# Supplementary material: use of neuraminidase inhibitors in influenza

## Introduction

This document supplements the Academy of Medical Sciences and Wellcome Trust's steering group report on the treatment of influenza. It reproduces the following evidence received throughout the course of the project:

- Three summaries of recent key studies, as provided by authors of the studies and circulated in advance of an evidence-gathering workshop held at the Wellcome Trust in February 2015.
- A series of slides, presented at the workshop by Professor Frederick Hayden (Professor of Medicine, University of Virginia), which give an overview of the diverse products in development and prospects for future therapies, including new medicines and combination approaches expected to come to the market over the next decade.
- Post-workshop comments from Professor Carl Heneghan (Professor of Evidence-Based Medicine, University of Oxford), and from Roche, the manufacturers of oseltamivir, who submitted a summary of their detailed analysis of the 2014 Cochrane Review, based on their report previously published on the Cochrane Collaboration website.

## Contents

# Evidence summary: Jefferson et al. (2014) and Heneghan et al. (2014)

**Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. BMJ. 2014 Apr 9;348:g2545. doi: 10.1136/bmj.g2545. Review.**
http://www.ncbi.nlm.nih.gov/pubmed/24811411
http://www.bmj.com/content/348/bmj.g2545.long

**OBJECTIVE:**
To describe the potential benefits and harms of oseltamivir by reviewing all clinical study reports (or similar document when no clinical study report exists) of randomised placebo controlled trials and regulatory comments ("regulatory information").
**DESIGN:**
Systematic review of regulatory information.
**DATA SOURCES:**
Clinical study reports, trial registries, electronic databases, regulatory archives, and correspondence with manufacturers.
**ELIGIBILITY CRITERIA FOR SELECTING STUDIES:**
Randomised placebo controlled trials on adults and children who had confirmed or suspected exposure to natural influenza.
**MAIN OUTCOME MEASURES:**
Time to first alleviation of symptoms, influenza outcomes, complications, admissions to hospital, and adverse events in the intention to treat population.
**RESULTS:**
From the European Medicines Agency and Roche, we obtained clinical study reports for 83 trials. We included 23 trials in stage 1 (reliability and completeness screen) and 20 in stage 2 (formal analysis). In treatment trials on adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% confidence interval 8.4 to 25.1 hours, P<0.001). There was no effect in children with asthma, but there was an effect in otherwise healthy children (mean difference 29 hours, 95% confidence interval 12 to 47 hours, P=0.001). In treatment trials there was no difference in admissions to hospital in adults (risk difference 0.15%, 95% confidence interval -0.91% to 0.78%, P=0.84) and sparse data in children and for prophylaxis. In adult treatment trials, oseltamivir reduced investigator mediated unverified pneumonia (risk difference 1.00%, 0.22% to 1.49%; number needed to treat to benefit (NNTB) 100, 95% confidence interval 67 to 451). The effect was not statistically significant in the five trials that used a more detailed diagnostic form for "pneumonia," and no clinical study reports reported laboratory or diagnostic confirmation of "pneumonia." The effect on unverified pneumonia in children and for prophylaxis was not significant. There was no significant reduction in risk of unverified bronchitis, otitis media, sinusitis, or any complication classified as serious or that led to study withdrawal. 14 of 20 trials prompted participants to self report all secondary illnesses to an investigator. Oseltamivir in the treatment of adults increased the risk of nausea (risk difference 3.66%, 0.90% to 7.39%; number needed to treat to harm (NNTH) 28, 95% confidence interval 14 to 112) and vomiting (4.56%, 2.39% to 7.58%; 22, 14 to 42). In treatment of children, oseltamivir induced vomiting (5.34%, 1.75% to 10.29%; 19, 10 to 57). In prophylaxis trials, oseltamivir reduced symptomatic influenza in participants by 55% (3.05%, 1.83% to 3.88%; NNTB 33, 26 to 55) and households (13.6%, 9.52% to 15.47%; NNTB 7, 6 to 11) based on one study, but there was no significant effect on asymptomatic influenza and no evidence of a reduction in transmission. In prophylaxis studies, oseltamivir increased the risk of psychiatric adverse events during the combined "on-treatment" and "off-treatment" periods (risk difference 1.06%, 0.07% to 2.76%; NNTH 94, 36 to 1538) and there was a dose-response effect on psychiatric events in two "pivotal" treatment trials of oseltamivir, at 75 mg (standard dose) and 150 mg (high dose) twice daily (P=0.038). In prophylaxis studies, oseltamivir increased the risk of headaches on-treatment (risk difference 3.15%, 0.88% to 5.78%; NNTH 32, 18 to 115), renal events with treatment (0.67%, -0.01% to 2.93%), and nausea while receiving treatment (4.15%, 0.86% to 9.51%; NNTH 25, 11 to 116).
**CONCLUSIONS:**
In prophylactic studies oseltamivir reduces the proportion of symptomatic influenza. In treatment studies it also modestly reduces the time to first alleviation of symptoms, but it causes nausea and vomiting and increases the risk of headaches and renal and psychiatric syndromes. The evidence of clinically significant effects on complications and viral transmission is limited because of rarity of such events and problems with study design. The trade-off between benefits and harms should be borne in mind when making decisions to use oseltamivir for treatment, prophylaxis, or stockpiling.

**Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. Heneghan CJ, Onakpoya I, Thompson M, Spencer EA, Jones M, Jefferson T. BMJ. 2014 Apr 9;348:g2547. doi: 10.1136/bmj.g2547. Review**
http://www.ncbi.nlm.nih.gov/pubmed/24811412
http://www.bmj.com/cgi/pmidlookup?view=long&pmid=24811412

**OBJECTIVES:**
To describe the potential benefits and harms of zanamivir.
**DESIGN:**
Systematic review of clinical study reports of randomised placebo controlled trials and regulatory information
**DATA SOURCES:**
Clinical study reports, trial registries, electronic databases, regulatory archives, and correspondence with manufacturers.
**ELIGIBILITY CRITERIA FOR SELECTING STUDIES:**
Randomised placebo controlled trials in adults and children who had confirmed or suspected exposure to natural influenza.
**MAIN OUTCOME MEASURES:**
Time to first alleviation of symptoms, influenza outcomes and complications, admissions to hospital, and adverse events in the intention to treat (ITT) population.
**RESULTS:**
We included 28 trials in stage 1 (judgment of appropriate study design) and 26 in stage 2 (formal analysis). For treatment of adults, zanamivir reduced the time to first alleviation of symptoms of influenza-like illness by 0.60 days (95% confidence interval 0.39 to 0.81, P<0.001, I(2)=9%), which equates to an average 14.4 hours' reduction, or a 10% reduction in mean duration of symptoms from 6.6 days to 6.0 days. Time to first alleviation of symptoms was shorter in all participants when any relief drugs were allowed compared with no use. Zanamivir did not reduce the risk of self reported investigator mediated pneumonia (risk difference 0.17%, -0.73% to 0.70%) or radiologically confirmed pneumonia (-0.06%, -6.56% to 2.11%) in adults. The effect on pneumonia in children was also not significant (0.56%, -1.64% to 1.04%). There was no significant effect on otitis media or sinusitis in both adults and children, with only a small effect noted for bronchitis in adults (1.80%, 0.65% to 2.80%), but not in children. There were no data to assess effects on admissions in adults and children. Zanamivir tended to be well tolerated. In zanamivir prophylaxis studies, symptomatic influenza in individuals was significantly reduced (1.98%, (0.98% to 2.54%); reducing event rates from 3.26% to 1.27%, which means 51 people need to be treated to prevent one influenza case (95% confidence interval, 40 to 103). In contrast, the prophylaxis effect on asymptomatic influenza cases was not significant in individuals (risk difference 0.14%, -1.10% to 1.10%) or in households (1.32%, -2.20% to 3.84%). In households treated prophylactically there was an effect on symptomatic influenza (14.84%, 12.18% to 16.55%), but this was based on only two small studies including 824 participants. Prophylaxis in adults reduced unverified pneumonia (0.32%, 0.09% to 0.41%; NNTB (number needed to treat to benefit) 311, 244 to 1086) but had no effect on pneumonia in children or on bronchitis or sinusitis in adults or children (risk difference 0.32%, 0.09% to 0.41%; NNTB 311, 244 to 1086).
**CONCLUSIONS:**
Based on a full assessment of all trials conducted, zanamivir reduces the time to symptomatic improvement in adults (but not in children) with influenza-like illness by just over half a day, although this effect might be attenuated by symptom relief medication. Zanamivir also reduces the proportion of patients with laboratory confirmed symptomatic influenza. We found no evidence that zanamivir reduces the risk of complications of influenza, particularly pneumonia, or the risk of hospital admission or death. Its harmful effects were minor (except for bronchospasm), perhaps because of low bioavailability.

***Details of the review***

1. Please outline the methodology of your review, including details of the inclusion criteria for the trials/data used.

Types of studies

We included evidence from randomised controlled trials (RCTs) testing the effects of NIs for prophylaxis, post-exposure prophylaxis (PEP) and treatment of influenza. Prophylaxis is the mode of use of NIs when there is expectation of possible near-future exposure to influenza. PEP is the use of NIs following probable exposure to influenza but before symptoms develop. Treatment is the use of NIs in persons showing probable signs of influenza.

Due to discrepancies between published and unpublished reports of the same trials, we decided to include only those trials for which we had unabridged clinical study reports (for example, with consecutively numbered pages), even though they may be parts of clinical study reports (i.e. Module 1 only) and information on reports of trials that were considered "pivotal" (i.e. first or second-line evidence to regulators in support of the registration application).

Types of participants

We included previously healthy people (children and adults). 'Previously healthy' includes people with chronic illness (such as asthma, diabetes, hypertension), but excludes people with illnesses with more significant effects on the immune system (such as malignancy or HIV infection). We included only trials on people exposed to naturally occurring influenza with or without symptoms. We targeted the intention-to-treat (ITT) and safety populations as our prior review discovered compelling evidence that the intention-to-treat-influenza-infected (ITTI), the sub-population deemed to be influenza-infected, 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).

Types of interventions

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

2. Please identify the strengths and limitations of your review. This will assist the workshop participants in thinking pragmatically about the full range of evidence, as well as future research priorities and methodological improvements.

**See**
**Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya I, Mahtani KR, Nunan D, Howick J, Heneghan CJ. Cochrane Database Syst Rev. 2014 Apr 10;4:CD008965. doi: 10.1002/14651858.CD008965.pub4. Review.**
http://www.ncbi.nlm.nih.gov/pubmed/24718923
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008965.pub4/abstract;jsessionid=D0952B85723A29FF11B3087DB5F71938.f03t02

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

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

Agreements and disagreements with other studies or reviews

Several reviews of NIs are now available (Burch 2009; Cooper 2003; Falagas 2010; Tappenden 2009; Turner 2003), including several separate versions of our previous reviews (Jefferson 2006; Jefferson 2009a; Matheson 2007; Shun-Shin 2009). All are mainly based on published information and reach similar conclusions to our 2006 review, which sparked the reader's comment and subsequent investigation and change of methods.

Following publication of our review update in December 2009, Roche asked the Harvard-based academics Hernan and Lipsitch to repeat the Kaiser analysis to confirm or reject Kaiser's conclusions (Hernan 2011). They were not provided with any funding to carry out this analysis and Roche ultimately provided them with patient-level data sets and Module 1 for the 10 Kaiser trials and one more treatment trial (WV16277). An important methodological difference between Hernan and Lipsitch's analysis and that of Kaiser was Hernan and Lipsitch's decision to privilege a true ITT

analysis over the sub-population analysis featured in the Kaiser analysis. Our Cochrane review also analyses the ITT population.

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

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

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

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

Unfortunately, the Hernan-Lipsitch analysis has been cited by influential bodies such as the European Centre for Disease Prevention and Control (ECDC) as "confirmation of the original Kaiser meta-analysis" (http://ecdc.europa.eu/en/activities/sciadvice/_layouts/forms/Review_DispForm.aspx?ID=561&List=a3216f4c%2Df040%2D4f51%2D9f77%2Da96046dbfd72) despite the fact that Hernan and Lipsitch did not confirm one of the key conclusions of the Kaiser paper (Kaiser 2003).

For complications, while Hernan and Lipsitch clearly produced similar results to Kaiser, we do not think that this means the result is more credible. In view of our findings, we suggest that these results should be interpreted with caution. We have published our preliminary comments (Cochrane Neuraminidase Inhibitors Review Team 2011). The approach Hernan and Lipsitch took in analysing data was insufficient to provide a credible, independent check on validity and reinforces the importance of detailed, critical assessment of entire trial programmes, with access to full-length study reports. Our analysis questions the coherence between the evidence and the proposed mode of action of oseltamivir.

The Ebell 2012 review concluded that there was "no evidence that oseltamivir reduces the likelihood of hospitalisation, pneumonia or the combined outcome of pneumonia, otitis media and sinusitis in the ITT population". This conclusion was based on Module 1 of the 10 Kaiser trials plus WV16277. These are the same 11 trials as Hernan 2011.

***Additional comments***

3. Please add any additional comments, not covered by the above, which may be of benefit to the workshop participants.

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

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

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# Evidence summary: Muthuri et al. (2014) and Okoli et al. (2014)

**Muthuri *et al*. (2014) Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med**
http://download.thelancet.com/flatcontentassets/pdfs/S2213260014700414.pdf

**Okoli GN, Otete HE, Beck CR, Nguyen-Van-Tam JS (2014) Use of Neuraminidase Inhibitors for Rapid Containment of Influenza: A Systematic Review and Meta-Analysis of Individual and Household Transmission Studies. PLoS ONE 9(12): e113633. doi:10.1371/journal.pone.0113633Okoli**
http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0113633&representation=PDF

***The use of existing antivirals***

1. Treatment for individuals with underlying health conditions that predispose them to complications from influenza (including pregnant women) who develop influenza.

*Individuals hospitalised with pandemic influenza A(H1N1)pdm09 are included in the PRIDE analysis, with and without comorbidities. Individuals with underlying health conditions are therefore included. But since the calculation of propensity scores was based partly on presence or absence of comorbidity we cannot specifically disentangle 'high-risk' individuals unless we adopt an alternative analytical approach that would allow for looking at high-risk groups as a subset. 38% of the PRIDE dataset had one or more comorbidities.*

2. Treatment for previously healthy people who develop severe influenza.

*Individuals hospitalised with pandemic influenza A(H1N1)pdm09 are included in the PRIDE analysis, with and without comorbidities. Previously healthy individuals are therefore included. But since the calculation of propensity scores was based partly on presence or absence of comorbidity we cannot specifically disentangle 'healthy' individuals unless we adopt an alternative analytical approach that would allow for looking at high-risk groups as a subset. 62% of the PRIDE dataset were patients free from documented comorbidity at the time of hospitalisation.*

*Overall: mortality reduction of 19% irrespective of NAI timing; early treatment vs. none 50% reduction in mortality. No clear evidence of effectiveness in children.*

3. Treatment for any previously healthy people with influenza that is not (currently) severe ('treat all' approach).

*All patients in the current PRIDE analysis were severe enough to have warranted hospital admission based on locally prevailing thresholds for hospitalisation. [within the wider PRIDE dataset is a large cohort of community patients; we are not sure yet but perhaps 80,000 useable case records – these data have not yet been analysed]*

4. Treatment in severely ill individuals more than 48 hours after onset of symptoms.

*The PRIDE analysis offers specific data on patients hospitalised with A(H1N1)pdm09 infection whose NAI treatment was initiated >48hrs after symptom onset. In critically ill adult patients, later treatment vs. none reduced mortality by 39% (not significant in children)*

5. In prophylaxis.

*The paper by Okoli et al. was funded by WHO specifically to look at rapid containment, which in practice will be a mixture of pre- and post- exposure prophylaxis. As such, pre- and post-exposure studies were combined. Larger residential settings excluded. Evidence for or against effectiveness of 'combined prophylaxis' was only available at household level. Overall: 89% individual protection but evidence limited to household-like settings not wider community.*

***Details of the reviews***

6. Please outline the methodology of your review, including details of the inclusion criteria for the trials/data used.

*PRIDE dataset: formally registered (PROSPERO) Individual Participant Data meta-analysis using propensity scores and adjustement for antibiotic and corticosteroid use in hospital; included all obtainable global datasets on patients with A(H1N1) infection. All hospitalised (for the data under discussion today). Conformity to a minimum dataset was required.*

*Okoli et al: formally registered (PROSPERO) standard meta-analysis. Included all obtainable published studies offering data on pre and post exposure prophylaxis, without limitation by study design.*

Please identify the strengths and limitations of your review. This will assist the workshop participants in thinking pragmatically about the full range of evidence, as well as future research priorities and methodological improvements.

*PRIDE dataset: W: retrospective, observational data; adjustment by propensity score was most extensive performed to date but will not have fully eliminated all confounding and has not fully adjusted for case severity. S: massive global dataset; 86% of all cases laboratory confirmed; sensitivity analysis including clinically diagnosed cases does not alter findings. Multiple alternative statistical approaches confirm generally robust findings.*

*Okoli et al: W: commissioned by WHO for a specific scenario; combining pre- and post-exposure data is a strength and a weakness (but appropriate for the WHO brief); no meaningful data above household level. S: highly consistent and strongly protective findings by individual and by household protection.*

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# Evidence summary: Dobson et al. (2015)

## 1. Publication

Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet*; online publication 30 January 2015. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)62449-1/fulltext

## 2. Review scope and methodology

- **Aim:** Individual patient data meta-analysis to assess efficacy and safety of oseltamivir for treatment of influenza in adults.

- **Selection criteria:** Published and unpublished randomised double-blind placebo-controlled trials in adults with naturally occurring influenza-like illness.

- **Included trials:**
  - 9 Roche-sponsored trials (12 protocols), including 2 trials in elderly participants (≥65 years) and 1 trial in participants with chronic cardiac or respiratory disease. Most trials were in otherwise healthy participants.
  - trials performed between 1997 and 2001
  - key inclusion criteria: ≤36 hours of feeling unwell, fever, 1 respiratory symptom (cough, sore throat, coryza) and 1 constitutional symptom (headache, myalgia, sweats/chills, fatigue)
  - all trials were in seasonal influenza. Majority of infected participants had influenza type A (88%).
  - trials performed according to good clinical practice criteria with relevant approvals from ethics committees and regulatory authorities
  - data and supporting documents (dataset specifications and clinical study reports) provided by Roche

- **Trials not included (not available):**
  - Li l et al (2003): Roche-supported trial in 451 Chinese adults
  - Dharan et al (2012): 19 adults / children

- **Analysis populations** (analysed by allocated treatment unless otherwise stated):
  - Efficacy analyses: i) Influenza-infected "Intention-to-treat influenza-infected population (ITTI)"
    ii) All participants "Intention-to-treat population (ITT)"
    iii) Additionally for main analyses, non-influenza-infected "Intention-to-treat not-infected population (ITTN)"
  - Safety analyses: All patients, analysed by treatment received (Safety population)

Note: definition of influenza infection = positive culture from a nasal or throat swab (viral shedding at baseline or during follow-up) or four-fold or greater increase from baseline in antibody titre (trial definition).

- **Intervention and follow-up**:
  - oseltamivir 75mg or placebo twice daily for 5 days. 21 days follow-up.
  - 2 trials had a third treatment arm of oseltamivir 150mg twice daily. We focused on the 75mg twice daily dose as this is the standard prescribed dose.

- **Main meta-analysis outcomes:**
  - primary efficacy outcome = time to alleviation of all 7 symptoms (nasal congestion, sore throat, cough, aches and pains, fatigue, headache and chills/sweats). Primary outcome for 8 out of 9 individual trials.

  - other efficacy outcomes =
    i) lower respiratory tract complication (LRTC) >48 hrs after randomisation requiring antibiotics. LRTCs identified via preferred terms containing "bronchitis", "pneumonia" or "lower respiratory tract infection". Diagnosis of complications was based on participant report and the investigator's clinical judgement. No diagnostic tests were needed.
    ii) Admittance to hospital for any cause.

  - safety outcomes included all adverse events, serious adverse events, adverse events by body system class, and preferred terms nausea, vomiting and diarrhoea. Adverse events analysed separately for on treatment and off treatment periods. On treatment was defined as up to 2 days after the last dose of study drug.

- **Analysis methods:**
- Fixed-effect methods of meta-analysis
- Time to alleviation of all 7 symptoms = accelerated failure time model adjusted for trial to obtain overall time ratio and estimate of difference in median time to alleviation of all symptoms.
- LRTC, hospitalisations and adverse events = meta-analysed with risk ratios and Mantel-Haenszel approach without continuity correction. Risk differences estimated by applying overall risk ratio (and 95% CI) to pooled placebo group risk.

**3. Summary of overall results of the review**

- ITT population (n) = 2402 oseltamivir vs 1926 placebo (one trial had 2:1 randomisation)
- ITTI population (n) = 1591 oseltamivir (66% infected) vs 1302 placebo (68% infected)

- **Time to alleviation of all symptoms:**
- ITTI population = 21% shorter time to alleviation of all symptoms for oseltamivir vs placebo (time ratio [TR]: 0·79, 95%CI 0·74, 0·85, p<0·0001). Median time to alleviation 97·5 hrs oseltamivir vs 122·7 hrs placebo, difference -25·2 hrs (95% CI -36·2, -16·0).
- ITT population = estimated treatment effect was attenuated but remained highly Significant (TR 0·85, 95%CI 0.80, 0.90, p<0.0001; median difference: -17·8 hrs, 95% CI -27.1, -9.3).
- ITTN population = estimated time ratio close to unity (TR 0.99, 95%CI 0.88, 1.12, p=0.91)

- **LRTC >48 hrs requiring antibiotics:**
- ITTI population = 44% reduction in risk of LRTC attributable to oseltamivir (Risk Ratio [RR] 0.56, 95%CI 0.42, 0.75, p=0.0001; Risk Difference [RD] -3.8%, 95%CI -5.0, -2.2; 4.9% oseltamivir vs 8.7% placebo)
  - *Bronchitis = RR 0.62 (95%CI 0.45, 0.85, p=0.0030), 56/1544 oseltamivir vs 87/1263 placebo*
  - *Pneumonia = RR 0.40 (95%CI 0.19, 0.84, p=0.015), 9/1544 oseltamivir vs 21/1263 placebo*
- ITT population = 38% reduction in risk of LRTC attributable to oseltamivir (RR 0.62, 95%CI 0.49, 0.79, p=0.0001; RD -3.0%, 95%CI -4.0, -1.7; 4.9% oseltamivir vs 7.9% placebo)
  - *Bronchitis = RR 0.71 (95%CI 0.54, 0.93 p=0.011), 90/2330 oseltamivir vs 111/1872 placebo*
  - *Pneumonia = RR 0.34 (95%CI 0.18, 0.64, p=0.0009), 13/2330 oseltamivir vs 32/1872 placebo*
- ITTN population = RR 0.82 (95%CI 0.53, 1.26), p=0.36

- **Admittance to hospital for any cause:**
- ITTI population = 9/1591 oseltamivir versus 22/1302 placebo. RR 0.37 (95%CI 0.17, 0.81), p=0.013. RD -1.1% (95%CI -1.4, -0.3), 0.6% oseltamivir vs 1.7% placebo.
- ITT population = 25/2402 oseltamivir vs 35/1926 placebo. RR 0.61 (95%CI 0.36, 1.03), p=0.066.
- ITTN population = RR 1.01 (95%CI 0.47, 2.15), p=0.99

- **Main on treatment adverse events (safety population):**
- Nausea = RR 1.60 (95%CI 1.29, 1.99), p<0.0001. RD 3.7% (95%CI 1.8, 6.1), 9.9% oseltamivir vs 6.2% placebo
- Vomiting = RR 2.43 (95%CI 1.83, 3.23), p<0.0001. RD 4.7% (95%CI 2.7, 7.3), 8.0% oseltamivir vs 3.3% placebo

- A number of pre-specified subgroup analyses and sensitivity analyses were also performed. The results of these and other analyses can be found in the published paper.

- **Overall conclusion:** oseltamivir accelerates clinical symptom alleviation in adults infected with influenza, and also reduces risk of lower respiratory tract complications and admittances to hospital. Whether the magnitude of these benefits outweigh the harms attributed to nausea and vomiting needs to be carefully considered.

**4. Strengths of review**
- use of individual patient data (more thorough analysis of outcomes, exploring patient subgroups, the ability to check data quality and performance of sensitivity analyses on key outcomes)

- includes both published and unpublished trial data including more treatment trials than previous meta-analyses
- the study was funded by Multiparty Group for Advice on Science Foundation through an unrestricted grant from Roche. However, neither party had a role in analysis, interpretation, reporting or the decision to submit for publication.

## 5. Limitations of review

- respiratory complications were not a pre-defined primary outcome for the original trials and specific diagnostic tests were not necessary. Some caution is warranted in interpreting these results, although incorporation of antibiotic use in the definition should enhance reliable reporting.
- For both pneumonia and hospitalisation for any cause, we noted significant differences but the numbers of events were small and so effect estimates are imprecise.
- The absence of a significant treatment difference for uncommon events might be explained by insufficient power to detect true effects even after data across studies was combined.
- this meta-analysis was for trials with a 5 day treatment duration. We did not study the benefits and harms of longer term use of oseltamivir e.g. in prophylaxis.
- Oseltamivir's effectiveness in the ITT population might not be generalisable because the percentage of participants infected might vary across populations in real-world experience. The balance of benefits and harms becomes less favourable if more non-infected participants are treated with oseltamivir. This highlights the value of additionally reporting results for the ITTI population.

## 6. Evidence for use of antivirals in specific scenarios

### *i. Seasonal and pandemic influenza:*

All trials in our meta-analysis were in seasonal influenza.

### *ii. Underlying health conditions that predispose to influenza complications (including pregnant women):*

All trials in our meta-analysis excluded pregnant women.
We performed subgroup analyses for high risk participants (65+ years, chronic obstructive airways disease at baseline, or in chronic illness trial) versus others in the intention-to-treat infected population. For the time to alleviation of all symptoms outcome, the time ratio of oseltamivir versus placebo was attenuated for high risk participants ('high risk' TR: 0.93 [95%CI 0.81, 1.07]; 'others' TR 0.75 [95% CI 0.69, 0.82], interaction p-value=0.0097). A (non-significant) attenuation in the relative risk reduction in high risk participants was also observed for the main LRTC outcome, although absolute risk reductions were greater in the high risk group ('high risk' RR: 0.70 [95%CI 0.49, 0.98], RD -5.4% [95%CI -9.0, -0.3], 12.5% oseltamivir vs 17.9% placebo) ; 'others' RR 0.39 [95% CI 0.23, 0.66], RD -2.7% [95%CI -3.4, -1.5], 1.7% oseltamivir vs 4.4% placebo, interaction p-value=0.070). Note: the majority of participants in the high risk group came from the elderly trials and chronic illness trial.

### *iii. Previously healthy people who develop severe influenza:*

The majority of the trials in our meta-analysis were in otherwise healthy individuals.

### *iv. Previously healthy people with influenza that is not (currently) severe ('treat all' approach):*

The majority of the trials in our meta-analysis were in otherwise healthy individuals. Thus our results should be generalisable to this population.

### *v. Severely ill individuals >48 hours after onset of symptoms:*

All trials in our meta-analysis were in participants who presented within 36 hours of onset of symptoms.

### *vi. Prophylaxis:*

All trials in our meta-analysis were treatment trials (not prophylaxis trials).

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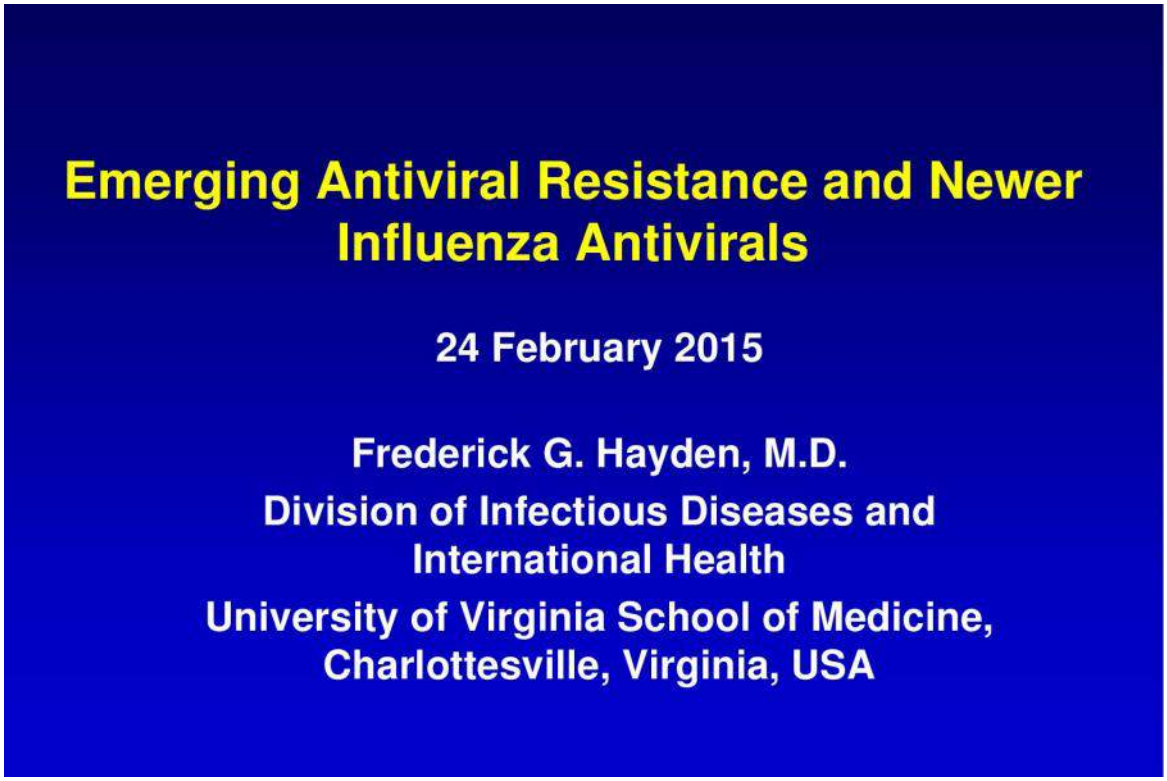
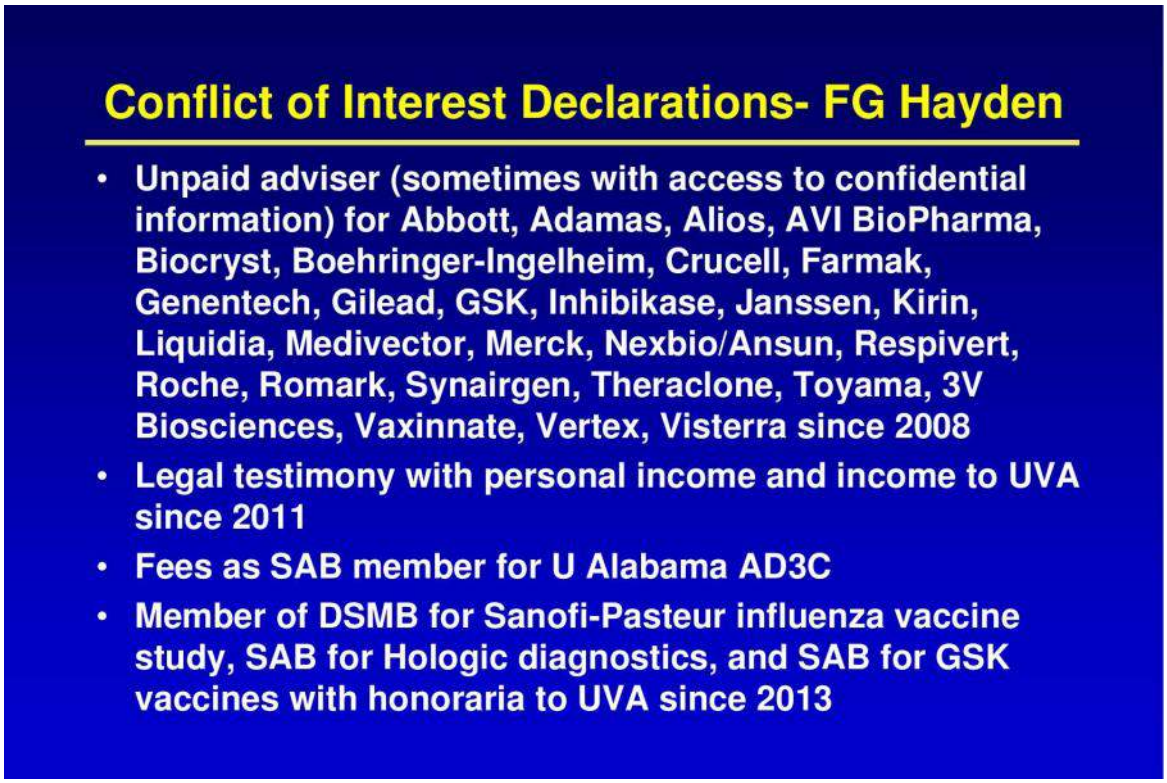
Professor Frederick G. Hayden's workshop slides:
Emerging Antiviral Resistance and Newer Influenza Antivirals



## Influenza Antiviral Resistance: *Comments*

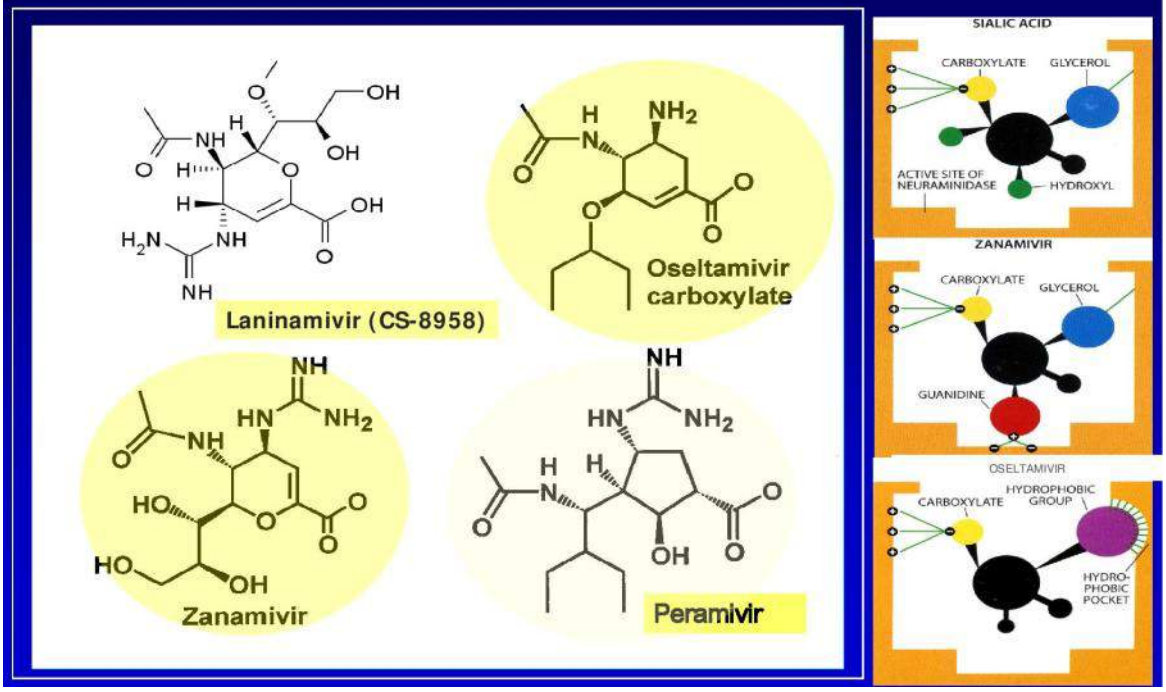
- Single nucleotide mutation → amino acid change in viral target can cause resistance.
- *In vitro* resistance to M2Is (S31N) or oseltamivir (e.g., H275Y in N1; R292K in N2/N9) is high-level and confers clinical resistance.
- Cross-resistance to entire M2I class, whereas NAI resistance is drug, NA, and substitution specific.
- Replication fitness and virulence of resistant variants is key to individual patient impact.
- Transmission fitness of resistant variants is key to public health impact.

## Features of Antiviral Resistant Influenza Viruses

| Feature | Seasonal A(H3N2) | Seasonal A(H1N1) | Pandemic A(H1N1)09 | Avian A(H7N9) |
|---|---|---|---|---|
| Resistance (substitution) | M2I (S31N) | Oseltam (H275Y) | M2I (S31N) | M2I (S31N) |
| Circulation | 2003- | 2007-9 | 2009- | 2013- (birds) |
| Sustained H2H transmission | Yes | Yes | Yes | No* |
| Virulence | Yes | Yes | Yes | Yes |
| Dual M2I + NAI resistance | Cases | Regional | Clusters | Cases |

*Inefficient respiratory ferret and GP of NAI-resistant (R292K) virus

## Neuraminidase Inhibitors




## Influenza A NAI Resistance Patterns

| NA change | NA subtype | Fold Δ in NA inhibition assay vs WT | | |
|---|---|---|---|---|
| | | Oseltamivir | Zanamivir | Peramivir |
| E119V | A/N2 | R (50->300) | S (1-3) | S (1) |
| R292K | A/N2 | R (>1,000) | S-R (1-35) | R (40-80) |
| R292K | A/N9 | R (>1,000) | I-R (11-62) | R (560->1,000) |
| H275Y | A/N1 | R (>300) | S (1) | R (50->300) |
| H275Y + I223R | A/N1 | R (>9,000) | I (22) | R (7,500) |

Mishin et al. AAC 49:4516, 2005; Wetherall et al. AAC 41:742, 2003; Yamashita et al. AAC 53:186, 2009; Baz et al., JID 201:740, 2010; Kiso et al., Lancet 364: 759, 2004; Nguyen et al., Antivir Ther 17:159, 2012; Yen et al., mBio 4(4): e00396-13, 2013; Sleeman et al., EID 19:521, 2013; Hai et al., Nat Comm 4:2854, 2013

## Treatment-Emergent Oseltamivir Resistance

| Study | No. treated | Group | Virus | % Resistance |
|---|---|---|---|---|
| RCT[1] | 598 | Outpt children + adults | A(H1N1)pdm09<br>H3N2 | 3.9<br>0 |
| Prospec-tive[2] | 1,041 | Outpt children 1-5<br><br>Outpt Adults | A(H1N1)pdm09<br>H3N2<br>A(H1N1)pdm09<br>H3N2 | 12.9<br>2.7<br>1.3<br>0.8 |
| RCT[3] | 151 | Outpt children | A | 6.7 |
| Prospec-tive[4] | 40 | Inpt children | H3N2 | 15.0 |

[1]Fry et al., Lancet ID 14:109, 2014; [2]Whitley et al., CID 56:1197, 2013; [3]Whitley et al., Ped Infect Dis J 20:127, 2001; [4]Kiso et al., Lancet 364: 759, 2004

## Recent Oseltamivir Resistance in Influenza A(H1N1)pdm09 Viruses

- 1.2% of 4,968 USA viruses had H275Y during 2013-14
  - Majority without drug exposure
- ↑ evidence for community transmission
  - Community cluster in Newcastle, Australia (2011)
- Since 2011, acquisition of enabling NA substitutions
  - V241I or N369K→ ↑ NA surface expression + activity
  - N386S/K→ loss of glycosylation site→ ? transmission
- Virus with H275Y/V241I/N369K- similar replication + illness and transmission fitness in ferrets

Okomo-Adhiambo et al., EID 21:136, 2015; Hurt et al., JID 206:148, 2012; Meijer et al., Euro Surveill 17:20266, 2012; Butler et al., PLoS Path 10(4): e1004065, 2014

## Influenza Antivirals in Clinical Development- Jan 2015

| Agent | Target | Spectrum | Route | Phase |
|---|---|---|---|---|
| Zanamivir | NA | A + B | IV | 3 |
| Peramivir *,+ | NA | A + B | IV | 4 |
| Laninamivir * | NA | A + B | Inhaled | 3 |
| Favipiravir * | Polymerase | A, B, C# | Oral | 3 |
| DAS181 | HA receptor | A + B, PIV# | Inhaled | 2 |
| Nitazoxanide | HA maturation | A + B# | Oral | 3 |
| VX-787 | Polymerase | A | Oral | 2 |
| MHAA4549A | HA | A | IV | 2 |
| AVI-7100 | M gene | A | IV | 1 |

Licensed in Japan*, S Korea + China + USA+

# Spectrum includes some non-influenza viruses

## Favipiravir: Summary of Pre-Clinical Findings


T-705

6-fluoro-3-hydroxy-2-pyrazinecarboxamide

Furuta et al., AAC 46:977, 2002; AVR 82:95, 2009; Smee et al., AAC 54:126, 2010; Baranovich et al., J Virol 87: 3741, 2013

- Inhibitory for influenza A, B, C viruses: $EC_{50}$s 0.01 - 0.5 µg/ml
  - Inhibitor of influenza RNA polymerase
  - Lethal mutagenesis
- Active orally in murine models of influenza
  - Additivity-synergy with NAIs
- Inhibitory for filo-, arena-, bunya-, flavi-, and picorna-viruses in animal models

## Favipiravir/T-705: *Comments*

- Approved in Japan (March 2014) for treating novel or re-emerging influenza infections when other drugs are ineffective or not sufficiently effective
- Oral administration
  - Complex human PK- loading doses
- Restricted use in pregnancy; no pediatric data
- RCTs in uncomplicated influenza in adults
  - Phase 3 study (Asia) – antiviral effects comparable to oseltamivir (Kobayashi et al., ICAAC 2011)
  - Phase 2 study in adults (ROW) – BID regimen with antiviral and clinical benefits (Epstein et al., Options 2013)

Journal of
Medicinal Chemistry



Article

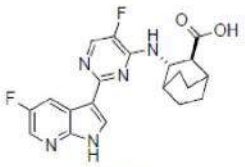
### The Discovery of a Novel, First-in-Class, Orally Bioavailable Azaindole Inhibitor (VX-787) of Influenza PB2

Michael Philip Clark, Mark Willem Ledeboer, Ioana Davies, Randal Byrn, Steven Jones, Emanuele Perola, Alice Tsai, Marc Jacobs, Kwame Nti-Addae, U Bandarage, Michael Boyd, Randy Bethiel, John Court, Hongbo Deng, John P Duffy, Warren Dorsch, Luc Farmer, Huai Gao, Wenxin Gu, Katrina Jackson, Dylan Jacobs, Joseph Kennedy, Brian Ledford, Jianglin Liang, Francois Maltais, Mark Murcko, Tiansheng Wang, Woods Wannamaker, Hamilton B Bennett, Joshua Leeman, Colleen McNeil, William Taylor, Christine Memmott, Min Jiang, Rene Rijnbrand, Christopher Bral, Ursula A Germann, Azin Nezami, Yuegang Zhang, Frank Salituro, Youssef L Bennani, and Paul S. Charifson

*J. Med. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/jm5007275 • Publication Date (Web): 14 Jul 2014

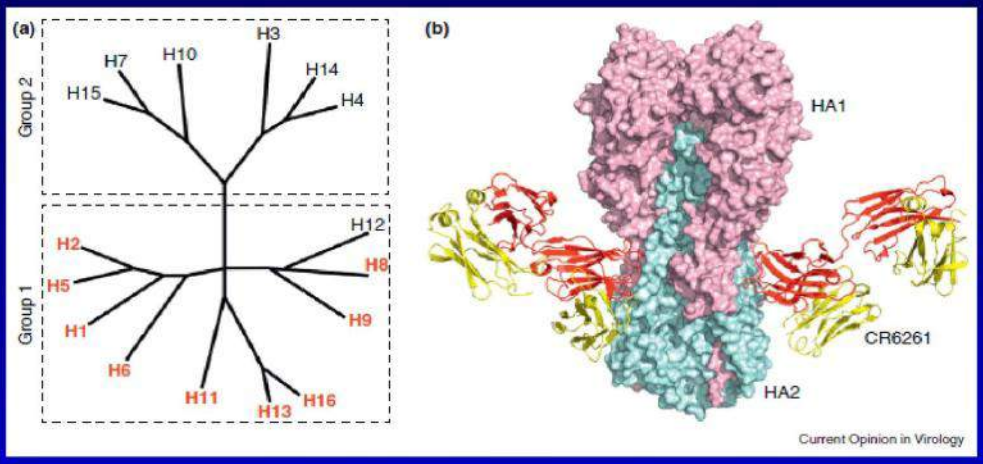


- 3-pyrimidine-azaindole derivative inhibitor of influenza A viruses
- Binds to PB2 cap-binding domain




VX-787 (2)

## Heterosubtypic Anti-HA Neutralizing MoAbs




- Human monoclonals that inhibit membrane fusion by binding to conserved regions in the HA stem in group 1, group 2, or both groups of influenza A HA subtypes

Ekiert + Wilson. Curr Opinion Virol 2:134, 2012

## Combination Antiviral Studies: *Comments*

- Increase antiviral potency→ ↓↓ replication → ↑ clinical effectiveness
- Prevent emergence of resistance
- Potential for dose sparing (↓ cost, ↓ AE risk)
- Ideally combine two (or three) agents with different mechanisms of action
  - Each effective when administered individually
  - Avoid adverse PK or AE interactions
- Proof of concept studies in pre-clinical models +/- phase 1 interaction studies

Dunning et al., Lancet Infect Dis 14:1259, 2014

## Ongoing Influenza Combination RCTs: Outpatients

| Combo | Control groups | Target population | Primary outcome | Trial phase |
|---|---|---|---|---|
| Amantadine + ribavirin + oseltamivir | Oseltamivir | High-risk 18+ yr (N = 1,200) | Viral clearance | 2 |
| Nitazoxanide + oseltamivir | Oseltamivir Nitazoxanide Placebo | Healthy 13-64 yr (N = 2,300) | Illness resolution | 3 |
| VX-787 + oseltamivir | Placebo VX-787 | Adults 18-64 yr (N = 500) | Illness resolution | 2 |

Source: ClinicalTrials.gov

## Ongoing Influenza Combination RCTs: Hospitalized Patients

| Agent | Control | Target population | Primary outcome | Trial phase |
|---|---|---|---|---|
| Immune plasma + SOC | SOC | Adults + SaO2 <93% or ↑ RR (N = 150) | LRT sign normalization | 2 |
| Hyperimmune IVIg + SOC | Placebo + SOC | Adults (N = 320) | Mortality, ICU care, suppl O2 | 3 |
| MHAA4549A + oseltamivir | Placebo + oseltamivir | Adults + suppl O2 or PPV (N = 334) | SpO2 >95% off suppl O2 | 2 |
| Azithromycin + NAI SOC | NAI SOC | Adults + LRTI (N = 100) | Cytokines + chemokines + mediators | 4 |

Source: ClinicalTrials.gov

## Newer Treatments for Influenza: *Comments*

- Progress in development of polymerase inhibitors, other novel antivirals, therapeutic antibodies, and combinations
- Need to identify more appropriate endpoints in studies of hospitalized patients
- Medical needs exist for more effective therapy of severe influenza and in at-risk patients, especially immunocompromised hosts.
  - Development of antiviral combinations
  - Selective host-directed or immunomodulatory interventions based on better understanding of disease pathogenesis

Thank You

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# Post-workshop comments: Professor Carl Heneghan

Professor Carl Heneghan
Nuffield Dept of Primary Health Care Sciences,
New Radcliffe House,
Oxford, OX2 6GG
Email: carl.heneghan@phc.ox.ac.uk
Evidence for Pandemic Influenza:

1. **Neuraminidase inhibitors for preventing and treating influenza in adults and children.**
   (Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya I, Mahtani KR, Nunan D, Howick J, Heneghan CJ. Cochrane Database Syst Rev. 2014 Apr 10;4:CD008965.)

- Oseltamivir and zanamivir have small, non-specific effects on reducing the time to alleviation of influenza symptoms in adults, but not in asthmatic children. These symptomatic benefits appear to be no better than common over the counter rescue medications.

> In eight zanamivir trials that reported on use of relief medication, in all participants the median days to alleviation in both the placebo and the treatment arms was less when compared to those who did not use relief medications (Table 6). In seven zanamivir trials, time to first alleviation of symptoms was also reported with and without rescue medication. Using these data we were able to compare zanamivir without rescue medication with placebo with rescue medication. Overall there was a non-significant 0.41 day decrease (95% CI 0.47 days lower to 1.29 days higher, $I^2$ statistic = 67%) in time to first alleviation of symptoms in the placebo with rescue medication group, suggesting that zanamivir itself is no better than rescue medication and possibly even less effective, although the varying levels of use of rescue medication in the seven trials did give rise to large heterogeneity (Analysis 3.68; Figure 6).

- It appears infection is not prevented but rather oseltamivir suppresses fever, reduces antibody response and viral shedding but does not reduce the risk of symptomatic illness. Classifying ILI as any occasion when patients had 2 or more of the symptoms (listed above). Based on that definition we found:
  a) Oseltamivir did not reduce ILI (RR 0.95, 95% CI 0.86 to 1.06);
  b) We found fever is reduced (RR 0.62, 95% CI 0.42 to 0.93);
  c) Proportion with lab confirmation is reduced (RR 0.59, 95% CI 0.41 to 0.85);
  d) Symptoms other than fever are not reduced (RR 0.96, 95% CI 0.86 to 1.07).

- Using either drug as prophylaxis reduces the risk of developing symptoms of influenza but both drugs have not been shown to prevent transmission. Similar to the FDA, because of the problems with the design of study WV15799 we could not draw any conclusions on the ability of oseltamivir to interrupt viral transmission.
  This is important, as the results of trial WV15799 formed part of the rationale for use of the drug to interrupt transmission from person to person and to allow time before the arrival of vaccines in the event of a pandemic, furnishing a seemingly powerful rationale for stockpiling oseltamivir.

a) All index cases were left untreated except for a paracetamol rescue pack (impossible to assess affects on nasal voidance);
b) Nasal viral voidance was measured only in symptomatic participants thereby missing out on potential asymptomatic infected people.

- Important populations including those admitted to hospital and those residing in nursing homes have been excluded from trials to date. (For example, Only 17 (1.8%) contact cases aged over 65 were included in trial WV15799 the household prophylaxis study used to underpin Public Health England's policy).

- Treatment trials with oseltamivir or zanamivir have not shown a reduction in complications of influenza (such as pneumonia). Most trials have a problem of a lack of diagnostic definition, IN oseltamivir trials 55% of event data - Self reported pneumonia (M76001; WV15670; WV15671; WV15707; WV15730; WV16277).

a) WV15670, secondary illnesses were patient reported;
b) No predefined list of secondary illnesses in the CSR (i.e. no mention of pneumonia, bronchitis, sinusitis or otitis in the protocol);
c) Nor did complications have anything to do with antibiotic treatment according to the protocol, nor does the CRF mention specific secondary illnesses by name;
d) There was no significant difference for the 5 trials that recorded "pneumonia" on a more detailed CRF (RR 0.69, 0.33 to 1.44).

- The use of oseltamivir increases the risk of adverse effects, such as nausea, vomiting, psychiatric effects and renal events in adults and vomiting in children.

- Lower bioavailability may explain the lower toxicity of zanamivir compared to oseltamivir.

**2. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials.**

(Dobson J, Whitley RJ, Pocock S, Monto AS. Lancet. 2015 Jan 30. pii: S0140-6736(14)62449-1. doi: 10.1016/S0140-6736(14)62449-1)

- If the results on hospitalisations were correct and we discounted the biases and the harms, then if the rate of circulating influenza in the population was 30%, (the rest was other viral infections referred to as influenza like illness) for every 1000 people treated 3 hospitalizations would be avoided.

- Rates of injury and poisoning were high.
*"injury and poisoning RR 3·37 (95% CI 1·08 to 10·47) P=0·036" (see table 2 in the paper).*

- There is no benefit of using oseltamivir in the elderly, given there was no symptom relieving effect in this age group (over 65 years).
*"The time ratio of oseltamivir versus placebo recipients was attenuated for high-risk participants (≥65 years or in chronic illness trial or chronic obstructive airways disease at baseline)." (See Figure 3 in the paper)*

- The main complication reported was lower respiratory tract complication more than 48 hours after randomisation requiring antibiotics. However, the Dobson paper confirms that the diagnosis of pneumonia was not based on a valid measure:
*"participant report and the investigator's clinical judgment" and not on objective measure such as x-ray*.
These lack of definitions were not originally reported in the earlier papers is a major issue that has led to confusion amongst those who make clinical decisions. But, the Dobson paper confirms there oseltamivir does not reduce pneumonia.

- The use of lower respiratory tract complications requiring antibiotics is not a clinically relevant outcome. Much of the reported effect on this outcome is driven by bronchitis, a condition for which antibiotics are not indicated, and acute bronchitis is often an indicator of respiratory syncytial virus (RSV) not influenza. We know from the results of a Cochrane systematic review "There is limited evidence to support the use of antibiotics in acute bronchitis.' (See box 1)

> Box 1: Antibiotics for acute bronchitis. Smith SM, Fahey T, Smucny J, Becker LA. Cochrane Database Syst Rev. 2014 Mar 1;3:CD000245. [2]Conclusions "There is limited evidence to support the use of antibiotics in acute bronchitis. Antibiotics may have a modest beneficial effect in some patients such as frail, elderly people with multimorbidity who may not have been included in trials to date. However, the magnitude of this benefit needs to be considered in the broader context of potential side effects, medicalisation for a self-limiting condition, increased resistance to respiratory pathogens and cost of antibiotic treatment."

- The Dobson paper used the same outcome as the Hernan study [3] of "oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms." This is puzzling as peer review should have picked up on the similarities of the analysis and that there was nothing new in this current paper, apart from one important deviation by Dobson, of only reporting complications beyond 48 hours, meaning the study had deviated from the important principle of intention to treat (see box 2).

> Box 2: Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomized clinical trials. Hernán MA, Lipsitch M. Clin Infect Dis. 2011 Aug 1;53(3):277-9. [3]Hernan methods:
>
> "Second, we included endpoints diagnosed during the first 2 days after randomization. These events were excluded by Kaiser et al [1] because they hypothesized that oseltamivir could have no effect during the first 2 days. Although reasonable, this approach deviates from the intention-to-treat principle used in many randomized trials, in which investigators refrain from making assumptions about the timing of effects and thus include all events after randomization in the analysis."

- The Dobson review analysed the infected group of patients separately, despite the fact our previous review had discovered compelling evidence that this population (the intention to treat influenza infected population) deemed to be influenza infected was not balanced between treatment groups in the oseltamivir trials. Furthermore results from the whole population (intention to treat population) are of use to clinical practice because routine testing for influenza is not used and is impractical.

- I am unsure how the definition of 21.5 hours was arrived at. Why not 22 or 23 hours? A more informative outcome, given the investigators had the IPD data would have been an analysis of those on and off rescue treatment (i.e. those taking paracetamol or not). There should be no reason why this analysis cannot and should not be done.

- From the Cochrane review results for the treatment of adults [4] there was no difference in rates of admission to hospital between treatment groups. (38/2663 in the hospital arm versus 32/1731 in the placebo arm). Dobson splits the results into the infected group, which is misleading as multiple subgroup results often leads to spurious findings. Even presenting this best-case scenario the absolute effect is small (1%) for those with influenza and non-existent for those with influenza like illness.

- In 2014 in the Annals of Internal Medicine, 7 out of 8 studies involving researchers with financial conflicts of interest came to positive conclusions about the effectiveness of neuraminidase inhibitors. But, only 5 of the 29 studies conducted by scientists who did not receive money had favorable outcomes. [5]

**Observational effects**

**3. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies.**
(Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, et al. Ann Intern Med. 2012 Apr 3;156(7):512-24.)

- The Hsu et al systematic review of observational data for antivirals for the treatment of influenza concluded therapy with NIs may provide a net benefit over no treatment.

- The confidence in the reported effects for decision making was rated by the authors as low to very low.

- The reported effect suggested oseltamivir is associated with a significant reduction in mortality (Odds Ratio [OR]: 0.23; 95% Confidence Interval [CI]: 0.13 to 0.43).

**Weaknesses that undermine the conclusions of this review.**

a) Many of the studies did not control for confounders (such as age or comorbid conditions);
b) Confounding by indication may have occurred, whereby likelihood of treatment varied by severity of disease or other important factors that were not measured. And even when adjusted analyses were available, there were author concerns that they did not use optimal adjustment;
c) For some outcomes, such as death, results only apply to hospitalized patients because the data were derived in this patient group;
d) a further critical weakness, is that the authors did not take account of the time-dependent nature of treatment exposure in their analysis; and
e) On further reading, the large reported effect on mortality in the Hsu et al review was based on only three studies of 681 hospitalized patients that adjusted for confounders (e.g., age, comorbid conditions or other known confounders).

- One of these studies, undertaken in Thailand, was a retrospective medical record review. The investigators called for caution in interpreting their results and report, 'Our small, retrospective, observational study has limitations with respect to establishing causality.' Only 22 fatal cases with laboratory confirmed influenza were included, and for all of these, the medical records were reviewed; however, of the 1466 non-fatal cases only 30% (n =445) were reviewed.

- The second study was also a retrospective review of clinical data. Medical data was obtained for 67 (72%) of 93 cases diagnosed with human influenza A (H5N1) in Vietnam. Oseltamivir was administered in 55 of the 67 cases. The effect was not statistically significant after stratification by age. The authors report, 'epidemiological data derived retrospectively from medical records are not robust.'

- The third study, of adult patients in Toronto requiring hospitalization, a population based surveillance study funded by contract with Hoffman-La Roche Ltd, was published initially as a supplement. The study noted a number of limitations. Only 63% of eligible patients were tested for influenza, data collection was by chart review which substantially limited the number of risk factors considered. The authors were concerned that 'undetected confounding may be present even in multivariable analyses.'

**4. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza A(H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients.**

(Muthuri SG, Myles PR, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam JS. J Infect Dis. 2013 Feb 15;207(4):553-63.)

- A second systematic review of observational studies on the impact of neuraminidase inhibitors (NIs) treatment during the 2009-2010 influenza pandemic 3 reported a non-significant effect of NIs when used at any time, OR 0.72 (95% CI 0.51 to 1.01), but observed a significant effect for early treatment upon mortality, OR 0.38 (95% CI 0.27 to 0.53). Treatment was not included as a time-dependent exposure in the analyses. Of the 44 studies that reported mortality included in the meta-analysis, only two compared NIs to no treatment and adjusted results for confounders. These two studies reported a non-significant effect upon mortality, OR 1.22 (95% CI 0.01 to 172.42).

- The first of these studies was a small observational study of 58 critically ill patients with A(H1N1) at 6 hospitals in Mexico. Of these, 52 (95%) were treated with antibiotics and 45 (78%) received NIs (oseltamivir [44], zanamivir [6]). No outcomes were provided on adjusted mortality rates apart from outcomes after excluding patients dying within 72 hours of onset. Confirmatory influenza testing was, however, often not available for patients who died rapidly. The second study was a cross-sectional study of 216 hospitalised patients in Iran with confirmed, probable, or suspected A (H1N1). The multivariate model of death reported a non-adjusted OR of 1.46 (95% CI 0.36 to 5.8) for oseltamivir use and an adjusted OR for death of 19.08 (95% CI 0.61 to 588).

**5. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data.**

(Muthuri SG, PRIDE Consortium Investigators, Nguyen-Van-Tam JS. Lancet Respir Med. 2014 May;2(5):395-404. doi: 10.1016/S2213-2600(14)70041-4. Epub 2014 Mar 19. Review.)

- Concluded that early instigation of NI treatment in adults admitted to hospital is warranted due to a significant effect on mortality, OR 0.81 (95% CI 0.70 to 0.93; p=0.0024).

**Weaknesses that undermine the conclusions of this review.**

a) The data collection to assemble the cohort was not systematic as it only included data from 78 (19%) of 402 potential centres;

b) the study was funded by Roche, the manufacturer of oseltamivir, which has been shown previously to be due to systematic bias favouring manufacturer products and leads to an industry bias that the authors of a Cochrane review on industry sponsorship and research outcome conclude cannot be explained by standard 'Risk of bias';

c) the investigators themselves acknowledge clear limitations in that they were unable to adjust specifically for disease severity due to the heterogeneity of severity measures;

d) There was a substantial amount of missing data (of 34,970 eligible patients 10% had missing data for exposure to NIs), missing patients were more likely to be older, treated with antibiotics and present later. This is further compounded as 2,095 (6%) of the 34,970 patients also had missing data for mortality status;

e) Investigators do not mention, and do not make an attempt to assess, the quality of the included studies, standard practice in systematic reviews, or for anyone assembling a retrospective cohort. This practice allows an assessment of the evidence and also subgroup analysis of the higher quality studies;

f) They were unable to adjust for vaccination and to adjust for steroid use prior and after admission; and

g) Of the included set of patients admitted to hospital only 1,600 (5%) were aged 65 years or older: an important at risk group of subjects that guidance is aimed at.

- In addition, early NI treatment compared with later treatment was associated with a reported reduction in mortality (adjusted OR 0.48 [95% CI 0.41 to 0.56]). However, later treatment with NIs led to increased mortality compared to no treatment (crude OR 1.27 [95% CI 1.00-1.61], adjusted OR 1.20 [95% CI 0.93-1.54]). This issue is further compounded when you consider the crude mortality rates were 9.2% (959/10 431) without treatment and 9.7% (1825/18 803) after exposure to neuraminidase inhibitor treatment.

- An inappropriate choice of analysis of time-dependent exposures in observational studies leads to time-dependent bias. We have known for some time that time-dependent bias is common amongst journal publications, often affects key factors, including the study's conclusions, and leads to changes in the conclusion in over half of studies.

**6. Assumptions that randomized trials are not feasible, or ethical, in pandemic situations are unjustified.**

- Based on a 10% mortality rate a sample of 864 patients is required to detect a decrease in the primary outcome measure from 10% in the control group to 5% (80% chance of detecting significance at the 5% level). This number falls to 382 patients assuming the 70% relative reduction observed in the Hsu et al review.2

**References**

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# Post-workshop comments:
# Summary of the Roche response to the Cochrane review

## Key points summary of the Roche response to the Cochrane acute respiratory infections group review of neuraminidase inhibitors.

The following summary information is based on the Roche detailed response to the Cochrane review of neuraminidase inhibitors (web link below) but focused on addressing a number of issues that were commented on during the Wellcome Trust and The Academy of Medical Sciences meeting in London Feb 24th 2015.

The full text of both the Cochrane review and the Roche full response can be found at the following link: http://editorial-unit.cochrane.org/cochrane-review-neuraminidase-inhibitors-influenza

With specific reference to the discussion in the recent meeting Roche would like to draw attention to the following points.

**Safety: (see Roche full response section 4.1 for more detail)**

**The gastrointestinal (GI) side effects** noted by Cochrane were not new findings and are clearly labelled adverse drug reactions. The observed rate of vomiting and/or nausea across key randomized treatment trials used for initial licensing was approximately 10%. It is also worth noting that these effects typically only occur with the first 1 or 2 doses and then subside and can be ameliorated by taking the medicine with food.

In the case of **renal effects**, the "marginal" significance observed by the Cochrane authors in prophylaxis studies (not seen in treatment studies) was based on a post-hoc analysis using a statistical model (Peto). The Peto methodology is known to produce biased estimates of an odds ratio when there is treatment allocation imbalance, as was the case for oseltamivir prophylaxis studies. Extensive pharmacovigilance monitoring over many years did not demonstrate any association between oseltamivir and renal impairment. Based on comprehensive analyses of the Roche safety database, clinical trial database and published literature, the EMA's Pharmacovigilance Risk Assessment Committee noted in April 2013 that no association between reported renal events and oseltamivir was observed. The oseltamivir label clearly states that no dose adjustment is required unless renal function drops below CrCL = 60ml/min, which is roughly half normal adult function, therefore typical renal function in an elderly patient without significant renal disease would not usually require any dose adjustment or assessment of renal function prior to dosing. Moreover, oseltamivir has a wide therapeutic window and treatment, even in patients with CrCL<60ml/min, would be expected to have an acceptable safety profile. This is supported by our experience in patients with end stage renal disease undergoing dialysis. In these patients, dose adjustment is indicated in the label, not for reasons of safety but to optimize exposure to the known efficacious range given their much diminished renal function. Their exposures tend to exceed that of patients with normal renal function but remain well tolerated and within a range for which we have clinical experience (Robson 2006).

**Neuropsychiatric adverse effects (NPAE), (see Roche full response section 4.3.3 and 4.3.6 for more detail)**

The Cochrane authors' conclusions are based on:

- A post-hoc analysis of adult prophylaxis studies, combining on- and off-treatment periods in an attempt to maximize the number of psychiatric events included in the analysis, given the planned analysis of on-treatment data approached but did not reach statistical significance (lower 95% confidence limit of RR= 0.97).
- A dose-response model based on psychiatric AE events data – the underlying data as verified by Roche do not indicate a monotonic response.

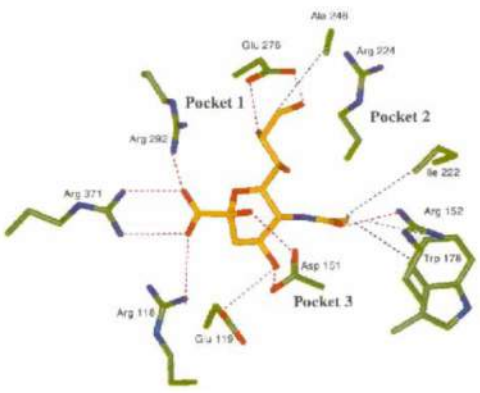
In addition, NPAEs have been the subject of close scrutiny both by Roche and global regulatory agencies over the years. As an example, minutes of the last of a series of FDA Paediatric Advisory Committee (PAC) meetings held in 2012 (link in references), noted that through the intensive pharmacovigilance periods, including the 2009 pandemic, no causal link could be established between oseltamivir and NPAEs. None of these regulatory agency reviews or their findings is mentioned in the Cochrane review. Our own internal analyses have found no evidence of a causal link either and these have been published (Toovey et al., 2008 and 2012).

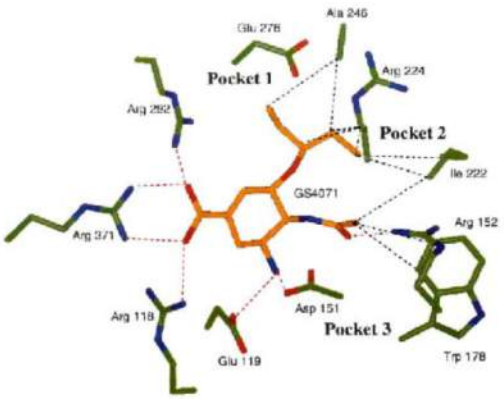
In summary the Cochrane findings are from post-hoc analyses of select studies, do not represent the totality of evidence and are inconsistent with the many other analyses conducted.

**Mode of action: (see Roche full response section 5.1 for more detail)**

The Cochrane authors have repeatedly asserted the idea that oseltamivir is not an influenza specific anti-viral. On p27 of the most recent Cochrane review they again state "the influenza virus specific mechanism of action proposed by the producers does not fit the clinical evidence". Roche would like to point out there is considerable evidence supporting the mode of action not mentioned in the Cochrane review. Specifically:

*Rational design:* oseltamivir was a product of rational drug design, with data from high-resolution X-ray crystal structures of the influenza receptor (sialic acid) bound to the viral neuraminidase used to identify oseltamivir as a potent and specific inhibitor of influenza A and B neuraminidases (Lew, 2000).



***Figures reproduced from Lew, 2000. On the left, the natural substrate sialic acid is shown bound in the active site of the viral neuraminidase. On the right side oseltamivir bound in the active site.***

*Highly specific*: a package of *in vitro* testing was performed to establish the specificity and potency of oseltamivir. Oseltamivir has been studied in *in vitro* cell-based assays, and shown to specifically inhibit influenza neuraminidases with little or no activity against other viral, bacterial or mammalian (including human recombinant origin) neuraminidases, tested up to high supra-therapeutic concentrations. Specificity of oseltamivir was also demonstrated by screening activity against a range of 155 molecular targets (including receptors, ion channels and other enzymes), confirming the lack of any relevant off-target activity (Lindemann et al., 2010). Enzyme sensitivity has been shown to represent a more predictive indicator of in vivo sensitivity, with electron microscopy studies showing the action of oseltamivir on viral particles.

*Efficacious: in vivo*, oseltamivir has shown efficacy when given as a treatment or prophylaxis against various influenza A and B virus strains in a range of models, including mouse, ferret and chicken (avian influenza) at clinically relevant doses of oseltamivir (systemic exposure similar to humans receiving a 75 mg dose of oseltamivir b.i.d.). Efficacy in animals translates to efficacy in humans with clinical data published for treatment and prevention in adults and children (Treanor et al. 2000; Nicholson et al. 2000, Whitley et al. 2001, Welliver et al. 2001; Hayden et al. 2004)

*Clinically specific:* moreover, despite commenting on the apparent lack of "fit" of the clinical data, the review does not consider data from patients who were confirmed as influenza negative by laboratory test. The lack of effect of oseltamivir treatment on alleviation of symptoms in these patients demonstrates the same influenza-specific anti-viral mechanism in patients as seen pre-clinically (see full response page 47, with findings corroborated in recent publication; Dobson et al., 2015).

**Central/off-target effects: (see Roche full response section 4.3.5 for more detail)**

The Cochrane authors stated that "animal toxicity study results firmly support the effect of oseltamivir on the central nervous system." This statement, based on two publications (Kimura et al., 2012; Freichel et al., 2009), is not presented in context. In summary, doses used in these studies would not allow the type of direct translation of adverse findings to the clinically approved dose suggested by the Cochrane authors. In the Kimura study oseltamivir phosphate (OP), the pro-drug, was dosed from 30-200 mg/kg intravenously and 500-1,000 mg/kg intraduodenally in anaesthetized animals, doses which would be estimated to result in plasma exposures (OP and oseltamivir carboxylate (OC) the active metabolite) substantially higher than those seen in patients receiving the approved therapeutic dose. The Freichel publication (a Roche toxicology study) aims to evaluate the effect of supra-therapeutic doses of OP (300 - 1,000 mg/kg, PO) on adverse effects, especially in younger children, and is part of the pre-clinical rationale supporting the safety of dosing infants. In the Cochrane review it is not pointed out that this study clearly shows the lowest dose of 300 mg/kg OP produced no observed adverse effects in juvenile rats and this dose produces exposures approximately 1000 and 45 fold above clinical therapeutic exposure for OP and OC respectively. Indeed the authors of the Freichel publication conclude that the effects observed at very high doses of OP (500 – 1,000 mg/kg) were likely due to general moribundity i.e. a non-specific systemic toxicity typical of that seen with extreme high dosing with many medicines, but of no clinical relevance whatsoever.

Exposure in the central nervous system (CNS) to both OP and OC were explored in animals (Hoffmann et al 2009; Freichel et al., 2009) and in healthy volunteers (Jhee et al.,2008) both showing very low penetration of the CNS. Specifically in healthy volunteers <3% of plasma levels could be measured in cerebrospinal fluid (CSF).

In addition, oseltamivir screening against a wide range of molecular targets, including assessment of activity of high concentrations of OP and OC against human neuraminidases and targets of high relevance for mood, cognition and behaviour (including $GABA_A$ binding and patch clamp experiments) was able to demonstrate no relevant interactions (Lindemann et al., 2010).

Collectively this data shows very limited penetration of oseltamivir and oseltamivir carboxylate into the CNS is expected in patients and a lack of any evidence that oseltamivir has an identifiable pharmacological mechanisms of action within the CNS that may result in abnormal neuropsychiatric findings.

**Impact on antibody production: (see Roche full response section 5.2 for more detail)**

Cochrane authors have proposed that oseltamivir *treatment* has an impact on a patient's ability to mount an antibody response to influenza infection. They argue that there is consequently an inherent bias in the efficacy analyses of oseltamivir trials as post-baseline serology data have been used to determine infection for some patients, Cochrane Analysis 1.3 [adult treatment] (Risk Ratio (RR) of 0.95 (95% Confidence Interval (CI), 0.91 – 0.99).

Roche conducted a similar analysis, differing from the Cochrane analysis 1.3 in the following ways: exclusion of the 150mg oseltamivir arm (not the licensed dose); correction of data anomalies observed in the Cochrane analysis; the use of a random effects model (R version 3.0.3). This yielded a RR of 0.96 (95% CI, 0.91-1.00), indicating that there is no statistical difference in the overall proportion of infected patients in the randomised placebo group compared with oseltamivir 75mg b.i.d.

Furthermore, even when Roche conducted an analysis including only patients whose infection was based on serology alone (i.e., no supporting virology infection), there was still no evidence of an imbalance between treatment groups (RR 0.96 (95% CI 0.87 – 1.06). In summary, there is no statistical evidence of bias introduced by the use of serology data in the efficacy analyses of oseltamivir trials.

The Cochrane authors have wrongly attempted to extend their analyses of a potential antibody effect in the setting of *prophylaxis*. There are 2 reasons it is inappropriate to attempt this analysis (1) the intended effect of prophylaxis confounds such an analysis (2) the studies were not designed to assess this putative effect.

With respect to point (1) above, given that an antibody response will only follow an infection and given that an effective prophylactic drug will show a reduction in the number of infections in the active group compared with the control in a properly designed clinical trial, it follows that there will also be a reduction in the number of patients with an antibody response in the active compared with the control. In other words, an imbalance of serological outcome in the prophylactic setting is expected, so such results cannot be used to support any claim on a detrimental impact of oseltamivir treatment on antibody response.

**Randomized controlled trials within the context of the total evidence base:**

RCTs are the accepted gold standard in terms of study design and the strength of evidence these types of studies provide. The RCTs Roche has conducted over the years for oseltamivir provide much of the basis for our product labelling. However no complete understanding of an established medicine can be achieved by only considering RCT data. For example, in order to make a robust assessment of safety, all data must be evaluated, including all relevant clinical studies (RCTs, observational studies, etc.), published literature and spontaneous safety reports. It is this total dataset that Roche and regulators worldwide review on a continuous basis to arrive at a thorough and reliable assessment of the safety of a medicine. Where treatment guidelines are concerned it is normal practice in any therapy area for expert bodies to consider the totality of evidence when arriving at recommendations. Of course evidence can and should be weighted but it comes in all forms from the non-systematic observations of a clinician in a case or case series to the RCT and all points in between and all forms warrant consideration. In the case of oseltamivir, the RCTs clearly describe its key benefits in uncomplicated seasonal influenza, e.g. reductions in duration of symptoms and viral shedding and point to additional benefits on complication reduction. These latter important observations have been corroborated by the many observational/real world data studies that have examined that question in larger datasets (Blumentals 2007; Gums 2008; Nordstrom 2005; Peters 2008; Piedra 2009; Shi 2014; Yu 2010). Most recently a highly valuable impact on mortality in the pandemic was demonstrated (Muthuri 2014). The totality of the evidence, has and still does, point to the appropriate use of oseltamivir as a valuable public health intervention. Finally, this is not an argument just for oseltamivir. The approach to medicine development is evolving and increasingly regulators and payers consider not just what RCTs tell us of the value of a medicine but also real world data. (Questions and Answers following the initial experience of the Adaptive Licensing Pilot project EMA/417706/2014; full link in references)

**Conclusion:**

Overall, Roche has identified many inaccuracies and inconsistencies with the approaches taken by the Cochrane authors in their review, including the methodology used and assumptions made; The Roche full response runs to some 70 pages and documents the main issues we have identified across the range of their analyses and interpretation. As a result, Roche believes that the Cochrane authors have made inappropriate statements about the mode of action, efficacy and safety of an important and long-established medicine. This has led to the Cochrane authors drawing conclusions that risk unnecessarily confusing both patients and physicians and could lead to public health risks owing to either patients not complying with their prescribed medicine or an antiviral doesn't get prescribed where it could be beneficial.

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