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protocol "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children - a review of unpublished data".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The title confused me: I expected it to be a review of unpublished trials to complement your review of published trials.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preventing and treating influenza in healthy adults and children - a review of clinical study reports for published and unpublished trials".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.

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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

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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.