83)	58/72 (81)	5 patients	Multivariable logistic regression
Javadi *et al.*[196]	Mean (range) 5 (1–15)	Not reported	Not reported	34/36 (94)	166/180 (92)	0 patients	Multivariable logistic regression
Miranda-Choque *et al.*[197]	5 (1–10)	Time of treatment unknown	Time of treatment unknown	11/12 (92)	50/62 (81)	0 patients	Multivariable logistic regression
Poeppl *et al.*[198]	Not reported	Not available	Not reported	9/14 (64)	232/327 (71)	2 patients	Multivariable logistic regression
Riquelme *et al.*[199]	Not reported	Not reported	Not reported	40/41 (98)	193/206 (93)	0 patients	Chi-squared test, Fisher's exact test, bivariate analysis
Yokota *et al.*[200]	5 (0–15)	Deaths 6 (1–16); survivors 5 (0–19)	Not reported	25/52 (48)	64/105 (61)	0 patients	Multivariate unconditional logistic regression
Thompson *et al.*[188]	Mean 2.1 days (95% CI 2.0 to 2.3 days)	Mean 3.2 days (95% CI 3.0 to 3.5 days)	Mean 1.3 days (95% CI 1.2 to 1.5 days)	23/32 (72)	646/869 (74)	25 patients	Multivariable Poisson regression
Bagdure *et al.*[201]	3 (IQR 1–5)	2 (IQR 1–4)	0 (IQR 0–1)	7/8 (88)	262/299 (88)	0 patients	Multiple logistic regression
Blumental *et al.*[202]	2 (IQR 1–4)	Not reported	79% started on admission	4/5 (80)	36/110 (33)	0 patients	Chi-squared test, Fisher's exact test
Chemaly *et al.*[203]	2 (0–21)	2 (0–24)	Not reported	11/11 (100)	89/104 (86)	0 patients	Survival analysis
Çiftçi *et al.*[204]	Not reported	Median 24 hours (range 3–240 hours)	Not reported	33/35 (91)	718/786 (91)	0 patients	Chi-squared test, Fisher's exact test
del Rosal *et al.*[205]	3 (IQR 1–5)	Not reported	Not reported	4/5 (80)	385/512 (75)	0 patients	Multiple logistic regression

Study	Time from symptom onset to admission[a]	Time from symptom onset to treatment[a]	Time from admission to treatment[a]	Oseltamivir exposure for deaths, *n*/*N* (%)	Oseltamivir exposure for survivors, *n*/*N* (%)	Not included because of missing data	Statistical analysis method used
Kusznierz *et al.*[206]	Not reported	Mean (range) 3 (0–30)	Not reported	70/81 (86)	157/161 (97)	0 patients	Mantel–Haenszel test, chi-squared test, bivariate analysis
Mickienė *et al.*[207]	2 (0–7)	3 (0–10)	Not reported	6/6 (100)	63/115 (55)	4 patients	Multivariate logistic regression
Moretti *et al.*[208]	Mean 2.3 days	Mean 4 days	Not reported	7/10 (70)	59/129 (46)	0 patients	Chi-squared test, Fisher's exact test
Brink *et al.*[209]	6 (IQR 3–7)	Not reported	Not reported	11/14 (79)	100/108 (93)	14 patients	Relative risk for death, Kaplan–Meier curves
Rahamat-Langendoen *et al.*[210]	2 (IQR 1–4)	Not reported	Not reported	7/7 (100)	58/78 (74)	0 patients	Multinomial logistic regression
Yang *et al.*[182]	Not reported	13% within 48 hours, 39% within 5 days	Not reported	7/10 (70)	485/531 (91)	0 patients	Survival analysis

IQR, interquartile range.
a Median (range) in days unless otherwise stated.
b Negative number implies prophylactic treatment.

hospital presentation. This may be important as, for example, NSAIDs have been shown to increase mortality in influenza-infected animals.[213]

Although a number of the included studies conducted analyses adjusting for potential confounding variables, such as patient comorbidities, they used logistic regression or standard survival analysis, which may not be appropriate for observational studies in which treatment exposure is time dependent. This type of analysis misallocates the time from initiation of the study (e.g. hospital admission) to start of antiviral treatment and leads to time-dependent bias. Beyersmann *et al.*[214] provide mathematical proof that analyses which ignore the time-dependent nature of an exposure variable lead to biased estimates of treatment effect in favour of treatment. Time-dependent bias is also referred to as immortal time bias,[215] survivor treatment selection bias[216] and survival bias.[217] It causes selection bias because patients who die early do not get an opportunity to receive treatment. In addition, patients who are extremely sick may not be given the opportunity to receive treatment because other more critical procedures take priority. Only two of the included studies[182,184] attempted to take account of time-dependent bias but they appeared to have used flawed approaches. One study excluded all deaths within 3 days of onset of symptoms and the other obtained results that appear incorrect because their analysis – taking into account time-dependent bias – increased the treatment effect in favour of oseltamivir. Only six studies reported data on time from hospital admission to treatment initiation (see *Table 17*). Beyersmann *et al.*[214] suggest that time-dependent bias can be avoided by proper hazard-based analyses. See *Appendix 15* for a detailed description and example of time-dependent bias.

Analysis of summary data from included studies

Table 17 shows a summary of the numbers and percentages of patients with oseltamivir exposure by survival status for each of the 30 included studies. In total there are 11,013 patients included and 1301 deaths (12%). Overall, the percentage receiving oseltamivir among deceased patients (1085/1301 = 83%) was similar to the percentage receiving oseltamivir among survivors (7918/9712 = 82%). Meta-analysis of the included studies showed moderate heterogeneity [$I^2 = 44\%$, $\chi^2 = 51.93$, degrees of freedom (df) = 29, $p = 0.006$, $\tau^2 = 0.217$] and no evidence of small study effects ($p = 0.25$). *Figure 17* shows a funnel plot of the 30 included studies.

To investigate heterogeneity we conducted a random-effects metaregression using the *metareg* command in Stata/IC. Factors investigated included age group (adults vs. children), severity of illness (critically ill vs. hospitalised), log-odds of death (another measure of severity of illness) and log-odds of treatment. This last factor was included to investigate the potential effect of time-dependent bias on treatment effects. If time-dependent bias is apparent then we would expect it to have a greater influence in cohorts that had higher odds of treatment. This is because if few patients were untreated then patients dying before initiation of treatment would tend to have a large influence on the odds of patients dying in the untreated group. Results showed no effect of age group ($p = 0.40$) or severity of illness ($p = 0.38$), but evidence of an effect of log-odds of death ($p = 0.024$) when, as odds of death increases, the treatment effect in favour of oseltamivir increases, and log-odds of treatment ($p = 0.003$), when, as odds of treatment increases, the treatment effect in favour of oseltamivir increases. These effects appear to be independent as *p*-values in multivariable analysis are 0.031 and 0.006, respectively.

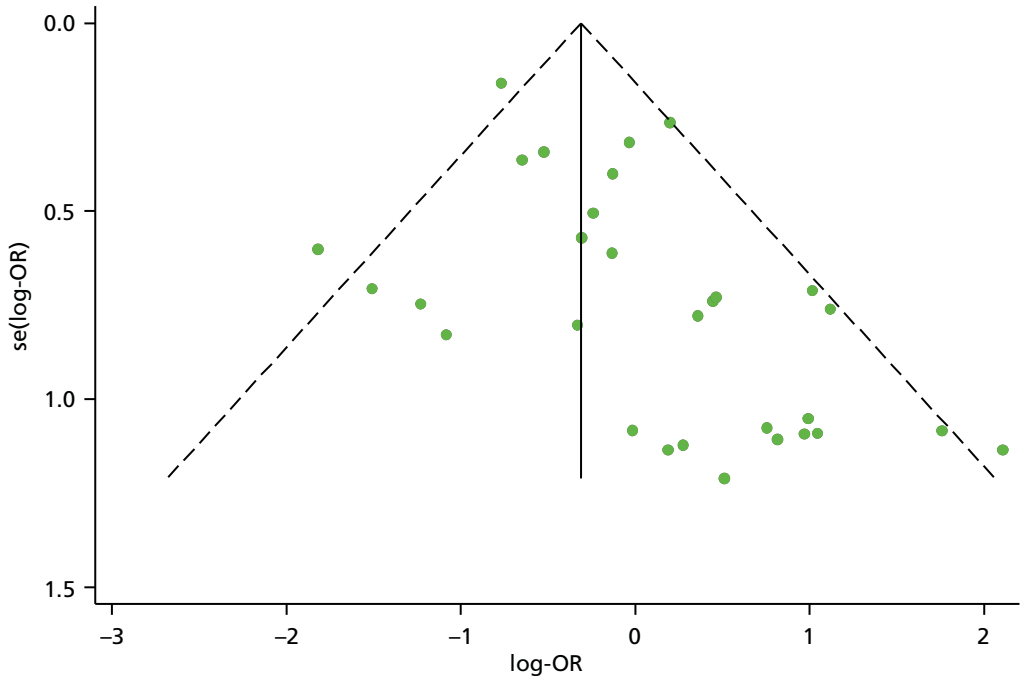


FIGURE 17 Funnel plot of the 30 included studies. Please note that the pseudo 95% confidence limits are shown by the dotted lines. The funnel shape, bounded by the confidence limits, represents the expected distribution of studies where, assuming no heterogeneity, 95% of the treatment effect estimates should lie.

To illustrate these effects we conducted subgroup analysis by odds of treatment: '< 5' compared with '≥ 5' and percentage of death: '< 10%' compared with '≥ 10%'. An odds of treatment of '≥ 5' equates to a percentage of ≥ 83.3%. Results show treatment effect is in favour of oseltamivir and more heterogeneous in cohorts when odds of treatment were '≥ 5'. Conversely, in cohorts for which odds were '< 5', heterogeneity is smaller and overall effect is in favour of no treatment (*Figure 18*). Similarly, treatment effect is in favour of oseltamivir and more heterogeneous in cohorts in which percentage of death was ≥ 10%; conversely, in cohorts in which the percentage is < 10%, heterogeneity is smaller and overall effect is in favour of no treatment (*Figure 19*).

Meta-analysis of individual patient data

We were able to obtain IPD from four included studies.[185–188] One was a German study of 93 critically ill children;[185] another was a UK study of 1520 hospitalised patients of all ages;[186] another was a Canadian study[187] of 605 critically ill adults; and the last study[188] was a US study of 926 hospitalised patients of all ages. After removing data from patients who received zanamivir and patients with missing death status ($n = 73$, 2%), we had data for 3071 patients, of whom 242 (8%) died, 1803 (59%) were discharged, 140 (4%) remained in hospital and 886 (29%) had missing date of discharge. Details of responses and non-responses from corresponding authors of included studies to our request for IPD are shown in *Table 18*.

In *Table 19* we present results of analysis of our primary outcome using five different methods. The first is logistic regression; the second is standard Cox regression; the third is Cox regression including treatment as a time-dependent exposure (td-Cox); the fourth is td-Cox with inclusion of potential confounders as covariates; and the fifth is td-Cox with inclusion of covariates as well as imputing missing time from hospital admission to death/discharge (for which 33% of values are missing, mainly due to the US study not providing date of discharge for survivors), time from hospital admission to oseltamivir exposure (for which 10% of values of the patients treated with oseltamivir are missing) and time from onset of symptoms to hospital admission (16% missing). The percentages of missing data were smaller for the deaths than the survivors (0.4% vs. 36% for time to death/discharge for example), suggesting that data collection was more thorough for patients who died.

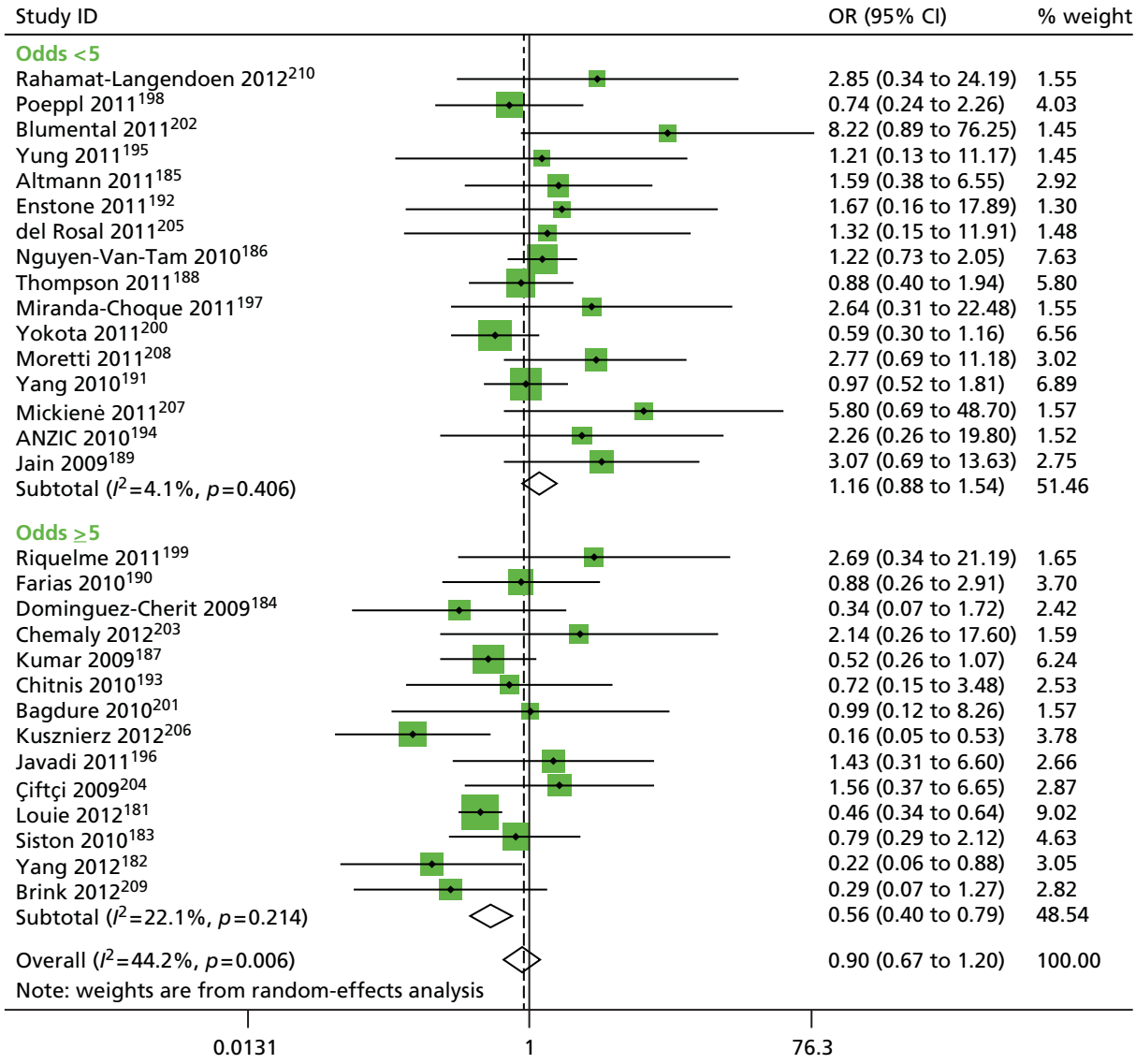


FIGURE 18 Meta-analysis of included studies by odds of treatment with oseltamivir.

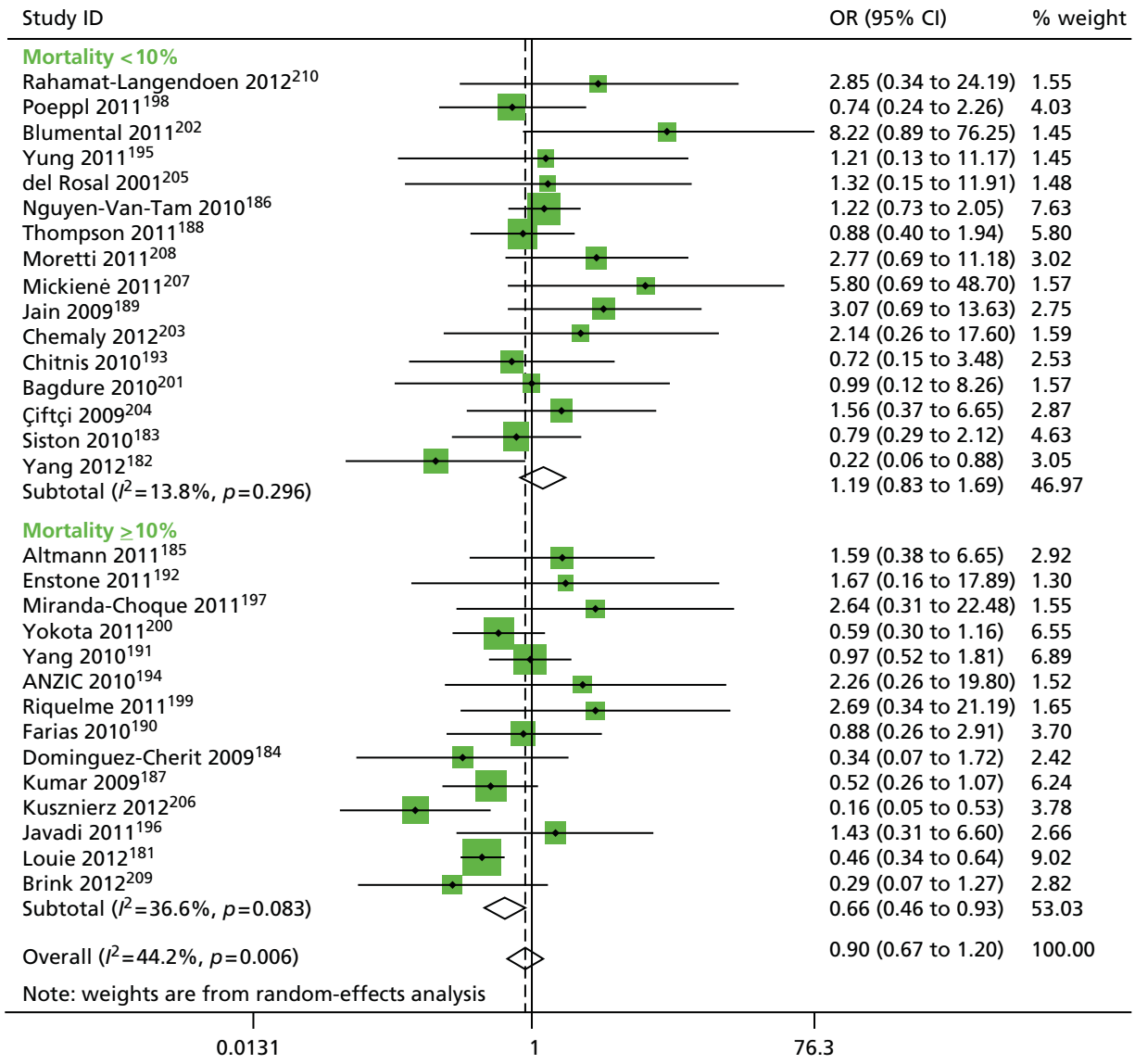


FIGURE 19 Meta-analysis of included studies by proportion of death.

TABLE 18 Responses and non-responses from corresponding authors of included studies to our request for IPD

Outcome from our request	Number of studies
Obtained IPD	4
No response to request	20
Response to our request but did not provide IPD[a]	6

a Reasons given for not providing IPD were as follows:
- 'We have no variables you need. We are epidemiologists, we didn't collect clinical data.'
- 'Unfortunately, the dataset is currently being used for a similar project.'
- 'Unfortunately we just didn't collect the data to be able to make a contribution.'
- 'We will not be able to contribute this time due to current overload of work.'
- 'The information we collected is less detailed than what you ask for.'
- 'Unfortunately it will be difficult to provide you the data as this was a multi-institutional study with centres from outside the US'.

TABLE 19 Results of analysis of primary outcome of death by oseltamivir exposure

Method		Estimate[a]	95% CI	*p*-value
1.	Logistic regression	0.93	0.65 to 1.33	0.71
2.	Standard Cox regression[b]	0.75	0.51 to 1.10	0.14
3.	Cox regression with time-dependent treatment exposure (td-Cox)[b]	1.11	0.75 to 1.65	0.59
4.	td-Cox adjusting for covariates[b]	1.10	0.74 to 1.63	0.64
5.	td-Cox with imputation and adjusting for covariates	1.11	0.77 to 1.62	0.57

a OR for logistic regression; HR for all other analyses.
b Based on the three studies for which date of discharge for survivors was available.

Results show that when the time-dependent nature of treatment is taken into account appropriately the treatment effects change direction, although none of the results is statistically significant. Adjusting for potential confounders and imputing missing data made little difference to the results. *Table 20* shows results of the first three analysis methods by study, and a detailed analysis of the Canadian study,[187] shown in *Appendix 15*, further illustrates why the time-dependent nature of treatment needs to be taken account of appropriately. This study was used for illustration because it had the most deaths and 93% of patients were treated, hence we would expect time-dependent bias to be large. However, bias is also apparent in the other studies if treatment is incorrectly assumed to be time independent (see *Table 20*). *Table 21* shows distributions of potential confounding variables by treatment received stratified by study with *p*-values based on the chi-squared test. Detailed examination suggests a possible explanation for the reason oseltamivir is associated with greater risk of mortality in the Altmann *et al.*[185] and Nguyen-Van-Tam *et al.*[186] studies. In these two studies,[185,186] comorbidities are generally more prevalent in the group that received treatment.

In *Table 22* we show the variables that were associated with oseltamivir treatment. Respiratory and neurological comorbidities, as well as cancer, were all associated with increased odds of treatment, whereas the ages of < 20 years and > 64 years, as well as missing time from symptom onset to hospital presentation, were associated with lower odds of treatment. Early presentation was not associated with increased odds of treatment. In multivariable competing risks analysis, respiratory comorbidity was protective for mortality irrespective of exposure to treatment (HR 0.60, 95% CI 0.43 to 0.84) and each 10 years increase in age was associated with increased risk of death by 22% (95% CI 10% to 35%). Respiratory comorbidity was also associated with 15% (95% CI 3% to 28%) increased likelihood of discharge suggesting despite the comorbidity these patients had a good prognosis. Furthermore, a two-sample *t*-test showed respiratory comorbidity was associated with slightly lower Acute Physiology and Chronic Health Evaluation (APACHE) II scores in the Kumar *et al.*[187] study [mean (SD) 20 (10)[10] vs. 22 (10);[10] $p = 0.014$].

The results of mortality analyses by timing of treatment (*Table 23*) further illustrate the importance of appropriate analysis of a time-dependent treatment exposure. Logistic regression shows a statistically significant reduced odds of death associated with early treatment compared with no treatment, and estimates from standard Cox regression suggest treatment reduces risk of death compared with no treatment, although the result is not statistically significant. However, when time-dependent exposure to treatment is included appropriately in the Cox model, the results show no evidence treatment is beneficial. There is a suggestion that patients receiving late treatment do worse than those who received early treatment; however, this can be at least partially explained by the patients receiving late treatment having worse prognosis due to being older and having increased likelihood of a number of comorbidities, including infection, cardiovascular, diabetes and obesity (*Table 24*).

TABLE 20 Results of IPD analysis by study

Study	Number of patients	Age in years[a]	Days admission to treatment[a]	Percentage treated	Percentage died	OR from logistic regression	HR[b] from Cox regression	HR[c] from td-Cox regression
Altmann *et al.*[185]	88	5 (0–14)	0.85 (0–6)	60	16	1.23	1.36	1.67
Nguyen-Van-Tam *et al.*[186]	1480	29 (0–95)	1.7 (0–79)	73	5	1.13	0.84	1.22
Kumar *et al.*[187]	583	47 (19–92)	0.62 (0–45)	93	20	0.54	0.52	0.87
[d]Thompson *et al.*[188]	936	30 (0–02)	1 (0–34)	74	4	0.99	[d]	[d]

a Mean (range).
b Time-independent treatment exposure.
c Time-dependent treatment exposure.
d Discharge date not available for survivors.

TABLE 21 Comorbidities and presentation timing by treatment and study

Variable	No-treatment group, *n* (%)	Oseltamivir group, *n* (%)	*p*-value
***Altmann* et al.**[185]			
Age group (years)			
< 20	35 (100)	53 (100)	–
20–64	0 (0)	0 (0)	
65+	0 (0)	0 (0)	
Presentation timing			
< 2 days	17 (48)	21 (40)	0.65
> 2 days	15 (43)	28 (53)	
Missing	3 (9)	4 (7)	
Infection	25 (71)	49 (92)	0.019
Cardiovascular	5 (14)	6 (11)	0.93
Neurological	17 (49)	37 (70)	0.075
Cancer	1 (3)	4 (8)	0.65
Immunosuppression	3 (9)	8 (15)	0.56
Respiratory	13 (37)	32 (60)	0.055
Obesity	0 (0)	0 (0)	–
Diabetes	0 (0)	0 (0)	–
***Nguyen-Van-Tam* et al.**[186]			
Age group (years)			
< 20	216 (54)	355 (33)	< 0.0001
20–64	163 (41)	656 (61)	
65+	18 (5)	72 (7)	
Presentation timing			
< 2 days	140 (35)	467 (43)	< 0.0001
> 2 days	97 (25)	346 (32)	
Missing	160 (40)	270 (25)	
Infection	–	–	–
Cardiovascular	31 (8)	159 (15)	0.0006
Neurological	39 (10)	170 (16)	0.005
Cancer	8 (2)	43 (4)	0.096
Immunosuppression	10 (3)	34 (3)	0.65
Respiratory	115 (29)	496 (46)	< 0.0001
Obesity	9 (2)	40 (4)	0.23
Diabetes	24 (6)	77 (7)	0.55

TABLE 21 Comorbidities and presentation timing by treatment and study (*continued*)

Variable	No-treatment group, *n* (%)	Oseltamivir group, *n* (%)	*p*-value
***Kumar* et al.[187]**			
Age group (years)			
< 20	0 (0)	8 (2)	0.23
20–64	32 (82)	480 (88)	
65+	7 (18)	56 (10)	
Presentation timing			
< 2 days	11 (28)	135 (25)	0.26
> 2 days	26 (67)	402 (74)	
Missing	2 (5)	7 (1)	
Infection	22 (56)	332 (61)	0.69
Cardiovascular	16 (41)	215 (40)	0.99
Neurological	1 (3)	30 (6)	0.67
Cancer	0 (0)	36 (7)	0.19
Immunosuppression	2 (5)	33 (6)	1.0
Respiratory	18 (46)	298 (55)	0.38
Obesity	8 (21)	135 (25)	0.68
Diabetes	9 (23)	138 (25)	0.90
***Thompson* et al.[188]**			
Age group (years)			
< 20	96 (40)	292 (43)	0.001
20–64	104 (43)	327 (48)	
65+	42 (17)	59 (9)	
Presentation timing			
< 2 days	137 (57)	362 (53)	0.048
> 2 days	90 (37)	295 (44)	
Missing	15 (6)	21 (3)	
Infection	–	–	–
Cardiovascular	46 (19)	94 (14)	0.071
Neurological	23 (10)	79 (12)	0.43
Cancer	3 (1)	22 (3)	0.16
Immunosuppression	10 (4)	73 (11)	0.003
Respiratory	89 (37)	275 (41)	0.34
Obesity	42 (17)	149 (22)	0.15
Diabetes	50 (21)	101 (15)	0.048

TABLE 22 Variables associated with oseltamivir treatment

Variable	OR for treatment	95% CI	*p*-value
Age (years)			
< 20[a]	0.61	0.50 to 0.74	< 0.0001
> 64	0.52	0.38 to 0.72	
Time from onset of symptoms to hospital presentation[b]	0.89 (early vs. late)	0.72 to 1.09	< 0.0001
	0.44 (missing vs. late)	0.34 to 0.57	
Neurological comorbidity	1.57	1.18 to 2.09	0.002
Cancer	2.93	1.55 to 5.54	0.001
Respiratory comorbidity	1.56	1.30 to 1.88	< 0.0001

a Reference group: age 20–64 years.
b Early ≤ 2 days; late > 2 days; missing = timing of treatment missing.

TABLE 23 Results of analysis of primary outcome of death by timing of oseltamivir exposure

Method	Estimate[a,b]	95% CI	*p*-value
1. Logistic regression	0.54 (early vs. none)	0.33 to 0.89	0.008
	1.12 (late vs. none)	0.76 to 1.66	
	1.11 (missing vs. none)	0.73 to 1.71	
2. Standard Cox regression[c]	0.68 (early vs. none)	0.40 to 1.16	0.12
	0.85 (late vs. none)	0.56 to 1.29	
	0.69 (missing vs. none)	0.44 to 1.06	
3. Cox regression with time-dependent treatment exposure (td-Cox)[c]	0.89 (early vs. none)	0.52 to 1.52	0.69
	1.15 (late vs. none)	0.74 to 1.77	
	1.25 (missing vs. none)	0.72 to 2.16	
4. td-Cox adjusting for covariates[c]	0.92 (early vs. none)	0.54 to 1.57	0.76
	1.16 (late vs. none)	0.75 to 1.79	
	1.14 (missing vs. none)	0.65 to 1.99	
5. td-Cox with imputation and adjusting for covariates	1.10 (early vs. none)	0.60 to 1.47	0.64
	1.28 (late vs. none)	0.86 to 1.90	

a OR for logistic regression; HR for all other analyses.
b Early ≤ 2 days; late > 2 days; missing = timing of treatment missing; none = no treatment given.
c Based on the three studies for which date of discharge for survivors was available.

TABLE 24 Comorbidities by treatment timing

Variable	Early treatment group, *n* (%)	Late treatment group, *n* (%)	*p*-value
Age group (years)			
< 20	313 (42)	237 (23)	< 0.0001
20–64	375 (51)	686 (68)	
65+	55 (7)	90 (9)	
Infection[a]	80 (19)	201 (30)	0.0001
Cardiovascular	106 (14)	235 (23)	< 0.0001
Neurological	101 (14)	133 (13)	0.83
Cancer	24 (3)	42 (4)	0.38
Immunosuppression	51 (7)	63 (6)	0.66
Respiratory	344 (46)	486 (48)	0.52
Obesity	87 (12)	179 (18)	0.0007
Diabetes	78 (11)	159 (16)	0.002

a Data not provided by Nguyen-Van-Tam *et al.*[186]

Competing risks survival analysis on the three cohorts that provided date of hospital discharge showed insufficient evidence that oseltamivir is associated with mortality (HR 1.03, 95% CI 0.64 to 1.65) but the results showed an association with increased likelihood of hospital discharge for survivors (HR 1.44, 95% CI 1.26 to 1.64).

Discussion

We have systematically reviewed the literature on the relationship between mortality from influenza 2009A/H1N1 and oseltamivir exposure. We included 30 studies in our review and obtained IPD for four of those studies. Analysis of both the summary data of the 30 studies, as well as the IPD, showed evidence of time-dependent bias, with bias increasing with increasing odds of treatment. Analysis of the IPD using Cox regression, with treatment exposure included as a time-dependent variable, adjusting for covariates and imputing missing data, has shown insufficient evidence that oseltamivir is associated with a reduction in mortality. Furthermore, early treatment with oseltamivir did not appear to have a beneficial effect on survival compared with no treatment. Competing risks survival analysis also showed insufficient evidence of association of treatment with mortality but the results showed an association with increased likelihood of hospital discharge for survivors.

Analysis of the IPD using logistic regression included 3071 patients and showed an OR of 0.93, whereas standard Cox regression on the 2056 patients with survival times gave a HR of 0.75, reflecting that untreated subjects who died did so earlier than those treated. When the time-dependent nature of oseltamivir exposure was incorporated into the Cox model, results showed a HR of 1.11, a marked difference from 0.75, illustrating the large time-dependent bias associated with standard Cox regression. After adjusting for covariates, the HR was virtually unchanged (1.10) and multiple imputation of the missing data had a negligible effect (HR 1.11). A competing risks survival analysis showed a consistent result, with a HR of 1.03 for mortality. We suggest that the competing risks analysis result may be the most appropriate because it takes into account the competing risk of discharge for treated patients, although a limitation is that it is based on only three studies because the fourth (US) study did not have data available for date of discharge.

The metaregression result that showed increasing mortality rate is associated with an increasingly favourable outcome for treatment is difficult to interpret because of the presence of time-dependent bias that cannot be quantified with access to only summary data. The metaregression result suggests that increasingly severe patients may lead to a better efficacy/toxicity trade-off of treatment. However, without the IPD it is unknown where, if anywhere, oseltamivir becomes a beneficial treatment. An alternative explanation is that cohorts with higher mortality rates were associated with greater time-dependent bias, as a greater proportion of patients died before they had the opportunity to receive antiviral treatment.

Confounding by indication is a possibility in observational studies and it is possible that sicker patients were more likely to get treatment. We were not able to adjust for severity of illness at baseline, as this information was not generally available for the included studies. However, APACHE II score was available for Kumar *et al.*[187] and comparison of treated with untreated patients showed no evidence of a difference in severity of illness (see *Appendix 15*). Prevalence of some comorbidities appeared higher for treated patients than untreated patients for two of the studies for which we had IPD, and this is reflected in the higher odds of mortality for treated patients in those studies. We adjusted for variables associated with treatment in the IPD analysis and this made little difference to the results. In addition, the competing risks survival analysis showed that treated patients who survived were discharged sooner than untreated patients. It is plausible that late treatment could indicate a sicker patient, as normally it takes time for patients to become severely ill. Patients who were treated late were older, and had greater prevalence of some comorbidities than patients who were treated early. This could at least partially explain why these patients had an increased risk of mortality.

Our results are different from those of three other recent reviews. Hsu *et al.*[172] included studies of seasonal influenza and 2009A/H1N1 influenza and based their primary analysis of mortality on three small studies of 681 patients, none of whom had 2009A/H1N1. They did not consider the time-dependent nature of treatment exposure and reported an OR of 0.23 (95% CI 0.13 to 0.43) based on summary data only. Muthuri *et al.*[171] focused on 2009A/H1N1 influenza, included 20 studies, did not consider time-dependent treatment exposure and reported an OR of 0.72 (95% CI 0.51 to 1.01) based on summary data only. Muthuri *et al.*[170] conducted an analysis of almost 30,000 patients from 78 studies using IPD; of the 78 studies included, only 22 would have been eligible for our study. For example, all included patients in 27 studies received NIs and 16 studies had no mortality. It is unclear how these studies were included in a mortality comparison between NIs and no treatment because, in meta-analyses, studies with no events and studies without a control group are dropped from the analysis. Muthuri *et al.*'s crude analysis results[170] are consistent with ours but the results from their analysis taking into account the time-dependent treatment exposure are different and appear to be incorrect, as they result in an increased protective effect of treatment. As Beyersmann *et al.*[214] show, mathematically time-dependent bias is always in the same direction (i.e. in the direction of showing a larger protective effect of treatment than is actually the case). Furthermore, the authors' reply to criticisms of their analysis[218] shows a crude HR of 0.36 (95% CI 0.32 to 0.41) for antiviral use modelled as a time-constant exposure without taking into account clustering or immortal time bias. However, this result is logically inconsistent with the descriptive data, which show that crude mortality in the antiviral group is larger than that of the no-treatment group (9.7% vs. 9.2%).

The results of this systematic review of observational studies are consistent with a recent Cochrane review[9] of NIs for influenza based on a full set of manufacturer compiled CSRs of RCTs and regulatory information. The Cochrane review[9] showed no evidence that NIs reduce the risk of hospitalisation or risk of complications classified as serious or leading to study withdrawal, a result consistent with oseltamivir not having a protective effect on mortality. The likelihood of treated survivors being discharged earlier is inconsistent with these findings, but is consistent with symptomatic relief that is not specific to influenza infection. The reasons for this inconsistency is unclear.

The problem of time-dependent bias is not confined to survival outcomes. For example, Beyersmann *et al.*[214] show time-dependent bias for the effect of hospital-acquired pneumonia on hospital length of stay. Yorifuji *et al.*[147] show the importance of taking account of time-dependent exposure of oseltamivir appropriately in a prospective observational study of Japanese children for which the outcomes related to abnormal behaviours. In the case of observational studies of 2009A/H1N1 influenza, outcomes by oseltamivir exposure – including pneumonia, hospitalisation and intensive care unit admission – have been compared and reported[171,172] without regard to the time-dependent nature of treatment exposure. Beyersmann *et al.*[214] state that 'because time-dependent bias inevitably leads to erroneous findings, it is a major concern that it is common in the clinical literature'. Van Walraven *et al.*[219] surveyed the medical literature and found that 'in medical journals, time-dependent bias is concerningly common and frequently affects key factors and the study's conclusion'. It is critical that analyses of all outcomes reported from observational studies with time-dependent exposures take account of time-dependent bias appropriately.

Strengths

We systematically searched five widely used databases over a 4-year period, as well as hand-searched relevant WHO documents and previous reviews. There were no restrictions on the type of research articles or studies considered for inclusion in the review. Studies from the Americas, UK and Europe, Australasia, Asia and the Middle East were included. We were able to obtain IPD for four studies that included > 3000 patients and more than 240 deaths. Using the IPD we were able to take account of the time-dependent nature of treatment exposure appropriately, impute missing time to event data and adjust for important covariates in the analysis. We were also able to take account of the competing risk of hospital discharge in estimating the effect of oseltamivir on mortality.

Limitations

Limitations of this review include the observational nature and quality of the included studies. All included studies were of hospitalised patients, and severity of illness of patients at baseline was not always reported. Limited information was provided on drug use prior to admission and no study reported NSAID use. Only two studies reported a definition for treatment and the comparison groups were assumed to be the subsets of patients who were not exposed to antivirals. The percentage of unexposed patients was often small (median 18%). Reasons for non-treatment with antivirals were not provided and none of the studies described a policy or criteria used for selecting patients for treatment. Our IPD analysis showed that patients with certain comorbidities were more likely to be treated, whereas children, the elderly and patients with unknown duration of symptoms were less likely to be treated.

We were able to obtain IPD for only four of the included studies, thus limiting the amount of statistical power that we had for our IPD analysis and potentially resulting in a biased subset of the 30 included studies. However, some of the responses to our request for IPD suggest critical data to assess the impact of oseltamivir on mortality were not collected. Furthermore, the IPD we obtained appears to be a representative sample of the 30 included studies as the ORs for mortality were similar for the IPD (0.93 – see *Table 19*) and the summary data (0.90 – see *Figure 19*). These estimates are also consistent with the crude OR of 0.92 reported by Muthuri *et al.*[170] Furthermore, the studies were from four different countries with varying mortality rates (4–20%), varying odds of treatment (60–93%) and included patients with ages from 0 to 102 years.

There were missing data for time to death/discharge and time to treatment (33% and 10% missing, respectively) in the four studies for which we had IPD. The majority of missing data for time to death/discharge was due to one study that did not report date of discharge for survivors. Analysis excluding this study showed similar results to those based on all four studies, hence we do not believe the missing time to discharge data has introduced a significant bias.

Conclusion

Our systematic review has found insufficient evidence that oseltamivir is associated with a reduced risk of mortality. However, this result is based primarily on an IPD analysis of just 4 of 30 eligible observational studies without adjustment for baseline severity of illness or other drug use. Analysis of all 30 included observational studies using summary data showed evidence of time-dependent bias that had an increasing effect with increasing odds of treatment. Observational studies with time-dependent treatment exposure are at high risk of time-dependent bias unless an appropriate analysis is conducted.

Acknowledgements

Thanks to Jon Deeks, Timothy Aoki, Carlo Di Pietrantonj, Vittorio Demicheli, Janet Wale, John Bartlett, Sree Nair, Tom Fahey, Matthew Shun-Shin, Anthony Harnden, Nigel Matheson, M Symmonds-Abrahams and Aziz Sheikh for input and advice on earlier versions of related reviews.

Thanks to Ruth Foxlee, Alex Rivetti and Nia Roberts for helping out with the searches.

Peter Collignon and Marcus Muellner helped us with aspects of the review.

Thanks to Nicola Ring and Ruth Jepson for advice on the inclusion of qualitative data.

We thank Toby Lasserson for providing advice and an independent check of our risk-of-bias judgements.

The EMA (formerly EMEA) provided all CSRs and reviewers' comments in their archive.

Hoffman-La Roche SA and GSK provided us with full CSRs and answered our queries.

Thanks also to the Australian National Health and Medical Research Council and the UK NHS Research and Development fund for grants to enable the 2009 healthy adults review update.

Philip Carter and Deborah Cohen shared some of their FOI material.

Eliana Ferroni helped develop and cross-check the TOC.

We are very grateful to Sarah Thorning (clinical librarian) for running the literature searches; Anand Kumar and Rob Fowler for providing the Canadian IPD; Jonathan Van Tam and Puja Myles for providing the UK IPD; Mathias Altmann for providing the German IPD; and Deborah Thompson for providing the US IPD.

Finally, we wish to thank the following people for commenting on the draft protocol: Maryann Napoli, Janet Wale, Paul Glasziou, David Boltz, Elaine Beller, Anca Zalmanovici Trestioreanu and Marcus Muellner.

We also thank the following people for commenting on:

- the draft 2012 review – Chris Cates, Janet Wale, Paul Glasziou, David Boltz and Robert Ware
- the draft 2014 review – Chris Cates, Elizabeth Dooley, Janet Wale, David Boltz and Robert Ware.

Contributions of authors

Carl J Heneghan (Professor, Evidence-Based Medicine) amended the review protocol, applied the inclusion criteria to the zanamivir CSRs and contributed to the draft.

Igho Onakpoya (Research Fellow, Evidence-Based Practice and Pharmacovigilance) applied the inclusion criteria to the zanamivir CSRs, extracted data from the CSRs and contributed to the draft.

Mark A Jones (Senior Research Fellow, Biostatistics) amended the review protocol, arbitrated the process for inclusion of studies where necessary, performed statistical analyses and contributed to the draft.

Peter Doshi (Assistant Professor, Pharmaceutical Health Services Research) amended the review protocol, applied the inclusion criteria to the oseltamivir CSRs and contributed to the draft.

Chris B Del Mar (Professor, Public Health) amended the review protocol, screened the electronic search updates and contributed to the draft.

Rokuro Hama (Chairperson, Japan Institute of Pharmacovigilance) amended the review protocol and contributed to the draft.

Matthew J Thompson (Helen D Cohen Endowed Professorship in Family Medicine) amended the review protocol, screened the electronic search updates and contributed to the draft.

Elizabeth A Spencer (Epidemiologist) extracted data from the CSRs and contributed to the draft.

Kamal R Mahtani (National Institute for Health Research Academic Lecturer in General Practice) extracted data from the CSRs and contributed to the draft.

David Nunan (Research Fellow, Evidence-Based Practice and Physical Activity) extracted data from the CSRs and contributed to the draft.

Jeremy Howick (Research Fellow, Centre for Evidence-Based Medicine) extracted data from the CSRs and contributed to the draft.

Tom Jefferson (Reviewer, Cochrane) amended the review protocol, applied the inclusion criteria to the oseltamivir CSRs and prepared the final text.

Publications

Doshi P, Jefferson T, Del Mar C. The imperative to share clinical study reports: recommendations from the Tamiflu experience. *PLOS Med* 2012;**9**:e1001201.

Heneghan CJ, Onakpoya I, Thompson M, Spencer EA, Jones M, Jefferson T. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;**348**:g2547.

Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ* 2014;**348**:g2545.

Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, *et al*. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2014;**4**:CD008965.

Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, *et al.* Risk of bias in industry-funded oseltamivir trials: comparison of core reports versus full clinical study reports. *BMJ Open* 2014;**4**:e005253.

Jones M, Jefferson T, Doshi P, Del Mar C, Heneghan C, Onakpoya I. Commentary on Cochrane review of neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Clin Microbiol Infect* 2015;**21**:217–21.

Data sharing statement

The full set of CSRs for the NI Tamiflu (Oseltamivir) and Reenza (Zanamivir) produced by Roche were made available to the Cochrane collaboration for the production of their meta-analysis of neuraminidase inhibitors for preventing and treating influenza in adults and children are available at http://datadryad.org/resource/doi:10.5061/dryad.77471. (Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, *et al*. Data from: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Dryad Digital Repository*, 2014. http://dx.doi.org/10.5061/dryad.77471).

References

1. UK Department of Health. *UK Influenza Pandemic Contingency Plan*. 2005. URL: www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4121744.Pdf (accessed 27 June 2013).
2. US Department of Health and Human Services. *HHS Pandemic Influenza Plan*. 2005. URL: www.pandemicflu.gov/planning-preparedness/federal/hhspandemicinfluenzaplan.pdf (accessed 27 June 2013).
3. World Health Organization. *WHO Interim Protocol: Rapid Operations to Contain the Initial Emergence of Pandemic Influenza*. URL: www.who.int/entity/csr/disease/avian_influenza/guidelines/RapidContProtOct15.pdf (accessed 27 June 2013).
4. 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;**63**:1667–72. http://dx.doi.org/10.1001/archinte.163.14.1667
5. 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. http://dx.doi.org/10.1016/S0140-6736(06)67970-1
6. Doshi P, Jefferson T, Del Mar C. The imperative to share clinical study reports: recommendations from the Tamiflu experience. *PLOS Med* 2012;**9**:e1001201. http://dx.doi.org/10.1371/journal.pmed.1001201
7. Thomas K. *Breaking the Seal on Drug Research. New York Times*, 29 June 2013. URL: www.nytimes.com/2013/06/30/business/breaking-the-seal-on-drug-research.html (accessed 20 October 2013).
8. Doshi P. Neuraminidase inhibitors: the story behind the Cochrane review. *BMJ* 2009;**339**:b5164 http://dx.doi.org/10.1136/bmj.b5164
9. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2014;**4**:CD008965. http://dx.doi.org/10.1590/1516-3180.20141324t2
10. Doshi P, Jones MA, Jefferson T. Rethinking credible evidence synthesis. *BMJ* 2012;**344**:d7898. http://dx.doi.org/10.1136/bmj.d7898
11. Doshi P, Jefferson T. Clinical study reports of randomised controlled trials: an exploratory review of previously confidential industry reports. *BMJ Open* 2013;**3**:e002496 http://dx.doi.org/10.1136/bmjopen-2012-002496
12. European Medicines Agency. *European Medicines Agency Policy on Access to Documents (Related to Medicinal Products for Human and Veterinary Use) POLICY/0043*. 2010. URL: www.ema.europa.eu/docs/en_GB/document_library/Other/2010/11/WC500099473.pdf (accessed 20 October 2013).
13. Godlee F. Clinical trial data for all drugs in current use. *BMJ* 2012;**345**:e7304. http://dx.doi.org/10.1136/bmj.e7304
14. Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database Syst Rev* 2010;**2**:CD001265. http://dx.doi.org/10.1002/14651858.cd001265.pub3
15. Hama R. Fatal neuropsychiatric adverse reactions to oseltamivir: case series and overview of causal relationships. *Int J Risk Saf Med* 2008;**20**:5–36.

16. Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? *JAMA* 2005;**8**:987–97. http://dx.doi.org/10.1001/jama.293.8.987

17. Sugaya N, Ohashi Y. Long-acting neuraminidase inhibitor laninamivir octanoate (CS-8958) versus oseltamivir as treatment for children with influenza virus infection. *Antimicrob Agents Chemother* 2010;**54**:2575–82. http://dx.doi.org/10.1128/AAC.01755-09

18. Hayden F. Developing new antiviral agents for influenza treatment: what does the future hold? *Clin Infect Dis* 2009;**48**(Suppl. 1):3–13. http://dx.doi.org/10.1086/591851

19. World Health Organization. Global Agenda on Influenza: Adopted Version. Part I. *Weekly Epidemiological Record/Health Section of the Secretariat of the League of Nations* 2002;**77**:179–82.

20. World Health Organization. Adoption of Global Agenda on Influenza. Part II. *Weekly Epidemiological Record/Health Section of the Secretariat of the League of Nations* 2002;**77**:191–5.

21. World Health Organization. *WHO Guidelines on the Use of Vaccines and Antivirals During Influenza Pandemics*. 2009. URL: www.who.int/csr/resources/publications/influenza/11_29_01_A.pdf (accessed 30 November 2009).

22. Matrosovich MN, Matrosovich TY, Gray T, Roberts NA, Klenk H. Neuraminidase is important for the initiation of influenza virus infection in human airway epithelium. *J Virol* 2004;**78**:12665–7. http://dx.doi.org/10.1128/JVI.78.22.12665-12667.2004

23. Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med* 2005;**353**:1363–73. http://dx.doi.org/10.1056/NEJMra050740

24. Ohuchi M, Asaoka N, Sakai T, Ohuchi R. Roles of neuraminidase in the initial stage of influenza virus infection. *Microbes Infect* 2006;**8**:1287–93. http://dx.doi.org/10.1016/j.micinf.2005.12.008

25. Liu C, Eichelberger MC, Compans RW, Air GM. Influenza type A virus neuraminidase does not play a role in viral entry, replication, assembly, or budding. *J Virol* 1995;**69**:1099–106.

26. Smith J, Dutkowski R, Ward P. Antivirals for influenza in healthy adults. *Lancet* 2006;**367**:1571;author reply 1573. http://dx.doi.org/10.1016/S0140-6736(06)68683-2

27. Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, *et al.* Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *JAMA* 1999;**282**:1240–6. http://dx.doi.org/10.1001/jama.282.13.1240

28. Li C, Yu Q, Ye Z, Sun Y, He Q, Li X, *et al.* A nonsynonymous SNP in human cytosolic sialidase in a small Asian population results in reduced enzyme activity: potential link with severe adverse reactions to oseltamivir. *Cell Res* 2007;**17**:357–62. http://dx.doi.org/10.1038/cr.2007.27

29. Cass LM, Efthymiopoulos C, Bye A. Pharmacokinetics of zanamivir after intravenous, oral, inhaled or intranasal administration to healthy volunteers. *Clin Pharmacokinet* 1999;**36**(Suppl. 1):1–11. http://dx.doi.org/10.2165/00003088-199936001-00001

30. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database Syst Rev* 2006;**3**:CD001265. http://dx.doi.org/10.1002/14651858.cd001265.pub2

31. Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ* 2009;**339**:b5106. http://dx.doi.org/10.1136/bmj.b5106

32. Shun-Shin M, Thompson M, Heneghan C, Perera R, Harnden A, Mant D. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2009;**339**:b3172. http://dx.doi.org/10.1136/bmj.b3172

33. World Health Organization. *WHO Model List of Essential Medicines. ADULTS, 18th edition (April 2013).* 2013. URL: www.who.int/medicines/publications/essentialmedicines/18th_EML_Final_web_8Ju_l13.pdf (accessed 25 November 2013).

34. World Health Organization. *WHO Model List of Essential Medicines for Children. 4th list (April 2013)*. 2013. http://apps.who.int/iris/bitstream/10665/93143/1/EMLc_4_eng.pdf (accessed 25 November 2013).

35. Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. *Cochrane Database Syst Rev* 200;**1**:CD002744.

36. M76001. McGarty T. *A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Efficacy Based on the Time to Treatment of Influenza Infection with the Neuraminidase Inhibitor Ro 64–0796 (also known as GS 4104)*. Data on file.

37. Gravenstein S, Peters P. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. *J Am Geriatr Soc* 2001;**49**:1025–31. [Erratum published in *J Am Geriatr Soc* 2013;**61**:478.] http://dx.doi.org/10.1111/jgs.12250

38. Peters PH, Jr, Gravenstein S, Norwood P, De Bock V, Van Couter A, Gibbens M, *et al.* Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. *J Am Geriatr Soc* 2001;**49**:1025–31. http://dx.doi.org/10.1046/j.1532-5415.2001.49204.x

39. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled Study of Ro 64–0796 (also known as GS4104) used in Elderly Subjects for the Prevention of Clinical Influenza during the Influenza Season*. Data on file.

40. Godlee F, Clarke M. Why don't we have all the evidence on oseltamivir? *BMJ* 2009;**339**:b5351. http://dx.doi.org/10.1136/bmj.b5351

41. McGauran N, Wieseler B, Kreis J, Schuler Y, Kolsch H, Kaiser T. Reporting bias in medical research: a narrative review. *Trials* 2010;**11**:37. http://dx.doi.org/10.1186/1745-6215-11-37

42. Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervölgyi V, Kohlepp P, *et al.* Completeness of reporting of patient-relevant clinical trial outcomes: comparison of unpublished clinical study reports with publicly available data. *PLOS Med* 2013;**10**:e1001526.

43. Cohen D. Complications: tracking down the data on oseltamivir. *BMJ* 2009;**339**:b5387. http://dx.doi.org/10.1136/bmj.b5387

44. Japanese Association for Infectious Diseases. *Question and Answers on the Japanese Association for Infectious Diseases Urgent Recommendation 'Handling Pandemic Influenza in Routine Care Institutions'*. 2010. URL: www.kansensho.or.jp/topics/090525influenza_qanda.html (accessed 9 May 2010).

45. Maugh TH, II. *British Medical Journal Questions Efficacy of Tamiflu for Swine Flu – Or Any Flu*. 2009. URL: http://latimesblogs.latimes.com/booster_shots/2009/12/british-medical-journal-questions-efficacy-of-tamiflu-for-swine-flu-or-any-flu.html (accessed 8 December 2009).

46. Nebehay S. *WHO Backs Findings on Tamiflu for Seasonal Flu*. 2009. URL: www.reuters.com/article/idUSGEE5BA0UY20091211?type=marketsNews (accessed 11 December 2009).

47. NHS Choices. *Antivirals and Swine Flu*. 2009. URL: www.nhs.uk/news/2009/12December/Pages/Antivirals-and-swine-flu.aspx (accessed 17 May 2010).

48. NHS Choices. *Swine Flu – Questions and Answers*. 2010. URL: www.nhs.uk/Conditions/Pandemic-flu/Pages/QA.aspx (accessed 17 May 2010).

49. US Centers for Disease Control and Prevention. Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine. *MMWR Morb Mortal Wkly Rep* 2009;**58**:521–4.

50. Itoh Y, Shinya K, Kiso M, Watanabe T, Sakoda Y, Hatta M, *et al.* In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. *Nature* 2009;**460**:1021–5. http://dx.doi.org/10.1038/nature08260

51. Rodgers MA, Brown JVE, Heirs MK, Higgins JPT, Mannion RJ, Simmonds MC, *et al.* Reporting of industry funded study outcome data: comparison of confidential and published data on the safety and effectiveness of rhBMP-2 for spinal fusion. *BMJ* 2013;**346**:f3981. http://dx.doi.org/10.1136/bmj.f3981

52. Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. *N Engl J Med* 2009;**361**:1963–71. http://dx.doi.org/10.1056/NEJMsa0906126

53. Vedula SS, Li T, Dickersin K. Differences in reporting of analyses in internal company documents versus published trial reports: comparisons in industry-sponsored trials in off-label uses of gabapentin. *PLOS Med* 2013;**10**:e1001378. http://dx.doi.org/10.1371/journal.pmed.1001378

54. Eyding D, Lelgemann M, Grouven U, Harter M, Kromp M, Kaiser T, *et al.* Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *BMJ* 2010;**341**:c4737. http://dx.doi.org/10.1136/bmj.c4737

55. Ioannidis JPA, Karassa FB. The need to consider the wider agenda in systematic reviews and meta-analyses: breadth, timing, and depth of the evidence. *BMJ* 2010;**341**:c4875. http://dx.doi.org/10.1136/bmj.c4875

56. Chou R, Helfand M. Challenges in systematic reviews that assess treatment harms. *Ann Intern Med* 2005;**142**:1090–9. http://dx.doi.org/10.7326/0003-4819-142-12_Part_2-200506211-00009

57. NV16871. No authors listed. *A Double-Blind, Randomized, Stratified, Placebo-Controlled Study of Oseltamivir in the Treatment of Influenza in Children with Asthma*. Data on file.

58. WV15671. Dorkings J. *Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial*. Data on file.

59. WV15673/WV15697. No authors listed. *Efficacy of RO 64–0796 when used as Chemoprophylaxis against Natural Influenza Infection*. Data on file.

60. WV15707. Grosse M. *A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study of Oseltamivir Treatment in Elderly Patients with Influenza*. Data on file.

61. WV15708. No authors listed. *A Double-Blind Randomised Placebo Controlled Study of RO 64–0796 (also known as GS4104) used in Elderly Subjects for the Prevention of Clinical Influenza during Influenza Season*. Data on file.

62. WV15730. Dorkings J. *A Double-Blind, Stratified, Randomized, Placebo Controlled Study of Ro 64–0796 (GS4104) in the Treatment of Influenza Infection in Adults*. Data on file.

63. WV15758. No authors listed. *A Double-Blind, Randomized, Stratified, Placebo-Controlled Study of Ro 64–0796 (also known as GS 4104) in the Treatment of Children with Influenza*. Data on File.

64. WV15759/WV15871. Gerster T. *A Double-Blind, Randomized, Stratified, Placebo-Controlled Study of Oseltamivir Phosphate (Ro 64–0796, also known as GS 4104) in the Treatment of Influenza in Children with Chronic Asthma*. Data on file.

65. WV15799. No authors listed. *A Double-Blind Randomised Placebo Controlled Study of Ro 64–0796 (also known as GS4104) for the Prevention of Clinical Influenza Post Exposure in Families*. Data on file.

66. WV15812/WV15872. McCarvil M. *A Double-Blind, Stratified, Randomised, Placebo Controlled Study of Ro 64–0796 (also known as GS4104) in the Treatment of Influenza in Chronically Ill Adults*. Data on file.

67. WV15819/WV15876/WV15978. No authors listed. *A Double-Blind, Randomized, Stratified, Placebo-Controlled Study of Ro 64–0796 (also known as GS4104) in the Treatment of Influenza Infection in Elderly Patients*. Data on file.

68. WV15825. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled Study of Ro 64–0796 (also known as GS4104) used in Elderly Subjects for the Prevention of Clinical Influenza during the Influenza Season*. Data on file.

69. WV16277. No authors listed. *A Double-Blind, Randomised, Stratified, Placebo-Controlled Study of Oseltamivir in the Treatment of Influenza Infection in Patients*. Data on file.

70. 167-101. GSK. *Investigation of the Efficacy of GG167 (Zanamivir) in the Treatment of Influenza Viral Infections (Late Phase II Study: Dose Comparison Study)*. Data on file.

71. JNAI-01. GSK. *Investigation of the Efficacy of CG167 in the Treatment of Influenza Viral Infections (Phase II Study) (Protocol NoJNAI-01). Double Blind, Double Dummy, Randomized, Placebo Controlled, Parallel Group, Multicenter Study to Investigate Safety and Route of Administration of CG167 when Inhaled, CG167 10 mg, or the Combination of Inhaled CG167 10 mg plus Intranasal CG167 6.4 mg, Administered Twice Daily for 5 days in the Treatment of Influenza A and B Viral Infections*. Data on file.

72. JNAI-04. GSK. *A Multicenter Two Way Layout Randomized Placebo-Controlled Double-Blind Trial Parallel Group Comparative Trial on the Efficacy and Safety of GG167 (zanamivir) 10 mg Twice a Day and 20 mg Twice a Day in the Treatment of Influenza Type A and Type B Infections (Late Phase II Study: Dose Comparison Study) (Protocol No. JNAI-04)*. Data on file.

73. JNAI-07. GSK. *A Multicenter Two Way Layout Randomized Placebo-Controlled Double-Blind Trial Parallel Group Comparative Trial on the Efficacy and Safety of GG167 (zanamivir) 10 mg Twice a Day and 20 mg Twice a Day in the Treatment of Influenza Type A and Type B Infections (Late Phase II Study: Dose Comparison Study) (Protocol No. JNAI-07)*. Data on file.

74. JV15823. No authors listed. *A Randomized, Placebo-Controlled, Multicenter Study of Oseltamivir (Ro 64–0796) in the Treatment of Influenza in Japanese Subjects (Translation of Summary Japanese Report – of 29 pages)*. Data on file.

75. JV15824. No authors listed. *Phase 3 Study for Prophylaxis of Influenza with Ro64–0796 (15 page Summary From Japanese)*. Data on file.

76. ML16369. No authors listed. *A Double-Blind, Randomized, Placebo-Controlled Multicenter Study of Oseltamivir Phosphate in the Treatment of Influenza Infection in China*. Data on file.

77. NAI30008. No authors listed. *A Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Multi-Center Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Administered Twice Daily for five Days in the Treatment of Influenza in Patients 12 years or over Diagnosed with Asthma or Chronic Obstructive Pulmonary Disease*. Data on file.

78. NAI30009. Alfors S, Keene O, Grice R, Hammond J, Hendricks V, Martin N, *et al. A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Efficacy and Safety of Zanamivir (GG167) 10 mg Administered by Inhalation Twice Daily for five Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Children ages 5–12*. Data on file.

79. NAI30010. Hunter S, Reilly L, Sharp S, West M, Alfors S, Hammond J, *et al. A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Efficacy and Safety of Inhaled Zanamivir (GG167) 10 mg Administered once a Day for 10 Days in the Prevention of Transmission of Symptomatic Influenza A and B Viral Infections within Families*. Data on file.

80. NAI30011. No authors listed. *A Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Impact of Inhaled Zanamivir Treatment on Workplace Attendance due to Influenza A and B Infections*. Data on file.

81. NAI30012. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multicentre Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Administered Twice Daily for five Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Subjects aged over 65 years*. Data on file.

82. NAI30015. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multicentre Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Administered Twice Daily for five Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Armed Services Personnel*. Data on file.

83. NAI30020. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled, Multicenter Study in 2 Parallel Groups, to Investigate the Efficacy and Safety of Inhaled Zanamivir (10 mg bd. via Diskhaler), for 5 Days, in High Risk Patients with Symptomatic Influenza A and/or B Infection*. Data on file. Synopsis only available.

84. NAI30028. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled, Multicenter Study in 2 Parallel Groups, to Investigate the Efficacy and Safety of Inhaled Zanamivir (10 mg bd via Diskhaler), for 5 Days, in Children aged 5 to 12 years with Symptomatic Influenza A and/or B Infection*. Data on file.

85. NAI30031. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multicentre Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Administered Once a Day for 10 days in the Prevention of Transmission of Symptomatic Influenza A and B Viral Infections within Households*. Data on file.

86. NAI30034. No authors listed. *A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicentre Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Administered Once a Day for 28 Days in the Prevention of Symptomatic Influenza A and B Viral Infections in Community-Dwelling High-Risk Populations*. Data on file.

87. NAIA/B2008. No authors listed. *A Double-Blind, Randomized, Placebo-Controlled, Multicenter, Parallel-Group Study to Investigate the Efficacy and Safety of Zanamivir Administered Twice or Four Times a Day for the Treatment of Influenza A and B Viral Infections*. Data on file.

88. NAIA/B2009. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled, Multicentre, Parallel-Group Study to Demonstrate the Efficacy and Safety of Zanamivir in the Prevention and/or Progression of Influenza A and B Viral Infections*. Data on file.

89. NAIA2005. MacLeod A, Gummer M, Raniga K, Hirst H, Keene O, Ossi M, *et al. A Double-Blind, Randomised, Placebo-Controlled Multi-Centre Study to Investigate the Efficacy and Safety of Inhaled and Intranasal Zanamivir in the Treatment of Influenza A and B Viral Infections*. Data on file.

90. NAIA2006. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled Multicentre Study to Investigate the Efficacy and Safety of Zanamivir Therapy in the Prevention of Progression of Influenza A and B Viral Infections*. Data on file.

91. NAIA3002. Elliott M, Flack N, Keene O, Szymborski P, Vega R (PharmaResearch, Inc.). *A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Efficacy and Safety of Inhaled Zanamivir (GG167) 10 mg Administered Twice a Day for five Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Adolescents and Adults*. Data on file.

92. NAIA3003. No authors listed. *A Double-Blind, Randomized, Parallel-Group, Multi-Center Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Administered Once a Day Compared to the Standard of Care in Controlling Nursing Home Influenza Outbreaks*. Data on file.

93. NAIA3004. No authors listed. *A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multi-Center Study to Investigate the Efficacy and Safety of Inhaled Zanamivir 10 mg Once a Day in Controlling Nursing Home Influenza Outbreaks*. Data on File.

94. NAIA3005. Elliott M, Hunter S, Flack N, Crisp A, Szymborski P, Vega R. *A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Efficacy and Safety of Zanamivir (GG167) 10 mg Administered Once a Day for 28 Days in the Prevention of Symptomatic Influenza A and B Viral Infections in Community Dwelling Adults*. Data on file.

95. NAIB2005. Leong J, Brennan J, Gummer M, Keene O, Wightman K. *A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multi-Centre Study to Investigate the Efficacy and Safety of Inhaled Plus Intranasal Zanamivir in the Treatment of Influenza A and B Viral Infections*. Data on file.

96. NAIB2006. No authors listed. *A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multicentre Study to Investigate the Efficacy and Safety of Inhaled Zanamivir in Preventing Progression of Influenza A and B Viral Infections*. Data on file.

97. NAIB2007. Perich R, Solterbeck A, Keene O, Leong J, Raniga K, MacLeod A. *A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multi-Centre Study to Investigate the Efficacy and Safety of Inhaled and Inhaled plus Intranasal Zanamivir in the Treatment of Influenza A and B Viral Infections*. Data on file.

98. NAIB3001. Campion K, Gummer M, Keene O. *A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Study to Investigate the Efficacy and Safety of Zanamivir Administered Twice Daily in the Treatment of Influenza A and B Viral Infections in Adults*. Data on file.

99. NAIB3002. Man CY, Keene ON, Challoner T (Challoner Associates). *A Double-Blind, Randomised, Placebo-Controlled, Parallel-Group, Multicentre Study to Investigate the Efficacy and Safety of Inhaled Zanamivir (GG167) 10 mg Administered Twice a Day for five Days in the Treatment of Symptomatic Influenza A and B Viral Infections in Adolescents and Adults*. Data on file.

100. PE-01. No authors listed. *A Trial to Investigate Efficacy to Reduce Development of Influenza Symptoms in Influenza Infected Patients treated with GG167 (protocol number PE-01 Phase II Clinical Trial). A Double-Blind Double-Dummy, Randomized, Placebo-Controlled, Parallel Group, Multicenter Study to Investigate the Efficacy Reducing Development of Influenza Symptoms and, Safety and Route of Administration of GG 157 when Orally Inhaled GG 167 10 mg, 6.4 mg Nebulized Intranasally or the Combination of Inhaled GG167 10 mg plus Intranasal GG167 6.4 mg was Administered Twice Day for 5 Days in the Treatment of Influenza A and B Viral Infections*. Data on file.

101. MacLean CH, Morton SC, Ofman JJ, Roth EA, Shekelle PG. How useful are unpublished data from the Food and Drug Administration in meta-analysis? *J Clin Epidemiol* 2003;**56**:44–51.

102. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011. URL: www.cochrane-handbook.org

103. Aronson JK, Ferner RE. Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ* 2003;**327**:1222–5. http://dx.doi.org/10.1136/bmj.327.7425.1222

104. WP16263. *A Randomized, Double Blind, Parallel Group, Placebo Controlled Study of the Effect of Oseltamivir on ECG Intervals in Healthy Subjects*. Data on file.

105. Dutkowski R, Smith JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. *Int J Antimicrob Agents* 2010;**35**:461–7. http://dx.doi.org/10.1016/j.ijantimicag.2009.12.023

106. Jefferson T, Jones, M, Doshi, P, Del Mar CB, Heneghan CJ, Hama R, *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;**1**:CD008965. http://dx.doi.org/10.1002/14651858.cd008965.pub3

107. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88. http://dx.doi.org/10.1016/0197-2456(86)90046-2

108. Feinberg J. *Wordle*. URL: www.wordle.net/2009 (accessed 15 September 2010).

109. Food and Drug Administration. *Tamiflu (Oseltamivir Phosphate) Capsule*. Medical Review Part 2 (Application No.: 021087). 1999. URL: www.accessdata.fda.gov/drugsatfda_docs/nda/99/21087_Tamiflu_medr_P1.pdf (accessed 26 August 2009).

110. Anekthananon T, Pukritayakamee S, Ratanasuwan W, Jittamala P, Werarak P, Charunwatthana P, *et al.* Oseltamivir and inhaled zanamivir as influenza prophylaxis in Thai health workers: A randomized, double-blind, placebo-controlled safety trial over 16 weeks. *J Antimicrob Chemother* 2013;**68**:697–707. http://dx.doi.org/10.1093/jac/dks418

111. Dharan NJ, Fry AM, Kieke BA, Coleman L, Meece J, Vandermause M, *et al.* Clinical and virologic outcomes in patients with oseltamivir-resistant seasonal influenza A (H1N1) infections: results from a clinical trial. *Influenza Other Respir Viruses* 2012;**6**:153–8. http://dx.doi.org/10.1111/j.1750-2659.2011.00312.x

112. Kashiwagi S, Watanabe A, Ikematsu H, Awamura S, Okamoto T, Uemori M, *et al.* Laninamivir octanoate for post-exposure prophylaxis of influenza in household contacts: A randomized double blind placebo controlled trial. *J Infect Chemother* 2013;**19**:740–9. http://dx.doi.org/10.1007/s10156-013-0622-9

113. NCT00419263. *A Phase II, Multicenter, Randomized, Double-Mask, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Intramuscular Peramivir in Subjects with Uncomplicated Acute Influenza*. Data on file.

114. NCT00453999. *A Phase II, Multicenter, Randomized, Double-Mask, Double-Dummy Study Comparing the Efficacy and Safety of Peramivir Administered Intravenously Once Daily versus Oseltamivir Administered Orally Twice Daily in Adults with Acute Serious or Potentially Life-Threatening Influenza*. Data on file.

115. NCT00486980. *A Phase 3 Multicenter, Randomized, Double Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Intramuscular Peramivir in Subjects with Uncomplicated Acute Influenza*. Data on file.

116. NCT00610935. *A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Intramuscular Peramivir in Subjects with Uncomplicated Acute Influenza*. Data on file.

117. NCT00705406. *A Phase II, Multicenter, Randomized, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of Intramuscular Peramivir 600 mg in Subjects with Uncomplicated Acute Influenza*. Data on file.

118. NCT00958776. *A Phase 3, Multicenter, Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of Peramivir Administered Intravenously in Addition to Standard of Care Compared to Standard of Care Alone in Adults and Adolescents who are Hospitalized due to Serious Influenza*. Data on file.

119. Food and Drug Administration. *Site Inspection Report in Review. Tamiflu (oseltamivir)*. NDA 021087 Supplement 002. 2000. URL: www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21–087SE1–002_review.pdf (accessed 26 August 2009).

120. WV16139. *(Oseltamivir trial. Title Unknown)*. Data on file. (Other: Mentioned in EMA EPAR dated 23 March 2006 pdf page 14 but possibly same trial as WV 16193).

121. Godlee F, Loder E. Missing clinical trial data: setting the record straight. *BMJ* 2010;**341**:c5641. http://dx.doi.org/10.1136/bmj.c5641

122. Jefferson T, Doshi P, Thompson M, Heneghan C. Ensuring safe and effective drugs: who can do what it takes? *BMJ* 2011;**342**:c7258. http://dx.doi.org/10.1136/bmj.c7258

123. Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med* 2010;**153**:158–66. http://dx.doi.org/10.7326/0003-4819-153-3-201008030-00006

124. Huic M, Marusic M, Marusic A. Completeness and changes in registered data and reporting bias of randomized controlled trials in ICMJE journals after trial registration policy. *PLOS ONE* 2011;**6**:e25258. http://dx.doi.org/10.1371/journal.pone.0025258

125. Van Driel ML, De Sutter A, De Maeseneer J, Christiaens T. Searching for unpublished trials in Cochrane reviews may not be worth the effort. *J Clin Epidemiol* 2009;**62**:838–44. http://dx.doi.org/10.1016/j.jclinepi.2008.09.010

126. Ghersi D, Clarke MJ, Reveiz L. *Do Cochrane Reviews Search Databases of Ongoing Trials, and How Well do they Report these Searches? Oral Presentation at the Joint Cochrane and Campbell Collaboration*. 2010;45–6. URL: www.cochrane.org/sites/default/files/uploads/abstract_book_keystone_2010.pdf (accessed 1 August 2015).

127. Food and Drug Administration. *Faxed Letter to Roche (file UCM166329) [NDA 21–087TAMIFLU (oseltamivir phosphate) MACMIS ID#8675].* 2000. URL: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166329.pdf (accessed 19 October 2010).

128. Food and Drug Administration. *Review. Tamiflu (Oseltamivir). NDA 021087 Supplement 002*. 2000. URL: www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21–087SE1–002_review.pdf (accessed 26 August 2009).

129. Food and Drug Administration. *Letter from FDA to Hoffman-La Roche Inc. Re 'NDA 21–087 TAMIFLU (Oseltamivir Phosphate) MACMIS ID#8675*. 2000. URL: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Enfo rcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166329.pdf (accessed 14 April 2000).

130. European Medicines Agency. *Annex I. Summary of Product Characteristics (Tamiflu 30 mg Hard Capsule)*. URL: www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500033106 (accessed 21 January 2010).

131. European Agency for the Evaluation of Medicinal Products. *Tamiflu. Oseltamivir Phosphate. (EMEA/H/C/402) CPMP Recommendation & Scientific Discussion Consolidated List of Questions (28 June 2001)*. URL: www.ema.europa.eu/ (1 August 2015).

132. Senn SJ. Added values: controversies concerning randomization and additivity in clinical trials. *Stat Med* 2004;**23**:3729–53. http://dx.doi.org/10.1002/sim.2074

133. Takahashi E, Kataoka K, Fujii K, Chida J, Mizuno D, Fukui M, *et al.* Attenuation of inducible respiratory immune responses by oseltamivir treatment in mice infected with influenza A virus. *Microbes Infect* 2010;**12**:778–83. http://dx.doi.org/10.1016/j.micinf.2010.04.013

134. Sawabuchi T, Suzuki S, Iwase K, Ito C, Mizuno D, Togari H, *et al.* Boost of mucosal secretory immunoglobulin A response by clarithromycin in paediatric influenza. *Respirology* 2009;**14**:1173–9. http://dx.doi.org/10.1111/j.1440-1843.2009.01639.x

135. Mendel DB, Tai CY, Escarpe PA, Li W, Sidwell RW, Huffman JH, *et al.* Oral administration of a prodrug of the influenza virus neuraminidase inhibitor GS 4071 protects mice and ferrets against influenza infection. *Antimicrob Agents Chemother* 1998;**42**:640–6.

136. Moore ML, Chi MH, Zhou W, Goleniewska K, O'Neal JF, Higginbotham JN, *et al.* Cutting edge: oseltamivir decreases T cell GM1 expression and inhibits clearance of respiratory syncytial virus: potential role of endogenous sialidase in antiviral immunity. *J Immunol* 2007;**178**:2651–4. http://dx.doi.org/10.4049/jimmunol.178.5.2651

137. Cox RJ, Mykkeltvedt E, Sjursen H, Haaheim LR. The effect of zanamivir treatment on the early immune response to influenza vaccination. *Vaccine* 2001;**19**:4743–9. http://dx.doi.org/10.1016/S0264-410X(01)00219-5

138. Fritz RS, Hayden FG, Calfee DP, Cass LM, Peng AW, Alvord WG, *et al.* Nasal cytokine and chemokine responses in experimental influenza A virus infection: results of a placebo-controlled trial of intravenous zanamivir treatment. *J Infect Dis* 1999;**180**:586–93. http://dx.doi.org/10.1086/314938

139. Ono H, Nagano Y, Matsunami N, Sugiyama S, Yamamoto S, Tanabe M. Oseltamivir, an anti-influenza virus drug, produces hypothermia in mice. *Biol Pharm Bull* 2008;**31**:638–42. http://dx.doi.org/10.1248/bpb.31.638

140. Ono H, Iwajima Y, Nagano Y, Chazono K, Maeda Y, Ohsawa M, *et al.* Reduction in sympathetic nerve activity as a possible mechanism for the hypothermic effect of oseltamivir, an anti-influenza virus drug, in normal mice. *Basic Clin Pharmacol Toxicol* 2013;**113**:25–30. http://dx.doi.org/10.1111/bcpt.12058

141. Hama R. Jones M, Hayashi K, Sakaguchi K. Oseltamivir and early deterioration leading to death. *Int J Risk Saf Med* 2011;**23**:201–15. http://dx.doi.org/10.3233/JRS-2011-0545

142. Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, *et al.* Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database Syst Rev* 2011;**7**:CD006207.

143. Toovey S, Rayner C, Prinssen E. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir. A comprehensive review. *Drug Saf* 2008;**31**:1097–114. http://dx.doi.org/10.2165/0002018-200831120-00006

144. Jones M, Hama R, Jefferson T, Doshi P. Neuropsychiatric adverse events and oseltamivir for prophylaxis. *Drug Saf* 2012;**35**:1187–8. http://dx.doi.org/10.1007/BF03262007

145. Toovey S. The author's reply. *Drug Saf* 2012;**35**:1188–90. http://dx.doi.org/10.1007/BF03262008

146. Hama R, Jones M, Hayashi K, Yanagi K, Sakaguchi K. *Oseltamivir: A Systematic Review and Meta-Analysis of Adverse Effects in Prospective Cohort Studies*. Presentation at the 16th Japanese Society for Pharmaco-epidemiology (JSPE) and 5th Activities and Co-operation for Drug Safety in Asia (ACPE) Joint Meeting, Tokyo, 2010.

147. Yorifuji T, Suzuki E, Tsuda T. Oseltamivir and abnormal behaviors: true or not? *Epidemiology* 2009;**20**:619–21. http://dx.doi.org/10.1097/EDE.0b013e3181a3d3f6

148. Fujita T, Fujii Y, Watanabe Y, Mori M, Yokota S. A pharmacoepidemiological study on the relationship between neuropsychiatric symptoms and therapeutic drugs after influenza infection. *Jpn J Pharmacoepidemiol* 2010;**15**:73–92. http://dx.doi.org/10.3820/jjpe.15.73

149. Kimura S, Niwa Y, Iwajima Y, Nagano Y, Yamamoto S, Ohi Y, *et al.* High doses of oseltamivir phosphate induce acute respiratory arrest in anaesthetized rats. *Basic Clin Pharmacol Toxicol* 2012;**111**:232–9. http://dx.doi.org/10.1111/j.1742-7843.2012.00889.x

150. Freichel C, Prinssen E, Hoffmann G, Gand L, Beck M, Weiser T, *et al.* Oseltamivir is devoid of specific behavioral and other central nervous system effects in juvenile rats at supratherapeutic oral doses. *Int J Virol* 2009;**5**:119–30. http://dx.doi.org/10.3923/ijv.2009.119.130

151. F. Hoffman-La Roche. *Tamiflu Label (for FDA NDA no. 021087*). 2011. URL: www.accessdata.fda.gov/drugsatfda_docs/label/2011/021087s057lbl.pdf (accessed 7 February 2011).

152. Roche. *Investigators Guide*. URL: www.roche.be/fmfiles/re7189007/CU056/10_Investigators_brochure.pdf (accessed 9 April 2014).

153. Food and Drug Administration. *Drug Approval Package. Tamiflu (Oseltamivir). Application No.: 021087-SE1–002*. 2000. URL: www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21–087SE1–002_review.pdf (accessed 27 August 2009).

154. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;**326**:1167–70. http://dx.doi.org/10.1136/bmj.326.7400.1167

155. Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2012;**12**:R000033. http://dx.doi.org/10.1002/14651858.mr000033.pub2

156. Burch J, Corbett M, Stock C, Nicholson K, Elliot AJ, Duffy S, *et al.* Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis. *Lancet* 2009;**9**:537–45. http://dx.doi.org/10.1016/S1473-3099(09)70199-9

157. Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. *BMJ* 2003;**326**:1235. http://dx.doi.org/10.1136/bmj.326.7401.1235

158. Falagas ME, Koletsi PK, Vouloumanou EK, Rafailidis PI, Kapaskelis AM, Rello J. Effectiveness and safety of neuraminidase inhibitors in reducing influenza complications: a meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2010;**65**:1330–46. http://dx.doi.org/10.1093/jac/dkq158

159. Tappenden P, Jackson R, Cooper K, Rees A, Simpson E, Read R, *et al.* Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): a systematic review and economic evaluation. *Health Technol Assess* 2009;**13**(11). http://dx.doi.org/10.3310/hta13110

160. 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). http://dx.doi.org/10.3310/hta7350

161. Hernan MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomized clinical trials. *Clin Infect Dis* 2011;**53**:277–9. http://dx.doi.org/10.1093/cid/cir400

162. Cochrane Neuraminidase Inhibitors Review Team. Does oseltamivir really reduce complications of influenza? *Clin Infect Dis* 2011;**53**:1302–3. http://dx.doi.org/10.1093/cid/cir706

163. Ebell MH, Call M, Shinholser J. Effectiveness of oseltamivir in adults: a meta-analysis of published and unpublished clinical trials. *Fam Pract* 2012;**30**:125–33. http://dx.doi.org/10.1093/fampra/cms059

164. Longini IM Jr, Halloran ME, Nizam A, Yang Y. Containing pandemic influenza with antiviral agents. *Am J Epidemiol* 2004;**159**:623–33. http://dx.doi.org/10.1093/aje/kwh092

165. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Structure and Content of Clinical Study Reports: E3 [Internet]*. 1995. URL: www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf (accessed 12 July 2012).

166. Jack A. Roche steps up production of Tamiflu after virus scare. *Financial Times*, 13 May 2009.

167. Chugai Pharmaceutical Company. *Summary Basis of Approval; Tamiflu Capsule for Treatment 2001*. URL: http://211.132.8.246/shinyaku/g0012/07/53039900_21200AMY00238.html (accessed 12 July 2012).

168. Chugai Pharmaceutical Company. *Summary Basis of Approval; Oseltamivir Capsule for Prevention (2004)*. 2004. URL: www.info.pmda.go.jp/shinyaku/P200400015/index.html (accessed 20 April 2009).

169. World Health Organization. *18th Expert Committee on the Selection and Use of Essential Medicines: Section 6.4.3: Other Antivirals. November 2010 Update*. 2010. URL: www.who.int/selection_medicines/committees/expert/18/en/index.html (accessed 16 November 2013).

170. Muthuri S, Venkatesan S, Myles P, Leonardi-Bee J, Al Khuwaitir TS, Al Mamum A, *et al.* Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med* 2014;**2**:395–404. http://dx.doi.org/10.1016/S2213-2600(14)70041-4

171. Muthuri S, Myles P, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam J. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009–10 influenza A(H1N1) pandemic: a systematic review and metaanalysis in hospitalized patients. *J Infect Dis* 2013;**207**:553–63. http://dx.doi.org/10.1093/infdis/jis726

172. Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, *et al.* Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Intern Med* 2012;**156**:512–24. http://dx.doi.org/10.7326/0003-4819-156-7-201204030-00411

173. Fiore A, Fry A, Shay D, Gubareva L, Bresee J, Uyeki T. Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2011;**60**:1–24.

174. World Health Organization. *Unedited Report of the 18th Expert Committee on the Selection and Use of Essential Medicines*. WHO Technical Report Series. 2011. URL: www.who.int/medicines/publications/unedited_trs/en/index.html (accessed 13 November 2013).

175. World Health Organization. *WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses*. Revised February 2010. URL: www.who.int/csr/resources/publications/swineflu/h1n1_use_antivirals_20090820/en/index.html (accessed 20 November 2013).

176. Harbord R, Egger M, Sterne J. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med* 2006;**25**:3443–57. http://dx.doi.org/10.1002/sim.2380

177. Rucker G, Schwarzer G, Carpenter J. Arcsine test for publication bias in meta-analyses with binary outcomes. *Stat Med* 2008;**27**:746–63 http://dx.doi.org/10.1002/sim.2971

178. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson D, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;**283**:2008–12. http://dx.doi.org/10.1001/jama.283.15.2008

179. Wolkewitz W, Schumacher M. Statistical and methodological concerns about the beneficial effect of neuraminidase inhibitors on mortality. *Lancet Respir Med* 2014;**2**:e8. http://dx.doi.org/10.1016/S2213-2600(14)70115-8

180. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509. http://dx.doi.org/10.1080/01621459.1999.10474144

181. Louie J, Yang S, Acosta M, Yen C, Samuel M, Schechter R, *et al.* Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1) pdm09. *Clin Infect Dis* 2012;**55**:1198–204. http://dx.doi.org/10.1093/cid/cis636

182. Yang SG, Cao B, Liang LR, Li XL, Xiao YH, Cao ZX, *et al.* Antiviral therapy and outcomes of patients with pneumonia caused by influenza A pandemic (H1N1) virus. *PLOS ONE* 2012;**7**:e29652. http://dx.doi.org/10.1371/journal.pone.0029652

183. Siston A, Rasmussen S, Honein M, Fry AM, Seib K, Callaghan WM, *et al.* Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. *JAMA* 2010;**303**:1517–25. http://dx.doi.org/10.1001/jama.2010.479

184. Dominguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, *et al.* Critically Ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA* 2009;**302**:1880–7. http://dx.doi.org/10.1001/jama.2009.1536

185. Altmann M, Fiebig L, Soyka J, von Kries R, Dehnert M, Haas W. Severe cases of pandemic (H1N1) 2009 in children, Germany. *Emerg Infect Dis* 2011;**17**:186–92. http://dx.doi.org/10.3201/eid1702.101090

186. Nguyen-Van-Tam J, Openshaw P, Hashim A, Gadd EM, Lim WS, Semple MG, *et al.* Risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza: United Kingdom first wave. *Thorax* 2010;**65**:645–51. http://dx.doi.org/10.1136/thx.2010.135210

187. Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, *et al.* Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA* 2009;**302**:1872–9. http://dx.doi.org/10.1001/jama.2009.1496

188. Thompson DL, Jungk J, Hancock E, Smelser C, Landen M, Nichols M, *et al.* Risk factors for 2009 pandemic influenza A (H1N1)-related hospitalization and death among racial/ethnic groups in New Mexico. *Am J Public Health* 2011;**101**:1776–84. http://dx.doi.org/10.2105/AJPH.2011.300223

189. Jain S, Kamimoto L, Bramley A, Schmitz AM, Benoit SR, Louie J, *et al.* Hospitalised patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* 2009;**361**:1935–44. http://dx.doi.org/10.1056/NEJMoa0906695

190. Farias J, Fernandez A, Monteverde E, Vidal N, Arias P, Montes MJ, *et al.* Critically ill infants and children with influenza A (H1N1) in pediatric intensive care units in Argentina. *ICM* 2010;**36**:1015–22. http://dx.doi.org/10.1007/s00134-010-1853-1

191. Yang P, Deng Y, Pang X, Shi W, Li X, Tian L, *et al.* Severe, critical and fatal cases of 2009 H1N1 influenza in China. *J Infect* 2010;**61**:277–83. http://dx.doi.org/10.1016/j.jinf.2010.07.010

192. Enstone J, Myles P, Openshaw P, Gadd E, Lim, W, Semple M, *et al.* Nosocomial pandemic (H1N1) 2009, United Kingdom, 2009–2010. *Emerg Infect Dis* 2011;**17**:592–8. http://dx.doi.org/10.3201/eid1704.101679

193. Chitnis A, Truelove S, Druckenmiller J, Heffernan R, Davis J. Epidemiologic and clinical features among patients hospitalized in Wisconsin with 2009 H1N1 influenza A virus infections, April to August 2009. *WMJ* 2010;**109**:201–8.

194. ANZIC. Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. *BMJ* 2010;**340**:c1279. http://dx.doi.org/10.1136/bmj.c1279

195. Yung M, Slater A, Festa M, Williams G, Erickson S, Pettila V, *et al.* Pandemic H1N1 in children requiring intensive care in Australia and New Zealand during winter 2009. *Pediatrics* 2011;**127**:e156–63. http://dx.doi.org/10.1542/peds.2010-0801

196. Javadi AA, Ataei B, Khorvash F, Babak A, Rostami M, Mostafavizadeh K, *et al.* Clinical features of novel 2009 influenza a (H1N1) infection in Isfahan, Iran. *J Res Med Sci* 2011;**16**:1550–4.

197. Miranda-Choque E, Ramírez C, Candela-Herrera J, Díaz J, Fernández A, Kolevic L, *et al.* [Niños hospitalizados con neumonía por influenza AH1N11/2009 pandémico en un hospital de referencia de Perú Children hospitalized with influenza pneumonia AH1N1/2009 pandemic in the INSN.] *Rev Peru Med Exp Salud Publica* 2011;**28**:610–16.

198. Poeppl W, Hell M, Herkner H, Stoiser B, Fritsche G, Schurz-Bamieh N, *et al.* Clinical aspects of 2009 pandemic influenza A (H1N1) virus infection in Austria. *Infection* 2011;**39**:341–52. http://dx.doi.org/10.1007/s15010-011-0121-9

199. Riquelme R, Jimenez P, Videla AJ, Lopez H, Chalmers J, Singanayagam A, *et al.* Predicting mortality in hospitalized patients with 2009 H1N1 influenza pneumonia. *Int J Tuberc Lung Dis* 2011;**15**:542–6. http://dx.doi.org/10.5588/ijtld.10.0539

200. Yokota R, Skalinski L, Igansi C, de Souza LR, Iser BP, Reis PO, *et al.* Risk factors for death from pandemic (H1N1) 2009, Southern Brazil. *Emerg Infect Dis* 2011;**17**:1467–71. http://dx.doi.org/10.3201/eid1708.101233

201. Bagdure D, Curtis DJ, Dobyns E, Glode MP, Dominguez SR. Hospitalized children with 2009 pandemic influenza A (H1N1): comparison to seasonal influenza and risk factors for admission to the ICU. *PLOS ONE* 2010;**5**:e15173. http://dx.doi.org/10.1371/journal.pone.0015173

202. Blumental S, Huisman E, Cornet MC, Ferreiro C, De Schutter I, Reynders M, *et al.* Pandemic A/H1N1v influenza 2009 in hospitalized children: a multicenter Belgian survey. *BMC Infect Dis* 2011;**11**:313. http://dx.doi.org/10.1186/1471-2334-11-313

203. Chemaly RF, Vigil KJ, Saad M, Vilar-Compte D, Cornejo-Juarez P, Perez-Jimenez C, *et al.* A multicenter study of pandemic influenza A (H1N1) infection in patients with solid tumors in 3 countries: early therapy improves outcomes. *Cancer* 2012;**118**:4627–33. http://dx.doi.org/10.1002/cncr.27447

204. Çiftçi E, Tuygun N, Ozdemir H, Tezer H, Sensoy G, Devrim I, *et al.* Clinical and epidemiological features of Turkish children with 2009 pandemic influenza A (H1N1) infection: experience from multiple tertiary paediatric centres in Turkey. *Scand J Infect Dis* 2011;**43**:923–9. http://dx.doi.org/10.3109/00365548.2011.598872

205. del Rosal T, Baquero-Artigao F, Calvo C, Mellado MJ, Molina JC, Santos MDM, *et al.* Pandemic H1N1 influenza-associated hospitalizations in children in Madrid, Spain. *Influenza Other Respir Viruses* 2011;**5**:e544–51. http://dx.doi.org/10.1111/j.1750-2659.2011.00272.x

206. Kusznierz G, Uboldi A, Sosa G, Torales S, Colombo J, Moyano C, *et al.* Clinical features of the hospitalized patients with 2009 pandemic influenza A (H1N1) in Santa Fe, Argentina. *Influenza Other Respir Viruses* 2012;**7**:410–17. http://dx.doi.org/10.1111/j.1750-2659.2012.00405.x

207. Mickienė A, Daniuseviciute L, Vanagaite N, Velyvyte D, Blauzdziuniene O, Nadisauskiene R, *et al.* Hospitalized adult patients with 2009 pandemic influenza A (H1N1) in Kaunas, Lithuania. *Medicina (Kaunas)* 2011;**47**:11–18.

208. Moretti ML, Sinkoc V, Cardoso LG, Camargo GJ, Bachur LF, Hofling CC, *et al.* Lessons from the epidemiological surveillance program, during the influenza A (H1N1) virus epidemic, in a reference university hospital of Southeastern Brazil. *Rev Soc Bras Med Trop* 2011;**44**:405–11. http://dx.doi.org/10.1590/S0037-86822011005000048

209. Brink M, Hagberg L, Larsson A, Gedeborg R. Respiratory support during the influenza A (H1N1) pandemic flu in Sweden. *Acta Anaesthesiol Scand* 2012;**56**:976–86. http://dx.doi.org/10.1111/j.1399-6576.2012.02727.x

210. Rahamat-Langendoen JC, Tutuhatunewa ED, Scholvinck EH, Hak E, Koopmans M, Niesters HG, *et al.* Influenza in the immediate post-pandemic era: a comparison with seasonal and pandemic influenza in hospitalized patients. *J Clin Virol* 2012;**54**:135–40. http://dx.doi.org/10.1016/j.jcv.2012.02.010

211. Herxheimer A, Clarke M, Edwards R, Jefferson T, Loke Y. A/H1N1 flu: time for case–control studies of NSAIDs and oseltamivir. *BMJ* 2009;**339**:b3048. http://dx.doi.org/10.1136/bmj.b3048

212. Hama R. *Potential Harm of Oseltamivir and NSAIDs Should be Discussed, Before the Threat of a 2009A/H1N1 Influenza-caused Pandemic is Feared. (Rapid Response)*. 2009. URL: www.bmj.com/cgi/eletters/338/may12_3/b1962#214206 (accessed 9 April 2014).

213. Eyers S, Weatherall M, Shirtcliffe P, Perrin K, Beasley R. The effect on mortality of antipyretics in the treatment of influenza infection: systematic review and meta-analysis. *J R Soc Med* 2010;**103**:403–11. http://dx.doi.org/10.1258/jrsm.2010.090441

214. Beyersmann J, Gastmeier P, Wolkewitz M, Schumacher M. An easy mathematical proof showed that time-dependent bias inevitably leads to biased effect estimation. *J Clin Epidemiol* 2008;**61**:1216–21. http://dx.doi.org/10.1016/j.jclinepi.2008.02.008

215. Suissa S. Immortal time bias in pharmacoepidemiology. *Am J Epidemiol* 2007;**167**:492–9. http://dx.doi.org/10.1093/aje/kwm324

216. Laupacis A. Observational studies of treatment effectiveness: some cautions. *Ann Intern Med* 2004;**140**:923–4. http://dx.doi.org/10.7326/0003-4819-140-11-200406010-00014

217. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol* 2005;**162**:1016–23. http://dx.doi.org/10.1093/aje/kwi307

218. Leonardi-Bee J, Venkatesan S, Muthuri S, Nguyen-Van Tam J, Myles P. Statistical and methodological concerns about the beneficial effect of neuraminidase inhibitors on mortality. *Lancet Respir Med* 2014;**2**:e10–12. http://dx.doi.org/10.1016/S2213-2600(14)70137-7

219. Van Walraven C, Davis D, Forster A, Wells G. Time-dependent bias was common in survival analyses published in leading clinical journals. *J Clin Epidemiol* 2004;**57**:672–82. http://dx.doi.org/10.1016/j.jclinepi.2003.12.008

220. Nicholson KG, Aoki FY, Osterhaus AD, Trottier S, Carewicz O, Mercier CH, *et al.* Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. *Lancet* 2000;**355**:1845–50. [Erratum published in *Lancet* 2000;**356**:1856.] http://dx.doi.org/10.1016/S0140-6736(00)02288-1

221. Treanor JJ, Hayden FG, Vrooman PS, Barbarash R, Bettis R, Riff D, *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. http://dx.doi.org/10.1001/jama.283.8.1016

222. Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. *BMJ* 2011;**342**:d2686. http://dx.doi.org/10.1136/bmj.d2686

223. Lefebvre C, Manheimer E, Glanville J. Searching for Studies. In Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. URL: www.cochrane-handbook.org/

224. Food and Drug Administration. *Drugs@FDA*. URL: www.accessdata.fda.gov/scripts/cder/drugsatfda/2011 (accessed 17 May 2016).

225. Food and Drug Administration. *Warning Letters*. URL: www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm 2011 (accessed 17 May 2016).

226. Brown JKM. *Experimental Design Generator and Randomiser*. URL: www.edgarweb.org.uk/2011 (accessed 24 August 2011).

227. Simon R, Makuch RW. Non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus non-responder bias. *Stat Med* 1984;**3**:35–44. http://dx.doi.org/10.1002/sim.4780030106

Appendix 1 The story of A159

The 2009 review: from A047 to A159

In the midst of the A/H1N1 influenza outbreak in June 2009, the Australian and UK governments commissioned an update of our long-standing Cochrane review on NIs for influenza in (otherwise) healthy adults (known as A047). Prior to the emergence of influenza A/H1N1 in 2009, governments worldwide stockpiled nearly CHF (Swiss francs) 7.6B worth of oseltamivir.[166] The WHO considered antivirals for influenza important (WHO has recently added oseltamivir to the list of essential medicines[169,174,175]). Oseltamivir and zanamivir have been prescribed for the treatment of influenza worldwide since the outbreak of 2009 A/H1N1 influenza. The review (on healthy adults) had first been published in 1999 (as A047) and was updated in 2006 and 2008. At the same time a similar review on children[32] (or A046) had also been published.

As the review had been updated the previous year, we initially anticipated that the commissioned 2009 update would not require substantial effort and would probably reflect only updated pharmacovigilance data and not the incorporation of new trial evidence.[6]

In the end, the 2009 update was inconclusive regarding whether or not oseltamivir reduced the risk of complications of influenza,[14] as we were unable to verify the data underlying manufacturer and government claims to this effect. The claims were based on clinical trial evidence included in a published pooled analysis of 10 manufacturer-funded clinical trials of oseltamivir for the treatment of influenza in people aged ≥ 13 years.[4] Eight of the 10 trials in the Kaiser *et al.*[4] pooled analysis have never been published,[31] and their complete data sets were not available from either the authors or the manufacturers. Some of the published trials had been ghost written.[43] The largest of the 10 Kaiser trials (M76001[36]), involving over 1400 people, had been briefly reported in conference abstract format but the person whose name appeared on the abstract could not recall ever presenting its results or being involved with the study.[43] Our early requests for data from the 10 Kaiser studies were met with an offer from Roche to sign a confidentiality agreement with an embedded secrecy clause preventing us from mentioning the existence of the agreement. The unsigned agreement can be seen at www.bmj.com/highwire/filestream/440792/field_highwire_adjunct_files/0.

At the time of publication of the 2009 update and its linked investigation by the BMJ, we were unaware of the size and depth of the oseltamivir evidence development programme. We thought it comprised around 36 trials and we expected that only a proportion of these would fit our inclusion criteria. We also did not realise the size and the level of detail that the CSRs contained.

On 31 December 2009, Roche released the core reports (or module 1s) of the 10 Kaiser trials with no legal agreement signed (only a web-based agreement that we would not share the documents with other commercial companies). After requesting Roche to provide us with the full study reports, Roche said that the module 1s were all that were needed for us to complete our job.[6] The missing modules (or parts), numbered 3–4 according to the trial in question, contained protocols, amendments, individual listings and demographic information. It seemed to us that these documents would have contained some important additional material for understanding the trials, their design and interpretation but we were not sure.

In 2010 we started exploring the relationship between the available module 1s for the only two Kaiser trials that had been published (Doshi[8] or Nicholson *et al.*,[220] and WV15671[58] or Treanor *et al.*[221]).

At about this time we started getting concerned that the oseltamivir trial programme was considerably larger than we first thought. Our interest was awakened by the casual discovery of a confidential 2009 Roche Tamiflu Investigator's Brochure, which was freely accessible on the web. This reported a clinical trial programme of over 60 studies. Searching for an unpublished and hitherto unseen data set requires

constructing a reasonably accurate list of all studies of the drug in question. The Roche Investigator's Brochure did not mention some studies that we were aware of and reinforced an idea that we had become clear was essential: the need to develop our own list of trials, because a single, authoritative, up-to-date and complete list of all clinical trials conducted on humans using both drugs did not seem to exist.

When thinking about our next update we decided not to use publications because the majority of treatment trial evidence for Tamiflu remained unpublished; we had found some discrepancies between CSRs and published equivalents; and, mostly, CSRs were so much more detailed and comprehensive than short journal articles, enabling a more thorough critical analysis of the trials. We also decided to expand the scope of A047 by including evidence relating to people of all ages except for immune-suppressed individuals. This, de facto, amounted to the creation of one new review (A159) with a new protocol subsuming A047 and A046. The protocol for A159 was publicly posted in December 2010.

A new source of evidence for A159

Today, the obvious source of information on CSRs would be trial registries and company websites, but most trials of both NIs were carried out before inception or wide acceptance of centralised registries and company websites. In 2009–11, company websites did not, and still do not, have extensive lists of trials with downloadable CSRs. Most people had never heard of CSRs before media coverage of our efforts.

We decided to construct our list by using multiple cross-referencing methods. We constructed a list beginning with clinical trials identified from previous review updates. To this end, we added additional trials in humans from multiple sources, including manufacturer submissions to regulators, drug product information sheets, previous published reviews, Health Technology Assessment (HTA) documents and public and manufacturers' registers,[5,156,157,159,160] such as www.ClinicalTrials.gov and www.roche-trials.com. Regulatory documents also aided the identification of unknown trials. Finally, we also conducted traditional database and grey literature searches (see *Appendix 3*) to identify previously unknown trials.

One of the first things we learned was that to ensure that the list did not include duplicate entries, we had to assign to each trial a unique trial ID. 'Author' is not a good choice of unique trial ID, as different authors can be present across different versions of the same trial (i.e. the authors of CSRs can be different from publications arising from the same clinical trial). Nor are any other details connected to publications a good option for unique trial ID because not all studies are published. Some trials will have company-specific codes and some will have public clinical trial registry numbers, or both, or neither. To simplify recognition and terminology we used the manufacturer protocol ID as our unique trial ID.

Our list was going to be useful only if it had sufficient details to enable us to decide whether or not it met our inclusion criteria. For each unique trial ID, we gathered the following details:

1. unique trial ID
2. other IDs
3. phase of study
4. sponsor
5. short description
6. official trial title
7. first authors (name and e-mail)
8. type of trial
9. comparator
10. outcomes assessed
11. date of trial
12. study period (days)
13. population

14. number of participants planned
15. number of participants enrolled
16. number of participants completing
17. trial status (e.g. completed, ongoing or early termination)
18. publication status (a citation or understanding of why it was not published)
19. how identified (to record how the trial was discovered)
20. notes.

Once we had as complete a list of trials as possible, we contacted manufacturers and sent them our draft list, asking them to check the accuracy and completeness of our list. Roche, GSK and BioCryst all did so and, in doing so, we learned of hitherto unknown trials.

Occasionally, the existence of further unknown trials was detected weeks and months after we thought we had a 'complete' list. This may be inevitable, given that trial identification often takes place in unpredictable ways, for example while reading through detailed regulatory reports.

We engaged in prolonged correspondence with Roche and GSK, and requested a series of regulatory documents under freedom of information policies from both the FDA and EMA. No substantial comments were made by Roche on the protocol of 159, which has been publicly available in one form or another since December 2010.

Specifically, we applied to EMA under their new release policy for 26 CSRs in their holdings relating to oseltamivir and GSK's zanamivir. The result was the delivery (starting in late March 2011) of 16 CSRs, all containing modules 1 and 2 plus one complete report for oseltamivir (trial WP16263[104]). (See table 1 in Doshi *et al.*[6]) None was available for zanamivir, as the EMA had not played a part in its market authorisation. These formed the basis for the 2012 version of A159.

At the date of completion of data searches for A159 (12 April 2011), Roche had provided us with only partial CSRs despite five requests for full CSRs. The material obtained from Roche included the first section (or so-called 'module 1' or 'core report') of a full CSR, each of which contain four to five modules (see *Appendix 9*) for the 10 oseltamivir treatment trials included in the Kaiser *et al.*[4] meta-analysis. Not contained in the provided module 1s are trial protocols with the list of amendments and original reporting analysis plans (RAPs). These module 1s comprise 3195 pages. Roche had not made available any further material and indicated that it did not intend to answer our requests for clarification on aspects of trials and for availability of the missing parts of complete CSRs. In addition we had a 53-page report in English of the treatment trial ML16369,[76] sponsored by Shanghai Roche Pharmaceutical Ltd. Regardless of success with our requests to obtain full CSRs, we decided to update our review with available material and subsequently update it as and when additional data became available.

Our searches of publication databases did not add any significant information.

Following a change of policy at the EMA, prompted by similar efforts of the Nordic Cochrane Centre,[222] we received an additional eight CSRs (10,737 pages) in response to a FOI request. An additional 14,700 pages of further CSRs and 33 pages of regulators' comments arrived after our search deadline. All of the materials received from the EMA are related to oseltamivir. The EMA has no access to information for zanamivir, as it is a nationally authorised product in Europe (correspondence with Xavier Luria, 23 March 2011, and David Mackay, 20 July 2011). At present, we hold all of the module 1s and module 2s of oseltamivir trials we have requested. From GSK we have received the promise of IPD. Many of the CSRs used in this review were obtained via FOI requests.

We still await a FDA decision regarding similar requests sent to FDA in January 2011.

We were able to download 2673 pages of SBA documents from the FDA website, 31 from EMA and 508 pages of Japanese SBA. We indexed the content and then constructed an extended table of contents, giving a summary of each file, thereby facilitating navigation of these complex documents. Once the table of contents had been constructed, we postulated that, given the huge work involved in reviewing lots of regulatory files, including CSRs, we needed new instruments to indicate which parts were more important than others, thus focusing our efforts. We experimented with a variety of methods reported in the earlier version of the review. We have now devised and used what, for us, is a satisfactory instrument for critically assessing CSRs in their entirety. We intend to publish this separately.

The EMA releases, coupled with documents from the FDA SBA for both drugs, formed the basis for the version of A159 that we eventually published in January 2012. The review reported our efforts to get to the bottom of the issue of the effects of NIs by appraising evidence from unpublished CSRs (see *Appendix 1*) and regulatory documents containing comments and reviews. We called the body of clinical studies and regulatory comments 'regulatory information', as all of these documents are either created for, or by, regulators. To our knowledge, this was the first Cochrane review ever conducted on the basis of regulatory documents only.

Owing to funding timelines and the sizeable amount of regulatory information already available to us, we decided to review material available as at 12 April 2011. This meant reviewing FDA SBA material and core reports (module 1s) in our possession from EMA data releases received by this time.

Study selection and extraction in 2011

In 2011 our methods were a mixture of established and novel, reflecting the size of the task, our lack of experience in dealing with large amounts of very detailed regulatory information and the lack of a complete set of CSRs. For example, scanning of titles and abstracts was doubled, but selection of studies for inclusion from the list constructed during our search was quadrupled, with disagreements resolved by discussion.

For many studies we had only titles and, in some cases, a very brief description of content, thus we assigned three categories to our trials:

1. definitely included
2. definitely excluded
3. trials for which we needed further information.

We excluded studies that were definitely not meeting the inclusion criteria on the basis of the available information (e.g. the title described the trial as a pharmacokinetic study). Where appropriate we requested further information from the trials' sponsor: usually copies of the CSRs (minus participant identification) for each trial that was definitely included or for which we needed further information. We did not contact first/corresponding authors of published versions of the trials on the basis of our experience with the 2009 review.

Data extraction and management reflected the lack of established methods for reviewing regulatory material. We subdivided the extraction, appraisal and analysis of the data into a two-stage exercise, including studies in the analysis phase only if we judged their reports to be reliable and complete. To help structure the information we used CONSORT statement-based extraction forms aimed at assembling a concise version of the CSRs, which included all of the important methods, as well as defined and extracted all relevant outcomes. We colour-coded the original text to flag up uncertainty or lack of clarity or need for more information from other (then inaccessible) parts of the CSR.

During this process we excluded all six peramivir trials, as we were informed by the manufacturers that no CSRs would be available. The 2012 A159 review was based on 15 oseltamivir clinical study core reports and 10 very brief zanamivir study reports. The former came from EMA, whereas the latter had been part of a GSK submission to UK NICE, which the BMJ had passed on to us together with the SBA material. Our 2010 protocol for A159 was not very detailed on how we would handle this mass of information for the simple reason that no one had ever done it before. We quite literally were learning as we were going along, and our understanding of the structure and content of CSRs evolved. We created and tested five post-protocol hypotheses (see *Appendix 8*), which had originated from the findings in the reports. The best example was our finding of an unnaturally high (up to 80%) influenza positivity rate in treatment trials, which, in some cases, had been pooled because of lack of viral circulation. We hypothesised that screening for influenza positivity had been carried out prior to enrolment of people with ILI. This was not borne out by the evidence available to us. We know now that a far simpler explanation is more likely: careful selection of the time period for trial participant enrolment, based on when surveillance data suggested that high influenza activity led to the recruitment of small numbers of participants from each of many centres with a high likelihood of influenza positivity, but at the time we had limited information available.

The 2012 A159 review analyses were based on the ITT population, which we had found to be the only reliable analysis unit, as oseltamivir appeared to have an effect on antibody production in people with influenza, leading to an imbalance in numbers of subjects in the influenza-infected (so-called ITTI) subpopulation. This, in effect, introduced confounding in what otherwise should have been well-designed double-blind trials. The only effect that was clearly identifiable was a modest shortening of ILI symptoms by less than a day. This led us to believe that oseltamivir had an aspecific powerful effect on symptoms, not mediated by any action on influenza viruses but possibly via an anti-inflammatory mechanism. Clearly, the trials had been designed with a commercial focus in mind and some of the claims made by the manufacturer (especially on the effect on interruption of transmission and on pneumonia) were not supported by the evidence in our possession.

2012 to the present day

Soon after the publication of the review, the BMJ agreed to publish our correspondence with Roche, GSK, the EMA, the CDC and WHO, recording our attempts at retrieving the full reports without any conditions attached and to understand the basis for promotion of the drugs (especially oseltamivir) by public health bodies. The correspondence (which is hundreds of pages long) formed the basis for what then became the BMJ Open Data Campaign and a stimulus for the later AllTrials campaign. Public exposure of our efforts and copious media coverage had the direct effect of ensuring the unconditional release of 77 reports of oseltamivir of 82 studies sponsored by Roche, and the equivalent of the 30 studies we had requested from GSK. For the full correspondence, see www.bmj.com/tamiflu and www.bmj.com/relenza.
The reports (amounting to over 140,000 pages) are made available with this review for the first time (at https://datadryad.org/resource/doi:10.5061/dryad.77471/2, p. 3), marking a small but significant victory for open science.

Before receiving the full reports, we resumed reviewing the remainder of the material that we had received in 2011. This mainly consisted of module 2s (Roche terminology for pre-study documents). Module 2s contained the information originally denied to us by Roche: study protocols with their amendments, randomisation lists, blank CRFs, certificates of analysis describing appearance and content of active and control capsules and, at times, SAPs. CRFs are containers for the rawest form of recorded data at the individual participant level.

We had no tools for reviewing and synthesising this information so, again, we had to create our own. The instrument is made up of three parts each with a separate function. In the first part there is a template for a brief summary description of the trial. The format fits into the RevMan (RevMan 5.3; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) Characteristics of Included Studies

Table (CIST) and is mainly descriptive. The second part is the appraisal of the trial following the Cochrane risk-of-bias format. The third part reconstructs the trial timeline and provides a checklist and position in the document of the various elements, such as protocol, protocol amendments and study period with dates. The last part aims to check the internal consistency and coherence of each element (such as numbers screened, numbers randomised, interventions, comparators) across all the different documents, starting from the earliest available version of the protocol. The form also contains suggestions on where to look for the information. This is based on our experience gained in this review and in a descriptive review[11] of 78 CSRs of 14 different drugs and biologicals.

While designing the tool, we also asked ourselves whether or not access to module 2 information (and later the full study reports) changed our perception of the trial and specifically our risk-of-bias assessment. We found that access to what are supposed to be full study reports should provide clarity and remove the rationale for 'unclear' risk-of-bias judgements, and, ideally, remove the concept of risk leaving just 'bias', at least for certain study design elements, such as attrition bias. Either a design element introduces bias or it does not. In the case of the 15 full oseltamivir CSRs we reviewed when constructing our tool, only one contained a protocol that predated the beginning of participant enrolment, only two had SAPs that clearly predated participants' enrolment and three had clearly dated protocol amendments. No CSR reported a clear date of unblinding.

During the latter part of 2013, we received from the manufacturers tens of thousands of pages of full CSRs for both programmes combined.

The history and conclusions form the backdrop to this version of A159.

Oseltamivir studies received from Hoffman La Roche SA in CSR format:

1. WV16277[69]
2. WV15819/WV15876/WV15978[67]
3. WV15707[60]
4. WV15812/WV15872[66]
5. WV15730[62]
6. M76001[36]
7. WV15670[8]
8. WV15671[58]
9. NV16871[57]
10. WV15759/WV15871[64]
11. WV16193
12. WV15825[68]
13. WV15708[61]
14. WV15799[65]
15. WV15673/WV15697[59]
16. WV15758[63]
17. NV20235
18. M76006
19. NV20236
20. NP15717
21. PV15616 (= GS-97-801)
22. PV15615 (= GS-97-802)
23. JV16284
24. WV15731
25. NV22155
26. NP15719
27. WP16254

28. WP16094
29. WP18308
30. WP16225
31. WP16134
32. PP15974
33. NP16472
34. NP15718
35. WP16226
36. NP25139
37. NP25138
38. NP15901
39. WP15525
40. NP25140
41. NP15728
42. NP15810
43. NP15826
44. PP16351
45. WP22849
46. NP22770
47. WP20727
48. PP16361
49. WP15517
50. NP15729
51. BP21288
52. WP21272
53. JP15735
54. WP15647
55. WP15648
56. WP15676
57. WP16263
58. NP15757
59. NV25118
60. NP15743
61. NP15881
62. NP15912
63. WP15979
64. WP16137
65. WP16295
66. NP15827
67. NV25655
68. JV21490
69. JP15734
70. NV22158
71. ML17713
72. ML22789
73. NV25182
74. ML17279 – publication only
75. ML19340 – publication only
76. JV15823[74] – English translation of Gaiyo summary
77. JV15824[75] – English translation of Gaiyo summary
78. ML17279 (= WV17052)
79. ML19340 (= COSMOS Study).

Zanamivir studies received from GSK in CSR format:

1. 167-101[70]
2. JNAI-01[71]
3. JNAI-04[72]
4. JNAI-07[73]
5. NAI30008[77]
6. NAI30009[78]
7. NAI30010[79]
8. NAI30011[80]
9. NAI30012[81]
10. NAI30015[82]
11. NAI30020[83]
12. NAI30028[84]
13. NAI30031[85]
14. NAI30034[86]
15. NAIA/B2008[87]
16. NAIA/B2009[88]
17. NAIA2005[89]
18. NAIA2006[90]
19. NAIA3002[91]
20. NAIA3003[92]
21. NAIA3004[93]
22. NAIA3005[94]
23. NAIB2005[95]
24. NAIB2006[96]
25. NAIB2007[97]
26. NAIB3001[98]
27. NAIB3002[99]
28. PE-01[100]
29. 167T3–11
30. NAIA2010.

Appendix 2 Compliharms: events alternatively recorded as complications or harms

Roche clinical study report of oseltamivir treatment trial

> *The following symptoms, signs and common sequelae associated with influenza were excluded from specific adverse event reporting if they occurred during the period of drug treatment provided their appearance was in conjunction with one or more other influenza-related symptoms. The recrudescence of single discrete signs/symptoms associated with influenza syndrome were recorded as adverse events.*[61]

[Event by body system]

Respiratory cough, pneumonia, bronchitis/tracheitis, sinusitis, dyspnoea/difficulty breathing

Cardiovascular tachycardia

Eyes, ears, nose and throat sore throat, nasal obstruction, earache, otitis, coryza, conjunctivitis

Central nervous system headache, fatigue

Musculoskeletal myalgia

Other fever, rigor, malaise/asthenia, chills

Source: 'Appendix 1. Events Associated with Influenza Syndrome'. Roche Clinical Study Report No. W-144117, Protocol WV15707, module I-43.

A 1999 Food and Drug Administration medical review of oseltamivir

> *As symptoms and common sequelae of influenza were collected as end point data, these symptoms, signs and common complications were specifically excluded from reporting as adverse events. The following table [above] lists events associated with influenza syndrome which were excluded from adverse event reporting. . .In addition, following the alleviation of influenza-like symptoms, the recurrence of a single respiratory or constitutional symptom was recorded as an adverse event; however, the reappearance of more than one symptom was recorded as influenza-like syndrome (i.e. secondary illness). Comment: As the applicant [Hoffman-La Roche] stated in a written response dated 6/11/99, some sites incorrectly reported symptoms occurring prior to the cessation of the primary illness as secondary illness.*[109]

Emphasis in the original. Oseltamivir Medical Review. US FDA Center for Drug Evaluation and Research, Application No. 021087, 25 October 1999, p. 15. www.accessdata.fda.gov/drugsatfda_docs/nda/99/21087_Tamiflu_medr_P1.pdf.

Appendix 3 Searches of the electronic databases

Although this review focuses on the primary data sources of manufacturers, we ran electronic searches in the following databases to check that there were no published RCTs from non-manufacturer sources:

- CENTRAL (2013, issue 6) limited to year published 2010–13 (20 search results).
- MEDLINE (January 2011 to July week 2, 2013) (56 search results) and MEDLINE (via Ovid) from 1 January 2011 to July week 2, 2013 (56 search results).
- EMBASE (January 2011 to July 2013) (90 search results) and EMBASE.com from 1 January 2011 to July 2013 (90 search results).
- PubMed (not MEDLINE) no date limit (21 records). We searched PubMed to identify publisher submitted records that will never be indexed in MEDLINE and the most recently added records not yet indexed in MEDLINE.

To identify reviews that may possibly have referenced further trials we searched:

- DARE (2013 issue 2 of 4 April; four search results)
- NHS EED (issue 2 of 4 April 2013; two search results) – both resources are part of The Cochrane Library, www.thecochranelibrary.com (accessed 22 July 2013).
- HEED (searched 22 July 2013; three search results).

Previously, we had searched CENTRAL (eight search results); MEDLINE (via Ovid) from 1 May 2009 to 12 April 2011 (31 search results); EMBASE from 1 January 2010 to 12 April 2011 (54 search results); DARE (five search results) and NHS EED (five search results). CENTRAL, DARE and NHS EED are part of The Cochrane Library, www.thecochranelibrary.com (issue 2, 2011, accessed 1 June 2011). All search results were loaded to an electronic library (EndNote X4; Thomson Reuters, CA, USA).

We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format.[223] We adapted the search strategy for EMBASE. We imposed no publication or language restrictions.

MEDLINE (via Ovid)

1. Influenza, Human/
2. exp Influenzavirus A/
3. exp Influenzavirus B/
4. (influenza* or flu).tw.
5. or/1-4
6. Oseltamivir/
7. Zanamivir/
8. neuraminidase inhibitor*.tw.
9. (oseltamivir or zanamivir or tamiflu or relenza or peramivir or gs4071).tw,nm.
10. or/6-9
11. 5 and 10

EMBASE.com

17 #13 AND #16
16 #14 OR #15 833616
15 random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti
14 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
13 #4 AND #12
12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
11 oseltamivir:ab,ti OR zanamivir:ab,ti OR tamiflu:ab,ti OR relenza:ab,ti OR peramivir:ab,ti OR laninamivir:ab,ti OR gs4071:ab,ti
10 'sialidase inhibitor':ab,ti OR 'sialidase inhibitors':ab,ti
9 'neuraminidase inhibitor':ab,ti OR 'neuraminidase inhibitors':ab,ti
8 'sialidase inhibitor'/exp
7 'peramivir'/de
6 'zanamivir'/de
5 'oseltamivir'/de
4 #1 OR #2 OR #3
3 influenza*:ab,ti OR flu:ab,ti
2 'influenza virus a'/exp OR 'influenza virus b'/de
1 'influenza'/exp

Appendix 4 Searches for regulatory information

We searched the following sources:

1. the FDA
2. the EMA
3. Roche
4. the Japanese regulator [Pharmaceuticals and Medical Devices Agency (PMDA)] SBA.

We conducted a search of the FDA regulatory documentation of the NDAs and supplementary NDAs (sNDAs) of both drugs.[224] The FDA NDA documentation includes medical, statistical, microbiological and other reviews, product labels, reports of site inspections, meetings with manufacturers and records of the decision-making leading to registration and post-marketing requirements. We also searched 'Warning Letters' dispatched by the FDA.[225]

To organise receipt of FDA materials, we created a TOC listing all of the regulatory and pharmaceuticals documents that were accessible to us. The TOC's function was that of an index, searchable quick reference guide and research tool to enable us to carry out quantitative (e.g. citation density analysis) and qualitative analyses (e.g. theme summaries) of the content. We also needed a rapid aide-memoire with brief summaries of the evidence contained in each regulatory document listed in the TOC. We called this aide-memoire the table of contents evidence (TOCE). As the TOCE contains copious working personal notes aiming to assist the understanding of the regulatory narrative, we have not reproduced it here but its content is woven into the narrative of this review.

Owing to the length and format of regulatory documents, we realised in building the TOC that there was a need to formalise the search and identification methods of trials referenced in the FDA documentation. We concentrated on where each trial is mentioned in the documentation by its pharmaceutical code. So, for example, if trial WV15670[8] is mentioned 60 times by that code in a particular file then the TOC will report the page numbers in which it is cited, which could be any number up to 60. The unit of search was the file, as a FDA PDF file can contain many different types of documents scanned into the same file. TOC and TOCE are among the tools we specifically constructed for the review (see *Appendix 1*).

We wanted to validate our new methods, therefore we compared the yield of OCR searching and hand-searching of the PDF files of the FDA regulatory material using the same trial ID as a working example.

We also searched the material sent to us by Roche for our 2009 update.

We searched the website of the Japanese PMDA (www.info.pmda.go.jp/shinyaku/shinyaku_previous_index.html) for data relating to NIs approved in 1999 and 2000 and www.info.pmda.go.jp/approvalSrch/PharmacySrchInit for NIs approved since 2001. We identified 1575 pages of documents relating to the regulatory review by the PMDA and the Japanese Ministry of Health, Labour and Welfare (JMHLW) and the Japanese SBA of oseltamivir capsules for treatment (2000), prophylaxis of oseltamivir dry syrup for children (2002) and oseltamivir capsules for prophylaxis of influenza (2004), and their re-examination results. The Japanese regulatory body introduced a system to disclose their examination results and SBA in 1999 instead of the prior system, 'full disclosure requirement system', which had been introduced in 1967. Although these documents included preclinical, methodological, clinical (pharmacological, toxicity and pharmacokinetics with metabolism) data and clinical (Phase I–III) studies and contain more precise data than the published papers, no complete CSRs were publicly available. Therefore, one review author (RH) asked the JMHLW on 29 July 2010 to disclose all of the documents reporting the evidence base for the approval of oseltamivir for these indications. The JMHLW sent RH a letter of refusal dated 2 September 2010, with the explanation 'because the disclosure of such documents might hurt the right, position or other fair benefit in the competition of the

corporation concerned'. We waited for 6 months to take further action hoping that the required CSRs would be forthcoming from the manufacturers. When this did not happen, RH filed a suit to overturn the JMHLW decision with the Osaka (Japan) District Court on 28 February 2011. The District Court petition was rejected on 19 April 2013 and the Osaka High Court rejected it on 29 November 2013. No appeal to the Supreme Court was made because substantial CSRs had already disclosed from various sources.

Appendix 5 Modified Consolidated Standards of Reporting Trials statement-based extraction template for clinical study reports

Title and drug name		
Include source documents used:		
Modified CONSORT extraction template www.consort-statement.org/		
Introduction CONSORT number		
Background and objectives	2a	Scientific background and explanation of rationale
	2b	Specific objectives or hypotheses
Insert text:		
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Insert text:		
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Insert text:		
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Insert text:		
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Insert text:		
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants and who assigned participants to interventions
Insert text:		
Blinding	11a	If done, who was blinded after assignment to interventions (e.g. participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes

Title and drug name Include source documents used:		
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
Insert text:		
Results		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Insert text:		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Insert text:		
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group and the estimated effect size and its precision (such as 95% CI)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Insert text:		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory
Insert text:		
Harms	19	All important harms or unintended effects in each group (*for specific guidance see CONSORT for harms*)
Insert text:		
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
Insert text:		
First author		
Date of completion		
Conflicts of interest		
Second author check		
Date of check		
Conflicts of interest		

Appendix 6 Stage 1 of the 2012 A159 review

Two review authors assessed each study (with studies allocated randomly to three pairs of review authors). The lists of included studies (33 for oseltamivir, 30 for zanamivir, six for peramivir) were randomly created by the program Edgar II (www.edgarweb.org.uk/2011).[226] Every study was openly allocated to each group according to its number.

We initially included six peramivir trials in the randomisation/allocation sequence but subsequently decided not to proceed further, as we were informed by the manufacturers that no CSRs would be available until after registration with the FDA (Bill Sheridan, BioCryst Pharmaceuticals Inc., 20 August 2010, personal communication). One review author (TJ) was assigned to the attempted reconstruction of CSRs from the FDA documents.

Two weeks before 'time lock' (see *Appendix 1*) we received the first batch of CSRs from the EMA (formerly EMEA), containing an additional four CSRs (including one complete four-module CSR) of studies we wanted to include. This time, random allocation was achieved by writing trial IDs on one set of tickets and asking an external researcher to allocate them to groups, the names of which had been written on another set of tickets.

Authors in pairs separately extracted data from the same CSRs of studies included in stage 1 of the review. When we had more than one copy of the same CSRs from different sources (e.g. CSRs submitted to a regulatory body and CSRs from a pharmaceutical company), we independently extracted data from each of the copies and then compared the results. We aimed to record and tabulate disagreements between data extracted from the same source and between different sources. We extracted data using a modified CONSORT statement-based extraction template (see *Appendix 5*).

The modified CONSORT-based extraction template aimed to assemble a concise version of the CSRs, which would include all important methods as well as define and extract all relevant outcomes. The CONSORT-based extraction template includes the features that would be expected to be found in a published trial report but in far greater detail. Our reconstructions do not include introduction or discussion sections. We extracted the following for each trial:

1. Background and objectives.
2. Methods: including trial design, important changes to methods after trial commencement (such as eligibility criteria), with reasons.
3. Participants: including eligibility criteria for participants and settings and locations where the data were collected.
4. Interventions: the interventions for each group with sufficient details to allow replication, including how and when they were actually administered.
5. Outcomes: prespecified primary and secondary outcome measures, including how and when they were assessed and changes to trial outcomes after the trial commenced, with reasons.
6. Sample size: how it was determined and explanation of any interim analyses and stopping guidelines.
7. Randomisation: including sequence generation and method used to generate the random allocation sequence.
8. Blinding: who was blinded after assignment to treatment groups.
9. Statistical methods: methods used to compare groups for primary and secondary outcomes and methods for additional analyses, such as subgroup analyses and adjusted analyses.
10. Results: participant flow, numbers of participants randomly assigned, losses and exclusions after randomisation, together with reasons. Baseline demographic and clinical characteristics for each group.
11. Outcomes: primary and secondary outcome results for each group.

12. Ancillary analyses: results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory.
13. Harms: all important harms or unintended effects in each group.

One review author completed the CONSORT-based extraction on the template in full (see *Appendix 5*), with the name and date of completion and a statement of conflict of interests. A second review author checked the extraction. We extracted data, text, tables and figures directly from the relevant sections of the CSRs into the appropriate section of the template. We did not change the text in any way apart from clarifying abbreviations or spellings, but we highlighted some text. We used three types of text highlighting in the document.

- *Yellow* Where text, figures or tables need to be checked with further information (e.g. if an adverse event is referred to in appendices or a further CSRs module).
- *Red* Where text or comments were inserted by one or both review authors but required an additional opinion because of concerns that there is the potential for discrepancies in the CSRs.
- *Green* Any text or tables added by us to the template (e.g. a reconstructed table of adverse events).

Two review authors (CH and MT) independently piloted the reconstruction method on oseltamivir trial WV15671[58] with data from module 1 of the CSR from Roche and data submitted to UK NICE. We discussed the pilot reconstruction among the whole review team for clarification. At a face-to-face meeting we discussed the reliability and completeness of each reconstructed trial in the light of comments and other information from regulatory sources with a view to inclusion of the trial in stage 2. We resolved all of the differences in opinion by consensus. We reached decisions on whether or not a trial moved to stage 2 by consensus. We planned to record dissent when consensus was not possible.

Appendix 7 Applying inclusion criteria for the A159 2012 review

For the 2012 A159 review, two review authors (CDM and MT) independently scanned the titles and abstracts identified from the searches of the published literature. None of the identified items was a published version of a trial unknown to us. Four review authors (TJ, CH, MJ and RH) independently read all of the data relating to the studies on the list constructed during our search and selected studies that seemingly fulfilled our inclusion criteria. One review author (PD) compiled the assessments into a single sheet for another review author (CDM). One review author (CDM) resolved disagreements by discussion.

We assigned three categories to identified trials from our complete list:

1. definitely included
2. definitely excluded
3. trials for which we needed further information.

We excluded studies definitely not meeting inclusion criteria on the basis of available information (e.g. the title described the trial as a pharmacokinetic study). Where appropriate, we requested further information from the trial's sponsor, usually copies of the CSRs (minus participant identification) for each trial that was definitely included or for which we needed further information. We did not contact first/corresponding authors of published versions of the trials on the basis of our experience with the 2009 A047 review.

Appendix 8 Post-protocol hypotheses: methods and results

This text is carried over from the 2012 version of this review and is provided for record completeness

Methods

The hypotheses (expressed as null hypotheses) are listed below, in order of their generation (not necessarily of importance). Their rationale is explained further down the text.

Hypothesis 1. Incidence of certain harms is not associated with placebo content.
Hypothesis 2. Oseltamivir (or zanamivir) does not affect antibody production in treatment trials.
Hypothesis 3. Oseltamivir does not affect antibody production in post-exposure (or secondary prophylaxis) trials.
Hypothesis 4. The number of trial centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size).
Hypothesis 5. In oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection.

Hypothesis 1. Incidence of certain harms is not associated with placebo content.
Rationale. While reviewing the US Food and Drug Administration (FDA) critique of zanamivir, we noted the regulators' concern over the apparent drop in forced expiratory volume (FEV) following zanamivir inhalation (FDA 1999a), which appeared to be enhanced by the lactose powder excipient content of the active blister (FDA 1999b). The powder, which causes bronchospasm in susceptible individuals, was contained in both the active and the placebo blisters. This principle of using a matching placebo is of course correct but may have had the effect of increasing the incidence of bronchospasm (or asthma-related episodes) in both arms. This is clearly reported as a warning in the 1999 FDA label "Because the placebo consisted of inhaled lactose powder, which is also the vehicle for the active drug, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation" (FDA 2000b p.10).

We reasoned by analogy and reviewed the medication content of the available clinical study reports of oseltamivir trials. The detailed information comparing content and physical characteristics and batch numbers is in Table 11. Roche's use of the word 'matching' is not strictly correct as two principles present in the placebo capsules (dehydrocholic acid and dibasic calcium phosphate dihydrate) are not listed as being present in the active oseltamivir capsules. We could not locate the reason for such a choice in the clinical study reports but both substances may have gastrointestinal action if consumed in large enough quantities.

On this basis we formulated two **hypotheses**:
1a. There is no association between incidence of gastrointestinal harms and a placebo containing dehydrocholic acid in oseltamivir trials.
1b. There is no association between incidence of asthma-related events and a placebo containing lactose powder in zanamivir trials.

To test hypothesis 1a we assessed the oseltamivir trials for which we had clinical study reports Module 1 (M76001; WV15670; WV15671; WV15707; WV15812/WV15872; WV15730; WV15819/WV15876/WV15978; WV15758; WV15799) for gastrointestinal tract (GIT) harms including nausea, vomiting and diarrhoea as well as participants withdrawing from the studies due to adverse events. We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the Chi^2 test and used Tau^2 to estimate between-study variance. To investigate whether placebo containing dehydrocholic acid may be associated with gastrointestinal harms we compared adverse event rates in placebo groups from the oseltamivir trials (where placebo contained dehydrocholic acid) with adverse event rates in the placebo groups from the zanamivir trials (where placebo did not contain dehydrocholic acid). This comparison was done informally using 1) data obtained from the FDA labels of oseltamivir and zanamivir (FDA 2000b; FDA 2011a) as well as 2) the trials for which we have clinical study reports. As a sensitivity analysis we assumed a similar gastrointestinal adverse event rate in the placebo groups of the oseltamivir trials as was observed in the placebo groups of the zanamivir trials and then repeated the meta-analysis (as described above). We also speculated that withdrawals in the placebo groups due to gastrointestinal adverse events were possibly related to dehydrocholic acid and removed these for the sensitivity analysis.

For hypothesis 1b we assessed asthma-related events in nine zanamivir trials for which we had clinical study reports (NAIA3002; NAIB3002; NAIA2005; NAIB2005; NAIB2007; NAIB3001; NAIA3005; NAI30010; NAI30009). We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the Chi^2 test and used Tau^2 to estimate between-study variance. To investigate whether placebo containing lactose powder may be associated with asthma-related events we informally compared event rates in placebo groups from the zanamivir trials (where placebo contained lactose powder) with event rates in the placebo groups from the oseltamivir trials (where placebo did not contain lactose powder). As a sensitivity analysis we assumed a similar asthma-related event rate in the placebo groups of the zanamivir trials as was observed in the placebo groups of the oseltamivir trials and then repeated the meta-analysis (as described above).

Hypothesis 2. Oseltamivir (or zanamivir) does not affect antibody production in treatment trials.
Rationale. All oseltamivir influenza treatment trials specify the primary efficacy analysis population as the influenza-infected population, not the randomised intention-to-treat (ITT) base population. The influenza-infected population (known as ITTI, or intention-to-treat-infected in clinical study reports) is determined post-randomisation based on the results of laboratory testing by culture and/or antibody rise (comparing paired sera from the same participant). The sample for culture and the first sample of sera are taken before commencement of trial product but the second or the third sera are taken after patients are treated with trial medication. It is vital that placebo and active groups of patients have the same odds of being classified as influenza-infected, otherwise any comparison between influenza-infected groups will be potentially affected by bias and will essentially be a non-randomised comparison. If trial medication affects the production of antibodies, the selection of the influenza-

infected population (which is partly based on antibody production) is confounded by taking the trial medication.

Roche have stated on multiple occasions (Smith 2006; Ward 2005; section 3.2.4.2 Serology WV15799) that ingestion of oseltamivir does not affect antibody production and the FDA supports this, stating that "In studies of naturally acquired and experimental influenza, treatment with TAMIFLU did not impair normal humoral antibody response to infection" (FDA 2011a).

However, we noticed unequal numbers of individuals in the influenza-infected population subgroup in numerous trials. In addition, Takahashi et al reported that oseltamivir significantly suppressed respiratory mucosal secretory immunoglobulin (Ig) A responses to antigen (Ag)-specific antibody (Ab) production and also the induction of Ag-specific IgA Ab-forming cells in an animal experiment (Takahashi 2010). If taking oseltamivir affects the production of IgG antibody as well, it may affect the selection of the influenza-infected population.

We are also unsure of the implication for immunisation with influenza vaccine. According to the FDA, no influenza vaccine interaction study has been conducted with oseltamivir (FDA 2011a).

To test the hypothesis we compared: (1) the odds of participants in the ITT population subsequently classified as influenza-infected; and (2) the odds of participants in the ITT population with a four-fold or more rise of antibody between the placebo and active arms of the trials. If ingestion of oseltamivir does not affect antibody production then we expect the odds of being classified as influenza-infected to be the same for the placebo and active arms. Therefore, we tested a null hypothesis that the odds of having a four-fold or more rise of antibody was the same for the placebo and active arms. We meta-analysed the results from these studies using the inverse variance random-effects method. We assessed heterogeneity using the Chi^2 test and used Tau^2 to estimate between-study variance. The trials included in this analysis were the 10 oseltamivir treatment trials analysed by Kaiser 2003 plus WV15758 for oseltamivir and NAIA3002, NAIB3002, NAIA2005, NAIB2005, NAIB2007, NAIB3001, NAI30009 for zanamivir. These are all the treatment trials for which we have clinical study reports Module 1. In an additional analysis we also assessed the oseltamivir trial conducted in China by Shanghai Roche Pharmaceutical Ltd for which we have a partial clinical study report (ML16369).

Hypothesis 3. Oseltamivir does not affect antibody production in post-exposure (or secondary prophylaxis) trials.
Rationale. According to the clinical study report of WV15799, the trial programme assessing the effects of oseltamivir in post-exposure prophylaxis (PEP) consisted of two trials: WV15799 and WV16139. The Module 1s of both trials together with copious FDA notes on trial WV15799 were available to us at 'time lock'. However the PEP trial WV16139 was not standard care or placebo-controlled and so we excluded it from the review.

WV15799 was a double-blind, cluster-randomised trial in which contact clusters of index cases were randomised to oseltamivir 75 mg a day or placebo for seven days. The trial formed an integral part of the "pivotal" trials package for the supplementary

application and review for prophylaxis use of oseltamivir 75 mg in people aged more than 13 years of age, submitted to the FDA on 22 May 2000, approved on 20 November 2000 (FDA 2000c). In the clinical study report Module 1 the manufacturer claimed that the trial provided evidence of the drug's capacity to prevent influenza in contacts by interrupting its transmission from index cases. Since all index cases were left untreated except for a paracetamol rescue pack, it is hard to see how such a claim can be made. The interruption of transmission claim has two components: reduction of viral spread from index cases (measured by nasal shedding of influenza viruses) and prevention of onset of influenza in contacts. This latter claim was based on the definition of (prevented) influenza cases: a mixture of symptoms signs and 'laboratory confirmation' (i.e. viral culture from the upper airways and/or at least a four-fold rise in antibody titres measured between baseline and two to three weeks later). The results of the trial later formed the basis for claims of the drug's effectiveness in interrupting transmission from person to person (WHO 2007) and allow time before the arrival of vaccines in the event of a pandemic. The interruption of transmission claim provided a powerful rationale for stockpiling oseltamivir (see for example vol 8, p.61-62 NICE 2000: "Ro 64-0796 successfully interrupts the transmission of influenza within households ... and suggests that Ro 64-0796 [oseltamivir] would control the spread of influenza in other closed communities associated with high risk of transmission, such as nursing homes" … "Ro 64-0796 also effectively interrupted virus transmission within households.")

The interruption of transmission indication was accepted by agencies such as the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC), but the US FDA refused to register and allow publicity based on any further indication beyond treatment and prophylactic effects on symptoms (FDA 2000f). Review of the evidence from the study protocol and Module 1 together with the FDA criticism explains the rationale for the FDA not supporting the manufacturers' claims. The design of the trial did not allow for comparison of the effects of treating index cases with oseltamivir versus placebo (as all index cases were not medicated) and a repeat viral culture was not performed for all participants. Viral culture was performed at baseline for all participants and thereafter only in participants with influenza-like illness symptoms (see Schedule of assessment for the contact case, WV15799, and the FDA Medical Officer report (FDA 1999c)). Any participants presenting at follow-up with symptoms of influenza had throat and nasal swabs taken in order to confirm the presence or absence of influenza infection (FDA 2000c), thereby missing out on potential asymptomatic infected people. However, a recent review of transmission studies has found no convincing evidence of spread from pre-symptomatic or asymptomatic subjects (Patrozou 2009), which might explain the FDA's caution in sanctioning any such claim for oseltamivir.

Our review of the clinical study report's Module 1 identified further problems with the conduct and reporting of the trial and discrepancies both within the clinical study reports and between the study and its protocol. In the protocol (version H) there is no mention of viral shedding measurement. This appears to be a post-protocol addition, which would explain the unsystematic nature of the viral excretion measurement remarked on by the FDA (i.e. taken from symptomatic contacts only). The primary population of analysis is the so called ITTIINAB population (contacts of ITT influenza-infected index cases who had negative virology at baseline). Although defined in the protocol, the selection and presentation of results for the intention-to-

treat contacts of the influenza-infected index case not infected at baseline (ITTIINAB) population has the effect of excluding 57% of the placebo (200/456) and 59% of the oseltamivir (205/497) participants. The effect of selection on the clustering was not formally tested in a sensitivity analysis. Nor is the potential weakness of such a choice discussed in the WV15799 clinical study report. We carried out an analysis using Fisher's exact test, which showed that there was no statistical evidence that the placebo and oseltamivir groups' cluster sizes were distributed differently based on households with an infected index case (P = 0.56) (Table 2). By analysing the population by influenza status of the index case, instead of unit of randomisations (all index cases), the beneficial effects of the cluster-randomisations are potentially lost, introducing unknown biases into the analysis. In addition, the generalisability of the conclusions may not be easily applied to clinical practice where testing of suspected influenza cases is often not practical. Cross-checking the definition of ITTIINAB with that reported in the protocol of the other PEP trial, WV16193 (excluded from this review) yields a different definition (PDF page 589) "The primary outcome in this study (WV15799) was the incidence of influenza occurring among contacts of influenza-infected index cases (the intent-to-treat-index-infected population)".

Throughout the clinical study report of trial WV15799 there are many other apparently contradictory statements on important aspects of the trial, for example, on how many viral swabs and paired sera tests were carried out. The text at page 50 of the Module 1 reports that "For 21 of the 26 contacts with laboratory-confirmed clinical influenza in the ITTIINAB population the diagnosis was confirmed by culture" but Table 19 shows the 26 contacts as shedding virus at days two to eight. The same table reports that 178 placebo contacts and 201 oseltamivir contacts were negative for virology (which suggests that they were tested) at days two and eight. However, viral testing only took place at baseline and thereafter only in symptomatic participants. The number of contacts in which influenza was diagnosed only by serology is unclear but it appears to be five (26 minus 21). These inconsistencies highlight one of the fundamental conceptual problems in understanding the whole oseltamivir prophylaxis trial programme: the mode of action of the drug. Our interpretation of the text suggests that oseltamivir does not prevent infection and does not affect influenza antibody response. As stated above, the claim that oseltamivir does not affect antibody responses has been made by the manufacturers. However, an antibody response is part of the definition of influenza. We are unsure how it is possible that oseltamivir could prevent influenza by stopping symptoms appearing and antibodies rising while at the same time leaving antibody production unaffected.

It is for this reason that we decided to test whether administration of oseltamivir for PEP affected the production of antibodies to influenza viruses. The distribution of change in antibodies from baseline to follow-up was compared between the arms of the trials for contacts of the index cases. Analysis was performed using Wilcoxon two-sample test separately for each type of antibody in each trial. An additional analysis of proportion of contacts having a four-fold or greater rise in influenza-specific antibody titre in antibodies was compared between groups using the Chi^2 test. Antibody data were not available for index cases, who were left untreated. In WV15799, antibody testing may have been undertaken at day 1, day 8 and at day 21 ± 4 days for all contacts. Day 8 blood samples for influenza antibody analysis were stored to measure influenza antibody levels only in those contacts who did not attend

the follow-up visit (day 17 to 25). Analysis was based on data from the ITTIINAB population at pages 59-60 and Appendix 60 of the clinical study report's Module 1.

Hypothesis 4. The number of trial centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size) and **Hypothesis 5.** In oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was effect size).
Rationale. The proportion of ITT population in the treatment trials of NIs that are subsequently diagnosed as infected with influenza is higher (~ 50% to 80%) than is usually seen in the course of the winter season in routine clinical care, although high peaks can occur for a very limited period. We know that in some treatment trials, such as WV15670 and WV15671, centres were activated to "recruit subjects during an influenza outbreak in the locality, detected using standardised surveillance techniques." We postulated that unreported procedures may also have been used in the trials to obtain these high proportions of influenza to ILI cases. Two procedures that may have been used are: 1) use of rapid influenza tests to screen out patients based on negative results; 2) dropping of centres that recruited low proportions of infected patients. The use of rapid testing of patients prior to randomisation has been reported in at least one of the zanamivir treatment trials (NAIB3001), in oseltamivir trial WV15670 as a means of excluding infection with H5N1 in the Hong Kong Centre, as a pilot surveillance in suburban London during the 1998 to 1999 winter (NICE 2000 vol.1) and in most oseltamivir paediatric trials to exclude respiratory syncytial virus (RSV) infection. In addition, the schedule of testing varies by trial for the oseltamivir trials with swabbing performed either before randomisation or after randomisation. In at least one oseltamivir treatment trial (WV15730) it was reported that no viral culture was performed at centres from South America (FDA 1999c). As a result of these observations we reformulated **Hypothesis 4** as follows: the number of centres and centre withdrawals does not affect the proportion of placebo patients subsequently diagnosed with influenza infection (originally the outcome was primary outcome effect size) in oseltamivir treatment trials and **Hypothesis 5** as in oseltamivir treatment trials there is no association between the order of randomisations and naso-pharyngeal swabbing (i.e. randomising participants first and then swabbing or swabbing first and then randomising) and the proportion of placebo patients subsequently diagnosed with influenza infection.

To test **hypothesis 4**, we used Spearman's rank method to estimate the correlation between average number of patients recruited per centre and the proportion of placebo patients subsequently diagnosed with influenza infection. The placebo patients were used for the proportion of patients subsequently diagnosed with influenza infection because, as we show later in the review, there is evidence that oseltamivir interferes with antibody production and antibody response was used to diagnose influenza infection. We did not analyse the number of centres dropped from studies because information on this variable was not available in Module 1s of the clinical study reports for the included trials (information on patients recruited to each centre is reported in Module 2 which we do not currently have access to).

Hypothesis 5 was generated to attempt to explain the seemingly high proportion of influenza-infected influenza-like illness cases in treatment trials. However, we did not formally test this hypothesis as there was only one clinical study report reporting randomisation first then swabbing second (WV15819/WV15876/WV15978) (see also Appendix 9).

Results

The results of our post-protocol analyses are also reported in Figure and/or Table format.

Hypothesis 1a tested in a sensitivity analysis whether the incidence of gastrointestinal harms may be associated with exposure of participants to a placebo containing dehydrocholic acid. The data obtained from the oseltamivir trials clinical study reports is shown in Table 15.

Overall, the crude adverse event incidence in the placebo groups of the oseltamivir trials was 5.5% for nausea, 3.6% for vomiting and 7.0% for diarrhoea. This compares with crude incidence in the nine zanamivir treatment trials' placebo groups of 4.1% for nausea and vomiting (reported as a combined outcome in the clinical study reports) and 2.8% for diarrhoea. Two studies (WV15670; WV15671) compared three treatment groups: oseltamivir 150 mg bid, oseltamivir 75 mg bid and placebo. To maintain the blinding in these trials, each participant took two pills twice daily. Therefore the participants in the oseltamivir 75 mg bid group took one placebo tablet twice daily. We note that in trial WV15671 there was evidence of a dose-response effect of placebo on incidence of diarrhoea: oseltamivir 150 mg bid (5.9%), oseltamivir 75 mg bid (8.7%) and placebo (11.8%) (P = 0.036). However, there was no evidence found of a similar trend in trial WV15670 (P = 0.88). We were unable to carry out a similar analysis for paediatric treatment trial WV15758 because a detailed content of the placebo preparations is not available (see Table 11).

Random-effects meta-analysis of the data in Table 15 provided the following results.

Nausea: increased odds of adverse events due to oseltamivir (OR 1.62, 95% CI 1.17 to 2.26, P = 0.004).
Vomiting: increased odds of adverse events due to oseltamivir (OR 2.32, 95% CI 1.62 to 3.31, P < 0.001).
Diarrhoea: decreased odds of adverse events due to oseltamivir (OR 0.72, 95% CI 0.53 to 0.97, P = 0.03).
Withdrawal from treatment due to adverse events: no evidence of a difference between treatment groups (OR 1.08, 95% CI 0.66 to 1.76, P = 0.75).

We carried out a sensitivity analysis by assuming placebo rates of gastrointestinal adverse events in oseltamivir trials based on those observed in placebo groups of similar zanamivir trials. Overall rates of nausea, vomiting and diarrhoea in placebo groups of zanamivir treatment trials for adults and adolescents were 3%, 2% and 4% compared to oseltamivir treatment trials for adults and adolescents where rates were 6%, 3% and 10% respectively based on FDA-reported data (FDA 2000b; FDA 2011a). Conversely, other common adverse events such as headaches, cough and dizziness had similar incidences of 2% to 3% in the placebo groups of zanamivir and

oseltamivir treatment trials (FDA 2000b; FDA 2011a). In the treatment trials of children the rates of nausea, vomiting and diarrhoea in placebo groups of zanamivir treatment trials were 2%, 3% and 2% compared to oseltamivir treatment trials of children where rates were 4%, 9% and 11% respectively. Our conservative estimate is that the oseltamivir placebo increased rates of nausea two-fold (risk ratio (RR) = 2), vomiting (RR 1.5) and diarrhoea (RR 2.5) compared to the placebo arms in zanamivir trials. Based on the adult and adolescent trials we could conservatively speculate that the substances in the oseltamivir trials placebo increase nausea, vomiting and diarrhoea by 100% (6%/3%), 50% (3%/2%) and 150% (10%/4%) respectively. This could also be considered a conservative assumption because it is plausible that the lactose powder used as the placebo in the zanamivir trials also induced gastrointestinal symptoms, especially in patients that were lactose intolerant. Adjusting the actual rates of these events in the oseltamivir trials placebo groups to be consistent with the zanamivir trials placebo group rates (as reported by the FDA (FDA 2000b; FDA 2011a) and re-running the random-effects meta-analysis we obtained the following results.

Nausea: increased odds of adverse events due to oseltamivir (OR 3.33, 95% CI 2.44 to 4.54, $P < 0.001$; test for heterogeneity $P = 0.33$).
Vomiting: increased odds of adverse events due to oseltamivir (OR 3.46, 95% CI 2.51 to 4.78, $P < 0.001$; test for heterogeneity $P = 0.37$).
Diarrhoea: increased odds of adverse events due to oseltamivir (OR 1.86, 95% CI 1.39 to 2.50, $P < 0.001$; test for heterogeneity $P = 0.50$).

The estimated effect sizes for nausea and vomiting have increased based on the sensitivity analysis. The effect on diarrhoea has reversed, indicating oseltamivir is possibly associated with increased odds of this adverse event. The results of our analysis support an alternative interpretation to that of the FDA.

Finally, we carried out a sensitivity analysis of withdrawal from treatment due to adverse events by assuming no withdrawals due to gastrointestinal events in the placebo group. In total there were nine patients in the oseltamivir trials' placebo groups that withdrew due to gastrointestinal events. When these withdrawals are not included the following result is obtained based on random-effects meta-analysis:

Withdrawal from treatment due to adverse events: no evidence of a difference between treatment groups (OR 1.48, 95% CI 0.87 to 2.51, $P = 0.15$; test for heterogeneity $P = 0.40$).

We conclude that participants in placebo arms of oseltamivir treatment trials experience a higher rate of gastrointestinal adverse events compared to their zanamivir counterparts. As the zanamivir trials' inclusion criteria were similar to the oseltamivir trials (fever and two additional symptoms of influenza-like illness (ILI)) this observation cannot plausibly be explained by an incremental role of influenza infection in the genesis of such heterogeneity. It is possible that the difference in reported gastrointestinal adverse events in the placebo groups of zanamivir and oseltamivir trials is due to differences in the collection of these events. However, other common adverse events such as headaches, cough and dizziness had very similar rates in the placebo groups of zanamivir and oseltamivir trials. Despite the results of this sensitivity analysis it is impossible without a clear statement of dosage

and rationale of use to assess the role of dehydrocholic acid and possibly calcium phosphate in the causation of such a high incidence of gastrointestinal adverse events.

For **hypothesis 1b** the data obtained from the zanamivir treatment trials clinical study reports are shown in Table 16.

Over all the nine zanamivir trials the incidence of asthma (including asthma exacerbation) in the placebo groups was 2.1% compared to 0.9% in the placebo groups of the oseltamivir trials. Random-effects meta-analysis of the data in Table 16 provided the following results for the combined outcome of any asthma event:

Asthma: decreased odds of adverse events due to zanamivir (OR 0.54, 95% CI 0.34 to 0.86, P = 0.01).

We carried out a sensitivity analysis by assuming placebo rates of asthma-related adverse events in zanamivir trials based on those observed in similar oseltamivir trials. If we assume a rate of asthma events in the placebo groups of the nine zanamivir trials similar to that observed in the oseltamivir trials we obtain the following result based on random-effects meta-analysis:

Asthma: no evidence of a difference between treatment groups (OR 1.27, 95% CI 0.71 to 2.26, P = 0.42; test for heterogeneity P = 0.68).

We conclude that zanamivir trial placebo recipients appear to have a higher incidence of asthma-related events than their oseltamivir counterparts. Again, as the inclusion criteria were similar for both trial programmes this finding is not likely to be due to severity of influenza infections but associated with exposure to lactose powder and possibly to the active principle. This is a point remarked on by the FDA.

For **hypothesis 2** (oseltamivir (or zanamivir) does not affect antibody production in treatment trials) the relevant trials showed strong and consistent evidence that patients randomised to active treatment had reduced odds of being classified as influenza-infected (OR 0.83, 95% CI 0.73 to 0.94, P = 0.003) with no evidence of heterogeneity (heterogeneity Chi^2 test = 2.80 (df = 7) P = 0.90; estimate of between-study variance Tau^2 = 0.00) (see Table 14). There was also strong evidence that patients randomised to active treatment had reduced odds of having four-fold or higher rise in antibody titres (OR 0.79, 95% CI 0.70 to 0.90, P < 0.001) with no evidence of heterogeneity (heterogeneity Chi^2 test = 4.61 (df = 7) P = 0.71; estimate of between-study variance Tau^2 = 0.00) (see Table 14).

In contrast, the zanamivir trials showed no evidence that patients randomised to active treatment had reduced odds of being classified as influenza-infected (OR 1.05, 95% CI 0.90 to 1.24, P = 0.52) with no evidence of heterogeneity (heterogeneity Chi^2 test = 3.03 (df = 6) P = 0.81; estimate of between-study variance Tau^2 = 0.00).

These results have important implications for the oseltamivir treatment trials programme and for all ongoing trials. All influenza-infected populations are selected post-randomisation and post-trial termination on the basis of laboratory findings (all ITT participants being symptomatic at entry, with aetiology unknown). However, as oseltamivir appears to affect antibody production (or perhaps testing, or both), there

may be some participants in the oseltamivir group who were infected with influenza but not diagnosed by the antibody rise and were therefore not counted in the influenza-infected population. These may have subsequently been excluded from the efficacy analysis. It is also possible that the strength of the antibody production limit to qualify for an influenza infection-induced antibody rise (four-four fold and above from baseline) had the effect of selecting the 'stronger' responders into the influenza-infected subgroup of the oseltamivir arm. This would mean that the best antibody producers were selected and this may have led to inflated treatment estimates of efficacy in influenza-infected populations.

To investigate this possibility we calculated the correlation between the odds of being classified as infected in the oseltamivir group compared to the placebo group and the size of the primary treatment effect (time to alleviation of symptoms in the ITTI population). In treatment trials all participants are recruited on the basis of symptoms of influenza-like illness. According to the mechanism of action proposed by the manufacturer, infected participants given oseltamivir up to 48 hours from symptom onset should have an antibody response which, given the effects of randomisation, should be similar to that of placebo recipients. Non-responders or weak responders should be spread evenly across the trial arms. All treatment trials of oseltamivir showing evidence of a treatment effect on the primary outcome of the study were included in the analysis. This included two trials for which we did not have clinical full study reports (ML16369; JV15823). We included these trials to increase variation in the two variables used for the analysis. In addition, two trials were excluded: WV15707 which had a total ITTI sample size of 12 participants; and WV15812/WV15872, which was a treatment trial in chronically ill adults that showed no evidence of a treatment effect. Results showed strong evidence of a correlation (Spearman rank correlation = -0.83, P = 0.01) (Table 19). The correlation was highly negative, indicating that lower odds of being classified as ITTI in the oseltamivir group compared to the placebo group is associated with larger treatment effects for the primary outcome of the studies. In contrast, there was no evidence of a correlation between the odds of being classified as infected in the oseltamivir group compared to the placebo group (Table 19) and the size of the treatment effect in the ITT population (Spearman rank correlation = -0.23, P = 0.66). A limitation of this analysis is that data for the ITT population for two trials were not available (WV15730; JV15823) (Table 19).

Thus, all influenza-infected comparisons are potentially confounded by the action of the drug (oseltamivir but probably not zanamivir) and are essentially non-randomised comparisons. Any analyses should be based on ITT populations in oseltamivir treatment trials. Analyses and data considered for inclusion in systematic reviews should be based on the ITT (or safety) populations only.

Our analysis of **Hypothesis 3** shows that the odds of having a four-fold rise in antibodies is 0.33 (95% CI 0.16 to 0.67) for the oseltamivir group compared to placebo (hence a much bigger effect compared to the treatment trials). Due to insufficient information provided in the clinical study report we were unable to take account of the clustering in this analysis, hence the confidence intervals are possibly under-estimated; however an analysis that takes into account clustering is unlikely to change the conclusions. These results show that oseltamivir prophylaxis is associated with lower odds of a four-fold rise in antibodies and this appears to be due to a

difference in the distribution of antibody rise in HIAAH3 antibodies but not HIAAH1 or HIB antibodies (see Table 14). In summary no conclusions can be drawn from the available evidence on the effects of the drug on viral transmission. The mode of action in prophylaxis appears mainly to be ascribed to symptom suppression or control. There is uncertainty around other possible effects of the drug especially given its interaction with the production of antibodies.

We rejected **Hypothesis 4** and are currently unable to test **Hypothesis 5**

We rejected **Hypothesis 4** as there was no evidence of correlation between average recruited subjects per centre and the proportion of placebo patients subsequently diagnosed with influenza infection (Spearman correlation = 0.26; P = 0.53). Two studies failed to reach their recruitment target (WV15707 and WV15730) and two clinical study reports were made up of multiple trials due to the original trial's poor recruitment (WV15819/WV15876/WV15978 and WV15812/WV15872). In addition the proportion of placebo patients subsequently diagnosed with influenza infection ranged from 63% to 75%, implying little between-trial variation.

We are currently unable to test **Hypothesis 5** as only one oseltamivir clinical study report (of three trials) reported randomisation first then swabbing second (WV15819/WV15876/WV15978). In this study the proportion of placebo patients that were confirmed as influenza-infected was 68.1%. This compares with the other seven clinical study reports where swabbing was carried out first and randomisation second and the proportion of placebo patients that were confirmed as influenza-infected ranged from 63.2% to 74.9% with mean 68.1%. Hence it seems that swabbing after randomisation made no difference in the treatment trial programme where this practice is reported. However, with only one clinical treatment study report randomising prior to swabbing available to us, the power to detect a difference in the proportion of placebo patients subsequently diagnosed with influenza infection is low. We hope to be able to retest this hypothesis as more data become available.

Appendix 9 Example of contents of a Clinical Study Report (from p. 1 of WV15670 report)

Final study report modules

This report consists of five modules. Those not supplied in this submission were obtainable from the sponsor on request.

Module 1: core report and study publications

Introduction.

Rationale.

Objectives.

Methodology.

Efficacy results.

Safety results.

Discussion/conclusions.

Appendices.

Module 2: prestudy documents and study methodology

Protocol and amendment history.

Blank CRF.

Subject information sheet.

Glossary of original and preferred terms.

Randomisation list RAP.

Certificates of analysis.

List of investigators.

List of responsible ethics committees.

Module 3: individual subject listings of demographic and efficacy data

Demographic data listings.

Previous and concomitant diseases.

Previous and concomitant medications.

Efficacy listings.

Module 4: individual subject listings of safety data

Laboratory parameters.

Vital signs data.

Module 5: statistical report

Appendix 10 List of excluded studies and reasons for exclusion

Study	Reason for exclusion
105934	Post-marketing study
107485	Dose-ranging study
108127	Non-randomised study
112311	Pharmaco-availability study
112312	Pharmaco-availability study
113268	Pharmaco-availability study
113502	Non-comparative study
113625	Pharmacokinetics study
113678	Non-comparative study
114045	Survey
114373	Not placebo/do nothing controlled
167-02	Dose-ranging Phase I in volunteers, no influenza exposure
167-03	Dose-ranging Phase I in volunteers, no influenza exposure
167-04	Dose-ranging Phase I in volunteers, no influenza exposure
167-05	Dose-ranging Phase I in volunteers, no influenza exposure
167T3-11	An open-label trial of 20 mg CG167 (zanamivir) in the treatment of influenza viral infection in children aged ≤ 5 and < 15 years old (open-label study). Non-randomised; the intervention group was compared with a survey group; 18-page summary available with no title
ADS-TCAD-PO206	Not placebo/do nothing controlled
BP21288	Pharmacokinetics study
C94–009	Pharmacokinetics study
C94–085	Pharmacokinetics study
GCP/95/045	Pharmacokinetics study
JNAI-02	Unknown study. Only ID traced
JNAI-03	Unknown study. Only ID traced
JP15734	Pharmacokinetics non-comparative study
JP15735	Does not test treatment, prophylaxis or PEP and there was no exposure to influenza
JV16284	Open-label, no control
JV21490	No influenza circulation, Phase IV study with unusual oseltamivir dosages
M76006	Not placebo/do nothing controlled
ML17279	CSR bears no title. Study of community pharmacist availability
ML17713	Non-comparative study

Study	Reason for exclusion
ML19340	Text in French. Community pharmacist availability study
ML20542	Not placebo/do nothing controlled
ML21954	Not placebo/do nothing controlled
ML22789	Not placebo/do nothing controlled
ML22872	Not placebo/do nothing controlled
ML22879	Not placebo/do nothing controlled
ML25018	Bioavailability study
ML25087	Not placebo/do nothing controlled
ML25094	Non-comparative study
ML25157	Pharmacokinetics study
ML25176	Pharmacokinetics study
ML25179	Not placebo/do nothing controlled
ML25265	Non-comparative observational study
ML25266	Pharmacokinetics study
MP20691	Pharmacokinetics study
MV20043	Transmission study
MV20050	Dose-ranging study
MV22926	Non-comparative study
MV22949	Pharmacokinetics study
MV22951	Pharmacokinetics study
MV22963	Pharmacokinetics study
MV22970	Pharmacokinetics study
NAI106784	Pharmacokinetics study
NAI108166	Pharmacokinetics study
NAI10901	Comparator is vaccine
NAI10902	Pharmacokinetics study
NAI40012	Instructional leaflet study
NAIA1009	Pharmacokinetics study
NAIA2010	Open-label, rimantadine-controlled, cluster randomised trial
NAIB1001	Pharmacokinetics study
NAIB1002	Pharmacokinetics study
NAIB1007	Pharmacokinetics study
NCT00297050	Dose-ranging study
NCT00416962	Not placebo/do nothing controlled
NCT00867139	Not placebo/do nothing controlled in immunocompromised people
NCT00957996	Peramivir study – does not have placebo/do nothing comparator
NCT01063933	Pharmacokinetics study

Study	Reason for exclusion
Not applicable (registry)	Unknown study. Only ID traced. Identified from Reddy D. *J Antimicrob Chemother* 2010;**65**(Suppl. 2):ii35–40 (doi: http://dx.doi.org/10.1093/jac/dkq014) table 2. http://jac.oxfordjournals.org/cgi/content/full/65/suppl_2/ii35/DKQ014TB2)
NP15525	Pharmacokinetics study
NP15717	Pharmacokinetics study
NP15718	Pharmacokinetics study
NP15719	Pharmacokinetics study
NP15728	Pharmacokinetics study
NP15729	Pharmacokinetics study
NP15743	Palatability study, open-label
NP15757	Pharmacokinetics study
NP15810	Pharmacokinetics study
NP15826	Pharmacokinetics study
NP15827	Pharmacodynamics study
NP15881	Palatability study in children
NP15901	Pharmacokinetics study
NP15912	Palatability study in children
NP16472	Not placebo/do nothing controlled
NP22770	Pharmacokinetics study
NP25138	Not placebo/do nothing controlled
NP25139	Not placebo/do nothing controlled
NP25140	Pharmacokinetics study
NV20234	Immunocompromised participants
NV20235	Immunocompromised participants
NV20237	Resistance study
NV22155	Not placebo/do nothing controlled
NV22158	Registry study
NV25118	Pharmacokinetics study
NV25182	Not placebo/do nothing controlled
NV25655	Open-label pharmacokinetics study
PP15974	Pharmacokinetics study
PP16351	Pharmacokinetics study
PP16361	Pharmacokinetics study
PV15615	Viral challenge study
PV15616	Viral challenge study
WP15517	Pharmacokinetics study
WP15525	Pharmacokinetics study

Study	Reason for exclusion
WP15647	Pharmacokinetics study
WP15648	Pharmacokinetics study
WP15676	Pharmacokinetics study
WP15979	Bioavailability study
WP16094	Pharmacokinetics study
WP16134	Bioequivalence study
WP16137	Bioequivalence study
WP16225	Bioequivalence study
WP16226	Pharmacokinetics study
WP16254	Pharmacokinetics study
WP16263	No influenza circulation, Phase IV study
WP16295	Open-label absorption study
WP17721	Pharmacokinetics study
WP18308	Pharmacokinetics study
WP20727	Pharmacokinetics study
WP20749	Not placebo/do nothing controlled
WP21272	Pharmacokinetics study
WP22849	Pharmacokinetics study
WV15731	No placebo arm
WV16139	Unknown study. Only ID traced. ID could be a typo
WV16193	Not placebo/do nothing controlled

ID, identity number.

Appendix 11 Symptomatic influenza-like illness in prophylaxis trials

Introduction

Among the CSRs of prophylaxis studies that we included, no oseltamivir study and only one study of zanamivir (NAI 30034[86]) reported the relevant primary outcome 'symptomatic ILI irrespective of positivity of laboratory testing'. In the zanamivir CSR (NAI 30034) no significant reduction was observed (9% vs. 10%). Furthermore, no definition was provided for ILI in the oseltamivir CSRs; however, individual patient data on symptoms of influenza were provided in module 3.

Methods

Examples of the definitions of categories for lab-confirmed influenza used in the oseltamivir trials (p. 33, CSR for WV15673–697;[59] p. 31, CSR for WV15825[68]) are given below:

TABLE 25 Definitions of categories for subjects with laboratory-confirmed influenza virus infection

Category	Oral temperature	Constitutional symptoms	Respiratory symptoms
Clinical influenza	≥ 99 °F	One or more	One or more
Non-clinical influenza			
Non-clinical URTI			
Febrile URTI	≥ 99 °F	None	One or more
URTI without systematic disturbance	< 99 °F	None	One or more
URTI with systematic disturbance	< 99 °F	One or more	None
Febrile constitutional	≥ 99 °F	One or more	None
Asymptomatic influenza	< 99 °F	None	None
	≥ 99 °F	None	None
	< 99 °F	One or more	None

URTI, upper respiratory tract infection.

TABLE 26 Definitions of categories for subjects with laboratory-confirmed influenza virus infection

Category	Oral temperature	Constitutional symptoms	Respiratory symptoms
Clinical influenza	≥ 99 °F	One or more	One or more
Non-clinical influenza			
Non-clinical URTI			
Febrile URTI	≥ 99 °F	None	One or more
URTI without systematic disturbance	< 99 °F	None	One or more
URTI with systematic disturbance	< 99 °F	One or more	One or more
Febrile constitutional	≥ 99 °F	One or more	None
Asymptomatic influenza	< 99 °F	None	None
	≥ 99 °F	None	None
	< 99 °F	One or more	None

URTI, upper respiratory tract infection.

These are complex and confusing definitions, in which, for example, the definition for 'URTI with systemic disturbance' is the same as one of the definitions for asymptomatic influenza in WV15673–697.[59] Furthermore, the definition for 'URTI with systemic disturbance' in WV15825[68] and WV15673/WV15697[59] is different. No definition is provided for ILI without confirmation of influenza. Asymptomatic influenza includes those with some symptoms.

In the absence of a definition provided in the CSRs for ILI and the complex and confusing definitions of categories for lab-confirmed influenza, we classified ILI as two or more symptoms out of nasal congestion, headache, chills/sweats, sore throat, cough, fatigue, myalgia and fever. Fever was defined as reported in the original protocols for each trial. We counted the number of patients with ILI during the trial follow-up for each prophylaxis study of oseltamivir in adults.

Results

Oseltamivir did not reduce ILI (RR 0.95, 95% CI 0.86 to 1.06) (*Figure 20*). In additional analysis we found that fever is reduced (RR 0.62, 95% CI 0.42 to 0.93) (*Figure 21*), proportion with laboratory confirmation is reduced (RR 0.59, 95% CI 0.41 to 0.85) (*Figure 22*) but symptoms other than fever are not reduced (RR 0.96, 95% CI 0.86 to 1.07) (*Figure 23*).

Interpretation

These results suggest oseltamivir suppresses fever, reduces antibody response and viral shedding but does not reduce the risk of symptomatic illness.

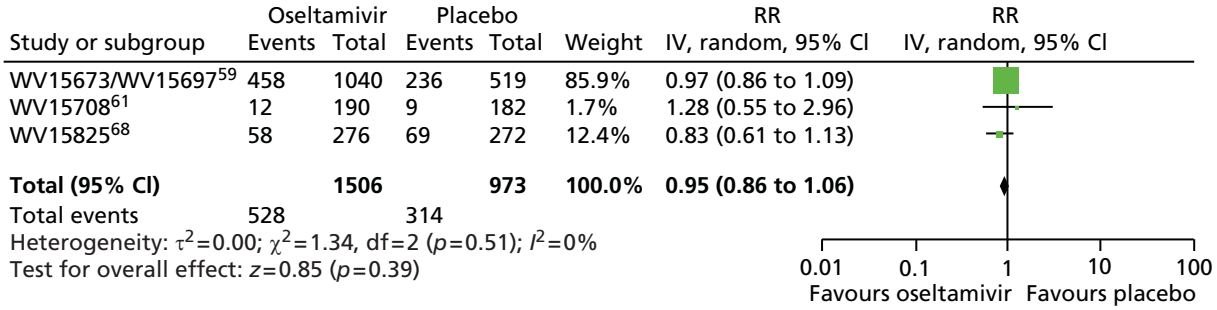


FIGURE 20 All symptomatic ILI in adult prophylaxis. ILI is classified as two or more symptoms out of: nasal congestion, headache, chills/sweats, sore throat, cough, fatigue, myalgia and fever (with or without lab confirmation). IV, inverse variance.

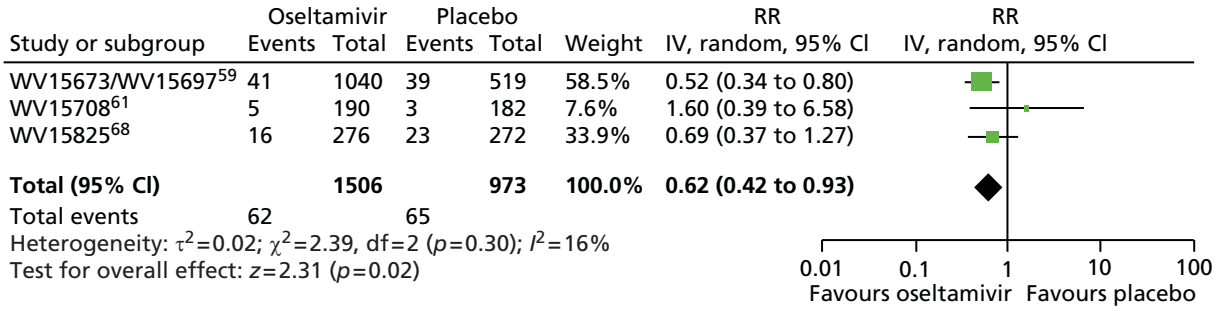


FIGURE 21 Fever in adult prophylaxis. Temperature ≥ 100 °F (WV15673/697[59]) or ≥ 37.5 °C (WV15825/15708) as originally defined in the trial protocols. IV, inverse variance.

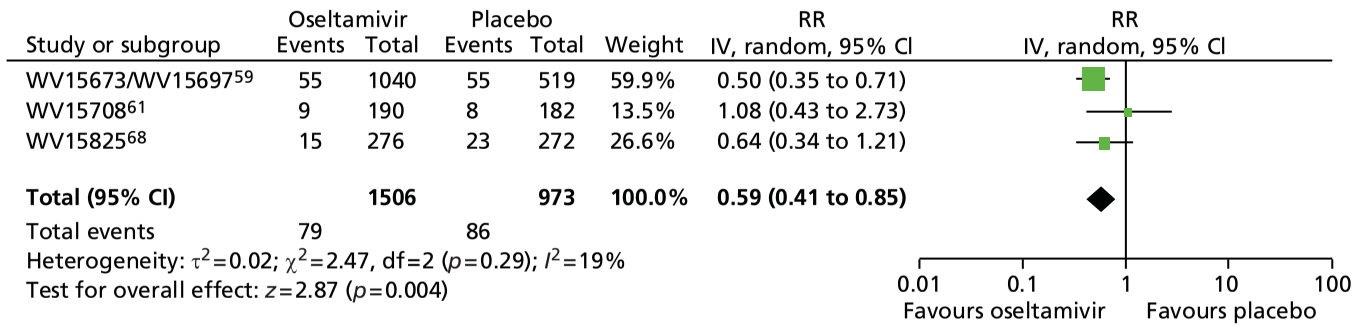


FIGURE 22 Lab confirmation of influenza (symptomatic and asymptomatic). IV, inverse variance.

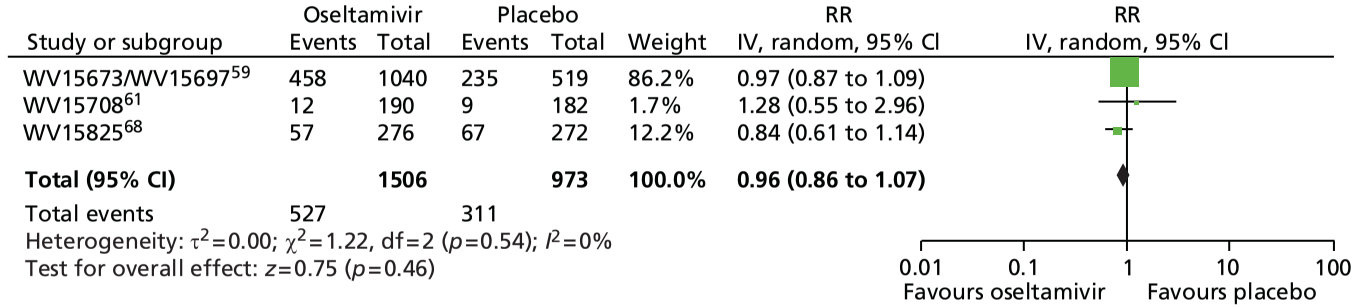


FIGURE 23 Two or more symptoms (other than fever) of ILI in adult prophylaxis. Other than fever defined as nasal congestion, headache, chills/sweats, sore throat, cough, fatigue and myalgia. IV, inverse variance.

Appendix 12 Oseltamivir observational studies review search strategies

Database: Ovid MEDLINE (1946 to February Week 1 2013)

Search strategy

1. Influenza, Human/
2. influenzavirus a/ or influenza a virus/ or influenza a virus, h1n1 subtype/
3. (influenza* or flu or h1n1).tw.
4. or/1-3
5. Oseltamivir/
6. (oseltamivir or tamiflu or neuraminidase inhibitor*).tw,nm.
7. Antiviral Agents/
8. antiviral*.tw.
9. or/5-8
10. 4 and 9
11. Hospitalization/
12. hospitali*.tw.
13. exp Mortality/
14. mortality.tw.
15. Death/
16. fatal outcome/
17. (death* or died or fatal*).tw.
18. Critical Illness/
19. (critical* adj2 ill*).tw.
20. or/11-19
21. 10 and 20
22. epidemiologic studies/
23. epidemiology.fs.
24. epidemiol*.tw.
25. exp case-control studies/
26. exp Cohort Studies/
27. cohort*.tw.
28. ((“follow up” or “follow-up”) adj2 (study or studies)).tw.
29. observational*.tw.
30. longitudinal*.tw.
31. retrospectiv*.tw.
32. prospectiv*.tw.
33. Cross-Sectional Studies/
34. (cross-section* or cross section*).tw.
35. (control* adj2 (group* or study or studies or patient* or case*)).tw.
36. or/22-35
37. 21 and 36

EMBASE (Elsevier)

#15 834		
	#15.34 #15.19 AND #15.33	#15.33 #15.20 OR #15.21 OR #15.22 OR #15.23 OR #15.24 OR #15.25 OR #15.26 OR #15.27 OR #15.28 OR #15.29 OR #15.30 OR #15.31 OR #15.32
		#15.32 'control group':ab,ti
		#15.31 'cross-sectional':ab,ti OR 'cross sectional':ab,ti
		#15.30 'cross-sectional study'/de
		#15.29 prospectiv*:ab,ti
		#15.28 retrospectiv*:ab,ti
		#15.27 longitudinal:ab,ti
		#15.26 observational*:ab,ti
		#15.25 (('follow up' OR 'follow-up') NEAR/2 (study OR studies)):ab,ti
		#15.24 cohort*:ab,ti
		#15.23 'cohort analysis'/de
		#15.22 'case control study'/exp
		#15.21 epidemiol*:ab,ti
		#15.20 'epidemiology'/de
		#15.19 #15.9 AND #15.18
		#15.18 #15.10 OR #15.11 OR #15.12 OR #15.13 OR #15.14 OR #15.15 OR #15.16 OR #15.17
		#15.17 (critical* NEAR/2 ill*):ab,ti
		#15.16 'critical illness'/de
		#15.15 death*:ab,ti OR died:ab,ti OR fatal*:ab,ti
		#15.14 'death'/de OR 'fatality'/de
		#15.13 mortality:ab,ti
		#15.12 'mortality'/exp
		#15.11 hospitali*:ab,ti
		#15.10 'hospitalization'/de
		#15.9 #15.3 AND #15.8
		#15.8 #15.4 OR #15.5 OR #15.6 OR #15.7
		#15.7 antiviral*:ab,ti
		#15.6 'antivirus agent'/de AND [embase]/lim
		#15.5 oseltamivir:ab,ti OR tamiflu:ab,ti OR 'neuraminidase inhibitor':ab,ti OR 'neuraminidase inhibitors':ab,ti
		#15.4 'oseltamivir'/de
		#15.3 #15.1 OR #15.2
		#15.2 influenza*:ab,ti OR flu:ab,ti OR h1n1:ab,ti
		#15.1 'influenza'/de OR 'influenza a'/de OR '2009 h1n1 influenza'/de OR 'influenza a (h1n1)'/de OR 'pandemic influenza'/de OR 'swine influenza'/de

Cumulative Index to Nursing and Allied Health Literature (EBSCO*host*)

Friday, February 15, 2013 2:30:38 AM

#	Query	Limiters/Expanders	Last Run Via	Results	Action
S35	S21 AND S34				
S34	S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33				
S33	TI ((control* N2 (group* or study or studies or patient* or case*))) OR AB ((control* N2 (group* or study or studies or patient* or case*)))				
S32	TI (cross section* or cross-section*) OR AB (cross section* or cross-section*)				
S31	TI prospectiv* OR AB prospectiv*				
S30	TI retrospectiv* OR AB retrospectiv*				
S29	TI longitudinal* OR AB longitudinal*				
S28	TI observational* OR AB observational*				
S27	TI (((“follow up” or “follow-up”) N2 (study or studies))) OR AB (((“follow up” or “follow-up”) N2 (study or studies)))				
S26	TI cohort* OR AB cohort*				
S25	(MH “Prospective Studies+”)				
S24	(MH “Case Control Studies+”)				
S23	TI epidemiol* OR AB epidemiol*				
S22	(MH “Epidemiological Research”)				
S21	S10 AND S20				
S20	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19				
S19	TI critical* N2 ill* OR AB critical* N2 ill*				
S18	(MH “Critical Illness”)				
S17	TI (death* or died or fatal*) OR AB (death* or died or fatal*)				
S16	(MH “Fatal Outcome”)				
S15	(MH “Death”)				
S14	TI mortality OR AB mortality				
S13	(MH “Mortality+”)				
S12	TI hospitali* OR AB hospitali*				
S11	(MH “Hospitalization”)				
S10	S4 AND S9				
S9	S5 OR S6 OR S7 OR S8				
S8	TI antiviral* OR AB antiviral*				
S7	(MH “Antiviral Agents”)				
S6	TI (oseltamivir or tamiflu or neuraminidase inhibitor*) OR AB (oseltamivir or tamiflu or neuraminidase inhibitor*)				
S5	(MH “Oseltamivir”)				
S4	S1 OR S2 OR S3				
S3	TI (influenza* or flu or h1n1) OR AB (influenza* or flu or h1n1)				
S2	(MH “Influenzavirus A”) OR (MH “Influenza A Virus”) OR (MH “Influenza A Virus, H1N1 Subtype”)				
S1	(MH “Influenza”) OR (MH “Influenza, Human”) OR (MH “Influenza, Pandemic (H1N1) 2009”)				

Latin American and Caribbean Health Sciences Literature (BIREME)

(mh:"Influenza, Human" OR grippe OR "influenza humana" OR "gripe humana" OR influenza* OR flu OR h1n1 OR mh:"Influenzavirus A" OR mh:"Influenza A virus" OR mh:"Influenza A Virus, H1N1 Subtype") AND (mh:oseltamivir OR oseltamivir OR tamiflu OR "neuraminidase inhibitor" OR "neuraminidase inhibitors" OR "inhibe la neuraminidasa" OR "inibe a neuraminidase" OR mh:"Antiviral Agents" OR antivirales OR antivirais OR antiviral*) AND (mh:"Epidemiologic Studies" OR "Estudios Epidemiológicos" OR epidemiol* OR mh:"Case-Control Studies" OR "Estudios de Casos y Controles" OR "Estudos de Casos e Controles" OR "Case-Base Studies" OR "Case-Comparison Studies" OR "Case-Referent Studies" OR "Matched Case-Control Studies" OR "Nested Case-Control Studies" OR "Combined Case-Control Studies" OR "Grupos de Estudio" OR "Estudios de Comparación de Casos" OR "Estudios de Referencia de Casos" OR "Estudios de Casos y Controles por Apareamiento" OR "Estudios de Casos y Controles Anidados" OR "Estudios de Casos y Controles Combinados" OR "Grupos de Estudo" OR "Estudos de Comparação de Casos" OR "Estudos de Referência de Casos" OR "Estudos de Caso-Controle com Emparelhamento" OR "Estudos de Caso-Controle Aninhados" OR "Estudos de Caso-Controle Combinados" OR mh:"Cohort Studies" OR "Estudios de Cohortes" OR "Estudos de Coortes" OR "Cohort Analysis" OR "Closed Cohort Studies" OR "Concurrent Studies" OR "Historical Cohort Studies" OR "Incidence Studies" OR "Análisis de Cohortes" OR "Estudios Cerrados de Cohortes" OR "Estudios de Concurrencia" OR "Estudios Históricos de Cohortes" OR "Estudios de Incidencia" OR "Análise de Coortes" OR "Estudos Fechados de Coortes" OR "Estudos Históricos de Coortes" OR "Estudos de Incidência" OR cohort* OR longitudinal OR retrospectiv* OR prospectiv* OR "follow up" OR "follow-up" OR "control group" OR mh:"Cross-Sectional Studies" OR "Estudios Transversales" OR "Estudos Transversais" OR "cross sectional" OR "cross- sectional") AND db:("LILACS")

Web of Science (Thomson Reuters)

#7	452	#6 AND #5 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*
#6	1,897,044	Topic=(epidemiol* or cohort* or (("follow up" or "follow-up") NEAR/2 (study or studies)) or observational* or longitudinal or retrospectiv* or prospectiv* or "cross section*" or "cross-section*" or (control* NEAR/2 (group* or study or studies or patient* or case*))) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*
#5	1527	#4 AND #3 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*
#4	1,158,683	Topic=(hospitali* or mortality or death* or fatal* or died or (critical* NEAR/2 ill*)) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*
#3	6592	#2 AND #1 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*
#2	56,113	Topic=(oseltamivir or tamiflu or "neuraminidase inhibitor" or "neuraminidase inhibitors" or antiviral*) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*
#1	86,524	Topic=(influenza* or flu or h1n1) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*

Appendix 13 Template of letter sent to corresponding authors of included studies

Dear Dr. X*,

We read with interest your paper:

(citation)*

We are conducting a systematic review of observational studies of antivirals for influenza and are contacting you in the hope of obtaining a copy of the patient data you analyzed, as we would like to conduct a further analysis of these data considering the time-dependent nature of antiviral exposure. Would this be possible? We would of course acknowledge your help in any papers or reports arising from this research. We recognize the need to protect patient privacy and hope that the data can be de-identified before sharing. Our protocol can be obtained from the following website:

Mark Jones, Rokuro Hama. Effect of oseltamivir on mortality in treatment of 2009A/H1N1 influenza patients. PROSPERO 2012:CRD42012002245 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002245

The variables we are particularly interested in for each patient are:

Patient ID

Hospital ID

Age and Sex of patient

Underlying Co-morbidities

Date of onset of symptoms (fever, or other symptoms in the case of no fever)

Date of first presentation at a medical facility

Date of admission to hospital

Antiviral treatment: start date (with time), type (oseltamivir/zanamivir/other/none), dose, duration

Antipyretic treatment: date, type (paracetamol/ibuprofen/aspirin/other NSAID) and dose

Corticosteroid treatment: date, type and dose

Date of admission to ICU

Date (with time) of start of artificial ventilation

Hospital outcome (death/discharge/unknown)

Date of death/discharge

Any other variable that is associated with hospital outcome

Yours sincerely,

CDM

Appendix 14 Reasons for exclusion of studies based on full manuscripts

Reason for exclusion	Number of studies	Citations[a]
Most (or all) patients received antiviral medication	77	1–57, 59–61, 63, 67, 68, 71–73, 102–111
Overlap with other included studies	10	58, 62, 64–66, 69, 70, 74–76
Did not provide a breakdown of numbers of patients dying by oseltamivir exposure	12	77–88
Fewer than five deaths	12	89–100
Not a clinical study	5	101, 112–115
Other reasons	8	116–123

a These citations refer to the reference numbers in this appendix and not the main reference list.

References

1. Metan G, Bozkurt I, Agkus C, Coskun R, Alp E, Sungur M, *et al.* Hospitalised pandemic influenza A (H1N1) patients in a university hospital. *Cent Eur J Med* 2010;**6**:83–8.
2. Chien Y, Su C, Tsai H, Huang AS, Lien CE, Hung MN, *et al.* Predictors and outcomes of respiratory failure among hospitalised pneumonia patients with 2009 H1N1 influenza in Taiwan. *J Infect* 2010;**60**:168–74.
3. Paredes G, Cevallos C. Acute respiratory distress syndrome during the 2009 H1N1 influenza A pandemic in Ecuador. *Med Intensiva* 2010;**34**:310–17.
4. Choi W, Kim WY, Kim S, Oh BJ, Kim W, Lim KS, *et al.* Clinical characteristics of pneumonia in hospitalised patients with novel influenza A (H1N1) in Korea. *Scand J Infect Dis* 2010;**42**:311–14.
5. Rello J, Rodriguez A, Ibanez P, Socias L, Cebrian J, Marques A, *et al.* Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care* 2009;**13**:R148.
6. Kumar S, Havens P, Chusid M, Willoughby RE Jr, Simpson P, Henrickson KJ, *et al.* Clinical and epidemiologic characteristics of children hospitalised with 2009 pandemic H1N1 influenza A infection. *Pediatr Infect Dis J* 2010;**29**:591–4.
7. Creanga A, Johnson T, Graitcer S, Hartman LK, Al-Samarrai T, Schwarz AG, *et al.* Severity of 2009 pandemic influenza a (H1N1) virus infection in pregnant women. *Obstet Gynecol* 2010;**115**:717–26.
8. Dubar G, Azria E, Tesniere A, Dupont H, Le Ray C, Baugnon T, *et al.* French experience of 2009 A/H1N1v influenza in pregnant women. *PLOS ONE* 2010;**5**:e13112.
9. Cui W, Zhao H, Lu X, Wen Y, Zhou Y, Deng B, *et al.* Factors associated with death in hospitalized pneumonia patients with 2009 H1N1 influenza in Shenyang, China. *BMC Infect Dis* 2010;**10**:145.
10. Estenssoro E, Rios FG, Apezteguia C, Reina N, Neira J, Cerasso D, *et al.* Pandemic 2009 influenza A(H1N1) in Argentina: a study of 337 patients on mechanical ventilation. *Am J Respir Crit Care Med* 2010;**182**:41–8.

11. Wei J, Chen F, Jin J, Mai WY, Qian WB, Meng HT, *et al.* Novel influenza A (H1N1) in patients with hematologic disease. *Leuk Lymphoma* 2010;**51**:2079–83.

12. Lee E, Wu C, Lee E, Mai WY, Qian WB, Meng HT, *et al.* Fatalities associated with the 2009 H1N1 influenza a virus in New York City. *Clin Infect Dis* 2010;**50**:1498–504.

13. Kute V, Godara S, Goplani K, Gumber M, Shah P, Vanikar A, *et al.* High mortality in critically ill patients infected with 2009 pandemic influenza A (H1N1) with pneumonia and acute kidney injury. *Saudi J Kidney Dis Transpl* 2011;**22**:83–9.

14. Paganini H, Parra A, Ruvinsky S, Viale D, Baumeister E, Bologna R, *et al.* Clinical features and outcome of 2009 influenza A (H1N1) virus infections in children with malignant diseases: a case–control study. *J Pediatr Hematol Oncol* 2011;**33**:e5–8.

15. Smud A, Nagel C, Madsen E, Rial Mdel C, Barcan LA, Gomez AA, *et al.* Pandemic influenza A/H1N1 virus infection in solid organ transplant recipients: a multicenter study. *Transplantation* 2010;**90**:1458–62.

16. Abdulkader R, Ho Y, De Sousa Santos S, Caires R, Arantes M, Andrade L. Characteristics of acute kidney injury in patients infected with the 2009 influenza A (H1N1) virus. *Clin J Am Soc Nephrol* 2010;**5**:1916–21.

17. Louriz M, Mahraoui C, Azzouzi A, El Fassy Fihri MT, Zeggwagh AA, Abidi K, *et al.* Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in an university hospital of Morocco. *Int Arch Med* 2010;**3**:26.

18. Tutuncu E, Ozturk B, Gurbuz Y, Haykir A, Sencan I, Kuscu F, *et al.* Clinical characteristics of 74 pandemic H1N1 influenza patients from Turkey: risk factors for fatality. *Saudi Med J* 2010;**31**:993–8.

19. Satterwhite L, Mehta A, Martin G. Novel findings from the second wave of adult pH1N1 in the United States. *Crit Care Med* 2010;**38**:2059–61.

20. Venkata C, Sampathkumar P, Afessa B. Hospitalized patients with 2009 H1N1 influenza infection: The Mayo Clinic experience. *Mayo Clin Proc* 2010;**85**:798–805.

21. Siau C, Law J, Tee A, Poulose V, Raghuram J. Severe refractory hypoxaemia in H1N1 (2009) intensive care patients: initial experience in an Asian regional hospital. *Singapore Med J* 2010;**51**:490–5.

22. Abouchacra S, Chaaban A, Gebran N, Hassan M, Paul A, Eid H, *et al.* Acute kidney injury in patients with H1N1 admitted to ICU: incidence, patient and renal outcomes. A multi-center perspective. *Anaesth Pain Intensive Care* 2010;**14**:13–16.

23. Miller R, Markewitz B, Rolfs R, Brown SM, Dascomb KK, Grissom CK, *et al.* Clinical findings and demographic factors associated with ICU admission in Utah due to novel 2009 influenza a(H1N1) infection. *Chest* 2010;**137**:752–8.

24. Koegelenberg C, Irusen E, Cooper R, Diacon A, Taljaard J, Mowlana A, *et al.* High mortality from respiratory failure secondary to swine-origin influenza A (H1N1) in South Africa. *QJM* 2010;**103**:319–25.

25. Mu Y, Zhang Z, Chen X, Xi X, Lu Y, Tang Y, *et al.* Clinical features, treatments and prognosis of the initial cases of pandemic influenza H1N1 2009 virus infection in Shanghai China. *QJM* 2010;**103**:311–17.

26. Al-Khuwaitir TS, Al-Abdulkarim AS, Abba AA, Yousef AM, El-Din MA, Rahman KT, *et al.* H1N1 influenza A: preliminary evaluation in hospitalized patients in a secondary care facility in Saudi Arabia. *Saudi Med J* 2010;**30**:1532–6.

27. Naseem A, Satti S, Khan M, Saeed W. A clinical account of hospitalized 2009 pandemic influenza a (H1N1) cases. *J Coll Physicians Surg Pak* 2011;**21**:97–102.

28. Binsaeed A. Characteristics of pandemic influenza A (H1N1) infection in patients presenting to a university hospital in Riyadh, Saudi Arabia. *Ann Saudi Med* 2010;**30**:59–62.

29. Anand R, Gupta A, Gupta A, Wadhawan S, Bhadoria P, *et al.* Management of swine-flu patients in the intensive care unit: our experience. *J Anaesthesiol Clin Pharmacol* 2012;**28**:51–5.

30. Bhatt KN, Jethw SC, Bhadiyadar D, Patel D, Joshi K, *et al.* Study of clinical profile in patients with H1N1 influenza in Surat district, June 2009-March 2010. *J Assoc Physicians India* 2012;**60**:15–19.

31. Camargo LFA, de Sandes-Freitas TV, Silva CD, Bittante CD, Ono G, Corrêa L, *et al.* Morbimortality of pandemic influenza a H1N1 infection in kidney transplant recipients requiring hospitalization: a comparative analysis with nonimmunocompromised patients. *Transplantation* 2012;**93**:69–72.

32. Carrillo-Esper R, Sosa-Garcia JO, Arch-Tirado E. [Experience in the management of the severe form of human influenza A H1N1 pneumonia in an intensive care unit.] *Cirugia y Cirujanos* 2011;**79**:409–16.

33. Choi WI, Yim JJ, Park J, Kim SC, Na MJ, Lee WY, *et al.* Clinical characteristics and outcomes of H1N1-associated pneumonia among adults in South Korea. *Int J Tuberc Lung Dis* 2011;**15**:270–5.

34. Cordero E, Aydillo T, Farinas MC, Panio-Pardo JR, Pachon J, Viasus D, *et al.* Immunosuppressed patients with pandemic influenza A 2009 (H1N1) virus infection. *Eur J Clin Microbiol Infect Dis* 2012;**31**:547–56.

35. Damak H, Chtara K, Bahloul M, Kallel H, Chaari A, Ksibi H, *et al.* Clinical features, complications and mortality in critically ill patients with 2009 influenza A(H1N1) in Sfax, Tunisia. *Influenza Other Respir Viruses* 2011;**5**:230–40.

36. Dashti-Khavidaki S, Khalili H, Gholamalipour F, Soudbakhsh A, Talazaz AH, Hajabdolbaghi M, *et al.* Approach to pandemic 2009 influenza: first report from a main referral hospital for Pandemic H1N1 influenza care in Iran. *J Infec Dev Ctries* 2010;**4**:629–35.

37. Ellington SR, Hartman LK, Acosta M, Martinez-Romo M, Rubinson L, Jamieson DJ, *et al.* Pandemic 2009 influenza A (H1N1) in 71 critically ill pregnant women in California. *Am J Obstetr Gynecol* 2011;**204**(6 Suppl. 1):21–30.

38. Farooq O, Faden HS, Cohen ME, Ramanathan M, Barrett H, Farkas MK, *et al.* Neurologic complications of 2009 influenza: A H1N1 infection in children. *J Child Neurol* 2012;**27**:431–8.

39. Han K, Ma H, An X, Su Y, Chen J, Lian Z, *et al.* Early use of glucocorticoids was a risk factor for critical disease and death from pH1N1 infection. *Clin Infect Dis* 2011;**53**:326–33.

40. Hung IFN, To KK, Lee CK, Lee KL, Chan K, Yan WW, *et al.* Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis* 2011;**52**:447–56.

41. Jung JY, Park BH, Hong SB, Koh Y, Su GY, Jeon K, *et al.* Acute kidney injury in critically ill patients with pandemic influenza A pneumonia 2009 in Korea: a multicenter study. *J Crit Care* 2011;**26**:577–85.

42. Kaya S, Yilmaz G, Arslan M, Oztuna F, Ozlu T, Koksal I, *et al.* Predictive factors for fatality in pandemic influenza A (H1N1) virus infected patients. *Saudi Med J* 2012;**33**:146–51.

43. Kim SH, Hong SB, Yun SC, Choi WI, Ahn JJ, Lee YJ, *et al.* Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. *Am J Resp Crit Care Med* 2011;**183**:1207–14.

44. Kirakli C, Tatar D, Cimen P, Edipoglu O, Coskun M, Celikten E, *et al.* Survival from severe pandemic H1N1 in urban and rural Turkey: a case series. *Resp Care* 2011;**56**:790–5.

45. Kumar D, Michaels MG, Morris MI, Green M, Avery RK, Liu C, *et al.* Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. *Lancet Infect Dis* 2010;**10**:521–6.

46. Kumar TCN, Shivakumar NS, Deepak TS, Krishnappa R, Goutam NS, *et al.* H1N1-infected patients in ICU and their clinical outcome. *N Am J Med Sci* 2012;**4**:394–8.

47. Lee N, Chan PK, Lui JC, Wong BC, Sin WW, Choi KW, *et al.* Complications and outcomes of pandemic 2009 influenza A (H1N1) virus infection in hospitalized adults: how do they differ from those in seasonal influenza? *J Infect Dis* 2011;**203**:1739–47.

48. Lenzi L, Wiens A, Pontarolo R. Clinical manifestations, outcomes and prognostic factors of the 2009 pandemic influenza A (H1N1) in children. *Rev Paulista Pediatr* 2012;**30**:346–52.

49. Li F, Chen G, Wang J, Liu H, Wu J. A case–control study on risk factors associated with death in pregnant women with severe pandemic H1N1 infection. *BMJ Open* 2012;**2**:e000827.

50. Linko R, Wiens A, Pontarolo R. Corticosteroid therapy in intensive care unit patients with PCR-confirmed influenza A(H1N1) infection in Finland. *Acta Anaesthesiol Scand* 2011;**55**:971–9.

51. Maravi-Poma E, Martin-Loeches I, Regidor E, Laplaza C, Cambra K, Aldunate S, *et al.* Severe 2009 A/H1N1v influenza in pregnant women in Spain. *Crit Care Med* 2011;**39**:945–51.

52. Minnema BJ, Patel M, Rotstein C, Mazzulli T, Hota S, Cole EH, *et al.* Comparison of hospitalized solid organ transplant recipients and nonimmunocompromised patients with pandemic H1N1 infection: a retrospective cohort study. *Transplantation* 2011;**92**:230–4.

53. Morales-Garcia G, Falfán-Valencia R, Garcia-Ramirez RA, Camarena Á, Ramirez-Venegas A, Castillejos-López M, *et al.* Pandemic influenza A/H1N1 virus infection and TNF, LTA, IL1B, IL6, IL8, and CCL polymorphisms in Mexican population: a case–control study. *BMC Infect Dis* 2012;**12**:299.

54. Nelliyanil M, Basha R, Sharada MP. Profile of novel flu patients admitted in two government hospitals in Bangalore. *Aus Med J* 2010;**3**:340–3.

55. Ormsby CE, de la Rosa-Zamboni D, Vasquez-Perez J, Ablanedo-Terrazas Y, Vega-Barrientos R, *et al.* Severe 2009 pandemic influenza A (H1N1) infection and increased mortality in patients with late and advanced HIV disease. *AIDS* 2011;**25**:435–9.

56. Paño-Pardo JR, Rodriguez-Baño A, Martinez-Sánchez N, Viasus D, Fariñas MC, Leyes M, *et al.* Prognosis of 2009 A(H1N1) influenza in hospitalized pregnant women in a context of early diagnosis and antiviral therapy. *Antiviral Ther* 2012;**17**:719–28.

57. Protheroe RE, Kirkland KE, Pearce RM, Kaminaris K, Bloor A, Potter MN, *et al.* The clinical features and outcome of 2009 H1N1 influenza infection in allo-SCT patients: a British Society of Blood and Marrow Transplantation study. *Bone Marrow Transplant* 2012;**47**:88–94.

58. Raboni SM, Stella V, Cruz CR, França JB, Moreira S, Gonçalves L, *et al.* Laboratory diagnosis, epidemiology, and clinical outcomes of pandemic influenza A and community respiratory viral infections in Southern Brazil. *J Clin Microbiol* 2011;**49**:1287–93.

59. Ramakrishna K, Sampath S, Chacko J, Chacko B, Narahari DL, Veerendra HH, *et al.* Clinical profile and predictors of mortality of severe pandemic (H1N1) 2009 virus infection needing intensive care: a multi-centre prospective study from South India. *J Glob Infect Dis* 2012;**4**:145–52.

60. Randolph AG, Vaughn F, Sullivan R, Rubinson L, Thompson BT, Yoon G, *et al.* Critically ill children during the 2009–2010 influenza pandemic in the United States. *Pediatrics* 2011;**128**:e1450–8.

61. Reyes S, Montull B, Martínez R, Córdoba J, Molina JM, Martí V, *et al.* Risk factors of A/H1N1 etiology in pneumonia and its impact on mortality. *Resp Med* 2011;**105**:1404–11.

62. Rhim JW, Go EJ, Lee KY, Youn YS, Kim MS, Park SH, *et al.* Pandemic 2009 H1N1 virus infection in children and adults: a cohort study at a single hospital throughout the epidemic. *Int Arch Med* 2012;**5**:13.

63. Rhim JW, Lee KY, Youn YS, Kang JH, Kim JC. Epidemiological and clinical characteristics of childhood pandemic 2009 H1N1 virus infection: an observational cohort study. *BMC Infect Dis* 2011;**11**:225.

64. Rice TW, Rubinson L, Uyeki TM, Vaughn FL, John BB, Miller RR III, *et al.* Critical illness from 2009 pandemic influenza A virus and bacterial coinfection in the United States. *Crit Care Med* 2012;**40**:1487–98.

65. Samra T, Pawar M, Yadav A. Comparative evaluation of acute respiratory distress syndrome in patients with and without H1N1 infection at a tertiary care referral center. *Indian J Anaesth* 2011;**55**:47–51.

66. Sertogullarindan B, Ozbay B, Gunini H, Sunnetcioglu A, Arisoy A, Bilgin HM, *et al.* Clinical and prognostic features of patients with pandemic 2009 influenza A (H1N1) virus in the intensive care unit. *Afr Health Sci* 2011;**11**:163–70.

67. Shah DP, El Taoum KK, Shah JN, Vigil KJ, Adachi JA, Granwehr BP, *et al.* Characteristics and outcomes of pandemic 2009/H1N1 versus seasonal influenza in children with cancer. *Pediatr Infect Dis J* 2012;**31**:373–8.

68. Souza TM, Salluh JIF, Bozza FA, Mesquita M, Soares M, Motta FC, *et al.* H1N1pdm influenza infection in hospitalized cancer patients: clinical evolution and viral analysis. *PLOS ONE* 2010;**5**:e14158.

69. Tabarsi P, Moradi A, Marjani M, Baghaei P, Hashemian SM, Nadji SA, *et al.* Factors associated with death or intensive care unit admission due to pandemic 2009 influenza A (H1N1) infection. *Ann Thorac Med* 2011;**6**:91–5.

70. Teke T, Coskun R, Sungur M, Guven M, Bekci T, Maden E, *et al.* 2009 H1N1 influenza and experience in three critical care units. *Int J Med Sci* 2011;**8**:270–7.

71. To KK, Wong SS, Li IW, Hung IF, Tse F, Woo PC, *et al.* Concurrent comparison of epidemiology, clinical presentation and outcome between adult patients suffering from the pandemic influenza A (H1N1) 2009 virus and the seasonal influenza A virus infection. *Postgrad Med J* 2010;**86**:515–21.

72. Torres SF, Iolster T, Schnitzler EJ, Farias J, Bordogna AC, Rufach D, *et al.* High mortality in patients with influenza A pH1N1 2009 admitted to a pediatric intensive care unit: a predictive model of mortality. *Pediatr Crit Car Med* 2012;**13**:e78–83.

73. Viasus D, Cordero W, Rodriguez-Bano, J, Oteo JA, Fernandez-Navarro A, Ortega L, *et al.* Changes in epidemiology, clinical features and severity of influenza A (H1N1) 2009 pneumonia in the first post-pandemic influenza season. *Clin Microbiol Infect* 2012;**18**:E55–62.

74. Vidovic J, Kovacevic P, Stanetic M, Rajkovaca Z, Zlojutro B. Treatment of critically ill patients with influenza a H1N1 in university hospital Banja Luka. *Acta Med Saliniana* 2011;**40**(Suppl. 1):49–51.

75. Zhang PJ, Li XL, Cao B, Yang SG, Liang AR, Gu L, *et al.* Clinical features and risk factors for severe and critical pregnant women with 2009 pandemic H1N1 influenza infection in China. *BMC Infect Dis* 2012;**12**:29.

76. Perez-Padilla R, De La Rosa-Zamboni D, Ponce De Leon S, Hernandez M, Quiniones-Falconi F, Bautista E, *et al.* Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009;**361**:680–9.

77. Schellongowski P, Ullrich R, Hieber C, Hetz H, Losert H, Hermann M, *et al.* A surge of flu-associated adult respiratory distress syndrome in an Austrian tertiary care hospital during the 2009/2010 influenza A H1N1v pandemic. *Wien Klin Wochenschr* 2011;**123**:209–14.

78. Louie J, Acosta M, Jamieson D, Honein M. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med* 2010;**362**:27–35.

79. Xi X, Xu Y, Jiang L, Li A, Duan J, Du B. Hospitalized adult patients with 2009 influenza A(H1N1) in Beijing, China: risk factors for hospital mortality. *BMC Infect Dis* 2010;**10**:256.

80. Louie J, Gavali S, Acosta M, Samuel M, Winter K, Jean C, *et al.* Children hospitalized with 2009 novel influenza A(H1N1) in California. *Arch Pediatr Adolesc Med* 2010;**164**:1023–31.

81. Libster R, Bugna J, Coviello S, Hijano D, Dunaiewsky M, Reynoso N, *et al.* Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. *N Engl J Med* 2010;**362**:45–55.

82. Altmann M, Fiebig L, Buda S, von Kries R, Dehnert M, Haas W. Unchanged severity of influenza A(H1N1)pdm09 infection in children during first postpandemic season. *Emerg Infect Dis* 2012;**18**:1755–62.

83. Bramley AM, Dasgupta S, Skarbinski J, Kamimoto L, Fry AM, Finelli L, *et al.* Intensive care unit patients with 2009 pandemic influenza A (H1N1pdm09) virus infection: United States, 2009. *Influenza Other Respir Viruses* 2012;**6**:e134–42.

84. Jain S, Benoit R, Skarbinski J, Bramley AM, Finelli L, 2009 Pandemic Influenza A(H1N1) Virus Hospitalizations Investigation Team. Influenza-associated pneumonia among hospitalized patients with 2009 pandemic influenza A (H1N1) virus: United States, 2009. *Clin Infect Dis* 2012;**54**:1221–9.

85. Peters PJ, Skarbinski J, Louie JK, Jain S, New York Department of Health Swine Flu Investigation Team, Roland M, *et al.* HIV-infected hospitalized patients with 2009 pandemic influenza A (pH1N1): United States, spring and summer 2009. *Clin Infect Dis* 2011;**52**(Suppl. 1):183–8.

86. Yen CJ, Louie JK, Schechter R. Infants hospitalized in intensive care units with 2009 H1N1 influenza infection, California, 2009–2010. *Pediatr Infect Dis J* 2012;**31**:e52–5.

87. Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, *et al.* Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA* 2009;**302**:1896–902.

88. Subramony H, Lai F, Ang L, Cutter J, Lim P, James L. An epidemiological study of 1348 cases of pandemic H1N1 influenza admitted to Singapore hospitals from July to September 2009. *Ann Acad Med Singapore* 2010;**39**:283–8.

89. Yates L, Pierce M, Stephens S, Mill AC, Spark P, Kurinczuk JJ, *et al.* Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant. *Health Technol Assess* 2010;**14**(34).

90. Donaldson L, Rutter P, Ellis B, Greaves FE, Mytton OT, Pebody RG, *et al.* Mortality from pandemic A/H1N1 2009 influenza in England: Public health surveillance study. *BMJ* 2010;**339**:b5213.

91. Sachedina N, Donaldson L. Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study. *Lancet* 2010;**376**:1846–52.

92. Santa-Olalla Peralta P, Cortes-Garcia M, Vicente-Herrero M, Castillo-Villamandos C, Arias-Bohigas P, Pachon-Del Amo I, *et al.* Risk factors for disease severity among hospitalised patients with 2009 pandemic influenza A (H1N1) in Spain, April-December 2009. *Euro Surveill* 2010;**15**:19667.

93. Moghadami M, Kazeroni P, Honarvar B, Ebrahimi M, Bakhtiari H, Akbarpour MA, *et al.* Influenza A (H1N1) virus pandemic in Fars province: a report from Southern Iran, July–December 2009. *Iran Red Crescent Med* J 2010;**12**:231–8.

94. Morgan O, Bramley A, Fowlkes A, Freedman DS, Taylor TH, Gargiullo P, *et al.* Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PLOS ONE* 2010;**5**:e9694.

95. Cortes Garcia M, Sierra Moros MJ, Santa-Olalla Peralta P, Hernandez-Baverra V, Jiminez-Garcia R, Pachon I, *et al.* Clinical characteristics and outcomes of diabetic patients who were hospitalised with 2009 pandemic influenza A H1N1 infection. *J Infect* 2012;**64**:218–24.

96. Gauzere BA, Bussienne F, Buchet B, Jabot J, Roussiaux J, Drouet D, *et al.* [Severe cases of A(H1N1) v2009 infection in Reunion Island in 2009 and 2010.] *Bull Soc Pathol Exot* 2011;**104**:97–104.

97. Hsann YM, Thang SP, Abdul Salam ZH, Yang Y, Su-Leong Lim V, Yang KS. Clinical characteristics and outcomes of hospitalized patients with 2009 H1N1 influenza in a large acute care tertiary hospital, Singapore. *Am J Infect Cont* 2011;**39**:e49–51.

98. Oersted I, Molvadgaard M, Linde Nielsen H, Nielsen H. The first, second and third wave of pandemic influenza A (H1N1) in North Denmark region, 2009–2011: a population-based study of hospitalisations. *Clin Microbiol Infect* 2012;**18**:217.

99. Pano-Pardo JR, Viasus D, Pachon J, Campins A, Lopez-Medrano F, Villoslada A, *et al.* Pandemic 2009 A(H1N1) infection requiring hospitalization of elderly Spanish adults. *J Am Geriatr Soc* 2012;**60**:740–4.

100. Aguirre E, Papenburg J, Ouakki M, Fontela PS, Guimont C, De Serres G, *et al.* Comparison of pandemic and seasonal influenza in the pediatric emergency department. *Pediatr Infect Dis J* 2011;**30**:633–9.

101. Cho JH, Kim CD, Kim MS, Kang ES, Kim YH, Kim JI, *et al.* The impact of A(H1N1)pdm09 infection on renal transplant recipients: a multicenter cohort study. *J Infect* 2012;**65**:88–90.

102. Choi SM, Boudreault AA, Xie H, Englund JA, Corey L, Boeckh M. Differences in clinical outcomes after 2009 influenza A/H1N1 and seasonal influenza among hematopoietic cell transplant recipients. *Blood* 2011;**117**:5050–6.

103. Fabbiani M, Sali M, De Cristo V, Pignataro G, Prete V, Farina S, *et al.* Prospective evaluation of epidemiological, clinical, and microbiological features of pandemic influenza A (H1N1) virus infection in Italy. *J Med Virol* 2011;**83**:2057–65.

104. Lee IK, Liu JW, Wang L, Yang KD, Li CC, Eng HL. 2009 pandemic influenza A (H1N1): clinical and laboratory characteristics in pediatric and adult patients and in patients with pulmonary involvement. *Influenza Other Respir Viruses* 2012;**6**:e152–61.

105. Morgan CI, Hobson MJ, Seger B, Rice MA, Staat MA, Wheeler DS. 2009 pandemic influenza A (H1N1) in critically ill children in Cincinnati, Ohio. *Pediatr Crit Care Med* 2012;**13**:e140–4.

106. Osoro EM, Munyua P, Muthoka P, Gikundi S, Njenga MK, Lifumo S, *et al.* Hospitalized patients with pandemic (H1N1) 2009, Kenya. *Emerg Infect Dis* 2011;**17**:1744–6.

107. Shlomai A, Nutman A, Kotlovsky T, Schechner V, Carmeli Y, Guzner-Gur H. Predictors of pandemic (H1N1) 2009 virus positivity and adverse outcomes among hospitalized patients with a compatible syndrome. *Isr Med Assoc J* 2010;**12**:622–7.

108. Bettinger J, Sauve L, Scheifele D, Moore D, Vaudry W, Tran D, *et al.* Pandemic influenza in Canadian children: a summary of hospitalised pediatric cases. *Vaccine* 2010;**28**:3180–4.

109. Hewagama S, Walker S, Stuart R, Gordon C, Johnson PD, Friedman ND, *et al.* 2009 H1N1 influenza A and pregnancy outcomes in Victoria, Australia. *Clin Infect Dis* 2010;**50**:686–90.

110. Stein M, Tasher D, Glikman D, Shachor-Meyouhas Y, Barkal G, Yochal AB, *et al.* Hospitalization of children with influenza A(H1N1) virus in Israel during the 2009 outbreak in Israel: a multicenter survey. *Arch Pediatr Adolesc Med* 2010;**164**:1015–22.

111. Bassetti M, Parisini A, Calzi A, Pallavicini F, Cassola G, Artioli S, *et al.* Risk factors for severe complications of the novel influenza A (H1N1): analysis of patients hospitalized in Italy. *Clin Microbiol Infect* 2011;**17**:247–50.

112. Chowell G, Viboud C, Simonsen L, Miller Ma, Echevarria-Zuno S, Gonzalez-Leon M, *et al.* Impact of antiviral treatment and hospital admission delay on risk of death associated with 2009 A/H1N1 pandemic influenza in Mexico. *BMC Infect Dis* 2012;**12**:97.

113. Gilca R, De Serres G, Boulianne N, Ouhoummane N, Papenburg J, Douville-Fradet M, *et al.* Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec, Canada. *Influenza Other Respir Viruses* 2011;**5**:247–55.

114. Gouya MM, Nabavi M, Soroush M, Haghdoust AA, Ghalehee S, Hemmati P, *et al.* Mortality from pandemic influenza A (H1N1) in Iran. *Iran Red Crescent Med J* 2011;**13**:698–701.

115. Rana H, Parikh P, Shah AN, Ghandi S. Epidemiology and clinical outcome of H1N1 in Gujarat from July 2009 to March 2010. *J Assoc Physicians India* 2012;**60**:95–7.

116. Schout D, Hajjar LA, Galas FR, Uip DE, Levin AS, Caiaffa Filho HH, *et al.* Epidemiology of human infection with the novel virus influenza A (H1N1) in the Hospital das Clinicas, Sao Paulo, Brazil: June-September 2009. *Clinics (Sao Paulo, Brazil)* 2009;**64**:1025–30.

117. Wilking H, Buda S, von der Lippe E, Altmann D, Krause G, Eckmanns T, *et al.* Mortality of 2009 pandemic influenza A(H1N1) in Germany. *Eur Surveill* 2010;**15**:19741.

118. Rodriguez A, Socias L, Guerrero J, Figueira JC, Gonzalez N, Maravi-Poma E, *et al.* Pandemic influenza A in the ICU: experience in Spain and Latin America. *Med Intensiva* 2010;**34**:87–94.

119. Adisasmito W, Chan P, Lee N, Oner AF, Gasimov V, Aghayev F, *et al.* Effectiveness of antiviral treatment in human influenza A(H5N1) infections: analysis of a global patient registry. *J Infect Dis* 2010;**202**:1154–60.

120. Marcelli D, Marelli C, Richards N. Influenza A(H1N1)v pandemic in the dialysis population: first wave results from an international survey. *Nephrol Dial Transplant* 2010;**24**:3566–72.

121. Nukiwa N, Kamigaki T, Oshitani H. Fatal cases of pandemic (H1N1) 2009 influenza despite their early antiviral treatment in Japan. *Clin Infect Dis* 2010;**51**:993–4.

122. Fuhrman C, Bonmarin I, Bitar D, Cardoso T, Duport N, Herida M, *et al.* Adult intensive-care patients with 2009 pandemic influenza A(H1N1) infection. *Epidemiol Infect* 2011;**139**:1202–9.

123. Echevarria-Zuno S, Mejia-Arangure J, Mar-Obeso A, Grajales-Muniz C, Robles-Perez E, Gonzalez-Leon M, *et al.* Infection and death from influenza A H1N1 virus in Mexico: a retrospective analysis. *Lancet* 2009;**374**:2072–9.

124. Martin-Loeches I, Rodriguez A, Bonastra J, Zaragoza R, Sierra R, Marques A, *et al.* Severe pandemic (H1N1)v influenza A infection: report on the first deaths in Spain. *Respirology* 2011;**16**:78–85.

Appendix 15 Illustration of time-dependent bias using individual patient data from the Canadian study

We illustrate the effect of time-dependent bias using the data from one of the included studies. Of 578 patients with a survival time, 540 received oseltamivir [of which 105 (19%) died] compared with 38 who did not receive an antiviral [of which 12 (32%) died]. A simple chi-squared test gives weak evidence of a difference in survival ($p = 0.072$) and Cox regression, assuming that treatment exposure uniformly occurs at hospital admission provides evidence of reduced risk of death for patients receiving oseltamivir (HR 0.52, 95% CI 0.29 to 0.95; $p = 0.033$). See *Table 27* for a life table and *Figure 24* for a Kaplan–Meier plot of the data assuming treatment exposure occurred at hospital admission.

An alternative analysis that takes into account the fact that treatment with oseltamivir does not occur at hospital admission but rather occurred at a mean of 0.62 days (range 0–45 days) after hospital admission shows a markedly different result. Cox regression assuming time-dependent treatment exposure gives no evidence of reduced risk of death for patients receiving oseltamivir (HR 0.87, 95% CI 0.48 to 1.61; $p = 0.66$). See *Table 28* for a life table and *Figure 25* for a survival plot of the data using the method of Simon and Makuch.[227]

The life tables and survival plots are shown for the first 11 days, as this is where most of the mortality occurred. When standard survival analysis is used there is an implicit assumption that treatment exposure begins at baseline, which, in this case, is hospital admission. Therefore, at baseline there were 540 patients at risk in the oseltamivir group and 38 patients at risk in the no-treatment group (see *Table 27* and see *Figure 24*). This incorrect assumption is what leads to time-dependent bias.

In the alternative analysis the timing of exposure to treatment is taken account of correctly by considering how many patients were exposed or unexposed to treatment on a daily basis. If the data were available the computation could be done more accurately, for example on an hourly basis. *Table 28* shows that in fact there were only 423 patients exposed to oseltamivir in the first 24 hours of hospital stay. By simple subtraction we also know that 155 patients had no exposure to oseltamivir during the first 24 hours of hospitalisation. This more accurate data then leads to more accurate estimates of the cumulative mortality. If we were to use hourly data then we would obtain more accurate estimates and reduce time-dependent bias further.

Severity of illness and competing risks analysis

Of 578 patients, 517 had an APACHE II score recorded, with the proportion missing being greater for the untreated patients than the treated patients (37% vs. 9%; $p < 0.0001$). Mortality was not significantly higher in the patients with missing APACHE II score (25% vs. 20%; $p = 0.35$). In those with an APACHE II score recorded there was no evidence of a difference between treated and untreated patients [untreated mean (SD) 19 (10)[12] vs. treated mean (SD) 21 (10);[10] $p = 0.39$]. Owing to the large difference in proportion missing between untreated and treated patients combined with similar observed scores in the two groups, unadjusted competing risks analysis was conducted using the method of Fine and Gray.[180] Results show insufficient evidence of a difference in mortality (HR 0.84, 95% CI 0.41 to 1.73; $p = 0.64$) or discharge (HR 1.41, 95% CI 0.73 to 2.74; $p = 0.31$).

TABLE 27 Time from admission to death by time-fixed treatment status

Days since admission	Number at risk (AV)	Number dead (AV)	Cumulative mortality (%) (AV)	Number at risk (no AV)	Number dead (no AV)	Cumulative mortality (%) (no AV)
1	540	4	0.7	38	3	7.9
2	536	14	3.3	35	3	15.8
3	519	4	4.1	32	0	15.8
4	507	2	4.5	31	0	15.8
5	498	3	5.0	29	0	15.8
6	485	4	5.8	27	1	18.9
7	467	6	7.0	26	1	22.0
8	449	4	7.9	25	0	22.0
9	441	4	8.7	23	1	25.4
10	422	8	10.4	22	0	25.4
11	394	7	12.0	22	1	28.8
12	375	6	13.4	20	0	28.8

AV, antiviral.

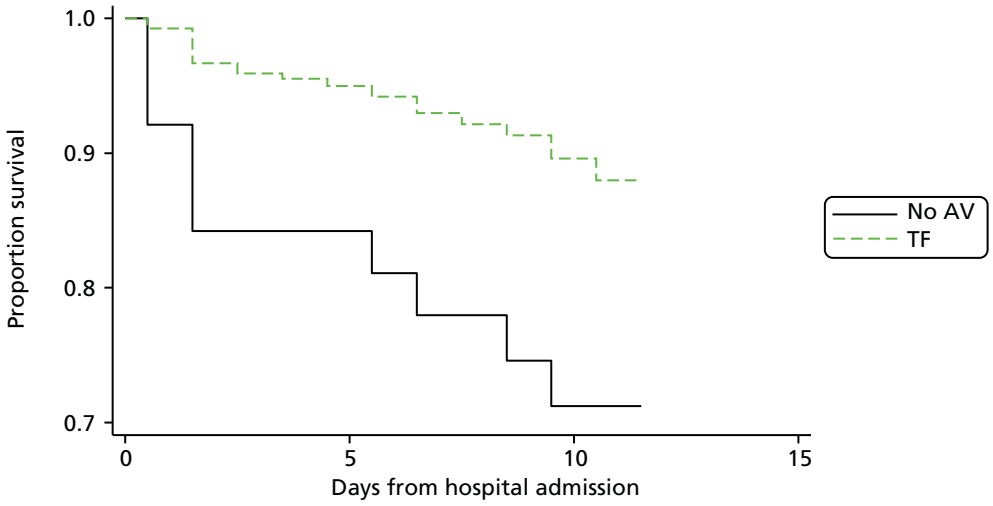


FIGURE 24 Kaplan–Meier plot of time to death. AV, antiviral; TF, Tamiflu (oseltamivir).

TABLE 28 Time from admission to death by time-dependent treatment status

Days since admission	Number at risk (AV)	Number dead (AV)	Cumulative mortality (%) (AV)	Number at risk (no AV)	Number dead (no AV)	Cumulative mortality (%) (no AV)
1	423	4	1.0	155	3	2.0
2	484	14	3.9	87	3	5.5
3	487	4	4.7	64	0	5.5
4	485	2	5.1	53	0	5.5
5	481	3	5.7	46	0	5.5
6	472	4	6.6	40	1	8.0
7	459	6	7.9	34	1	11.0
8	442	4	8.8	32	0	11.0
9	434	4	9.7	30	1	14.4
10	415	8	11.7	28	0	14.4
11	388	7	13.5	28	1	18.0
12	370	6	14.8	25	0	18.0

AV, antiviral.

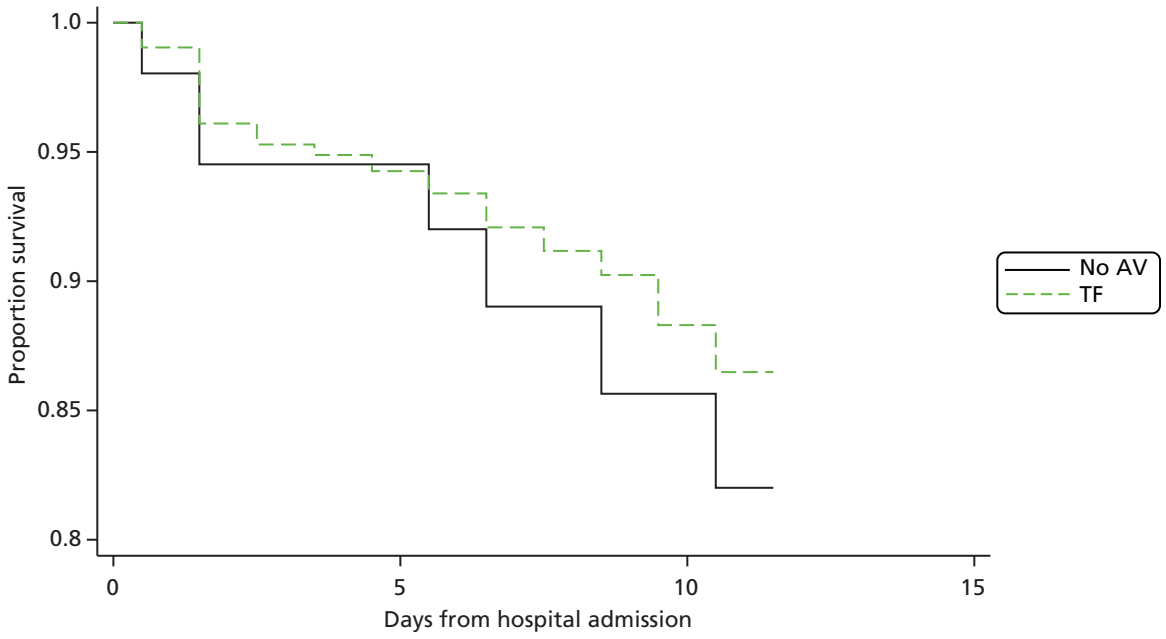


FIGURE 25 Survival plot for time-dependent treatment exposure. AV, antiviral; TF, Tamiflu (oseltamivir).

Appendix 16 Feedback

1 From Michael Power, Sowerby Centre for Health Informatics at Newcastle, 15 December 2010

Summary

From: Michael Power <michael.power@schin.co.uk>
Date: 15 December 2010 18:51
Subject: Neuraminidase inhibitors for influenza - HTA project
To

Hi
I picked up Carl's Twitter request for comments on your draft protocol "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data". So, here are my two comments on the content.

The title confused me: I expected it to be a review of unpublished trials to complement your review of published trials. It would be longer but clearer if you could call it "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of clinical study reports for published and unpublished trials".

The section "How the intervention might work" could be reorganized along the lines of:
0) Metabolism: oseltamivir phosphate (OP), Tamiflu, is the pro-drug of oseltamivir carboxylate (OC), the effective form. OP dissociates in the gastrointestinal tract to form oseltamivir (OT) which is absorbed and metabolised into OC by hepatic carboxylesterase (h-CE).
1) Reducing the ability of the virus to penetrate the mucus in the very early stage of infection (Bhatia 2007; Matrosovich 2004; Moscona 2005; Ohuchi 2006).
2) Inhibiting neuraminidase, which enables influenza viruses to exit host cells (Liu 1995; Moscona 2005).
3) Central depression by OT (Hama 2008) may cause hypothermia (Ono 2008).
4) Inhibition by NIs of human sialidase may cause abnormal behaviour (Li 2007).

You have obviously put a huge amount of work and expertise into developing the protocol, and have an even bigger task ahead to complete the review. Congratulations for taking this on.

Best wishes
Michael

Reply

Thanks for the constructive comments.

We have re-titled the Protocol to address this concern (and that of feedback from GSK, see below);

We have re-examined the "How the intervention might work" section but made only small adjustments in the interest of keeping this section short;

We are not sure what problems you might have had printing the pdf file, and hope they are resolved with this new version.

Contributors

Chris Del Mar

2 From Juan C. Vergara, Intensive Care, Hospital Cruces, 48901 Barakaldo, Spain, 24 February 2011

Summary

From: JUAN CARLOS VERGARA SERRANO <JUANCARLOS.VERGARASERRANO@osakidetza.net>
Date: 24 February 2011 12:48
Subject: oseltamivir
To:

I've read your Intervention Protocol: Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data. And may be you can be interested in this letter I wrote to de BMJ: http://www.bmj.com/content/340/bmj.c789.extract/reply
1. Early use of oseltamivir does not reduce swine flu mortality, Juan C. Vergara, MD. Intensive Care Unit, Hospital Cruces. 48901 Barakaldo. Spain

As you say, in July the National Pandemic Flu Service started providing oseltamivir to anybody who telephoned with a plausible set of symptoms. From 23rd July to 1st December, the National Pandemic Flu Service (NPFS) in the UK, has provided more than one million courses of antiviral medication. By that time the Spanish Health Secretary General, José Martínez Olmos, at the Congress of Deputies, announced that only 6.000 patients (most of them hospitalised) had received oseltamivir in Spain. At the end of January there have been 411 deaths reported due to pandemic (H1N1) 2009 in the UK, and about 300 in Spain. That means 6.7 and 6.5 deaths per million, respectively. These data create serious doubts about the real utility of early use of oseltamivir in preventing deaths from Influenza A H1N1.
http://www.nhsdirect.nhs.uk/article.aspx?name=SbSwineflu
http://www.congreso.es/public_oficiales/L9/CONG/DS/CO/CO_411.PDF

Competing interests: None declared

Yours sincerely;
J. C. Vergara

Reply

Thank you for your interest.

Contributors

Chris Del Mar

3 From Dr Helen Steel, GSK, UK, 30 March 2011

Summary

GSK comments on Cochrane Collaboration protocol: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data

General:

The term **'unpublished data'** is used extensively in the protocol. However, it does not appear to be clearly defined either in the protocol or in Jefferson's comment in the 15 Jan 2011 edition of the BMJ. Additionally, the term **'unpublished data'** is misleading. It appears the Cochrane Group use this term interchangeably with Clinical Study Reports, regardless of whether a primary manuscript is available for a given study. We suggest this is clarified or preferably replaced, especially since the term appears extensively in the protocol including the title. Readers are likely to use the terms 'unpublished data' and 'unpublished trials' (trials for which no primary publication appears in the scientific press) interchangeably. A suggested replacement is 'Clinical Study Reports' since this term is not easily misinterpreted and is clearly defined in Jefferson's BMJ comment.

The 'scope of clinical trial data' are defined in Jefferson's BMJ 15 Jan 2011 comment, as mentioned above (i.e. definitions for clinical study reports, raw data, unpublished trial, published trial, regulatory data). It would seem important that these and any other definitions introduced in the protocol are included in the protocol.

Description of Intervention

This section incorrectly describes Relenza as 'nebulized zanamivir'. Relenza is formulated in Rotadisks containing foil blisters with a powder mixture of zanamivir and lactose. Relenza is administered by oral inhalation using a breath-activated device called the Diskhaler. Earlier clinical studies explored several methods of administration, including nebulized and intranasal routes but marketing approval in nearly all countries is currently available only for oral inhalation via Rotadisk/Diskhaler.

Types of Studies

To meet the objective of providing a comprehensive review of neuraminidase inhibitors in preventing and treating influenza, it would seem appropriate that clinical trials from all sources (including sponsors other than industry) be included in this meta-analysis. Please clarify if this is your intent.

Outcome Measures

More details should be provided on the outcome measures section in the final protocol.

For example, broad outcome measures are stated in the protocol but specific endpoints are not provided. The primary and secondary endpoints of the meta-analysis should be clearly defined in the final protocol.

e.g.1. A stated primary outcome in the treatment studies is 'symptom relief'. Does this refer to 'the time to alleviation of symptoms' or 'reduction in symptom score' or another endpoint? Time to alleviation of clinically significant symptoms was the primary endpoint used in the majority of GSK treatment studies.

e.g.2. Another stated primary outcome is 'Harms'. Please provide the specific endpoints. Will this refer to 'incidence of most common AEs' or 'incidence of common SAEs', 'incidence of complications' or another endpoint? It is not clear if 'harms' are the same as 'compliharms'. It is not clear what specific events will comprise compliharms.

Prophylaxis studies: Several types of prophylaxis studies were conducted by GSK: household prophylaxis (post-exposure prophylaxis), community prophylaxis and outbreak control in nursing homes, and as such the

designs and/or endpoints are different. It is possible to measure 'prevention of onset of influenza in contacts' in these studies but not 'reduction in viral spread from index cases' in the majority of prophylaxis studies.

Hospitalisations: As studies were generally conducted in the setting of acute uncomplicated influenza, limited hospitalisation data were collected, and are available only for some studies.

Extracting compliharms: There is a statement that 'AEs are reported for all participants while complications are only reported for infected subjects'. This statement is not accurate for GSK trials. AEs are reported for all study participants. However, AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness. Without knowing the specific safety endpoints, it is unclear whether this will affect the outcome of some of the harms analyses.

Data collection and analysis:

The protocol indicates that clinical study reports will be requested (minus participant identification). In fact many documents for each study will need to be redacted not just to remove participant identification but any personally identifiable information including author and investigator identification.

Missing Data. The protocol states "*At the participant level (i.e. within a trial) we will not make any assumptions about missing data.*" This is not possible, because an analysis of data that is collected in a trial can only be done in the context of assumptions about potential mechanisms that led to data being missing (e.g., missing completely at random, or missing at random).

Meta-analysis Method. Little detail is given in the protocol. The protocol states that "*Whether or not heterogeneity is detected, we will perform a random effects meta-analysis. Random-effects methods will be used to compare the dichotomised outcomes (RR and absolute risk reduction (ARR) for efficacy and safety).*" There are several different Random Effects methods available (Bayesian or frequentist, DerSimonian & Laird or Maximum-likelihood or REML), and different approaches to handling rare events (various "corrections" to include trials with zero counts). Furthermore, would random-effects methods also used to compare the continuous outcomes?

Fixed-effects Model. The protocol also states that fixed-effects models will be used in a sensitivity analysis. No details are given with regard to which fixed-effects models will be used. There are several fixed-effects models available including Inverse Variance, Mantel-Haenszel, and Peto's method. The appropriate method used should also depend on the outcome measures (dichotomous vs. continuous; relative vs. absolute). The approach and choice of models for sparse data and rare events should be provided. Furthermore, various methods in the framework of fixed-effects model may be explored to evaluate the robustness of the results.

Hazard Ratio. The protocol states "*We will convert medians of treatment groups into (log) hazard ratios (estimating the variance of these) to enable meta-analysis of time to event outcomes.*" Although hazard ratio (HR) is a standard analysis and widely recommended approach for time-to-event data in clinical trials, the HR analysis may not be suitable for the Relenza studies with relatively short follow-up time because the assumption of proportional hazards required for the proportional hazards model may not hold. GSK did not follow this approach for the original analysis due to the concern stated above. Further the clinical and regulatory interest centred on differences in the time to alleviation not in the relative hazard between treatments. The above issues would be best addressed by using subject level rather than summary data, which GSK have offered to provide to the Cochrane Group.

Analysis Populations. The protocol does not specify which populations will be used for the various analyses, for example, intent-to-treat or influenza-positive or other. We believe that influenza positive population is appropriate, especially for the efficacy analysis using time to alleviation of influenza symptom as a primary endpoint consistent with the prescribing information for Relenza.

Study Duration. No details are given in the protocol with regard to how studies with different follow-up times will be handled.

Trials with no Events. No details are given in the protocol with regard to how to deal with trials in which there are no events (such as death). By excluding studies with no events will make the event appear more common than it actually is. There are various techniques: Bayesian approach, continuity correction, combining similar trials to avoid having any components of the analysis that have no events.

Sensitivity Analyses. Sensitivity analyses using different outcome measures, statistical models and/or continuity correction factors to assess the robustness of the results are strongly encouraged.

Reply

General:

'unpublished data'. We agree that this term is confusing, and are attracted to the proposal of using 'clinical study reports' instead.

We have attempted to ensure all terms are clear.

Description of intervention

Description of zanamivir (Relenza): we have corrected 'nebulized zanamivir' to 'powder inhalation'.

Types of studies

Yes, we intend to comprehensively review clinical trials from all sources (including sponsors other than industry). This intent is clear from the subsection '***Electronic searching'*** under the '**Search methods for identification of studies'** section.

Outcome measures

Our specified outcomes are those of interest to patients, and their clinicians and policy-makers. They are therefore likely to be broader than the more specific endpoints selected by trialists. The purpose of Cochrane Reviews are usually to set clinically relevant review questions, and search the literature (or other sources) for answers to them. Sometimes answers to some questions are not available, and this is also documented. Where possible we report outcomes as pre-specified in the trial protocols, or as pre-specified in the review protocol, or otherwise reported as a post-hoc analysis.

e.g. 1. 'symptom relief' may refer to 'the time to alleviation of symptoms' or 'reduction in symptom score', or any other endpoint (including 'area under the curve of symptom score and time').

e.g. 2. 'Harms' include common adverse events (AEs) as well as serious AEs. We agree about the confusion of harms and complications, and have tried to capture the totality of these with the neologism 'compliharms' to avoid classification errors between their different labellings.

Prophylaxis studies: We understand that it is possible to measure 'prevention of onset of influenza in contacts' in some GSK studies but not 'reduction in viral spread from index cases' in others.

Hospitalisations: We understand that hospitalisation data may only be available for some studies. However patient hospitalisation is usually classified as a serious adverse event therefore we expect to identify hospitalisations (not reported separately) in that way.

Extracting compliharms: Your statement that "AEs of ILI were not collected in the treatment studies unless the symptoms were considered to be worse than expected for the normal progression of illness" underlies the complexity of analysing AEs and complications (our 'compliharms'). We have noted in the protocol that the limitation of complications only reported for the infected patients is relevant to the Roche trials only.

Data collection and analysis:

We are interested that not only subject identification would be required to be removed from any documents of clinical study reports but also information personally identifying authors and investigators. We wonder why.

Missing data. We have removed this statement.

Meta-analysis method. DerSimonian & Laird method will be used. Note that in the case of zero cells (e.g. no events in one group) the RevMan software (which we will use for the analysis) automatically adds 0.5 to each cell of the 2×2 table for any such study. There are no continuous outcomes specified in this review.

Fixed-effects model. Mantel-Haenszel method will be used except in the case of sparse data, in which case Peto's method will be used (as recommended in the Cochrane Handbook).

Hazard ratio. We note the concerns with this outcome hence we will also consider analysis of this outcome as a continuous outcome noting that the data are likely to be skewed. We will use the inverse-variance random-effects method for this analysis.

Analysis populations. All analysis will be using the intent-to-treat population as this is the most methodologically rigorous and clinically relevant.

Study duration. We have specified in the protocol, where appropriate, that we will report outcomes for the on-treatment and off treatment time periods. If data are not available in the clinical study reports for any time period of the study then we will write to the relevant manufacturer to request the missing data.

Trials with no events. As stated above the RevMan software automatically adds 0.5 to each cell of the 2×2 table for any such study.

Sensitivity analyses. We note this point and agree. Where appropriate, a realistic sensitivity analyses will be conducted.

Contributors

Chris Del Mar

4 Feedback from Wolfgang Becker-Brueser, 30 January 2012

Summary

Dear Tom Jefferson,

I read your review about NI for prevention and treating influenza with interest. It's an important work. In the chapter "Why it is important to do this review" I found a small mistake concerning the worldwide stockpiling of oseltamivir which is mentioned to be "CHF 7.6 billion worth of oseltamivir (JACK 2009)". This would be an enormous amount "prior (!) to the emergence of influenza A/H1N1 in 2009". But Andrew JACK wrote in the cited Financial Times (May 13, 2009): "Governments around the world had stockpiled 220m treatments to date, swelling sales since the start of 2003 to SFr7.6bn, largely on the basis of preparation for a pandemic virus that has yet to appear." So 7.6 billion SFr represent sales and not stockpiling.

Wolfgang Becker-Brueser (physician and pharmacist)

Reply

Thank you. The extent of stockpiling is a closely guarded secret this is why these are estimates. We will probably never know.

Contributors

Tom Jefferson MD

5 From Frederick G. Hayden, M.D., 02 February 2012

Summary

I am writing to comment on the recently updated meta-analysis by Jefferson and colleagues published through the Cochrane Collaboration and to request clarifications on several points, as well as to suggest some additional analyses that would be helpful in terms of taking greater advantage of this useful database. While I fully support access of Jefferson and other interested investigators to all of the published and unpublished data from the RCTs of oseltamivir and zanamivir for further analyses, this analysis only focuses on RCTs in ambulatory patients with uncomplicated influenza (the vast majority of whom were previously healthy) and on the period before the 2009 H1N1 pandemic. Consequently, I would urge these investigators to extend their efforts to other populations and datasets examining the risks and benefits of using neuraminidase inhibitors (NAIs) for treatment and prophylaxis. Furthermore, the authors should acknowledge the limitations of their analyses more explicitly and avoid inappropriate extrapolation to populations and influenza events that the RCTs did not adequately address. Differences in disease pathogenesis related to virus and host factors, as well as time to treatment, have important effects on the utility of antiviral agent interventions. My specific comments and recommendations for additional analyses follow:

1. Use of Intention to Treat (ITT) and ITTI-Infected Groups. The exclusive focus in the current treatment analysis on the ITT population is a readily rectified shortcoming. Outcomes in all three groups of relevance (ITT, ITT-infected, and ITT-noninfected) should be presented, so that readers can examine both clinical effectiveness and efficacy for the key endpoints, as well as events in those without documented influenza. Because NAI treatment would not be expected to provide any benefit in non-influenza illness, not presenting the ITT-infected outcomes in the analysis underestimates possible beneficial drug effects. Assessment of the non-infected group provides a valuable control and also enables a determination of whether there was a potential drug-disease adverse interaction of NAI treatment in non-influenza patients. Of note, our earlier pooled analysis of physician-diagnosed lower respiratory tract complications leading to antibiotic use found a significant benefit of oseltamivir in the influenza-infected patients but not in those enrolled in whom influenza infection was not detected by culture or serology [Kaiser 2003].

2. Sample size considerations. Severe outcomes of influenza infection are sufficiently uncommon in previously healthy people that even large RCTs or combining multiple RCTs would be very unlikely to detect them with confidence. The same point applies to very uncommon endpoints like microbiologically documented bacterial complications and rare adverse effects of treatment. Consequently, conclusions that there is no evidence (from trials) that NAIs reduce the risk of pneumonia, hospitalisations, deaths are overstated, as the evidence considered in this analysis is insufficient to properly address these questions.

The US CDC has estimated age-related influenza-related hospitalisation and mortality rates for both seasonal epidemics and the 2009 pandemic [Shrestha 2011]. Jefferson and colleagues should use such event estimates and others to make calculations of the necessary sample sizes to detect reductions in these severe outcomes with NAI therapy in a controlled RCT across a range of clinically relevant effect sizes (e.g., 20%, 35%, 50% reductions). In a related fashion, they should also provide more quantitative estimates for their ability to detect such outcomes with their existing database and comment more precisely on their power to capture particular endpoints.

3. Complications in ambulatory patients. Other clinically relevant endpoints in these previously healthy and at-risk persons warrant investigation. With regard to influenza-related complications, the most frequent in previously healthy children and adults are respiratory tract infections (otitis media, bronchitis) leading to antimicrobic use. These are usually not severe and typically not microbiologically documented with respect to etiologies but physician-diagnosed complications leading to antibiotic use is an outcome that has important clinical and public health implications (i.e., cost, antibiotic resistance, side effects) and also is sufficiently frequent to demonstrate effects of antivirals. We showed such a benefit in adults in our earlier pooled analyses

of the then available RCT data on inhaled zanamivir [Kaiser 2000] and oral oseltamivir [Kaiser 2003]. The oseltamivir effect was confirmed in a recent meta-analysis [Hernan 2011], and another recent Cochrane report confirms an effect on otitis media in children [Wang 2011].

Given the large amount of data available to the investigators, it would be a valuable contribution to also explore the clinical outcomes in greater detail and to clarify the use of terms like severe outcomes. Although uncommon in the populations enrolled in these RCTs, endpoints such as radiographically documented pneumonia, microbiologically documented infections, and hospitalisation or death are clear and should be listed separately in those with or without proven influenza infection. Because of the importance of hospitalisations as an endpoint, it would be helpful to examine not only all-cause hospitalisations but also relevant subgroups based on likely causation (e.g., events in which influenza was documented or likely implicated including exacerbations of co-morbidities vs others like accidents, elective surgeries, conditions unlikely to be influenza-related). In addition to these events, exacerbations of underlying conditions (e.g., asthma, COPD, diabetes, CHF) are of medical importance in influenza outpatients with co-morbidities and should be examined.

4. Data from observational studies. Typically the patients who are most at risk of severe outcomes (older people, infants and young children, those with underlying chronic conditions) are not included in RCTs. In this regard, the current analysis is limited to placebo- or active-controlled RCTs largely done in previously healthy persons and does not consider the multiple observational studies from different countries that have consistently showed protective effects against severe outcomes like pneumonia and hospitalisation, particularly in those with co-morbidities, as well as reduced mortality if patients have been hospitalised. A considerable amount of new treatment data was generated in many countries during the 2009 H1N1 pandemic that found timely NAI treatment to be associated with a lower risk for intensive care admission and death (reference list available upon request).

While such data and analyses are weaker than RCT data and subject to bias, these observational studies address key endpoints in at-risk and seriously ill populations, including patients admitted to a hospital at the time of initiating therapy, that the available RCTs cannot and do not address. Furthermore, the standard of care has evolved such that placebo-controlled RCT in such patient groups would not be acceptable to investigators or ethics committees. The decision by Jefferson and colleagues not to consider and critically analyse the large amount of observational data with modern techniques means that they are not incorporating key information and many important patient groups in which the available data suggests medically important benefits from early NAI therapy. Such findings from observational data can inform antiviral treatment in more severely ill patients when no other data are available. As discussed above, not to include observational data means that conclusions of no effect on uncommon events or no severe adverse events being detected are almost inevitable. This should be made explicit in the design and the conclusion of the current report.

4. Influenza diagnosis and serologic results. The Jefferson report raises questions about the possible inhibitory effects of oseltamivir therapy on influenza-specific serologic rises and introduction of bias into the outcomes analysis. Further analyses might help to assess these possibilities. They should compare the primary endpoint of illness alleviation between the oseltamivir and placebo subgroups that were culture-positive (irrespective of serologic findings) at enrolment, and separately those that were culture-negative but had serologic evidence of infection.

Of note, one prior study of oseltamivir treatment in pandemic 2009 H1N1 patients, although not in seasonal influenza patients, suggested that early treatment could reduce antibody responses [Cowling 2010]. Jefferson and colleagues should examine the age-related frequencies of HAI seroconversions and the GMT titre rises in those with influenza-culture positive illness and separately in those with such HAI rises in absence of culture positivity. Of course, if still available, it would be interesting to test the culture-negative enrolment samples by RT-PCR.

The RCT data were generated over multiple seasons in which different influenza A and B viruses were circulating. Influenza B neuraminidases are generally less susceptible to oseltamivir carboxylate and several observational studies indicate that oseltamivir is less effective in influenza B- than influenza A-infected children

[Sugaya 2007; Sato 2008]. It would be useful to examine the primary outcome in relation to virus type (A vs. B) and if possible A subtype (H3 vs. H1) in those with documented infections to expand on this point.

5. Other treatment endpoints of interest. Since those enrolled in the RCTs were outpatients, it would be useful to explore other endpoints that reflect patient recovery and impacts on the healthcare system (e.g., nonscheduled return visits for complications or adverse events). Perhaps more important than the time to alleviation endpoint used in the registrational trials might be the times to resumption of usual activities and return to pre-morbid status.

The authors raise the possibility that oseltamivir might have non-specific antipyretic effects, and one animal model study has also suggested possible adverse immunomodulatory effects of oseltamivir in RSV infection [Moore 2007]. Consequently, it would be interesting to examine the course of fever resolution (a much earlier event than cough resolution) and of symptoms in oseltamivir- and placebo-treated patients with and without documented influenza infections. In addition, it would be valuable to examine the correspondence (or lack thereof) between influenza virologic measures (e.g., enrolment virus titre, time to culture negativity, change in viral titres over time) and symptom resolution measures in both oseltamivir and placebo groups.

Various cost-effectiveness analyses on NAI therapy in low-risk populations have been published with widely divergent outcomes, largely depending on the input assumptions. Using this large database, a more refined analysis that incorporates both the direct and indirect (productivity losses) costs of influenza would be informative.

6. Adverse events with treatment. With regard to drug tolerability, it is important to examine not only the frequencies of reported adverse events but also assess indicators of their severity and interference with compliance (e.g., symptom days, patient reported severity, premature cessation of study drug).

Comparisons of AEs in the placebo groups across zanamivir and oseltamivir studies need to be interpreted with caution, since these studies were performed in different influenza seasons viruses and locations, with different protocols and case record forms, and by different investigators. Only one head-head RCT of treatment comparing these drugs has been published to date to my knowledge but the design did not include placebo only groups [Duval 2010]. In particular, comparisons in children (page 24) need to be age-adjusted as there were major differences in those enrolled into the zanamivir (5 years and older) and oseltamivir trials (1 year and older), and the frequencies of gastrointestinal manifestations are much higher in younger children with influenza and other acute illnesses.

7. Prophylaxis endpoints of interest. The analysis of prophylaxis outcomes and the associated discussion requires clarification. The statement on page 5 says: "The FDA has also not allowed an indication for interference of viral transmission within households (the key concept behind post-exposure prophylaxis)." The key concept behind post-exposure prophylaxis is prevention of illness in exposed persons, and the primary endpoint in most prophylaxis studies has been symptomatic, laboratory-confirmed influenza illness. FDA and other regulatory agencies have approved both NAIs for post-exposure prophylaxis in households and also for longer duration pre-exposure chemoprophylaxis [reviewed in Khazemi 2009].

The Jefferson analysis seems to focus exclusively on the effect of chemoprophylaxis in "preventing the spread" of influenza, with endpoints presumably determined by evidence of culture or serologically confirmed infection irrespective of illness. While this is one endpoint of interest in such studies, the primary outcome of medical interest is prevention of influenza illness in those exposed. There is abundant RCT data, as well as observational data from the 2009 pandemic, that both inhaled zanamivir and oral oseltamivir have both statistically significant and medically important effects on preventing influenza-specific illness. Of note, the development of serologic evidence of infection without illness is advantageous in those receiving chemoprophylaxis, as it likely is an immunizing event that protects against future infection and illness by that strain. In addition several oseltamivir RCTs have shown significant but lesser effects on influenza infection in prophylaxis recipients [Welliver 2001; Hayden 1999]. The authors should present all of the relevant endpoints in their analysis of the prophylaxis trials.

8. Adverse effects with prophylaxis. The prophylaxis studies are particularly useful in assessing drug tolerability as symptoms of acute illness present in treatment studies are not confounders and there is a more prolonged duration of drug exposure. However, it is essential to examine not only the frequencies of reported adverse events but also indicators of their severity and possible interference with compliance (e.g., symptom days, patient reported severity, premature cessation of study drug).

For example, the Jefferson posting states that "Similarly, a published prophylaxis trial (Hayden 1999a, known by its trial ID WV15673/WV15697) describes headache as having "occurred in similar proportions of subjects in the three groups (39 to 47 per cent)." but indicates that Japanese regulatory documents reached a different conclusion. My own review of the adverse event tabulations from our 6-weeks prophylaxis study (tables provided by the sponsor) indicates that the proportions of subjects reporting headache (not otherwise specified) that might have been related to study drug (unrelated reports excluded) during the treatment phase were similar across the placebo (N=116, 22.4%), oseltamivir 75 mg once (N=124, 23.8%), and oseltamivir 75 mg twice (N=132, 25.4%) daily dose groups [Hayden 1999]. Most of these reports indicated mild or moderate intensity and were self-limited. As indicated in the published paper [Hayden 1999], study withdrawals for AEs or illness occurred infrequently across these same groups (N=10, 1.9%; N= 8, 1.5%; N= 7, 1.3%). Of note, the specified causes for AE-related withdrawals included three reports of headache associated with other symptoms in the placebo group. In contrast, there were no reports of headache as reason for the withdrawals receiving oseltamivir; gastrointestinal complaints accounted for withdrawals in 4 of 8 oseltamivir 75 mg and 3 of 7 oseltamivir 75 mg twice daily recipients. The total numbers of patients with premature study withdrawal for any reason was 21 (4.0%), 17 (3.3%), and 16 (3.1%) across the three groups, respectively. Overall, severe AEs were reported in 82 (15.8%) of placebo, 75 (14.4%) of oseltamivir 75 mg, and 77 (14.8%) of oseltamivir 75 mg twice daily recipients. We were unable to include these details in the paper because of space limitations but my interpretation remains that no excess of clinically relevant oseltamivir-related headache occurred during this study. This type of detailed AE analysis incorporating severity measures provides necessary context in interpreting the possible importance of AEs.

9. Peer review. The questions raised and opinions expressed in this and earlier Cochrane reports on NAIs by Jefferson and colleagues have resulted in debate and sometimes confusion among practitioners and policy makers regarding the appropriate use of NAIs in seasonal and pandemic influenza responses. Given the importance of these issues, it would be helpful for any future updates to have proper independent review before posting or publication by the Collaboration, as the Cochrane methodology of publication and then independent peer review is not well understood by many people.

Thank you for the opportunity to provide comments. I look forward to seeing the responses from Dr. Jefferson and his colleagues on these points.

Sincerely,

Frederick G. Hayden, M.D.
Stuart S. Richardson Professor of Clinical Virology
Professor of Medicine
University of Virginia School of Medicine
Charlottesville, Virginia, USA

Reference List

1. Cowling BJ, Chan KH, Fang VJ, Lau LL, So HC, Fung RO, Ma ES, Kwong AS, Chan CW, Tsui WW, Ngai HY, Chu DW, Lee PW, Chiu MC, Leung GM, Peiris JS. Comparative epidemiology of pandemic and seasonal influenza A in households. N Engl J Med 2010 June 10;362(23):2175-84.

2. Duval X, van der WS, Blanchon T, Mosnier A, Bouscambert-Duchamp M, Tibi A, Enouf V, Charlois-Ou C, Vincent C, Andreoletti L, Tubach F, Lina B, Mentre F, Leport C. Efficacy of oseltamivir-zanamivir

combination compared to each monotherapy for seasonal influenza: a randomised placebo-controlled trial. PLoS Med 2010:7(11):e100362.

3. Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, Huson L, Ward P, Mills RG. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med 1999 October 28;341(18):1336-43.

4. Hernan MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomised clinical trials. Clin Infect Dis 2011 August 1;53(3):277-9.

5. 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 November 27;160(21):3234-40.

6. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalisations. Arch Intern Med 2003 July 28;163(14):1667-72.

7. Khazeni N, Bravata DM, Holty JE, Uyeki TM, Stave CD, Gould MK. Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. Ann Intern Med 2009 October 6;151(7):464-73.

8. Moore ML, Chi MH, Zhou W, Goleniewska K, O'Neal JF, Higginbotham JN, Peebles RS, Jr. Cutting Edge: Oseltamivir decreases T cell GM1 expression and inhibits clearance of respiratory syncytial virus: potential role of endogenous sialidase in antiviral immunity. J Immunol 2007 March 1;178(5):2651-4.

9. Sato M, Saito R, Sato I, Tanabe N, Shobugawa Y, Sasaki A, Li D, Suzuki Y, Sato M, Sakai T, Oguma T, Tsukada H, Gejyo F, Suzuki H. Effectiveness of oseltamivir treatment among children with influenza A or B virus infections during four successive winters in Niigata City, Japan. Tohoku J Exp Med 2008 February;214(2):113-20.

10. Shrestha SS, Swerdlow DL, Borse RH, Prabhu VS, Finelli L, Atkins CY, Owusu-Edusei K, Bell B, Mead PS, Biggerstaff M, Brammer L, Davidson H, Jernigan D, Jhung MA, Kamimoto LA, Merlin TL, Nowell M, Redd SC, Reed C, Schuchat A, Meltzer MI. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009-April 2010) Clin Infect Dis 2011 January 1;52 Suppl 1:S75-S82.

11. Sugaya N, Mitamura K, Yamazaki M, Tamura D, Ichikawa M, Kimura K, Kawakami C, Kiso M, Ito M, Hatakeyama S, Kawaoka Y. Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza A infection in children. Clin Infect Dis 2007 January 15;44(2):197-202.

12. Wang K, Shun-Shin M, Gill P, Perera R, Harnden A. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev 2012;1:CD002744.

Welliver R, Monto AS, Carewicz O, Schatteman E, Hassman M, Hedrick J, Jackson HC, Huson L, Ward P, Oxford JS. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomised controlled trial. JAMA 2001 February 4;285(6):748-54

Submitter has modified conflict of interest statement: Disclosures to BMJ (Updated 4 June 2012)

Dr. Hayden received lecture and/or consulting honoraria from GSK until 2002 and from Roche until 2005. Gilead Sciences from 1996-1999 and Roche from 1999-2005 provided grant support to the University of Virginia for oseltamivir studies on which he was PI. Similarly GSK provided grant support to the University of Virginia for zanamivir studies from 1994-2001. Dr. Hayden served as medical officer in the Global Influenza Programme from 2006-2008 with funding provided to the University of Virginia through the National Institute of Allergy and Infectious Diseases (NIAID). Since 2008 to present the University of Virginia has received funding from the Wellcome Trust for his part-time work as influenza research coordinator at the Trust and

through NIAID for his work as consultant the Southeast Asia Infectious Diseases Clinical Research Network. From 2008-11 the University also received honoraria for his participation in the Neuraminidase Inhibitor Susceptibility Network which received funding from Roche and GSK. Since 2008 to present, Dr. Hayden has been an unpaid consultant to multiple companies engaged in the development or marketing of influenza antivirals including Roche and GSK.

Dr. John Treanor reports receiving compensation as a member of the scientific advisory boards of Novartis and Immune Targeting Systems, and has performed consulting work for Pfizer. Within the last 3 years, his group has been funded to perform laboratory assays or conduct clinical trials for Sanofi, GlaxoSmithKline, Protein Sciences Corp, Wyeth, PaxVax, Ligocyte, and Vaxinnate.

Dr. Kaiser reports no financial disclosures.

Frederick G. Hayden

Reply

Response to Dr. Hayden's comments of 2 February 2012.

We thank Dr. Hayden for his detailed feedback. However nothing he writes allays our basic concerns that:

(1) despite the 16,000 pages we analysed, we currently only have access to a very limited dataset hence cannot carry out many of the analyses Dr. Hayden suggests;
(2) analysing the "influenza infected" population in Roche oseltamivir trials, as Dr. Hayden proposes, will lead to misleading results because the treatment groups are not comparable for this population;
(3) the observational studies Dr. Hayden urges us to consider are generally of poor quality and only represent the small proportion of patients who are hospitalised with influenza;
(4) the Kaiser et al (2003) analysis is seriously flawed;
(5) data have been selectively reported.

Below, we provide point-by-point responses to Dr. Hayden's concerns. (Please note that point 4 appears twice, to follow the numbering in Dr. Hayden's letter.)

1. Use of intention to treat (ITT) and ITTI-infected [sic] groups

We agree, in principle, to conduct analysis using the ITT-infected (ITTI) sub-population provided that it is appropriately selected by the results of testing completed before the start of the trial (for example by using only the results of viral culture or rapid testing before randomisation).

However we argue that this is not possible in Roche oseltamivir trials. In these trials, the selection of "infected" or "non-infected" was dependent on the results of serology that is affected by "use" and "non-use" of oseltamivir. And the selection of those with "serology-positive results" appears to have given advantage to the oseltamivir group. Hence the method of selecting the ITT-Infected population in the trials has fundamental flaws and therefore the results are less reliable than those obtained using the ITT population.

2. Sample size considerations

The Kaiser et al analysis has a number of fundamental problems. First, analyses were performed on the ITT-infected sub-population which we have shown to be non-comparable between treatment groups. Second, the authors analysed an outcome that was different to that pre-specified in the trials. In the trials, complications included otitis media and sinusitis but in the Kaiser et al paper these were not included. This is an example of selective reporting or "cherry picking". Third, complications were not objectively or consistently measured in the trials. Fourth, outcomes such as pneumonia and bronchitis could be either reported as a complication or as an adverse event according to a classification criteria we do not understand and is not discussed in the Kaiser et al paper. And finally the data from the 10 trials was not meta-analysed, rather, it was combined as if generated from one single trial.

We could potentially address most of these limitations (except for the third) but we have not been given access to the data despite repeated requests to the manufacturer. However we were able to compare hospitalisations as those data were available to us for the ITT population.

We found 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). This result is quite different to that reported by Kaiser et al based on the (non-comparable) ITT Infected population.

In terms of power analysis, to detect a significant difference at this level of difference of 0.84% (placebo) vs 0.80% (oseltamivir), with alpha of 0.05 and power of 0.8, a RCT with approximately 800,000 participants is required.

3. Complications in ambulatory patients

As we have illustrated above the Kaiser et al (2003) analysis has fundamental flaws that we cannot address because the manufacturer refuses to provide us with the data necessary to conduct a proper analysis.

Analysis of the "population with proven influenza infection" (ITT-infected population) is not appropriate (see above). Data for the analysis of "population without proven influenza infection" are not available to us.

As we have shown above, the power to detect a difference in all-cause hospitalisation is very small hence to do a subgroup analysis on this outcome seems unwarranted.

The pharmacological/toxicological adverse effects of oseltamivir can be classified into two major types [3]. One is sudden type occurring during the hypercytokinemic state in the early phase of infection including sudden death [3,4], accidental death after abnormal behaviours and vomiting induced by the central depressing action of unchanged oseltamivir [4]. The second are delayed type of reactions including recurrence or exacerbation of influenza and/or other infection, diabetes, bleeding, renal impairment and delayed type neuropsychiatric reactions related to inhibition of the host's neuraminidase [3]. Sudden type adverse effects should be collected and analysed only during the early phase of influenza (for example, vomiting was only significantly increased within one day of treatment in the paediatric RCTs). However, delayed type adverse effects should be collected and analysed for a longer period to detect those reactions after a full course of treatment (for example the increase of pneumonia in the off-treatment period in the paediatric RCTs).

A recently published proportional mortality study has indicated that oseltamivir increases sudden type of death (odds ratio: 5.9) compared with zanamivir users by analysing all death cases among approximately 20 million 2009A/H1N1 influenza patients in Japan. This effect was also true for the comparison of oseltamivir users with non-users of antivirals [4].

4. Data from observational studies

Observational studies during the 2009 H1N1 influenza outbreak have assessed the effects of oseltamivir on a selected population of hospitalised patients. These represent a very small proportion of the total population who get influenza. While subgroup analyses are important, it is important to not lose sight of the fact that the use and governmental stockpiling of oseltamivir is for its routine use in asymptomatic and symptomatic members of the community. Our review thus considers the evidence base that applies to the vast majority of people.

In addition, the studies Dr. Hayden appears to be referring to are retrospective observational studies in which apparent treatment effects may be the result of an effective treatment but could also be due to confounding effects. Unfortunately there is no way to determine which of these possibilities is true. That is why drug regulators require evidence from RCTs to determine whether or not a drug is approved for use. According to the analysis by Jones and Hama [5], apparent protective effects against severe outcomes like pneumonia, hospitalisation and mortality are possibly derived from survivor treatment selection bias (or immortal time-bias). This is not an issue for randomised controlled trials because follow up begins at the time of randomisation which is the same for patients allocated to active drug and patients allocated to placebo. However in the case of

observational studies treatment can begin at varying times (up to several days) after the onset of symptoms. Therefore a naive comparison that compares a binary outcome, such as death (or other adverse event), or time to an event (survival time) is at high risk of survivor treatment selection bias (also referred to as immortal time bias or simply time dependent bias). This bias can occur, for example, because patients who die early are not given the opportunity to receive treatment. In addition patients who are extremely sick may not be given the opportunity to receive antivirals because other treatments and procedures take priority. This bias can be addressed with an appropriate analysis however this has not been done in any of the observational studies of antiviral use for influenza that we have seen.

4. Influenza diagnosis and serologic results

We do not have access to the data required to conduct all these analyses.

5. Other treatment endpoints of interest

We do not have access to the data required to conduct these analyses (time to resumption of usual activities and return to pre-morbid status) using the ITT population.

By mentioning the evidence and possible mechanism of action for oseltamivir, we are arguing that fever alleviation and symptom reduction may not be caused by the reduction of viral load but may be the result of inhibition of host's immune functions including induction of cytokines and antibody production by inhibition of the host's neuraminidase in addition to central depression by oseltamivir.

Analysis of the population with documented influenza infection (ITT-Infected population) is not valid (see above). Hence we are unable to conduct a valid analysis in the influenza positive population and data for the influenza negative population has not been provided.

Antibody titre is one of the ways of selecting only subjects infected with influenza. However we have shown that the production of antibodies was consistently lower in the oseltamivir group compared to the placebo group in the treatment trials. Therefore the use of antibody production to confirm influenza in prophylaxis trials is not valid. Moreover comparison of the proportion with confirmed infection between the oseltamivir group(s) and the placebo group will provide misleading results.

Nor are "virus titre", "time to culture negativity" or "change in viral titres over time" a true measure of viral load, because oseltamivir as a neuraminidase inhibitor may conceal positivity by inhibiting the influenza virus from leaving the surface of host respiratory cells (which are covered by a mucous layer on the surface of the cells).

6. Adverse events with treatment

In principle we agree. However, there are many data that show the classification of severity is questionable: for example, we believe that *psychosis* or *hallucinations* should be classified as "severe" but this has not always been followed. Therefore, we are planning to propose using new classification methods for the analysis of adverse events in the next update of our review.

We agree that comparisons of adverse events in the placebo groups across zanamivir and oseltamivir studies need to be interpreted with caution.

We agree that the spectrum and severity of adverse events/reactions are different among age groups. Therefore, we propose analysing adverse events/reactions stratified by age, if possible, according to the data in the Clinical Study Reports or individual patients' data in the next step of our systematic review.

7. Prophylaxis endpoints of interest

As described on page 7 of our systematic review, the primary outcome measures for prophylaxis studies are:

influenza (both symptomatic and asymptomatic and laboratory-confirmed) and influenza-like illness (ILI);

hospitalisation and complications;

interruption of transmission (in its two components, reduction of viral spread from index cases and prevention of onset of influenza in contacts);

harms.

We did not meta-analyse data from the prophylaxis trials in this systematic review because the substantial documents for prophylaxis trials were obtained after the time lock of 12 April 2011.

Due to the problems we have illustrated above on using virus titre to confirm influenza infection we plan to amend the primary endpoint for prophylaxis trials to influenza-like illness (ILI).

There is some fear that those with serologic negative infection without symptoms may be more easily infected with influenza virus in the future, because evidence from animal experiments shows that IgA antibody in the respiratory mucosa is reduced (to about 20% of the control group), while reduction of those of systemic IgG antibody (HI antibody) was slight and not statistically significant [6].

8. Adverse effects with prophylaxis

We agree that the prophylaxis studies are particularly useful in assessing drug tolerability.

As we discussed above ("7. Adverse events with treatment"), there are many data that show the classification of severity is questionable. For example, we believe that psychosis or hallucinations should be classified as "severe" but this has not always been followed. Therefore, we are planning to propose using new classification methods for the analysis of adverse events in the next step of the review.

We mentioned the statement "occurred in similar proportions of subjects in the three groups (39 to 47 per cent)" as an example of reporting bias present in the paper (Dr. Hayden's reference no. 3; known by its trial ID WV15673/WV15697).

The numbers for headache are 47% (242/520) in high-dose oseltamivir group, 43% (335/520) in low-dose oseltamivir group and 39% (202/519) in placebo group. These proportions are not similar and show a significant linear trend of increase with oseltamivir dose ($P = 0.013$).

In addition, we would be grateful if Dr. Hayden were to supply the definition of "drug related headache among headaches reported as adverse events"? In particular, how was it decided whether a headache was drug-related or not? We cannot suggest signs or symptoms to distinguish oseltamivir-induced headache from placebo-induced headache.

We propose analysing adverse events in clinical study reports, including those for prophylaxis trials.

9. Peer review

We agree that there is confusion among policy-makers and practitioners but believe this to be justified: the data published and accessible to them appear to have some flaws that need to be resolved. We are encouraged by Dr Hayden's support for our obtaining all the data necessary to clear the confusion.

Cochrane systematic reviews are stringently peer-reviewed. Not only are they peer-reviewed by independent experts prior to publication but the protocols are also peer-reviewed before being undertaken, to reduce a priori biases. In addition, protocols are available for comment from outside the internal review process – Dr Hayden himself, or employees of Roche the manufacturer of oseltamivir, could have provided input about suggested alterations to the protocol which we would have been glad to receive. To this extent the peer-review process is more stringent than that employed by most other scientific journals.

RH, MJ, TJ, CDM, PD

References

[1] Moore ML, Chi MH, Zhou W, Goleniewska K, O'Neal JF, Higginbotham JN, Peebles RS Jr. Cutting Edge: Oseltamivir decreases T cell GM1 expression and inhibits clearance of respiratory syncytial virus: potential role of endogenous sialidase in antiviral immunity. J Immunol. 2007 Mar 1;178(5):2651-4.

[2] Hama R, Jones M et al. An overview of neuraminidase inhibitors on inhibitory effect of immune response including cytokines and antibody production (under submission for publication)

[3] Hama R, Fatal neuropsychiatric adverse reactions to oseltamivir: case series and overview of causal relationships. The International Journal of Risk & Safety in Medicine 20 (2008) 5-36. Available at http://npojip.org/english/no11.html

[4] Hama R, Jones M, Okushima H, Kitao M, Noda N, Hayashi K, Sakaguchi K. Oseltamivir and early deterioration leading to death: a proportional mortality study for 2009A/H1N1 influenza. Int J Risk Saf Med. 2011;23(4):201-15. Available at http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf

[5] Jones M, and Hama R et al. Survivor treatment selection bias in a cohort of 2009A/H1N1 influenza patients from Japan (manuscript in preparation)

[6] Takahashi E, Kataoka K, Fujii K, Chida J, Mizuno D, Fukui M, Hiro-O Ito, Fujihashi K, Kido H. Attenuation of inducible respiratory immune responses by oseltamivir treatment in mice infected with influenza A virus. Microbes Infect. 2010 Sep;12(10):778-83.

Contributors

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

6 Additional feedback from Frederick G. Hayden, 10 August 2012

Summary

I am writing to respond to the comments and questions raised by Jefferson and his colleagues to my letter of 2 February 2012 about their report published through the Cochrane Collaboration. While the authors have provided helpful clarifications to many points, I remain concerned about their selective approach to data analysis and presentation. Resolution of these issues is important in anticipation of future analyses by Jefferson and colleagues or by others. Many of their responses indicate that analysis of the cohorts with proven influenza infection (ITT-infected) are not appropriate but further analyses of patient level data should be able to address their concerns (see below). Also they identify biases that could make oseltamivir look better but not those that could make it look worse than its effectiveness and tolerability likely are in reality. An impartial analysis would identify biases in both directions and attempt to deal with them in a balanced appraisal.

My specific comments and recommendations for additional analyses follow:

1. **Use of intention to treat (ITT) and ITTI-infected groups.** One obvious means of addressing the concern about selection bias in defining the ITT-infected (ITTI) population for analysis is to focus on those who were influenza virus-positive (irrespective of serologic results) at enrolment. These individuals (ITTI-virus) represented approximately 70-85% of those enrolled into the ITTI cohorts across the various RCTs.

In addition, those who were included in the ITTI group solely on the basis of seroconversion could be analysed separately to assess overall comparability in terms of symptom resolution and complications to those who were both virus-positive (ITTI-virus) and showed serologic rises. This might also help determine whether inclusion of data from virus-negative seroconverters would affect overall findings.

In contrast to the Cochrane statement that "And selection of those with "serology-positive results" appears to have given the advantage to the oseltamivir group", it might alternatively be disadvantageous (bias toward the null) or neutral in effect. If oseltamivir is most beneficial in preventing lower respiratory tract (LRT) complications leading to antibiotic use in those in whom it also prevents seroconversion, as one might expect if its overall treatment effect varies between patients based on timing of administration, individual pharmacokinetics or other factors, then its protective effect on complications will be underestimated because the benefits in those for whom it prevents seroconversion will not be counted. If, on the other hand, treatment works effectively only in those infected who seroconvert and has little or no effect in those in whom it prevents seroconversion, this would increase the apparent benefit. However, the only way in which this sequence seems possible would be if late treatment does not interfere with seroconversion but early treatment does AND late treatment is more effective than early. This is biologically implausible and inconsistent with the observed effects on time to treatment for other outcomes, in which early treatment is associated with greater effects. Alternatively, if oseltamivir treatment has a similar effect on LRT complications in infected who seroconvert and those who do not, this would reduce the numbers in the treated group with and without outcomes in a non-differential way.

In addition to a possible non-specific immunomodulatory effect of oseltamivir on serologic responses or possible confounding effect of prior inactivated influenza vaccine which might blunt antibody responses in those with proven influenza (1), one explanation for the apparently lower seroconversion rate in oseltamivir recipients would be that some oseltamivir recipients had low viral replication levels at enrolment that were quickly reduced by treatment and did not stimulate antibody rises, so that in these persons treatment prevented seroconversion. If one assumes that clinical outcomes are linked to viral replication levels as other reports suggest, such individuals would probably have shorter illness duration and also be less likely to develop LRT complications. Consequently, not counting them in the oseltamivir group would bias towards the null and under-estimate the effect of treatment on both illness resolution and complications. In this regard, comparing outcomes in the ITTI-virus seroconverters vs non-seroconverters would be of interest if sufficient numbers are available. Also, as stated previously, analysis of the serologic responses based on time from symptom onset to

enrolment, including both frequency of seroconversion and observed titres rises in the ITTI-virus group compared to placebo, might help address this possibility.

If I have interpreted their report correctly, the post-hoc analyses by Jefferson and colleagues found an absolute difference of 3.4% in overall infection rates between placebo (68.9%) and oseltamivir (65.5%) groups across the studies they analysed (Figure 5, Table 14). This difference presumably approximates the fraction of virus-negative, non-seroconverting but possibly influenza-infected subjects in oseltamivir group. To what extent this difference might bias outcomes is uncertain but its relatively modest size suggests that misclassification would not be a major confounder in either the ITTI or ITT-non-infected groups. Optimally in future studies more sensitive nucleic acid amplification testing will be used to detect infection by influenza and other respiratory viruses and facilitate more clear delineation of the groups of interest.

In summary, further analyses of the RTCs on oseltamivir and zanamivir, the outcomes in all groups of relevance (ITT, ITTI, ITTI-virus, and ITT-non-infected) are important and should be presented as fully as possible. As stated previously, separate assessment of the ITT-non-infected group provides a valuable control and also enables a determination of whether there was a potential drug-disease interaction of NAI treatment in non-influenza patients. As specific antiviral treatment would not be expected to provide benefit on illness resolution or complications in non-influenza illness, examining the ITT-non-infected groups allows this point to be tested directly. An analysis of 11 oseltamivir RCTs (2) confirmed lack of treatment effect on LRT complications in non-influenza-infected subjects compared to placebo. The failure to present outcomes in the ITT-infected or ITT-virus cohort underestimates possible beneficial drug effects, whereas full data presentation would enable readers to examine the event rates and magnitude of treatment effect sizes for key outcomes across all relevant groups for themselves.

2. Sample size considerations. The endpoint used in our pooled analysis of oseltamivir RCTs (3) was prospectively defined before the analysis was undertaken and was based on findings in our earlier study of zanamivir treatment effects (4) that indicated inhaled zanamivir reduced LRT illnesses leading to antibiotic prescriptions (RR, 0.60; 95% CI 0.42-0.85) but not upper respiratory tract ones (RR 0.90; 95% CI 0.63-1.27). The oseltamivir analysis used all studies available to us at the time, including unpublished clinical study reports, in order to avoid selection bias. The other endpoints of upper respiratory tract complications leading to antibiotic use (6.8% oseltamivir vs 5.9% placebo) and overall antibiotic use (14.0% oseltamivir vs 19.1% placebo; P <.001) were described in our 2003 paper (page 1760). Of note, the reductions in overall antibiotic use in influenza outpatients were similar for zanamivir (28%) and oseltamivir (27%) treatment. The limitations of the clinical diagnoses and retrospective approach used in these studies were described more fully in the earlier zanamivir paper (4). However, the simple pooled analysis we undertook in the oseltamivir paper did not correct for the higher proportion of influenza-infected, at-risk individuals in the placebo group, and this was a shortcoming. In any case, we pointed out this difference in the paper (page 1669) and presented the data by each group of interest (previously healthy or at risk) in Tables 3 and 4.

More importantly, our finding that early oseltamivir treatment reduced the likelihood of physician-diagnosed LRT complications leading to antibiotic use has been confirmed and extended (37% reduction in oseltamivir group; risk ratio 0.63 [95% CI 0.48, 0.82]) in a subsequent meta-analysis (that controlled for pre-enrolment risk status and included events from the time of enrolment) of the same 10 RCTs included in our paper and one additional one (2). Furthermore, this analysis found that the unpublished trials for which Jefferson and colleagues apparently do not have data were found to be no more favourable to oseltamivir than the published ones. When only the two published trials in previously healthy persons were considered, the reduction in the 24-day risk of LRT complications treated with antibiotics was 65% (risk ratio, 0.35; 95% CI 0.15, 0.82) in the oseltamivir arms.

3. Complications in ambulatory patients. Their comments on possible oseltamivir adverse events, including sudden death and neuropsychiatric adverse events (NPAEs), raises important points about the effects of influenza infection itself and possible drug-disease interactions. A well-documented relationship exists between NPAEs and influenza infection itself. Differing age-related patterns of influenza-associated encephalopathy/encephalitis and NPAEs have been reported in Japanese children and adolescents, and also age-

related differences exist in NAI prescribing patterns in Japan. Consequently, careful analysis is required to assess possible associations. It is important to point out that causal relationships between oseltamivir use and such events remain to be proven. Some analyses have indicated comparable or lower NPAEs rates in oseltamivir-treated compared to non-treated influenza patients (reviewed in (5)) and no higher rates of NPAEs have been found in hospitalised infants in the USA (6). Oseltamivir administration to those with influenza-associated NPAEs does not appear to worsen manifestations (7;8). Of note, the crude reporting rates for possible oseltamivir-associated NPAEs in Japan and USA were significantly lower during the 2009 pandemic than during preceding influenza seasons (9).

As pointed out by Jefferson and colleagues, the possibility of late-onset adverse events requires that sufficient follow-up be incorporated into study design to examine both possible adverse and beneficial effects. However, the low frequencies of such events would likely require much larger numbers of subjects than enrolled in most RCTs. One approach is retrospective examination of large databases that link healthcare visits, clinical diagnoses, and drug administration registries. For example, one cohort study involving over 150,000 subjects (49,238 oseltamivir recipients, 102,692 control patients) reported that oseltamivir treatment of presumed influenza was associated with lower risk of TIA or stroke in the subsequent six months (10). This kind of observational study approach has been undertaken for investigation of outcomes and possible adverse events following influenza immunisation and should also be extended to antivirals.

4. Data from observational studies. Jefferson and colleagues indicate that possible survivor treatment selection bias in observational studies can occur because patients who die early are not given the opportunity to receive treatment. However, there is also the opposite concern that sicker patients, especially in a rapidly evolving illness like influenza, are more likely to initiate therapy at any given time after symptom onset than less ill ones. This would be a conservative bias and reduce the likelihood of observing a treatment effect. Clinical experience during the 2009 H1N1 pandemic indicated that late NAI treatment in critically ill or non-surviving influenza patients was frequently due to delayed consideration of the diagnosis or failure to appreciate the potential value of starting treatment beyond two days after symptom onset in those with progressive illness or high-risk conditions. This occurred often despite some of these patients having had prior outpatient contact for their acute illness. Although the published reports indicate that most critically ill patients ultimately received antiviral therapy, delayed treatment commonly led to initiation of NAI administration as part of a salvage effort in a deteriorating patient. In part because of critical care support, even those patients who died in hospital usually survived into the second week of illness or later. Those analysing the large amount of observational data that has been generated in recent years, particularly in the context of the 2009 H1N1 pandemic, need to keep these clinical observations in mind. Of note, a recent analysis of critically ill pandemic H1N1 patients in California compared mortality in untreated patients who survived at least to the day after symptom onset when NAIs were first given to the NAI-treated ones and found that cases who received NAI up to 4 days after symptom onset were more likely to survive ($P < 0.05$ for each day 0-4) (11).

An independent report on the observational studies of influenza antivirals published up to November 2010 (12) conducted a meta-analyses of the few studies providing effects adjusted for confounders and, while acknowledging the low quality of the evidence based on the GRADE assessment approach, concluded that in high-risk populations, oral oseltamivir may reduce mortality (odds ratio, 0.23 [95% CI 0.13 to 0.43]) and hospitalisation (odds ratio, 0.75 [95% CI 0.66 to 0.89]). In addition, as reported in multiple studies of hospitalised pandemic 2009 A(H1N1) patients, including high-risk ones like pregnant women and those admitted with pneumonia, treatment with oseltamivir up to 4 days and in some studies later after illness onset has been associated consistently with better outcomes (11;13-21). Such observations have served to reinforce US CDC recommendations for using influenza antivirals as early as possible in those with severe or progressive illness, those hospitalised with suspected or proven influenza, and outpatients at higher risk for influenza complications (22). Furthermore, given that the circulating influenza viruses have continued to change, with the pre-2009 A(H1N1) seasonal viruses being entirely replaced by A(H1N1)pdm09 and now antigenically drifted A(H3N2) and B viruses, ignoring observational data means that only information concerning NAI treatment for influenza viruses that are now no longer circulating is being considered.

5. Other treatment endpoints of interest. The possibility that oseltamivir might have non-specific antipyretic or immunomodulatory actions unrelated to its antiviral effects has been raised in part on the basis of murine studies (23;24). These possibilities or other symptom- modifying effects could be addressed by comparison of the course of fever and individual symptom resolution between oseltamivir and placebo recipients for those enrolled in the RTCs who did not have laboratory evidence for influenza (ITT-non-infected). Of note, antipyretics were provided to participants in these trials, so that use of paracetamol (acetaminophen) needs to be included as a confounder in such analyses.

In the published pivotal RCTs of oseltamivir treatment in adults, the fever and symptom reductions observed in oseltamivir recipients were in addition to the effects of paracetamol (acetaminophen). One previous RCT in adults with uncomplicated influenza compared amantadine to aspirin and found faster fever resolution in aspirin recipients but slower resolution of other symptoms and higher rates of adverse effects leading to drug cessation (25). While fever resolution is an objective endpoint of interest, it is generally short-lived and of limited clinical importance relative to other endpoints like time to symptom alleviation, time to return to usual activities/premorbid status, and complications reductions.

The comment by Jefferson and colleagues on measuring viral loads is confusing. Virologic endpoints like quantitative virus titres (infectious and in recent studies viral RNA), time to culture negativity, and changes in titres over time are essential to determining whether a putative influenza antiviral treatment is exerting an antiviral effect and the magnitude of that effect. Failure to detect an antiviral effect raises questions about issues like compliance, drug absorption and disposition, lack of potency, and resistance emergence. Examining such virologic measures also serves to confirm the likely mechanism of antiviral action of NAIs, inhibiting release from infected cells and spread in respiratory tract secretions to initiate subsequent rounds of replication. Several observational studies during the 2009 pandemic found that early antiviral treatment (<2-3 days from symptom onset) was associated with reduced duration of viral RNA detection (26-28). Consequently, in the context of the oseltamivir RCTs, it would be valuable to examine the correspondence between upper respiratory tract influenza virologic measures and symptom resolution and LRT complications in both oseltamivir and placebo groups.

7. Prophylaxis endpoints of interest. As indicated in my initial letter, the key efficacy endpoint for an influenza antiviral used for prophylaxis should be symptomatic, laboratory-confirmed influenza illness. Given the potential for other respiratory viruses to cause febrile respiratory illness, a focus on ILI as the primary endpoint will inevitably underestimate the protective effects of an influenza-specific chemoprophylactic agent. Of note, various definitions of symptomatic illness and ILI have been used in the influenza prophylaxis RCTs to date, so that further analyses using standardised definitions would be a helpful contribution. Other secondary endpoints of interest include laboratory documented infection (irrespective of symptoms), ILI, virus-positive ILI, and laboratory-confirmed illnesses not meeting the ILI definition. Laboratory confirmation based on both viral culture and in future studies viral RNA detection would take advantage of the greater sensitivity of RNA detection.

8. Adverse effects with prophylaxis. As detailed in the oseltamivir seasonal prophylaxis study protocols and report, the relationship between drug receipt and adverse events, including headache, in these trials (29) was determined by the study staff and investigators during the trial under blinded conditions before data lock. The assessment of causality in adverse events (unrelated, remote, possible, probable) as related to drug administration was made using pre-specified criteria in the protocol (see Appendix 1) on an individual basis by both interviewing the affected participant and considering various factors including past patterns of headaches, associated symptoms, duration and severity, timing in relation to study drug, and whether the symptom persisted during drug administration. Because of its background frequency in the population, headache is a very common event in longer term studies. When it is mild or transient despite continued drug administration, or when it occurs in context of other events (URI, trauma, stress), headache is unlikely to be drug-related. Using these criteria and the analysis report provided by the sponsor Roche, we observed headache (not otherwise specified, NOS) that was probably, possibly, or remotely related to study drug administration in 22.4% of placebo, 23.8% of once daily oseltamivir, and 25.4% of twice daily oseltamivir recipients during the 6 weeks of prophylaxis

(29). The proportions were 10.2%, 8.7%, and 10.8%, respectively, for headache (NOS) that was possibly or probably related to study drug administration.

Headache is a good example of where it is essential to examine not only the frequencies of reported adverse events but also their severity and functional impact, including premature cessation of study drug. In our 6-week prophylaxis trial (29), severe headache (NOS) irrespective of relationship to study drug administration was reported in 5.0% of placebo, 3.3% of once daily oseltamivir, and 6.9% of twice daily oseltamivir, respectively. Overall premature study withdrawals were found in 21 (4.4%) of placebo, 17 (3.3%) of once daily oseltamivir, and 16 (3.1%) of twice daily oseltamivir recipients. In three placebo but no oseltamivir recipients, headache was listed as a contributory factor. However, headache was reported to be a factor leading to cessation of oseltamivir prophylaxis in one subject in another prophylaxis study (30) and was also reported at a higher frequency during 6-weeks prophylaxis in a nursing home-based RCT (5.5% placebo vs 8.3% oseltamivir)(31), so that further analyses are warranted.

9. Peer review. I thank Jefferson and his colleagues for their clarifications on the Cochrane peer review process, and as indicated above, I have provided my own suggestions on the design of future analyses by them and others. In addition, I have provided a list to the Cochrane Editorial Unit of several dozen potential expert reviewers for future protocols and reports on influenza antivirals.

Thank you for the opportunity to provide these responses and comments.

Sincerely,

Frederick G. Hayden, M.D.
Richardson Professor of Clinical Virology
Professor of Medicine
University of Virginia School of Medicine
Charlottesville, Virginia, USA

Reference List

(1) Ohmit SE, Petrie JG, Cross RT, Johnson E, Monto AS. Influenza hemagglutination-inhibition antibody titres as a correlate of vaccine-induced protection. J Infect Dis 2011 Dec 15;204(12):1879-85.
(2) Hernan MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomised clinical trials. Clin Infect Dis 2011 Aug 1;53(3):277-9.
(3) Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalisations. Arch Intern Med 2003 Jul 28;163(14):1667-72.
(4) 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.
(5) Okamoto E. Is oseltamivir (Tamiflu) safe? Re-examining the Tamiflu 'ado' from Japan. Expert Rev Pharmacoecon Outcomes Res 2010 Feb;10(1):17-24.
(6) Kimberlin DW, Shalabi M, Abzug MJ, Lang D, Jacobs RF, Storch G, et al. Safety of oseltamivir compared with the adamantanes in children less than 12 months of age. Pediatr Infect Dis J 2010 Mar;29(3):195-8.
(7) Huang YC, Li WC, Tsao KC, Huang CG, Chiu CH, Lin TY. Influenza-associated central nervous system dysfunction in Taiwanese children: clinical characteristics and outcomes with and without administration of oseltamivir. Pediatr Infect Dis J 2009 Jul;28(7):647-8.
(8) Tanabe T, Hara K, Nakajima M, Shimakawa S, Tamai H. Oseltamivir treatment for children showing abnormal behavior during influenza virus infection. Brain Dev 2010 Jun;32(6):440-4.
(9) Donner B, Bader-Weder S, Schwarz R, Peng MM, Smith JR, Niranjan V. Safety profile of oseltamivir during the 2009 influenza pandemic. Pharmacoepidemiol Drug Saf 2011 May;20(5):532-43.
(10) Madjid M, Curkendall S, Blumentals WA. The influence of oseltamivir treatment on the risk of stroke after influenza infection. Cardiology 2009;113(2):98-107.

(11) Louie JK, Yang S, Acosta M, Yen C, Samuel MC, Schechter R, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A(H1N1)pdm09. Clin Infect Dis 2012 Jul 26.
(12) Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med 2012 Apr 3;156(7):512-24.
(13) Yang SG, Cao B, Liang LR, Li XL, Xiao YH, Cao ZX, et al. Antiviral therapy and outcomes of patients with pneumonia caused by influenza A pandemic (H1N1) virus. PLoS One 2012;7(1):e29652.
(14) Higuera Iglesias AL, Kudo K, Manabe T, Corcho Berdugo AE, Corrales BA, Alfaro RL, et al. Reducing occurrence and severity of pneumonia due to pandemic H1N1 2009 by early oseltamivir administration: a retrospective study in Mexico. PLoS One 2011;6(7):e21838.
(15) Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol 2011 Jul;205(1):10-8.
(16) Dubar G, Azria E, Tesniere A, Dupont H, Le RC, Baugnon T, et al. French experience of 2009 A/H1N1v influenza in pregnant women. PLoS One 2010;5(10).
(17) Rodriguez A, Zaragoza R, Daz E, Daz JJ, Marques A. Early oseltamivir treatment was associated with improved outcomes in 2009 pandemic influenza A (H1N1)v in Spain. Intensive Care Med 2010;36:S136.
(18) Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 2010 Apr 21;303(15):1517-25.
(19) Sugaya N, Shinjoh M, Mitamura K, Takahashi T. Very low pandemic influenza A (H1N1) 2009 mortality associated with early neuraminidase inhibitor treatment in Japan: analysis of 1000 hospitalised children. J Infect 2011 Oct;63(4):288-94.
(20) Yu H, Feng Z, Uyeki TM, Liao Q, Zhou L, Feng L, et al. Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. Clin Infect Dis 2011 Feb 15;52(4):457-65.
(21) Viasus D, Pano-Pardo JR, Pachon J, Riera M, Lopez-Medrano F, Payeras A, et al. Timing of oseltamivir administration and outcomes in hospitalised adults with pandemic 2009 influenza A(H1N1) virus infection. Chest 2011 Oct;140(4):1025-32.
(22) "Have you heard?": CDC recommendations for influenza antiviral medications remain unchanged. http://www.cdc.gov/media/haveyouheard/stories/Influenza_antiviral.html. 2012.
(23) Ono H, Nagano Y, Matsunami N, Sugiyama S, Yamamoto S, Tanabe M. Oseltamivir, an anti-influenza virus drug, produces hypothermia in mice. Biol Pharm Bull 2008 Apr;31(4):638-42.
(24) Wong ZX, Jones JE, Anderson GP, Gualano RC. Oseltamivir treatment of mice before or after mild influenza infection reduced cellular and cytokine inflammation in the lung. Influenza Other Respi Viruses 2011 Sep;5(5):343-50.
(25) 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 Apr;23(4):577-82.
(26) Cao B, Li XW, Mao Y, Wang J, Lu HZ, Chen YS, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. N Engl J Med 2009 Dec 24;361(26):2507-17.
(27) Ling LM, Chow AL, Lye DC, Tan AS, Krishnan P, Cui L, et al. Effects of early oseltamivir therapy on viral shedding in 2009 pandemic influenza A (H1N1) virus infection. Clin Infect Dis 2010 Apr 1;50(7):963-9.
(28) Li IW, Hung IF, To KK, Chan KH, Wong SS, Chan JF, et al. The natural viral load profile of patients with pandemic 2009 influenza A(H1N1) and the effect of oseltamivir treatment. Chest 2010 Apr;137(4):759-68.
(29) Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med 1999 Oct 28;341(18):1336-43.
(30) Welliver R, Monto AS, Carewicz O, Schatteman E, Hassman M, Hedrick J, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomised controlled trial. JAMA 2001 Feb 14;285(6):748-54.
(31) Peters PH, Jr., Gravenstein S, Norwood P, De B, V, Van CA, Gibbens M, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. J Am Geriatr Soc 2001 Aug;49(8):1025-31.

Appendix 1 Definition of Adverse Event Relationship to Treatment

Probable

This category applies to those adverse events which are considered, with a high degree of certainty, to be related to the test drug. An adverse event may be considered **probable** if:
1. It follows a reasonable temporal sequence from administration of the study drug.
2. It cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It disappears or decreases on cessation or reduction of dose. (There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug- relatedness clearly exists; e.g., (1) bone marrow depression, (2) tardive dyskinesias).
4. It follows a known pattern of response to the study drug.
5. It reappears upon re-challenge.

Possible

This category applies to those adverse events in which the connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An adverse event may be considered **possible** if or when:
1. It follows a reasonable temporal sequence from the administration of study drug.
2. It may have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It follows a known pattern of response to the study drug.

Remote

In general, this category is applicable to an adverse event which meets the following criteria:
1. It does **not** follow a reasonable temporal sequence from administration of the study drug.
2. It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
3. It does not follow a known pattern of response to the study drug.
4. It does not reappear or worsen when the drug is re-administered.

Unrelated

This category is applicable to those adverse events which are judged to be clearly and incontrovertibly due only to extraneous causes (disease, environment, etc.) and do not meet the criteria for drug relationship listed under **remote**, **possible**, or **probable**.

	Probable	**Possible**	**Remote**	**Unrelated**
Clearly due to extraneous causes	-	-	-	+
Reasonable temporal association with drug administration	+	+	-	-
May be produced by subjects clinical state	-	+	+	+
Known response pattern to suspected drug	+	+	-	-
Disappears or decreases on cessation or reduction in dose	+	-	-	-
Reappears on re-challenge	+	-	-	-

Reply

Reply to Hayden Letter 10 August 2012

Thank you for taking the trouble to provide further feedback to our responses to your first set of feedback comments.

You remain concerned about 1) "…selective approach to data analysis and presentation…", especially with respect to our concern that ITT-infected (ITTI) criteria are inappropriate; and 2) our identification of biases that may exaggerate the effectiveness of oseltamivir. You detail these concerns in more detail:

1. ITT and ITTI
You propose an analysis of ITTI in which patients are categorised not by an immune response (which we regard as potentially flawed because our interpretation of the data suggests the drug may interfere with the immune response) but instead by determining whether patients were seroconverting excreting influenza virus at enrolment.

This sounds sensible, and were the data of symptoms and baseline infectivity (by serology or even virus shedding) available to us in suitable format, we would include this analysis. By this, we would expect the randomisation of patients into the two groups to be independent of the initiation of the drug (that is the "influenza-positive" or "-negative") before the drug was administered, in case (as may be with the immune response) the drug interferes with virus excretion (as the manufacturer claims in some of its literature).

You also propose an analysis of those grouped by ITTI from serological conversion with those grouped by virus excretion. This also would be useful, to determine whether or not a bias exists in the current data (in either direction, as you point out – the possible mechanisms you outline are plausible).

However, your hypothesis "If oseltamivir is most beneficial in preventing lower respiratory tract (LRT) complications" IS one of the main issues to be confirmed.

As already described in our review, you reported a reduction of cytokine production in response to influenza infection by oseltamivir in humans:

Hayden FG, Atmar RL, Schilling M, Johnson C, Poretz D, Paar D, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. New England Journal of Medicine 1999;341(18):1336-43

These findings suggest that reduction of antibody production cannot simply be assumed to be the result of reduced viral load.

2. Sample sizes
You describe in more detail the Kaiser 2003 pooled analysis of complications:

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

This was central to the start of our unease, after it was pointed out to us (in this Feedback section!) by Hayashi that over half of the data in it were of unpublished trials. You state that the end-points were established a priori and not post hoc. You admit to shortcomings of the paper but point out that they were declared in the paper itself. You suggest that because the two published trials meta-analysed had no more favourable drug results than the unpublished, bias is less likely.

We think this is to misunderstand our central concern: we are unable to critically appraise the trials in the usual way because they are not available to us, nor, apparently, any other group unselected by the manufacturer. Incidentally we note that you yourself, even as an author, admit you were unable to locate the data for this paper on request, referring us instead to the sponsoring manufacturer, Roche:

Cohen D. Complications: tracking down the data on oseltamivir. BMJ 2009;339:b5387.

This inability by you (authors) or sponsoring manufacturer to provide data for independent scrutiny is disgraceful, a view shared by others, http://bmj.com/tamiflu.

3. Adverse effects of NIs
We find it interesting that you call these adverse events 'complications'. You point to our concerns about

neuropsychiatric adverse events (NPAEs), and (correctly) state that any association recorded in the literature "…remains to be proven…" with some references (all were retrospective studies and mostly sponsored by the manufacturer) that suggest that there is no increase over control groups. We have other references suggesting the opposite:

Hama R. Fatal neuropsychiatric adverse reactions to oseltamivir: case series and overview of causal relationship. Int J Risk Safety Med: 20 (2008): 5-36: http://npojip.org/english/no11.html

Nakamura K, Schwartz BS, Lindegårdh N, Keh C, Guglielmo BJ. Possible neuropsychiatric reaction to high-dose oseltamivir during acute 2009 H1N1 influenza A infection. Clin Infect Dis. 2010 Apr 1;50:e47-9.

Kruker AT, Krause M. ["Oseltamivir-induced delirium"]. Ther Umsch. 2010 Dec;67(12):613-5. German.

Chung S, Joung YS. Oseltamivir (Tamiflu) induced depressive episode in a female adolescent. Psychiatry Investig. 2010 Dec;7(4):302-4. Epub 2010 Nov 11.

The following are prospective cohort studies that aimed to analyse the association of NPAEs and administration of NIs, in particular oseltamivir.

Fujiwara F, Ikushima S, Hibi N et al. An analysis of risk factors of abnormal behavior in two seasons (07, 08) of influenza infection. Presentation at the 40th annual meeting of the Japanese Society for Paediatric Infectious Diseases held on 15 and 16 (2008)

Fujita T, Fujii Y, Watanabe Y, Mori M, Yokota S. A pharmacoepidemiological study on the relationship between neuropsychiatric symptoms and therapeutic drugs after influenza infection. Jap J Pharmacoepidemiol 2010; 15: 73-92.

This preliminary report on the analysis of randomised controlled trials of oseltamivir for prophylaxis contains our response to Roche's report discussing NPAEs and oseltamivir:

Jones M, Hama R, Jefferson T, Doshi P. Neuropsychiatric adverse events and oseltamivir for prophylaxis (letter). Drug Safety, 2012, 35 (12): 1187-90.

A proportional mortality study indicates that oseltamivir increases sudden death (odds ratio: 5.9) compared with zanamivir users in an analysis of all deaths among ~ 20 million 2009A/H1N1 influenza patients in Japan. This effect is also observed for the comparison of oseltamivir users with non-users.

Hama R, Jones M, Okushima H, Kitao M, Noda N, Hayashi K, Sakaguchi K. Oseltamivir and early deterioration leading to death: a proportional mortality study for 2009A/H1N1 influenza. Int J Risk Saf Med. 2011;23(4):201-15. http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf

We have presented many of these studies in our previous reply to you, without response.

Of course the uncertainty about causation is true for many drug adverse events: our duty is to ensure that any such uncertainty is clearly articulated.

Nevertheless we entirely agree that "…observational studies … undertaken for investigation of outcomes and possible adverse events following influenza immunisation … should also be extended to antivirals." However, because this Cochrane review is limited to randomised data, such observational studies would be conducted outside this particular review.

4. Observational data
You point to our concerns about observational data in general for answering intervention questions. We acknowledge the plethora of observational data available, and even the meta-analysis of some of them. This does not detract from our continued concern that the best data for answering these questions are randomised, and to leave most of these data unavailable for independent scrutiny is unforgivable.

Moreover, the observational studies are regarded as poor in quality. A recent 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 J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, et al. Ann Intern Med. 2012 Apr 3;156(7):512-24. doi: 10.1059/0003-4819-156-7-201204030-00411. Epub 2012 Feb 27. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies

Incidentally, we are interested in rigorously meta-analysing these data ourselves, and have put in a protocol to do just that. (Jones M, Hama R. Effect of oseltamivir on mortality in treatment of 2009A/H1N1 influenza patients. PROSPERO 2012:CRD42012002245. Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002245

The proportional mortality study (above), analysing all influenza deaths in Japan and estimating populations who took antivirals and did not take them as the denominators, provides far more reliable estimates of risk from drug exposures than retrospective analysis of surveillance cases without exposed populations (denominators). Contrary to your suggestion "…there is also the opposite concern that sicker patients, especially in a rapidly evolving illness like influenza, are more likely to initiate therapy at any given time after symptom onset than less ill ones…", no such tendency was detected in this study. Proportions of patients treated with antivirals within 12 hours from the onset of fever were significantly lower in the "not mild" cases (26.5%) than "mild" cases (35.4%) at the time when antiviral was prescribed [Table 2b]. However, no patients who deteriorated before the first presentation at medical facilities were treated with antivirals before deterioration [Table 2a], while 78% of "mild" cases and 55% of "not mild" cases were prescribed antivirals within 48 hours from onset of fever [Tables 2a and 2b]. These may be related to the lower positive results (45%) of rapid testing for influenza virus in the "not mild" cases than that in the "mild" cases (60%) at the first consultation:

Hama R, Jones M, Okushima H, Kitao M, Noda N, Hayashi K, Sakaguchi K.Oseltamivir and early deterioration leading to death: a proportional mortality study for 2009A/H1N1 influenza. Int J Risk Saf Med. 2011;23(4):201-15. http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf

5. Other treatment endpoints of interest
Does oseltamivir have non-specific antipyretic or immune-modulatory actions unrelated to its antiviral effect?

We have already noted the hypothermic and immune-suppression effect of oseltamivir in humans, some from your own writing.

Hama R. Fatal neuropsychiatric adverse reactions to oseltamivir: case series and overview of causal relationship. Int J Risk Safety Med 2008:20:5-36

Hayden FG, Treanor JJ, Fritz RS, Lobo M, Betts RF, Miller M, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomised controlled trials for prevention and treatment. JAMA 1999;282:1240-6.

Your suggestion that antipyretic actions of oseltamivir be tested by comparing those randomised to oseltamivir against those not in the non-ITTI group is worth consideration (although the results might be difficult to interpret). Again, as mentioned above, it would be good to have access to sufficient data to allow this analysis and others we have outlined in the protocol.

We note your criticism about over-focusing on fever as a proxy for symptom resolution. We are of course interested in any good measure of the latter that is not only objective but also common to all trials. Nevertheless, despite your criticism, fever is a reasonable marker of 'illness' from infections such as influenza, and probably correlates reasonably well with symptom resolution (especially in the prophylaxis trials) and in the treatment trials (if fever is measured until complete resolution) – it is, after all, a cardinal symptom – and has the great advantage of being clearly measured.

You suggest that we test whether viral excretion correlates with symptoms of influenza. We agree that this would be an interesting analysis, were the data available to us (see above).

7. (Note there was no Point 6) Should we be focusing so much on influenza-like illness (ILI)?

Of course, if oseltamivir neither reduces antibody production to influenza virus nor conceals testing positivity, selecting only laboratory-confirmed influenza might be a reasonable end point for prophylaxis trials. However the facts suggest these cannot be assumed.

In any case, the Cochrane Collaboration is dedicated to finding the best available evidence to enable patients and their clinicians to make best-informed decisions. To that end, ILI is what the vast majority of clinicians and their patients will be facing. Therefore this is an end-point of direct relevance to them, and we make no apology for including it.

8. Adverse events in prophylactic trials
Thanks for this detailed information. Further analyses are indeed what we would like to undertake according to our protocol.

9. Peer review
Thanks for offering a list of your own colleagues to act as peer reviewers. We adhere to the principle of ensuring there is methodological expertise as well as content expertise. Your list will be useful to consider when finding peer reviewers.

As you may be aware, because this particular Review Group (Acute Respiratory Infections) has its Co-ordinating Editor as an Author on this review, the handling of the manuscript is managed by the Central Editorial Unit to minimise any potential conflict of interest.

Contributors

Chris Del Mar, Tom Jefferson, Rokuro Hama, Mark Jones, Peter Doshi, Carl Heneghan, Matthew Thomson.

7 Feedback from Adam Jacobs, 13 February 2013

Summary

Comment: The selection criteria in the review seem highly unusual. The authors describe a 2-stage process for including trials.

In the first stage, they require that the trial reports they analyse have "external consistency". As far as I can tell, this means that they must be able to verify the contents of the report from an external source.

This seems an extraordinarily high bar to set. I am not aware that it is part of standard Cochrane methodology. If it were applied across Cochrane reviews more generally, I imagine that very few Cochrane reviews would include any evidence at all, especially given that most Cochrane reviews are done perfectly happily with published papers, whereas this one had the advantage of clinical study reports, which are generally far more reliable and comprehensive than published papers.

It is almost as if the authors have gone out of their way to exclude the evidence, which does not help to answer important questions about the efficacy of neuraminidase inhibitors.

It is also noteworthy that no specific reasons were given for exclusion of studies from stage I of the process: we are only told that "insufficient information was available". In the interests of transparency, it would be better to know specifically what information was lacking.

May I suggest that the authors either explain the reason why they felt the need to use far stricter inclusion criteria than is normal in Cochrane reviews, or revisit their inclusion criteria so that the studies can be analysed.

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.

Adam Jacobs, Director, Dianthus Medical Limited

Reply

Adam Jacobs writes:

"The selection criteria in the review seem highly unusual. The authors describe a 2-stage process for including trials. In the first stage, they require that the trial reports they analyse have "external consistency". As far as I can tell, this means that they must be able to verify the contents of the report from an external source."

At page 11 of the review we provide the definition: "External consistency. Consistency of data as reported in regulatory documents, other versions of the same clinical study reports/unpublished reports and other references, to be established by cross-checking"

"This seems an extraordinarily high bar to set. I am not aware that it is part of standard Cochrane methodology. If it were applied across Cochrane reviews more generally, I imagine that very few Cochrane reviews would include any evidence at all, especially given that most Cochrane reviews are done perfectly happily with published papers, whereas this one had the advantage of clinical study reports, which are generally far more reliable and comprehensive than published papers".

And

"May I suggest that the authors either explain the reason why they felt the need to use far stricter inclusion criteria than is normal in Cochrane reviews, or revisit their inclusion criteria so that the studies can be analysed."

Our review is the first systematic review that we are aware of to be completely based on regulatory information. As our basic element of data synthesis was different, we had to develop new methods which we did transparently and are described in the review. It was a fact that we had received partial clinical study reports for the same trials from both Roche and EMA. We felt the need to ensure these reports were consistent. Whether our methods were an "extraordinarily high bar" or a reasonable bar or too low a bar is a judgement readers can make for themselves.

The background history which informed our methodology is explained in the review itself. At pages 4 and 5 of the review we write:

"In 2009, a reader posted a comment in response to the (then current) 2006 version of this review (Jefferson 2006). He pointed out that the review had endorsed the claim regarding a reduction in complications based on the uncritical inclusion of the Kaiser meta-analysis (Doshi 2009). The reader pointed out that only two of the 10 'Kaiser trials' had been published (Nicholson 2000; Treanor 2000) and the information provided by the Kaiser text about the remaining eight was insufficient for their appraisal. Our subsequent efforts to retrieve and review the eight unpublished trials (representing 2691 patients) were unsuccessful, raising the possibility that the findings of our previous review were not an accurate estimate of the benefits and safety of the drug. In addition, we found clear evidence of possible publication bias (see below) amid concern that some evaluations have not been available to scrutiny by the scientific community (Cohen 2009; Doshi 2009; Freemantle 2009; Godlee 2009)."

"This review is focused on healthy adults and children. It represents the amalgamation of two long-standing Cochrane reviews on the effects of NIs for influenza in healthy adults (Jefferson 2010a, also published as Jefferson 2009a) and children (Matheson 2007). The reviews were combined to pool our collective expertise and time in extracting and assessing data from clinical study reports, which in the case of some oseltamivir trials, report both adult and paediatric outcomes. Cochrane reviews of NIs in both children and adults generated intense interest from clinicians and media during the influenza outbreak declared a pandemic by the WHO in 2009. The Cochrane review of NIs in healthy adults highlighted the high risk of publication bias (Jefferson 2010a). In 2009, a reader posted a comment in response to the (then current) 2006 version of this review (Jefferson 2006). He pointed out that the review had endorsed the claim regarding a reduction in complications based on the uncritical inclusion of the Kaiser meta-analysis (Doshi 2009). The reader pointed out that only two of the 10 'Kaiser trials' had been published (Nicholson 2000; Treanor 2000) and the information provided by the Kaiser text about the remaining eight was insufficient for their appraisal. Our subsequent efforts to retrieve and review the eight unpublished trials (representing 2691 patients) were unsuccessful, raising the possibility that the findings of our previous review were not an accurate estimate of the benefits and safety of the drug. In addition, we found clear evidence of possible publication bias (see below) amid concern that some evaluations have not been available to scrutiny by the scientific community (Cohen 2009; Doshi 2009; Freemantle 2009; Godlee 2009).

Our attempts to reconcile published and unpublished evidence by contacting the manufacturer and study authors failed (the latter were unable to provide us with the necessary data; some were not in possession of the data and others may have been restricted by confidentiality agreements). Together with the *British Medical Journal* (BMJ)we ascertained that ghostwriters had been involved, which means the named authors may not have been in full control of the trial publications (Cohen 2009). We also identified several key differences in licensed indications for oseltamivir between regulatory systems (mainly between the US, Europe and Japan) and under-reporting of harms. The differences are detailed elsewhere (Doshi 2009) but of particular concern was the insistence of the FDA that oseltamivir has not been shown to reduce complications (FDA 2011a). The FDA has also not allowed an indication for interference of viral transmission within households (the key concept behind post-exposure prophylaxis). This undermined our confidence in published data and in the findings of our previous Cochrane reviews. In the background of all this were suggestions that NIs may not be as safe as

previously assumed, with associations between oseltamivir use and neuropsychiatric adverse reactions of particular concern (Hama 2008)."

Adam Jacobs writes:

"It is almost as if the authors have gone out of their way to exclude the evidence, which does not help to answer important questions about the efficacy of neuraminidase inhibitors."

A page 5 of the review we write:

"During the preparation of the 2010 review and of the current review, we realised that there were multiple sources and different levels of granularity of clinical trial data (see 'The Scope of Clinical Trial Data' table in Jefferson 2011). We decided that clinical study reports and regulatory comments were likely to provide the least biased, most complete and most insightful set of data for our review".

And

"We identified that 60% (3145/5267) of patient data from randomised, placebo-controlled phase III treatment trials of oseltamivir have never been published. This includes M76001, the biggest treatment trial ever undertaken on oseltamivir (with just over 1400 people of all ages). Exclusion of unpublished data changed our previous findings regarding oseltamivir's ability to reduce complications of influenza (Doshi 2009; Jefferson 2009a)."

Our attempts at identifying and retrieving all available evidence from regulators and manufacturers since 2009 are documented at http://bmj.com/tamiflu.

Adam Jacobs writes:

"*It is also noteworthy that no specific reasons were given for exclusion of studies from stage I of the process: we are only told that "insufficient information was available". In the interests of transparency, it would be better to know specifically what information was lacking.*"

In Table 9 (page 186) we list all studies included in Stage 1 and report details of what data for each were available to us. For, example for trial MV22940 we know that it is likely to be a randomised trial assessing effects of oseltamivir on post exposure prophylaxis but no other data are available to us. In these circumstances we cannot proceed to assessment until the information is available, as explained in the text of the review. However these studies are not excluded but are marked as pending assessment.

We invite Adam Jacobs to read the review and the references which document the history of the review, background and rationale for withdrawing the original review and developing the current version. We also invite Mr Jacobs to clarify what business relation his firm has if any with Roche, GSK and BioCryst Ltd.

It is possible that future Cochrane reviews will include an increasing proportion of regulatory information to minimize the effects of reporting bias. This type of speculation is however beyond the scope of the review.

Contributors

Cochrane Neuraminidase Inhibitors Review Team, 5 March 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

8 Feedback from Harri Hemilä, 06 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

[1] Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev 2013:CD000980. http://dx.doi.org/10.1002/14651858.CD000980.pub4

[2] Hemilä H. Zinc lozenges may shorten the duration of colds: a systematic review. Open Respir Med J 2011;5:51-8. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969/

[3] Buffinton GD, Christen S, Peterhans E, Stocker R. Oxidative stress in lungs of mice infected with influenza A virus. Free Rad Res Commun 1992;16:99-110 http://www.ncbi.nlm.nih.gov/pubmed/1321077, http://dx.doi.org/10.3109/10715769209049163

[4] Li W, Maeda N, Beck MA. Vitamin C deficiency increases the lung pathology of influenza virus-infected gulo-/- mice. J Nutr 2006;136:2611-6. http://www.ncbi.nlm.nih.gov/pubmed/16988135, http://jn.nutrition.org/content/136/10/2611

[5] Kimbarowski JA, Mokrow NJ. Colored precipitation reaction of the urine according to Kimbarowski as an index of the effect of ascorbic acid during treatment of viral influenza [in German]. Deutsche Gesundheitswesen 1967;22:2413-8. http://www.ncbi.nlm.nih.gov/pubmed/5614915, Translation: http://www.mv.helsinki.fi/home/hemila/T4.pdf

[6] Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. Cochrane Database Syst Rev 2007:CD005532. http://dx.doi.org/10.1002/14651858.CD005532.pub2

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

9 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 time lock. We will assess additional evidence from oseltamivir Module 2s, evidence on adverse events following exposure to neuraminidase inhibitors (NIs) and clinically relevant outcomes.

A rationale and description of our methods follows.

Evidence from Module 2s (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 Module 2s (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 committees and study sites' addresses, the Reporting Analysis Plan (Roche's term for the Statistical Analysis Plan or SAP detailing the types of data analyses to be carried out), randomisation list (used to allocate participants and the study Protocol with its amendments when appropriate or available.

1.2 Methods

We received 12 CSR Ms2 from 31 studies requested from EMA by July 2011. Before we reviewed Ms2 we knew they contained protocols, with their amendments, certificate of analyses, blank case report forms, randomisation and participating centres' lists. However, we had no precise idea whether this was a comprehensive list or whether further items would be identified once we started reviewing. We also noted that the same info was reported elsewhere in the CSRs (for example in the core report) but in a different level of detail. A good example of this is the statistical analysis section of the core report which is a few pages long chapter, compared to the Statistical Analysis Plan (SAP), which is a self contained document included in M2. In addition we were not aware of the existence of any readily available tool to allow us to extract, organise and appraise the information contained in the Ms2.

As consequence we decided to develop our own tool. Our plan is to do this by identifying the types of items contained in the Ms2 available to us and their location in the Ms2. The outline content of all items identified will be checked in the Ms2 because of the potential for differing titles for the same item. For example we have already noticed that Research Analysis Plan (RAP) is sometimes called Data Analysis Plan (DAP) or Statistical Analysis Plan (SAP). Another example are the Protocol Amendment Histories and Protocol Modification History Document. These represented different ways of identifying the same item and need to be given a single identifier. Items such as Data Reporting and Analysis Manual (DRAM) are only cited in one M2. We will also conduct a pilot to identify with certainty which items are present more frequently. We will make a list of what we thought were most present and important items contained in the Ms2 and create a grid based on the sequence of development of the trial design and analysis plan. For example, we want to track whether the reporting of the trial study design in the relevant section of the protocol and its amendments (in M2) is consistent with that described in the core report (in M1). We will also make an initial extraction frame to reconstruct the timeline of

the study documents, summarising the number of protocol changes and their dates in sequence. This has the purpose of giving an overview of the main timeline points of the key items of study design and analysis.

We will then pilot our extraction sheet and make changes following discussion with all authors. We will extract the data in the same groups we worked in the original review.

We will define the impact of adding M2 information by measuring the change in risk of bias (ROB) assessment in our review as well as reporting our summary description and appraisal of each trial before and after addition of the data and comparing it with the manufacturer's assessment.

The detailed questions addressed by our analysis are:

Does addition of M2 to M1 change the risk of bias evaluation compared to M1 alone?

Does reading M2 and M1 in CSRs change the risk of bias evaluation compared to using published papers?

Is the current risk of bias tool adequate for assessing trials based on reading M2 then M1 in the CSRs?

Does reading M2 and M1 in the CSRs identify additional useful relevant information for systematically reviewing a trial programme?

We will primarily use descriptive methods to answer the questions. To answer question 1 we will compare the risk of bias in our 2012 review with risk identified after addition of M2 information to our current review using a 3 by 3 contingency table. We will repeat this procedure to answer question 2, by comparing risk of bias in our 2009 *BMJ* review to our current assessment. This analysis will be based on the subset of trials that were published and included in our 2009 review.

To answer question 3 we will list all the components of other risk of bias in the current review and compared these with previous reviews (2012 and 2009).

To answer the final question we will provide a summary of the items that were identified in our assessment of the trials using the new M2 tool. This will allow us to summarise discrepancies between what was planned in the protocol, what was carried out (RAP, protocol amendments), what was reported in M1, and what was reported in the published papers. The focus would be on the trial programme of research i.e. issues that appeared consistently over the trials.

Adverse events

2. Summary and background

This document outlines how we will conduct the analysis of adverse events as part of the wider Cochrane review of neuraminidase inhibitors (NIs) for prophylaxis and treatment of influenza in healthy adults and children (A159).

We use the term 'adverse events' throughout this document rather than harms or adverse reactions as these latter terms imply causality which may or may not be appropriate.

In keeping with the methods of our previous review we will not use data from journal publications for this proposed analysis. We now have access to multiple clinical study reports (CSRs) for both oseltamivir and zanamivir. To our knowledge this is the first time some of these data have been available outside manufacturers and regulators, and allows for the exploration of events in more detail than is possible using the limited information on safety reported in journal publications. This potentially allows us to address some of the concerns that have arisen in the post marketing period about the possible relationship between neuraminidase inhibitors, oseltamivir in particular, and neuropsychiatric and other harms. The documents available to us contain listings and summaries of adverse events recorded in the trials including narrative summaries of serious adverse events and adverse events leading to study withdrawal.

The adverse events are classified by relationship to the study drug and also, by intensity (mild, moderate, severe, life-threatening and death). The duration of events is reported and they are also lumped into body systems such as gastrointestinal, neurological, etc.

2.1 Methods

All CSRs of oseltamivir and zanamivir will be included in our analysis. CSRs for prophylaxis, for treatment of adults and for treatment of children will be analysed separately. Adverse events will be initially descriptively compared over the entire treatment and follow-up period but then potentially stratified by on-treatment and off-treatment periods if it appears there may be a difference between treatment groups.

2.2 Adverse events for comparison

2.2.1 Common events

For common events of any intensity with an overall incidence of 2% or more we will compare the incidence between treatment groups. The cut-off of 2% is based on a power analysis where assuming 4000 patients in total (this is approximately how many patients we have access to in oseltamivir treatment trials of adults as well as in oseltamivir prophylaxis trials of adults), we will have 80% power to detect an odds ratio of 1.75 with 5% level of significance.

2.2.2 Uncommon events

Due to a lack of data to compare uncommon events we will compare events lumped into body systems between treatment groups. If we find evidence of a difference in incidences between groups lumped into a body system we will conduct further analysis if appropriate. This further analysis is to determine whether the difference in incidence is due to any common events included in that body system. For example, in the case of neurological body system, if we found evidence of a difference between treatment groups we would remove all common neurological events such as headaches and repeat the analysis.

2.3 Severe, serious events and events leading to study withdrawal

As well as the analysis described in section 2.2 above we will also conduct a subgroup analysis of just the events with severe intensity, serious events and events leading to study withdrawal. We will use the same definitions of "severe" and "serious" as specified in the CSRs. However we will check the classifications using all the information available in the CSRs including line listings of events, narratives provided for serious events and also for events leading to study withdrawal. Any disagreements with the original classifications will be recorded and any reclassifications will be assessed in a sensitivity analysis. Given it is unlikely there will be sufficient events to conduct separate statistical analysis at the level of body system we will compare the overall distribution of events by body system between treatment groups.

2.4 Incidence of adverse events in the CSRs

As a further check on the validity of the data on adverse events contained in the CSRs we will conduct descriptive comparisons of the incidence of adverse events in the prophylaxis and treatment trials.

This is because of the unclear methods of collecting and classifying adverse events in the trials. A potential adverse event could have been classified as a symptom of influenza, an efficacy outcome (such as complication of influenza) or an adverse event. Hence an informal comparison of the incidence of adverse events in the trials where participants had influenza (or influenza-like-illness) and the trials where participants did not have influenza may help show where adverse events could have been under-reported. We will take into account factors such as age of participants and duration of treatment exposure for these informal analyses. In addition if it is clear that an adverse event was not reported as an adverse event but was included elsewhere in the CSR (e.g. in the efficacy section), we will include that data in our adverse event analyses.

We will also construct a table showing the definitions specified in each CSR for classifying potential adverse events as adverse events, complications or symptoms of influenza.

2.5 Antibody titre

We have already reported that antibody production was lower in the oseltamivir group than in the placebo group in the systematic review of treatment trials of oseltamivir (2012). We will update this analysis by including additional oseltamivir trials as well as assess antibody production in the zanamivir trials.

We will assess antibody production in the prophylaxis trials of oseltamivir and zanamivir by the following methods.

We will first identify the participants who had influenza-like illness (ILI) or pyrexia. If the proportion is similar between active group and placebo group, the proportion of participants who had four times or higher increase of antibody will be compared between groups.

2.6 Dose-response analysis

A number of trials included two or more active treatment arms with different doses of study medication given to participants in each of the arms. For these trials we will investigate the dose-response relationship for common adverse events (as defined above).

2.7. Details of analysis

Initial analysis will be descriptive only where we will report the numbers and percentages of events by treatment group. If there is a potential difference in the pooled percentages between treatment groups (e.g. if there is more than a two standard error difference between percentages) then we will conduct formal meta-analysis. If indicated we may also conduct additional analyses taking into account event intensity and/or duration.

2.8 Limitation and exploratory analysis

The methods presented above are those that we have pre-specified prior to formal analysis of the data. A limitation of these methods is that we may fail to detect differences in rare adverse events because these events will be compared along with other types of events within body systems. Therefore in the process of conducting our formal analysis we may generate further hypotheses or conduct additional exploratory analyses. If this is the case then we will clearly label these analyses as exploratory and interpret the findings accordingly.

Types of outcome measures

3. Background

For most people, influenza is a self-limiting illness. However the disease can at times lead to serious complications such as pneumonia and hospitalisations, and if treatment with neuraminidase inhibitors can reduce the risk of severe outcomes, this would be an important public health benefit. Another potentially important public health benefit would be the ability of antivirals to interrupt person to person transmission of influenza. Current evidence for these outcomes is scarce or inconclusive. A positive balance of effects on complications and viral spread versus harm profile is the main reason for using NIs in a public health context, especially the orally administered oseltamivir.

All analysis will be based on the intention-to-treat (ITT) or safety populations as our prior review discovered compelling evidence that the ITTI (the subpopulation deemed to be influenza-infected) populations were not balanced between treatment groups in the Roche oseltamivir trials. In addition, estimates from the ITT population will be more generalisable to clinical practice where routine testing for influenza is not common in many countries (and even where used, remains of variable accuracy). Analysis will be conducted separately for prophylaxis trials, treatment trials of adults and treatment trials of children.

The list of outcomes given below includes all potential outcomes that we believe are clinically important. However a number of them may not be formally comparable in this review because there are insufficient numbers of events (e.g. mortality) or they were not adequately measured or reported (e.g. drug resistance).

3.1 Outcome measures for treatment studies

Complications~
Harms*
Symptom relief
Hospitalisation
Viral excretion
Drug resistance
Mortality

3.2 Outcome measures for prophylaxis studies

Influenza-like-illness^
Complications~
Harms*
Hospitalisation
Viral excretion
Drug resistance
Mortality

~Complications (secondary illnesses) include pneumonia, bronchitis, otitis media, sinusitis or other respiratory tract infection after influenza-like illness. Initially we will construct a table to illustrate the design methodology used for each study. The table will include the following variables:

Study/trial ID
Where complications are first defined in the CSR (e.g. "as secondary endpoint in 3rd version of protocol six months into trial and two months prior to trial unblinding")
Definition of "complication" including types of events, population and time period at risk
How complications were measured (see diagnosis methods criteria shown below)
Availability of complications data for the ITT population

We will then stratify our analysis by method of diagnosis with three possible criteria:
a. Lab-confirmed diagnosis (e.g. based on radiological or microbiologically confirmed evidence of infection).
b. Clinical diagnosis without laboratory confirmation (diagnosed by a doctor after a clinical examination).
c. Other type of diagnosis such as self-reported by patient

*A separate section provides the details of our proposed analysis of harms.

^The main outcome of interest is any symptomatic influenza-like-illness (ILI). However, we will also conduct separate analyses of influenza (symptomatic and asymptomatic) and non-influenza ILI.

Reply

TJ

Contributors

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

10 From Peter Gross, Hackensack University Medical Center, USA, 17 April 2014

Summary

Comment: Can Cochrance compare their results on influenza neuraminidase inhibitors with the reduction in symptoms when penicillin is given for strep throat? I think they may be comparable. That would be an important perspective.

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.

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library