

Table of contributions

European Centre for Disease Prevention and Control. Table of contributions for the expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza – review of recent systematic reviews and meta-analyses. Stockholm: ECDC; 2017

Number	Name/organisation	Contribution	ECDC assessment
1	Chris Butler, University of Oxford	Primary care clinicians are coming under increasing pressure to prescribe neuraminidase inhibitors in primary care, despite a sub-optimal evidence base from primary care to support this. We know from your review of reviews that neuraminidase inhibitors shortens the duration of ILI and influenza. However, there has never been an open, pragmatic, publically funded trial of cost effectiveness in routine care to guide whether or not these agents provide useful benefit in routine primary care, and if they do provide benefit, identifying which patient subgroups are most likely to benefit. Open trials (i.e. not placebo controlled) are the best design for determining cost effectiveness. Your focus for recommendations is largely on placebo controlled trials. My view is that you should also consider commenting on the research gap that exists regarding publically funded, large, open, pragmatic trials of cost effectiveness in primary care. Please see http://www.prepare-europe.eu	While this expert opinion did not assess the evidence related to cost-effectiveness, a passage on this is added to page 20.
2	Barry Clinch, Roche Products Ltd.	<p>Roche welcomes this new report addressing the utility of neuraminidase inhibitors for the treatment and prevention of influenza. The findings of the ECDC assessment of recent systematic reviews and meta-analyses are in line with previous evaluations and current treatment guidance, and support the value of neuraminidase inhibitors, including oseltamivir, as part of the armamentarium for tackling seasonal and pandemic influenza.</p> <p>Influenza remains a significant cause of morbidity and mortality globally, and Roche continues to be active in the field of antiviral medicines for influenza. More than 16 years after the first registration of Tamiflu, we continue to generate new evidence in support of Tamiflu in special populations, with studies ongoing to address unmet needs and knowledge gaps in immunocompromised adults and children (CT.gov identifiers: NCT00545532 and NCT01715909; EudraCT identifiers: 2006-002468-24 and 2012-002633-11).</p> <p>In addition, Roche continues to pursue research into new influenza antivirals. Of note, a phase II trial of a novel antiviral for the management of severe influenza is ongoing (CT.gov identifier: NCT02293863; EudraCT number: 2014-000461-43). Roche has also entered a licensing agreement to co-develop a new small molecule drug with a novel mode of action. Roche is committed to developing these new medicines to improve outcomes for patients and to reporting the results of trials to the scientific community.</p> <p>Roche is aware of the criticism levelled at Tamiflu by the Cochrane review in 2014 and has previously provided a detailed response to that review directly to the Cochrane editorial board. This detailed response can be found at the following location: http://editorial-unit.cochrane.org/cochrane-review-neuraminidase-inhibitors-influenza.</p>	Added passage on page 20 on studies in immunocompromised persons. Section 'New antivirals' on p 37 already refers to work ongoing with novel antivirals. ECDC cannot refer to development of small molecule drugs without knowledge of which molecule is being discussed. ECDC is aware of the correspondence published on the Cochrane website.
3	Wouter Havinga, NHS Primary Care	(p. 11 line 386): as such similar to antibiotics considering the RCGP's antibiotic advice leaflet http://www.rcgp.org.uk/clinical/target-antibiotics-toolkit/~media/Files/CIRC/TARGET/Patient-Antibiotic-leaflet.ashx which discourages antibiotic use (also to prevent resistance) when there seems to be a similar 'benefit' of reducing time of 'ill health' e.g. see Del Mar's evaluation of antibiotic for sore throat which also mentions a reduction of duration of symptoms by 16 hrs http://www.ncbi.nlm.nih.gov/pubmed/15106140 - antivirals should be discouraged in primary care.	Current evidence does not support the view that use of neuraminidase inhibitors is a strong driver of the development of antiviral resistance (see page 3), therefore this comparison with antibiotics appears not to apply to neuraminidase inhibitors.
4	Marianne van der Sande, RIVM Centre for Infectious Disease Control	Just one comment on page 15: the statement 'pregnancy is a known risk factor for severe influenza disease' seems to be only supported by data from the pandemic. I think this is insufficient to extrapolate to risks for pregnant women from seasonal influenza. Risk groups are known to differ for pandemic and seasonal, so it cannot be assumed this will be the same for pregnant women and there are definitely studies which did not find an increased risk for pregnant women in seasonal influenza (eg Merk et al, Vaccine 2014). So the verdict may still be out on that?	We agree and have reflected this in changes to the text on p.3 and p.15. Furthermore, we have changed the recommendations for pregnant women in Table 6, based on other public comments.

Number	Name/organisation	Contribution	ECDC assessment
5	Dr Rachel Quinn Director, Medical Science Policy The Academy of Medical Sciences	Could our report [http://www.acmedsci.ac.uk/file-download/38069-561595082cd83.pdf] be considered as our contribution to your consultation please?	The joint report from the Academy of Medical Sciences and the Wellcome Trust is considered and a reference added to page 22.
6	Rokuro Hama, NPO Japan Institute of Pharmacovigilance; Tom Jefferson, Centre for Evidence-Based Medicine, Oxford Carl Heneghan, Centre for Evidence-Based Medicine, Oxford	<p>Introduction As the ECDC advice has many limitations, we would like to comment on it as follows:</p> <p>Contents of our comments:</p> <p>1. On the analysis methods</p> <p>1.1. On the principles of analysis methods in general 1.2. For the systematic review of treatment 1.2.1. The population: ITT population should be used for efficacy analysis. 1.2.2. Exclusion or inclusion of high dose groups 1.2.3. All hospitalizations 1.2.4. Pneumonia and bronchitis 1.2.5. Note that reduction of antibody production is related to the mechanism of action of symptom relief 1.2.6. Efficacy in non-influenza ILI 1.3. For the systematic review of prophylaxis: Discussions are needed by taking ‘false negative effect’ into account both for ECDC advice and for our own.</p> <p>2. On the data of individual results</p> <p>2.1. Treatment trials 2.1.1. Efficacy: complication especially on serious events leading to treatment withdrawal and hospitalization. 2.1.2. Harm: antibody production, QT interval, cardiovascular events. 2.1.2.1. Antibody production 2.1.2.2. QT interval and other cardiovascular events 2.1.2.3. Psychiatric events, injury and poisoning 2.2. Prophylaxis trials 2.2.1. Efficacy in prophylaxis trials: 2.2.2. Harm in prophylaxis trials: 2.2.2.1. Psychiatric reactions 2.2.2.2. Injury and poisoning 2.2.2.3. Other adverse reactions 2.2.2.3.1. Renal impairment 2.2.2.3.2. Hyperglycemic of diabetic events, and pain in limbs 2.2.2.3.3. Headaches</p>	Numbering below according to comments by Hama et al.

3. Evidence from non-randomised studies

3.1. Epidemiological studies suggesting neuropsychiatric adverse reactions to oseltamivir:

3.1.1. Prospective cohort studies and their systematic review and meta-analysis.

3.1.2. Proportional reporting ratio for abnormal behaviours especially of fatal outcome.

3.2. Adverse effects on mortality

3.2.1. Observational studies do not support protective effect on mortality

3.2.2. Epidemiological evidence suggesting sudden deterioration leading to death following oseltamivir use:

3.3. Adverse effect on pregnant women, foetus and newborns

4. No discussion on the mechanisms of action and reactions of oseltamivir

4.1. Oseltamivir act on the central nervous system (CNS) both as depressant and as stimulants.

4.1.1. Juvenile (7-day-old) rats and mature rats (intraduodenally and intravenously)

4.1.2. Oseltamivir has hypothermic effect on animals by inhibiting nicotinic acetylcholine receptor.

4.1.3. Oseltamivir induces abnormal behaviours by inhibiting MAO-A.

4.1.4. Oseltamivir has various other effects on CNS such as impairment of sensory system, impairment of cognition, impairment of alertness other than respiratory depression.

4.2. Oseltamivir has symptom relieving effects by inhibiting host's endogenous neuraminidase, not by inhibiting viral load.

4.2.1 Label of oseltamivir does not state viral load reduction

4.2.2. Experiments indicate inhibition of host's endogenous neuraminidase, but not viral load

4.3. Inhibiting host's endogenous neuraminidase may be related with adverse effects of NIs

5. Efficacy and effectiveness in risk groups

6. Conflict of Interest

7. Conclusion

Note: we cite the same reference number as in the ECDC report if the document is cited in the ECDC report. We cite the reference number serially after 51 if they are not referred in the ECDC report.

1. On the analysis methods

1.1. On the methods of systematic review and analysis

On Cochrane's systematic review, ECDC reported:

267 In 2014, Jefferson et al. published a meta-analysis of study-level data gathered from reports of published and
268 unpublished randomised, placebo-controlled trials and regulatory comments and presented the results in the
269 Intervention Review 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children
270 (Review)' [14-16]. This is the fifth and most extensive review of NAIs by the Cochrane group.

271 The review team identified study reports through trial registries, electronic databases and regulatory archives and
272 corresponded with manufacturers to identify all randomised, placebo-controlled trials on adults and children with
273 confirmed or suspected exposure to naturally circulating influenza. Many study reports had, until then, been
274 confidential and available only to respective manufacturer and reviewing regulators. For inclusion, studies were
275 evaluated for quality using CONSORT criteria, and risk of bias in each analyses was quantified using a Cochrane
276 'risk of bias' tool.

277 Data from 46 clinical trial study reports were analysed for time to first alleviation of symptoms, influenza outcomes,
278 complications, hospitalisations and adverse events in the intention-to-treat (ITT) population. The analysis included
279 20 studies which assess oseltamivir with 9 623 participants, and 26 studies which assess zanamivir with 14 628
280 participants.

On Dobson's review, ECDC reported:

299 In 2015, Dobson et al. published 'Oseltamivir treatment for influenza in adults: a meta-analysis of randomised
300 controlled trials' [17].

301 This report is a meta-analysis of individual adult patient data from twelve randomised placebo-controlled clinical

	<p>302 trials with a total of 4 328 participants using the dose of 75 mg twice a day. They report data on an intention to 303 treat population (ITT) as well as on an intention to treat (influenza) infected population (ITT-I). 307 A comparison of clinical trials included in the analyses by Jefferson et al. and Dobson et al. are presented in Table 4. 308 These meta-analyses included 11 RCTs in common. As ECDC described above, unlike Cochrane systematic reviews [14], Dobson’s report [17] (1) did not review prophylaxis trials (2) did not disclose protocol pre-specified at the outset, which the authors should not deviate from, or if they do should be explained. (3) did not perform a quality assessment of the evidence, and as such, the Roche funded study doesn’t meet the criteria for a systematic review.</p> <p>1.2. For the systematic review of treatment ECDC compared Cochrane’s review [14] and Dobson’s [17], but picked up only the results that favors oseltamivir and did not discuss the difference of methodology and rationality of methods. Dobson’s results [17] are different from our results [14]. It seems the difference is due to (1) The difference of populations analysed, (2) Exclusion or inclusion of high dose groups, and (3) We included all hospitalisations; rather than the availability of individual patient data (IPD).</p> <p>1.2.1. The population: ITT population should be used for efficacy analysis. One of the most important things that we found during the analysis process of oseltamivir, is the fact that oseltamivir use affected not only the outcome but also the initial inclusion or exclusion of analysis population by affecting the diagnosis of influenza, if ITT-I (intention to treat infected) population is used as population for the assessment of efficacy. This is derived from one of the most important action of oseltamivir on antibody production due to suppression of host’s endogenous neuraminidase. We reported that oseltamivir reduced the odds of patients having four-fold antibody rise by almost 20 % [51]. In the recent review [14], we reported RR=0.92 by expressing relative risk. If it is expressed by odds ratio, OR= 0.82 (95%CI: 0.70, 0.95, p= 0.01). Influenza-infection was diagnosed by the results of antibody testing which is affected by oseltamivir but not by placebo. This means that some influenza patients were miss-classified from the ‘infected population’ to the ‘non-infected population’ in the oseltamivir group due to false negative testing. As a result, the ITT-infected population is biased: patients with influenza whose antibody response were poor were excluded from the ITT-infected population in the oseltamivir group leading to greater apparent benefit compared to the ITT-non-infected population. 51: Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev. 2012 Jan 18;1:CD008965. doi: 10.1002/14651858.CD008965.pub3</p> <p>1.2.2. Exclusion or inclusion of high dose groups The excluded high dose group in WV15671 included four hospitalized patients, while there were two in the 75mg b.i.d group and one in the placebo group. If oseltamivir decreases hospitalization, high dose groups should exhibit a more beneficial effect but they did not. Moreover, the trends were the reverse.</p> <p>1.2.3. All hospitalisations To resolve the confusing number of hospitalizations in the clinical study reports, we obtained the complete list of hospitalized patients from Roche. In comparison, the numbers in Dobson’s review are generally smaller in the oseltamivir group. Even if we include the Japanese data (which is the only different RCT that we did not include because of unavailability of CSRs), we get pooled RR (0.85: 95% CI: 0.53 to 1.34, p= 0.48) compared to Dobson’s results (RR: 0.61, p>0.05) [17]</p> <p>1.2.4. Complication: pneumonia and bronchitis Pneumonia: 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. Why these lack of definitions were not originally reported in</p>	<p>1.2.1 Added sentence into penultimate paragraph of page 8 to acknowledge the possible effect of oseltamivir on decreasing antibody production and subsequent potential for misclassification.</p> <p>1.2.2 The comments on this single trial are acknowledged and do not affect the text of the Expert Opinion that is based on an overall assessment of the cited systematic reviews.</p> <p>1.2.3 Comments on acknowledged and do not affect the text of the Expert Opinion which is based on assessment of the published peer-reviewed systematic review findings.</p> <p>1.2.4 Comments are acknowledged and a reference to Hernán and Lipsitch added on p. 10.</p>
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the earlier papers is a major issue that has led to confusion amongst those who make clinical decisions.

Bronchitis-antibiotic:

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. 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

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.'
Ref. Smith SM, Fahey T, Smucny J, Becker LA. Cochrane Database Syst Rev. 2014 Mar 1;3:CD000245 [52]

Furthermore, the Dobson paper [17] used the **same outcome** as the Hernan study 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 randomised clinical trials.

Hernan methods:

'Second, we included endpoints diagnosed during the first 2 days after randomization. These events were excluded by Kaiser et al 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.'
Ref. Hernán MA, Lipsitch M. Clin Infect Dis. 2011 Aug 1;53(3):277-9 [53]

References

52. Smith SM, Fahey T, Smucny J, Becker LA. [Antibiotics for acute bronchitis](#). Cochrane Database Syst Rev. 2014 Mar 1;3:CD000245. doi: 10.1002/14651858.CD000245.pub3.
53. Hernán MA, Lipsitch M. [Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomized clinical trials](#). Clin Infect Dis. 2011 Aug 1;53(3):277-9. doi: 10.1093/cid/cir400. Epub 2011 Jun 15.

1.2.5. Note that reduction of antibody production is related to the mechanism of action on symptom relief (as described later in the section 4.2 Oseltamivir has symptom relieving effects by inhibiting host's endogenous neuraminidase, not by inhibiting viral load).

1.2.6. Efficacy in non-influenza ILI

ECDC report:

381 Neuraminidase inhibitors treatment does not show any efficacy in those with ILI due to pathogens other than 381 influenza virus (non-influenza ILI) [14].

We have no data for adequate assessment of influenza-like illness (ILI) in any treatment CSRs of oseltamivir. In addition, oseltamivir induce false negative results of influenza testing (antibody production, culture and PCR) and negative results do not mean 'ILI due to pathogens other than influenza virus (non-influenza ILI)'. Hence, it is inappropriate for ECDC to say in the line 380 to 381 'NI treatment does not show any efficacy in those with ILI due to pathogens other than influenza virus (non-influenza ILI)'.

In subgroup analysis of time to first alleviation of symptoms in adults by infection status, we found no evidence of a difference in treatment effect

1.2.5

Comment acknowledged, however these interesting experimental observations require further investigation and it remains our understanding that the more generally held view - that oseltamivir's symptom-relieving effects are due to the decrease in virus replication and viral load - is valid. (The text cited in 4.2.1 does not appear to be a direct refutation of that mechanism).

1.2.6

Comments are acknowledged and text on p.11 under 'efficacy' changed accordingly.

for zanamivir on the influenza-infected (positive testing) subgroup compared to the non-influenza-infected (negative testing) subgroup ($P = 0.53$). The treatment effect was 0.67 days (95% CI 0.35 to 0.99 days, I^2 statistic = 17%) for influenza-infected (positive testing) patients and 0.52 days (95% CI 0.18 to 0.86 days, I^2 statistic = 0%) for non-influenza-infected (negative testing) patients (Analysis 3.69). Zanamivir did not reduce odds of patients with 4 fold or more rise of antibody production.

Hence, these results suggest that zanamivir show some efficacy in non-influenza ILI. The implications are that efficacy in reducing time to alleviation of symptoms is independent of the property of neuraminidase inhibition which is specifically targeted at influenza viruses but is related to the nonspecific inhibition of neuraminidase (see the section 4.2 Oseltamivir has symptom relieving effects by inhibiting host's endogenous neuraminidase, not by inhibiting viral load).

1.3. For the systematic review of prophylaxis: Discussions are needed by taking 'false negative effect' into account both for ECDC advice and for our own.

ECDC does not take into account the property of oseltamivir to reduce antibody production and to conceal positivity of influenza virus by testing culture and/or PCR.

In the amended protocol published on 16th May 2013 (p539-543 [14]), 'Outcome measures for prophylaxis studies' of the systematic review issued on 10th April 2014, the primary outcome measure for prophylaxis trials is defined as 'Influenza-like-illness' (p.542).

There is a note: '*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*' (p543 [14]). 'Symptomatic influenza-like-illness' means 'symptomatic influenza-like-illness irrespective of positivity of laboratory testing'.

We would like to emphasize that the protocol was amended to describe the endpoints more clearly after two feedback comments and our replies (see the feedback from Frederick G. Hayden, M.D., 2 February 2012 and Additional feedback from Frederick G. Hayden, 10 August 2012 and replies: Cochrane review [14] p520-536).

The outcome measure of symptomatic influenza-like-illness is biologically relevant, because neuraminidase inhibitors induce false negative testing results for influenza not only by reducing production of host's antibody (p25 [14]) but also by concealing the positivity of viral culture results by their mechanism of action of reducing viral shedding but not viral load of the lungs or nasal washings of infected animals (module 2 of [WV15670](#), [WV15671 \[14\]](#)) and in mice with experimental mild influenza infection (Wong [54]). This outcome measure is also of primary interest for patients wishing to reduce the risk of having symptomatic illness.

Among the CSRs that we included, no oseltamivir study and only one study of zanamivir (NAI 30034) reported the relevant primary outcome 'symptomatic influenza-like-illness irrespective of positivity of laboratory testing'. In the zanamivir CSR (NAI 30034) no significant reduction was observed (9% versus 10%) (p37 [14]).

We added our own analysis of oseltamivir for the primary outcome: 'in prophylaxis trials we could not analyse effects on influenza-like illness because of a lack of definition in the clinical study reports. However, using our definition (see methods), oseltamivir did not reduce influenza-like illness in participants (RR 0.95, 95% CI 0.86 to 1.06)' (p24 [14]).

References

14. 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. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD008965. DOI: 10.1002/14651858.CD008965.pub4.

54. 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 and Other Respiratory Viruses 2011;5(5):343-50.

2. On the data of individual results

2.1. Treatment trials

2.1.1. Efficacy: complication especially on serious events leading to treatment withdrawal and hospitalisation.

See the methods section (1.2. For the systematic review of treatment: 1.2.1.to 1.2.6.)

2.1.2. Harm: antibody production, QT interval, cardiovascular events

1.3

We note with interest the comments on the influence of oseltamivir on suppression of endogenous non-specific neuraminidase and antibody response. However, our assessment is that the impact of this mechanism on the results presented in the reviews remains hypothetical.

2.1.2.1. Antibody production

Osetamivir significantly reduced the odds of patients having a 4-fold antibody rise, by 18% (risk ratio by 8%), according to a meta-analysis of 8 reports (10 studies) [14, 51]. Heterogeneity was not significant ($I^2=4\%$).

Attenuation of secretory IgA (sIgA) was more marked [55-58]. Sawabuchi et al. reported that lower induction of sIgA against the influenza A virus was observed in children treated with oseltamivir in comparison with children treated without oseltamivir. The odds of a child's sIgA level increasing more than 5-fold were significantly lower in children treated without oseltamivir: OR=0.11 (95%CI: 0.02, 0.61, $p=0.008$) [55]. Anti-influenza A virus sIgA attenuation was observed in children treated both with oseltamivir or with zanamivir [56].

These findings are consistent with evidence from animal tests using sub-clinical doses of oseltamivir in influenza A/H1N1 infected mice [57,58].

Non-significant slight reduction of hemagglutinin (HA) specific IgG antibody in the serum and spleen was reported, while HA specific secretory IgA antibody (s-IgA Ab) in nasal wash and bronchoalveolar fluids (BALF) was significantly reduced: by approximately 80% on day 12 [57].

In human clinical trials, zanamivir at the usual dosage did not reduce antibody (anti-HA Ab) production [14], but attenuated sIgA antibody significantly [56]. In a double blind, placebo controlled trial with healthy volunteers designed to investigate the effect of zanamivir treatment (20 mg/day for 14 days) on the humoral immune response to influenza, the zanamivir group responded with significantly lower antibody titres to the H1N1 [59]. Levels of pro-inflammatory cytokines including IL-6, TNF- α , IFN- γ , and other chemokines were almost completely suppressed in the viral challenge RCT using a very high dose (600 mg) of intravenous zanamivir before inoculation of influenza virus in human adults [60].

Shinahara et al. [56] reported: 'Even under the spread of a new virus subtype in 2009/2010, only 8.6% of the children of the no-treatment group were re-infected. However, the proportions of children treated the previous year with oseltamivir and zanamivir who developed re-infection in 2009-2010 were significantly higher at 37.3% and 45.0%, respectively ($P<0.01$), than those of the no-treatment group.'

Several cases of re-infection with the same influenza virus within one season were reported [61, 62]. Kopel et al. [61] reported a 13-year-old boy with cerebral palsy who 3 times had episodes of fevering with positive 2009A/H1N1 influenza detected by the RT-PCR method. He was treated with the standard dose (75mg b.i.d for 5 days) of oseltamivir at the time of the first episode. A second course of oseltamivir was administered for 10 days with the dosage adjusted for age and doubled from that of the previous regimen. His HI titres were high, but the level of secretory IgA was not determined.

References

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56. Shinahara W, Takahashi E, Sawabuchi T, Arai M, Kido H et al (2013) [Immunomodulator clarithromycin enhances mucosal and systemic immune responses and reduces re-infection rate in pediatric patients with influenza treated with antiviral neuraminidase inhibitors: a retrospective analysis.](#) *PLoS One* 8: e70060.
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62. Perez CM, Ferres M, Labarca JA (2010) [Pandemic \(H1N1\) 2009 reinfection, Chile.](#) *Emerg Infect Dis* 16: 156-7.

2.1.2.1

We note with interest the comments on the influence of oseltamivir on suppression of endogenous non-specific neuraminidase and antibody response. However, our assessment is that the impact of this mechanism on the results presented in the reviews remains hypothetical.

2.1.2.2. QT interval and other cardiovascular events**ECDC reported:**

367 Cardiovascular events and gastrointestinal events can occur as both an adverse event from medication but also as 368 complications or symptoms of influenza infection. In the Jefferson et al. analysis, oseltamivir use was associated 369 with a decrease in 'cardiac body system adverse events' (RR 0.49; 95% CI 0.25–0.97) and a decrease in risk of 370 diarrhoea (RR 0.67; 95% CI 0.46–0.98).

In the Cochrane review we report 'The cardiac effects of oseltamivir are unclear. Exposure to oseltamivir may reduce cardiac general events compared to placebo (RR 0.49, 95% CI 0.25 to 0.97, I² statistic = 0%; RD 0.68%, 95% CI 0.04 to 1.00; NNTB = 148, 95% CI 101 to 2509), excluding WV16277 in which ECG was included in the safety parameters (Analysis 1.27). However, exposure to oseltamivir may increase QTc prolongation (including borderline) as reported in trial WV16277 (RD 4.0%, 95% CI 0.71 to 7.30; NNTH = 25, 95% CI 14 to 140) compared to placebo during on-treatment periods.'

Occurrence of **QTc prolongation** was closely related to the timing of the increase in the concentration of oseltamivir carboxylate [14]. This is consistent with the findings from animal toxicity tests. Oseltamivir decreased heart rate in the 9-month repeated toxicity test using marmoset monkeys. The average heart rate during treatment period with oseltamivir was 328 beats/min, which was an 11% and 16% decrease compared with the control group (368 beat/min) and the average of baseline and recovery phase (392 beat/min), respectively [63]. In an experiment using beagle dogs to test the effects on cardiac functions such as QT time [64], mean baseline QTc intervals (msec ± SE) were 417±16 in the control (vehicle) group (n=4) and 374±2 in the oseltamivir carboxylate (OC) group (n=4). This difference was significant (p=0.0372) according to the summary data t-test. Other evidence suggested that variation was higher in the control group (P=0.005; Bartlett's test) [65]. The average ± standard error of QTc interval of anesthetized dogs intravenously infused with 100 mg/kg OC over 30 minutes significantly increased (390±4) compared with that before infusion (376±2). The average QTc recovered (374±6) at 1.5 hours after discontinuation, but the standard error became larger. QTc prolongation is closely related to the serum concentration of OC [63-65]. The reasons for such large and systemic imbalances are not known, but they are unlikely to have occurred by chance.

References

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<http://www.pmda.go.jp/drugs/2000/q001202/index.html>

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65. Hama R, Jones M and Jefferson T (2015) Concerns about the randomization in the prophylaxis trials of oseltamivir (rapid response): Accessed on 30/5/2015, available at: <http://www.bmj.com/content/348/bmj.g2545/rr>

2.1.2.3. Psychiatric events, injury and poisoning.

Psychiatric events were more reported in the prophylaxis trials. 'Injury and poisoning' may be related to the psychiatric events and these are discussed in the section for prophylaxis trials (2.2.2. Harms in prophylaxis trials)

2.2. Prophylaxis trials**2.2.1. Efficacy in prophylaxis trials:**

We have no data for adequate assessment of influenza-like illness (ILI) in any CSRs of prophylaxis trials of oseltamivir analyzed. Oseltamivir induce false negative results of influenza testing (antibody production, culture and PCR) and negative results do not mean 'ILI due to pathogens other than influenza virus (non-influenza ILI)'.

For oseltamivir prophylaxis, a Japanese trial which is only available as a published paper (in Japanese, Kashiwagi et al 2001 [66]) provided the data from which we could report 'symptomatic influenza-like-illness irrespective of positivity of laboratory testing'. By using these data, 'symptomatic influenza-like-illness irrespective of positivity of laboratory testing' was compared showing no difference between the oseltamivir (34/155=22%) and placebo groups (36/153=24%) (Hama 2009 [67]). Moreover, 29 persons with negative testing ILI were significantly more

2.1.2.2

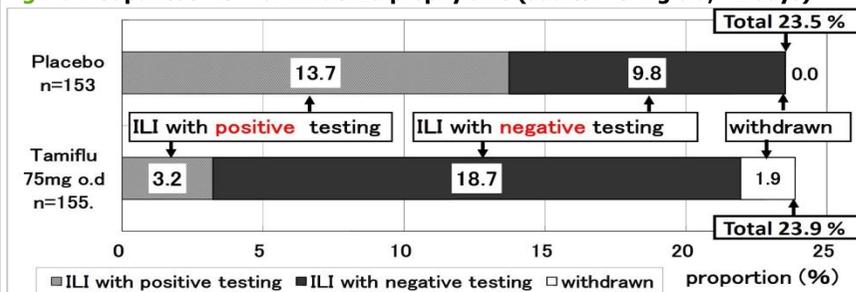
We acknowledge the comment. However, we consider the safety signal from the studies presented to be insufficient to guide public health decision-making.

2.2.1

We note with interest the results summarised from the study by Kashiwagi et al. (2001). In our view, outcome measures for RCTs on influenza, should, whenever possible, relate to laboratory-confirmed influenza, due to the specific mechanism of action of NAIs.

observed in oseltamivir group (29/155=18.7%) than in the placebo group (15/153=9.8%) (OR=2.18; 95% CI: 1.09, 4.13, p=0.026). These may be the results derived by the oseltamivir's false negative effects on the laboratory testing.

Figure 1. Japanese RCT for influenza prophylaxis (adults: 75 mg o.d, 42 days)



Total percent of persons with flu symptoms who had positive testing and negative testing and those withdrawn were 23.5 % for placebo group and 23.9 % for the Tamiflu 75mg o.d. group (for 42 days): no difference between both groups.

#1: ILI (Influenza-like illness): if one or more of the following symptoms were seen

1) fever 37.5°C or more, 2)respiratory symptoms, 3)general symptoms

#2: Positive testing: if virus was detected from nasal swab by culture or hemagglutination inhibition (HI) antibody titer increased 4-fold or more. This is consistent with the results of NAI 30034 and our own analysis of oseltamivir trials. In additional analysis of the oseltamivir prophylaxis trials we found fever is reduced (RR 0.62, 95% CI 0.42 to 0.93), proportion with laboratory confirmation is reduced (RR 0.59, 95% CI 0.41 to 0.85) but symptoms other than fever are not reduced (RR 0.96, 95% CI 0.86 to 1.07). These results suggest oseltamivir suppresses fever, reduces antibody response and viral shedding but does not reduce the risk of symptomatic illness.

References

66. Kashiwagi S, Kudoh S, Watanabe A, Yoshimura I. Efficacy and safety of the selective oral neuraminidase inhibitor oseltamivir for prophylaxis against influenza: placebo-controlled double-blind multicenter phase III trial. *Kansenshogaku Zasshi*. 2000 Dec;74(12):1062-76. (in Japanese).
 67. Hama R. [Neuraminidase inhibitors for prophylaxis and outcome measure: How efficacy claimed? What can we learn from the Japanese study?](#) Rapid response (on 24th Dec 2009) to Jefferson T et al. 'Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis' *BMJ* 2009; 339 <http://www.bmj.com/content/339/bmj.b5106?tab=responses>

2.2.2. Harms in prophylaxis trials:

ECDC report:

The Expert Group concluded that on the basis of their review of the evidence presented, oseltamivir or zanamivir use was not associated with an increase in serious adverse events or events leading to withdrawal from treatment or prophylaxis among previously healthy adults or children [14,17].

We challenge this conclusion.

2.2.2.1. Psychiatric reactions

ECDC might ignore our important findings indicating that oseltamivir may induce 1.8 times more psychiatric symptoms than placebo group in prophylaxis trials. The psychiatric symptoms include hallucination, aggravation of schizophrenia, psychosis, aggression and depressions and so on. Aren't these serious enough?

2.2.2

The reference by Hama et al. to safety sections of the pre-exposure prophylaxis (p.15) and post-exposure prophylaxis (p.17) are incorrect and the commentators refer to the safety section of treatment here. Please see responses above. Under post-exposure prophylaxis we refer to findings in Jefferson et al. on risk of headaches and neuropsychiatric events (p.15).

2.2.2.1

We note the concerns raised. However, our conclusion remains valid: 'The Expert Group concluded that on the basis of their review of the evidence presented, oseltamivir or zanamivir use was not associated with an increase in serious

	<p><i>We reported in the Cochran systematic review that</i></p> <p><i>'Figure 11 (Analysis 2.54) shows that in prophylaxis trials of oseltamivir there was a significant increase in patients with psychiatric adverse events over the on- and off-treatment periods (RR 1.80, 95% CI 1.05 to 3.08, I² statistic = 0%; RD 1.06%, 95%CI 0.07 to 2.76; NNT_H = 94, 95% CI 36 to 1538). Initial analysis of patients with psychiatric adverse events in the on-treatment period showed a borderline statistically significant result (P = 0.06), hence we conducted sensitivity analysis using Peto's method (P = 0.05) as well as the analysis reported in Figure 11. Table 15 shows a summary of all psychiatric adverse events in oseltamivir prophylaxis trials. Of particular note was an oseltamivir patient in study WV15825 who had severe confusion on day 27 and was hospitalised. On day 28 the patient was taken off medication and the event resolved. On day 29 the patient was discharged from hospital and subsequently resumed medication. However, confusion reappeared on day 32. The initial event was misclassified in the clinical study report as 'mental impairment' but has since been corrected in an erratum published in the same journal that published the original trial manuscript (Gravenstein 2013; Peters 2001).'</i></p> <p>In the treatment RCTs of oseltamivir and zanamivir, definition of adverse event was defined 'any adverse change from the subject's baseline (pre-treatment) condition, which occurred during the course of the study after treatment had started, whether considered related to treatment or not'. This is different from the ordinary definition of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2D guideline.</p> <p>As a consequence, adverse events that are similar to the symptoms of influenza (such as headache, mild gastrointestinal adverse events and mild psychiatric events) tend to be excluded from the treatment trials.</p> <p>However, we found that:</p> <p><i>'there was a dose-response effect in the two 'pivotal' treatment trials. In the identically designed trials WV15670 and WV15671 there were two active treatment groups: 150 mg (standard dose) and 300 mg (high dose) oseltamivir per day. In the dose-response analysis there was an increased risk of psychiatric body system adverse events over the entire follow-up period (P = 0.038 based on likelihood ratio test). In trial WV15670, the event rates were: 1/204, 1/206 and 4/205 in the placebo, 75 mg and 150 mg arms respectively, whereas trial WV15671 had rates of 2/235, 0/242 and 5/242, respectively.'</i></p> <p><i>Is it appropriate to state that there were 'no serious adverse effects'?</i></p> <p>2.2.2.2. Injury and poisoning</p> <p>Although, oseltamivir increased 'injury and poisoning' in the treatment trials, we discuss here, because it may be related to the psychiatric reactions.</p> <p>In the Dobson review [17], risk of 'injury and poisoning' was higher in the oseltamivir group than in the placebo group: RR 3.37 (95% CI 1.08 to 10.47) P=0.036. (see Table 2 in Dobson's paper [17]).</p> <p>By our own analysis excluding Japanese trial, we have similar results:</p> <p>Pooled relative risk (by Random effects, DerSimonian-Laird) = 3.04 (95% CI = 1.02 to 9.05, p=0.046. As many zero cells were reported especially in the placebo group, we conducted some sensitivity analyses:</p> <p>Pooled odds ratio (by Fixed effects, conditional maximum likelihood) = 6.54 (95% CI = 1.51 to 59.34, P = 0.0051),</p> <p>Pooled odds ratio (by Peto's method) = 4.08 (95% CI = 1.55 to 10.71, P = 0.0043).</p> <p>Although, the risk did not increase dose-dependently (in WV15670 and WV15671 trials) and was not evident in the prophylaxis trials, most of the events of 'injury and poisoning' reported in the treatment trials were 'injury' and these might occur as accidents. Considering the relation between abnormal behaviours and accidents, these should not be ignored.</p> <p>2.2.2.3. Other adverse reactions</p> <p><i>Other than psychiatric events, we reported in the Cochrane review that oseltamivir increased renal, diabetic or hyperglycemic events, pain in limbs and headaches, but that zanamivir did not. However, ECDC ignored these findings.</i></p> <p>2.2.2.3.1. Renal impairment</p> <p>Renal event was marginally non-significant by random effects (DerSimonian-Laird) (RR= 3.17 [95% CI= 0.96, 10.49, p=0.058] but significantly</p>	<p>adverse events or events leading to withdrawal from treatment or prophylaxis among previously healthy adults or children [14,17], (p. 11).'</p> <p>2.2.2.2 We note the concerns raised. However, our conclusion remains valid: 'The Expert Group concluded that on the basis of their review of the evidence presented, oseltamivir or zanamivir use was not associated with an increase in serious adverse events or events leading to withdrawal from treatment or prophylaxis among previously healthy adults or children [14,17], (p. 11).'</p>
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different by Fixed effects (Mantel-Haenszel, Rothman-Boice: RR= 3.47 [95% CI = 1.06, 11.32, p=0.039]) and by Peto's methods (OR = 2.93 [95% CI = 1.16 to 7.43, p=0.023]) as sensitivity analysis.

We also noticed two patients in oseltamivir groups who experienced renal failure prior to death **[14]**: one in trial WV15825 and on in trial WV15708. The two participants who died in the oseltamivir arms both experienced acute renal failure while on-treatment, although only one of those events was listed as an adverse event. The unlisted event was in a 91-year old female who was withdrawn from the study on Study Day 15 because her estimated creatinine clearance was less than 30 mL/min. The screening laboratory examinations that were carried out 10 days before the start of study treatment were normal **[14]**.

Moreover, while assessing the evidence in individual patient data in prophylaxis trials, we found significant and serious imbalance of baseline renal disorders between the oseltamivir and placebo groups **[68]**. We independently extracted the data on baseline creatinine level and concomitant renal and urinary tract diseases (renal/UTD) for five studies in total: two in adults (WV15673/WV15697), two in the elderly (WV15708; WV15825) and one in households (WV15799).

Participants with high baseline creatinine level (154µmol/L or more) were significantly less reported in the oseltamivir group than in the placebo group: pooled odds ratio was 0.29 (95% CI = 0.12 to 0.69, P = 0.005, I²= 0%). In trial WV15708 which was never published, participants with high baseline creatinine level (154µmol/L or more) were significantly less reported (OR 0.23; 95%CI: 0.06, 0.82. P = 0.0168). Participants with concomitant renal/UTD were less reported (OR 0.38; 95%CI: 0.14, 0.93, p=0.0269). In trial WV15708, Proportions of participants with high baseline creatinine level and/or concomitant renal/UTD were 5.8% (11/190) and 16.5% (30/182) for oseltamivir group and placebo group respectively: odds ratio 0.31 (95%CI = 0.14 to 0.67, P = 0.0014).

We don't know the reason why such large and systemic imbalances occurred, but they are unlikely to have occurred by chance **[68]**.

References

68. Hama R, Jones M, Jefferson T. Concerns about the randomization in the prophylaxis trials of oseltamivir.

<http://www.bmj.com/content/348/bmj.q2545/rapid-responses>

2.2.2.3.2. Hyperglycemic of diabetic events, and pain in limbs

Hyperglycaemic adverse events (aggravated diabetes mellitus or hyperglycaemia) were also more common in the oseltamivir arms, with eight events in total (one in WV15673/WV15697, two in WV15708 and five in WV15825) compared to none in the corresponding placebo arms. These data are only presented descriptively as they are too few (< 10) to meta-analyse formally, as prespecified in our analysis plan **[14]**.

2.2.2.3.3. Headaches

Oseltamivir caused headaches and psychiatric harms in adult prophylaxis trials. Headaches are one of the most prominent harms of oseltamivir. There is evidence of a dose-response effect in prophylaxis trials WV15673/WV15697 (P = 0.013), in which headaches were observed in 202/519, 225/520 and 242/520 participants in the placebo, oseltamivir 75 mg once daily and 75 mg twice daily arms, respectively **[14]**.

It should be emphasised that in the published report of trial WV15673/WV15697 **[69]**, the authors did not mention the dose-response increase of headaches but **denied the difference** and wrote that: 'The most commonly reported adverse event was headaches, which occurred in **similar proportions** in the three groups (39 to 47 percent).'

Headaches may be related to the increased intra-cranial pressure except in infants less than 1 year-old, in whom it may induce bulging of fontanelle. A typical case with increased intra-cranial pressure was reported as a spontaneous report from Japan that was reported to the Food and Drug administration **[70]**. A 5-month-old male infant who was treated with oseltamivir for prophylaxis vomited one and a half hours after receiving the drug. His mother noticed that his fontanel bulged repeatedly throughout the treatment period of eight days.

References

69. 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.

70. Edwards Et and Truffa MM (2005) (Division of Drug Risk Evaluation: DDRE) One-Year Post Pediatric Exclusivity Postmarketing Adverse Events Review (Drug: Oseltamivir phosphate): Department of Health and Human Services, Public Health Services, Food and Drug administration: Center for Drug Evaluation and Research=FDA CDER. Accessed on 28/5/2015 available at:

http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4180b_06_01_Tamiflu%20AE_reviewed.pdf

3. Evidence from non-randomized studies**3.1. Epidemiological studies suggesting neuropsychiatric adverse reactions to oseltamivir:****3.1.1. Prospective cohort studies and their systematic review and meta-analysis.**

A systematic review and meta-analysis of three prospective cohort studies of neuropsychiatric adverse events (NPAEs) in Japanese children show a pooled odds ratio for abnormal behaviours due to oseltamivir exposure of 1.55 (95% CI 1.21 to 1.98; $P = 0.0005$) without significant heterogeneity [71] [14].

The largest prospective cohort study among the tree was conducted by Fujita et al (2011) [72] but the results were first reported by Hirota Y et al [73] referred by Yorifuji et al [74]. It was conducted in the winter of 2006–2007 to assess the relationship between oseltamivir use and abnormal behaviors. An interim report was released on 10 July 2008 [73]. In the report, the research group concluded that no positive associations were detected between oseltamivir use and abnormal behaviors. However, the analytic method used in the study was flawed. A correct analysis (based on person-time) shows a rate ratio of 1.57 (95% confidence interval 1.34, 1.83, $p < 0.0001$). Abnormal behaviours were reported in 889 among 25844 person-days (3.4 per 100 person day or 13.8%) in oseltamivir taker and 187 were reported among 8516 person days (2.2 per 100 person-days or 8.8%) in no oseltamivir takers [74].

Reanalysis of this study population, focusing on delirium and unconsciousness, also showed a significant association between oseltamivir and neuropsychiatric events, especially in the very early phase of the illness within a day of commencement of fever [70]. For example, the risk ratio for delirium associated with oseltamivir use was up to 7.0 about 12 hours after commencement of fever or multivariate hazard ratio during 21:00 to 24:00 was up to 5.58 (95% CI: 1.94, 16.06), while the overall hazard ratio was 1.51 ($p = 0.084$) by multivariate analysis. These indicate that prospective and intentional collection with this scale of participants may be necessary in treatment RCTs.

References

71. Hama R, Jones M, Hayashi K, Yanagi T, Sakaguchi K. Oseltamivir: A systematic review and meta-analysis of adverse effects in prospective cohort studies (a preliminary report was presented at the 16th JSPE and 5th ACPE joint meeting Tokyo 29-30th 2010 Tokyo).

72. 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. Available from:

http://www.istage.ist.go.jp/article/ijpe/15/2/73/_pdf

73. Hirota Y. Interim report of investigations about the frequency of associated symptoms with influenza (in Japanese). Available at:

<http://www.mhlw.go.jp/shingi/2008/07/dl/s0710-6ak.pdf>. Accessed July 23, 2008

74. Yorifuji T, Suzuki E, Tsuda T. Oseltamivir and abnormal behaviors: true or not? *Epidemiology* 2009; 20(4): 619-21.

3.1.2. Proportional reporting ratio for abnormal behaviours especially of fatal outcome.

Association of age and gender with neuropsychiatric adverse events (NPAEs) in patients treated with oseltamivir was analysed by reporting odds ratio (ROR) using a logistic regression model (after duplicates were excluded) [75]. NPAE data were obtained from the U.S. Food and Drug Administration Adverse Event Reporting System (2004 to 2013).

Adjusted ROR of 'abnormal behavior' was 96.4 (95% CI, 77.5–119.9) in male patients aged 10–19 years treated with oseltamivir [75].

If we use data of FDA from Rxisk.org [76] that may contain duplicates, number of reports and PRRs of abnormal behavior were 1140, 31.3 for oseltamivir and 753, 61.7 for zanamivir. However all reports of zanamivir were from Japan only. In addition, abnormal behaviours with fatal outcome were 30 reports for oseltamivir and none for zanamivir. Odds ratio of fatal case among abnormal behaviours from oseltamivir compared with zanamivir was 41.39 (95%CI: 2.53, 677.9, $p < 0.0001$). These data mean abnormal behaviour leading to death may be induced by oseltamivir but not by zanamivir.

References

75. Ueda N, Umetsu R, Abe J, Kato Y, Nakayama Y, Kato Z, Kinosada Y, Nakamura M. [Analysis of Neuropsychiatric Adverse Events in Patients Treated with Oseltamivir in Spontaneous Adverse Event Reports](#). *Biol Pharm Bull*. 2015;38(10):1638-44.

76. <http://rxisk.org/drugs-a-z/> accessed on March 9 2016

3.1

We acknowledge the comments. However, these reviews and studies were not included in our original remit and the results do not appear to be sufficiently conclusive to guide public health recommendations.

3.2. Adverse effects on mortality**Line number 520 to 537: ECDC report describes as follows:****520 Mortality**

521 In the individual patient level meta-analysis done by Muthuri et al. (2014) in patients hospitalised with influenza
 522 A(H1N1)pdm09 virus infection, decreased mortality was associated with the use of NAIs among hospitalised
 523 patients (OR 0.81; 95% CI 0.70–0.93) [18]. Among adults, treatment was associated with a 25% reduction in
 524 likelihood of death, irrespective of the timing of treatment (OR 0.75; 95% CI 0.64–0.87); among children under the
 525 age of 16, a similar association was observed but the reduction was not significant (OR 0.82; 95% CI 0.58–1.17).
 526 Similar results were observed when restricting the analysis to adult critical care patients
 527 (OR 0.72; 95% CI 0.56–0.94) and pregnant women (OR 0.46; 95% CI 0.23–0.89). Late treatment (started after 48
 528 hours of symptom onset) was associated with reduced risk of death only among adult critical care patients
 529 (OR 0.65; 95% CI 0.43–0.93).
 530 For patients for whom exact timing of NAI treatment from symptom onset was available, when antiviral use was
 531 modelled as a time-dependent covariate to overcome potential immortal time bias (i.e. survivor bias), NAI
 532 treatment was significantly associated with decreased hazard rate of mortality within 30 days of illness onset
 533 (adjusted HR 0.51 [95% CI 0.45–0.58], $p < 0.0001$) as compared with no antiviral treatment. Among treated cases,
 534 there was an increase in the hazard with each day's delay in initiation of treatment up to day five as compared with
 535 treatment initiated within two days of symptom onset (HR 1.23 [95% CI 1.18–1.28], $p < 0.0001$ for the increasing
 536 HR with each day's delay). The unadjusted and adjusted survival curves comparing survival by time to treatment
 537 initiation are shown in Figure 2.

3.2.1. Observational studies do not support protective effect on mortality

Raw data of the study by Muthuri et al [18] shows that 959/10,431 (9.2%) died without treatment while 1825/18,803 (9.7%) died after exposure to NAI treatment. The effect size is, however reported as a Relative risk, RR, of 0.81 without taking account of time-dependent treatment exposure and as a Hazard Ratio, HR, of 0.51 after taking account of time-dependent treatment exposure. Including treatment as a time-dependent treatment exposure must move the treatment effect estimate in the opposite direction to that shown. This is because the time from initiation of follow up to initial treatment exposure is incorrectly allocated to the treatment group in an analysis that incorrectly includes treatment exposure as time-independent. This makes the estimates of mortality over time too low for the treatment group and too high for the non-treatment group [77].

To examine the effects of oseltamivir on 2009A/H1N1 influenza mortality, we included observational studies with at least 5% of patients untreated and five or more deaths overall. We requested individual patient data (IPD) from corresponding authors of all included studies.

Analysis of summary data of 30 studies as well as IPD of four studies showed evidence of time-dependent bias. After adjusting for time-dependent bias and potential confounding variables, competing risks analysis of the IPD showed insufficient evidence that oseltamivir reduced the risk of mortality (HR 1.03, 95% CI: 0.64 to 1.65) [78]. In conclusion, oseltamivir has no protective effect on mortality among 2009A/H1N1 influenza patients [78].

References

77. Jones M, Del Mar C, Hama R. Statistical and methodological concerns about the beneficial effect of neuraminidase inhibitors on mortality. *Lancet Respir Med.* 2014 Jul;2(7):.

78. Heneghan CJ, Onakpoya I, Jones M, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Mahtani KR, Nunan D, Howick J and Jefferson T. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. *Health Technology Assessment.* 2016 (in press)

3.2.2. Epidemiological evidence suggesting sudden deterioration leading to death following oseltamivir use:**Comparative mortality analysis by Hama et al (2011) [79].**

Hama et al [79] conducted a comparative mortality study utilizing all disclosed data of died persons with influenza 2009A/H1N1 during 09/10

3.2 We acknowledge the comments and have added a reference to Heneghan et al. (2016) on page 10 and refer to the mortality results of this review on page 14.

winter season and consumption data of oseltamivir and zanamivir during the season. Age stratified mortality was calculated and compared between oseltamivir prescribed people and zanamivir prescribed people. Of 119 deaths after Tamiflu was prescribed, 38 deteriorated within 12 hours (28 within 6 hours), while of 15 deaths after Relenza, none deteriorated within 12 hours. Pooled OR for early deterioration was 5.88 (95% CI: 1.30 to 26.6, $p = 0.014$) (Pooled OR of overall death was 1.91, $p = 0.031$). Baseline characteristics including risk factors did not contribute to early deterioration after Tamiflu use [79].

References

79. Hama R, Jones M, Hayashi K, Sakaguchi K. Oseltamivir and early deterioration leading to death. *International Journal of Risk & Safety in Medicine* 2011; **23**: 201–15. (accessed on 27/5/1013. <http://iospress.metapress.com/content/5257410q24403m68/fulltext.pdf> (note, this is not a proportional mortality study but comparative mortality study)

3.3. Adverse effect on pregnant women, fetus and newborns

ECDC report state as follows on pregnant women:

548 **Severe outcomes in pregnant women**

549 Pregnancy is a known risk factor for severe influenza disease, as also noted for the 2009 influenza A(H1N1)pdm09
 550 pandemic, and a systematic review published by Mosby et al in 2011 was drawn to the attention of the group by
 551 one of the experts [24]. This systematic review identified five observational studies, in which neuraminidase
 552 inhibitors administered within 48 hours from onset of symptoms compatible with influenza, conferred decreased
 553 risk of severe disease [24]. No meta-analysis was conducted, but in the identified studies Louie et al. in 2010
 554 reported an increased risk of being admitted to the intensive care unit (ICU) or to die if treatment was initiated
 555 later than 48 hours from onset of symptoms (RR 4.3 95% CI 1.4–13.7) [33]. Creanga et al. reported 3.3% of
 556 pregnant women who received oseltamivir treatment within two days of symptom onset had severe illness
 557 compared with 21.4% and 44.4% pregnant women who started treatment three to four days and five days,
 558 respectively or more after symptom onset ($P = .002$ for trend) [34]. Siston et al. reported that pregnant women who
 559 had treatment initiated more than four days from onset of symptoms were more likely to be admitted to the ICU
 560 (RR 6.0 05% CI 3.5–10.6) [35].

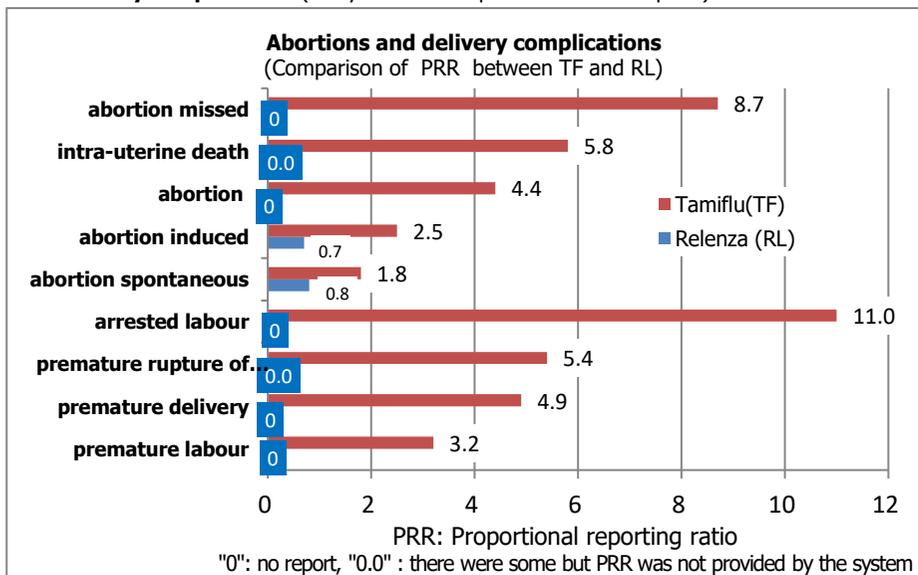
The reports above (Louie et al [33], Creanga et al [34] and Siston et al[35]) did not consider the time dependent bias (immortal time bias) and have flaws as pointed out in the mortality section (**3.2.1 Observational studies do not support protective effect on mortality**).

Analysis of FDA’s data from Rxisk.org (accessed on November 16 2012) shows increased proportions of abortion related reactions (especially of **abortion missed**), intra-uterine fetal death and complicated delivery (**Figure 2**), **still birth and neonatal death or asphyxia (Figure 3)** related to Tamiflu but not to Relenza. Note that a proportional reporting ratio of 2 or more indicates at least a doubling in the proportion of those ADRs reported for the drug in question (e.g. oseltamivir) compared to all other drugs in the FDA database. A PRR of 2 or greater is a signal that the drug in question may cause these types of reactions.

3.3

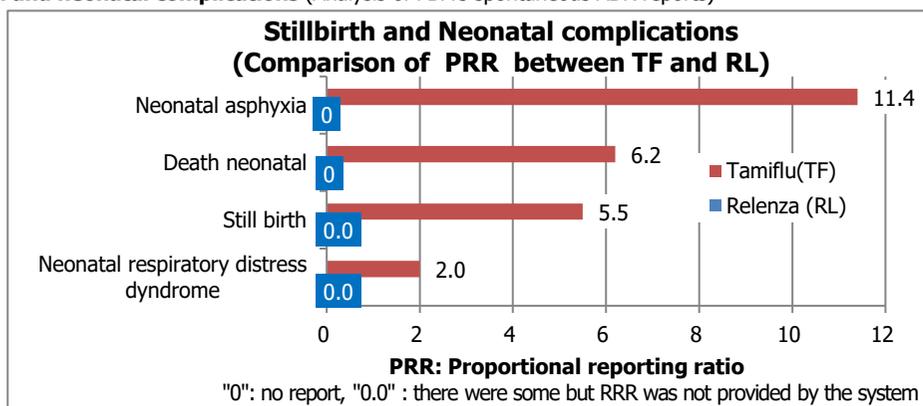
Reviewing regulators safety databases was not within the scope of this Expert Opinion and ECDC is not aware of any concerns regarding safety signals as described. However, we take note of the concerns and will communicate these to EMA. We urge Hama et al. to also bring forward these concerns to regulators. Emerging evidence also does not appear to strongly support pregnant women being at higher risk of severe outcomes than others during seasonal influenza epidemics. We have therefore amended passages on p.3, p.15 and in Table 6.

Figure 2. Abortions and delivery complications (Analysis of FDA's spontaneous ADR reports)



Based on the data from RxISK.org (<https://www.rxisk.org/Default.aspx>) accessed on Nov 16 2012

Figure 3. Stillbirth and neonatal complications (Analysis of FDA's spontaneous ADR reports)



Based on the data from RxISK.org (<https://www.rxisk.org/Default.aspx>) accessed on Nov 16 2012

In addition, these findings are all supported by animal toxicity tests. Hence, it may be harmful to use oseltamivir for pregnant women with influenza infection. **Therefore, ECDC should reconsider the recommendation of oseltamivir to use in pregnant women with influenza infection or at least express caution in its use.**

4. No discussion on the mechanisms of action and reactions of oseltamivir

ECDC report did not discuss on the mechanisms of actions and reactions of oseltamivir. Here we briefly summarise them.

4.1. Oseltamivir act on the central nervous system (CNS) both as depressants and as stimulants.

4.1.1. Juvenile (7-day-old) rats [80-84] and mature rats (intraduodenally and intravenously) [85] died dose-dependently after one dose of oseltamivir as shown in Figure 4. They die from respiratory arrest followed by cardiac arrest as shown in Figure 5 [85].

4. We acknowledge the comments on mechanism of action and reactions. However, pre-clinical studies were beyond the scope of this Expert Opinion.

Figure 4. Dose of oseltamivir and mortality trend in juvenile (7-day-old) rats

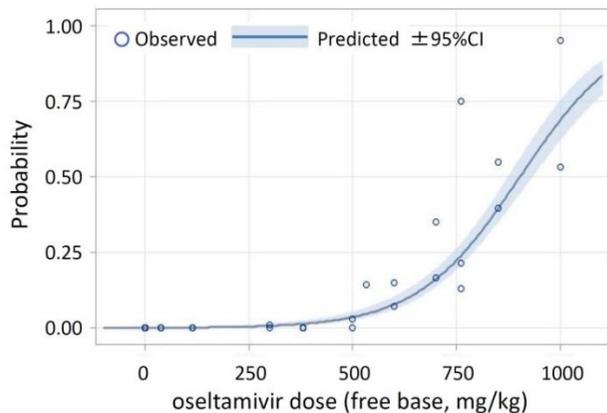
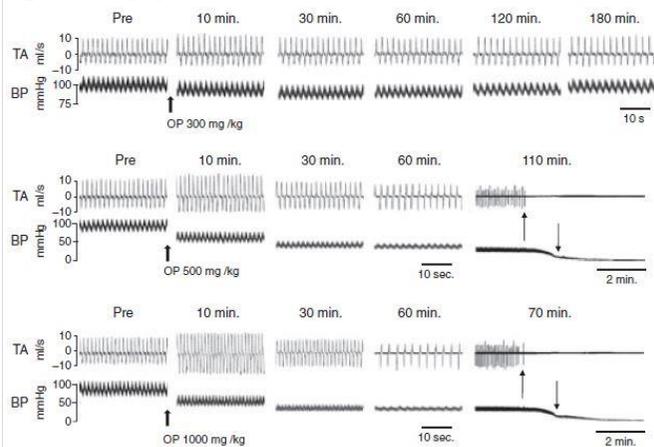


Figure 5. Effect of intraduodenal injection of oseltamivir phosphate (OP) on respiration and blood pressure in rats (Kimura's Figure 3 on p4)



Data from ref [80-84]. In the TK tests, the proportion of deaths is underestimated because rats were withdrawn for determination of plasma and brain concentration. The results show that for each additional dose of 100 mg/kg, the odds of death more than double (OR = 2.26, 95% CI: 2.01 - 2.54, P<0.0001).

Figure 3 (of ref [85]): intraduodenal injection of oseltamivir phosphate (OP) at higher doses (500–1000 mg/kg) provoked ventilatory arrest followed by cardiac arrest in spontaneously breathing anaesthetized rats. Traces of tracheal airflow (TA) and blood pressure (BP) were taken before (pre) and several times (min.) after the injection of OP. Thin arrows indicate the time lag between ventilatory arrest and cardiac arrest.

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4.1.2. Oseltamivir has hypothermic effect [86-89] on animals by inhibiting nicotinic acetylcholine receptor [89].

4.1.3. Oseltamivir induces abnormal behaviours [80-93] by inhibiting MAO-A [93].

4.1.4. Oseltamivir has various other effects on CNS such as impairment of sensory system, impairment of cognition, impairment of alertness other than respiratory depression [82, 83].

Figure 6. Proportion of rats lacking olfactory orientation at 2 hours after dosing oseltamivir

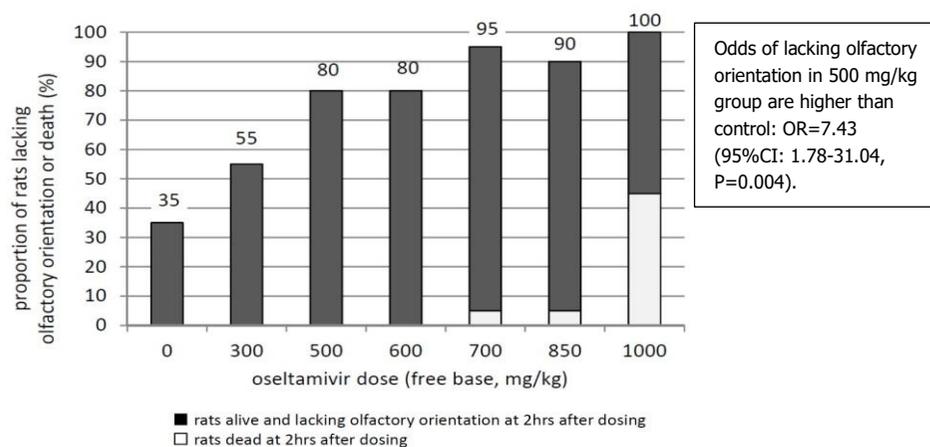
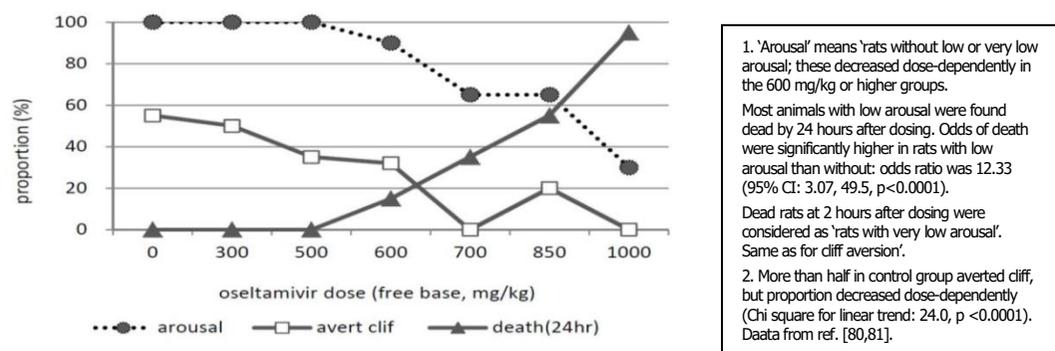


Figure 7. Cliff aversion, arousal at 2 hours after dosing, and proportion of death at 24 hours**References**

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4.2. Oseltamivir has symptom relieving effects by inhibiting host's endogenous neuraminidase, not by inhibiting viral load.**4.2.1 Label of oseltamivir does not state viral load reduction**

It may be generally believed that oseltamivir most likely reduces symptom duration by reducing viral load, and via the spread and release of cytokines [94]. However, the full prescription information of oseltamivir (revised in April 2010) states: '*The concentrations of oseltamivir carboxylate required for inhibition of influenza virus in cell culture were highly variable depending on the assay method used and the virus tested. (...) The relationship between the antiviral activity in cell culture, inhibitory activity in the neuraminidase assay, and the inhibition of influenza virus replication in humans has not been established*' [95].

4.2.2. Experiments indicate inhibition of host's endogenous neuraminidase, but not viral load.

A significant but slight reduction of the proportion with serum antibody (mostly hemagglutination inhibition (HAI) antibody) titre rise by four-fold or more among those who were tested was shown in the Cochrane review [14]. These findings are also consistent with the evidence on the mode of action of oseltamivir from animal models (Module 2 of most of the CSRs including WV15670 and WV15671 and from viral challenge, randomised, placebo-controlled studies in humans [94]. Pro-inflammatory cytokines, including interleukin 6 (IL-6), tumour necrosis factor alpha

4.2

We note with interest the comments on the influence of oseltamivir on suppression of endogenous neuraminidase and antibody response. However, our assessment is that the impact of this mechanism on the results presented in the review within our scope remains hypothetical.

(TNF- α) and interferon gamma (IFN- γ), were completely suppressed by oseltamivir administered 28 hours after the experimental inoculation of influenza virus, while the reduction of viral titre in nasal lavages was partial [94].

There is decisive evidence that administration of oseltamivir in animals challenged by respiratory syncytial virus (RSV) that lacks a neuraminidase gene showed a symptom-relieving effect (decreased weight loss) and inhibition of viral clearance [96]. These effects were accompanied by a decreased CD+8 T cell surface sialoglycosphingolipid GM1 level, which is regulated by the endogenous sialidase/neuraminidase in response to viral challenge along with suppression of cytokine expression [96]. They are consistent with those findings from the pharmaceutical company and their investigators. The findings of the study by Moore2007 [96] suggest a risk of infection and exacerbation of infection by pathogens other than influenza virus in spite of the apparent reduction of symptoms from infection [14].

In a study by Wong et al. [54] using mice infected with mild influenza (inoculated with a non-lethal dose of influenza virus), which is a better model for testing the effects of oseltamivir in human seasonal influenza, a clinically compatible dose of oseltamivir (10 mg/kg=approximately 0.8 mg/kg as HED) administered (in 3 different experiments) at 4 hours before inoculation, 24 hours after inoculation, or 48 hours after inoculation showed no significant effect on viral titres at day 5 post-inoculation.

Wong et al [54] observed that oseltamivir markedly and significantly reduced lung inflammatory cell response and induction of pro-inflammatory cytokines and chemokines such as TNF- α , IL-1 β , IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), keratinocyte-derived chemokine (KC), Macrophage inflammatory protein-1 α (MIP-1 α), and Monocyte chemoattractant protein-1 (MCP-1) whether administered prophylactically or therapeutically. However, these were accompanied by small non-significant effects on viral titres. Based on these findings, the researchers discussed the possibility of intrinsic anti-inflammatory effects of oseltamivir [54].

No animal study has been conducted of the infection model with mild and non-lethal doses of the influenza virus for zanamivir, laninamivir, or peramivir. Only animal studies of the infection model using lethal doses of the influenza virus are available.

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4.3. Inhibiting host's endogenous neuraminidase may be related with adverse effects of NIs

ECDC cites our results only on the findings that oseltamivir use was associated with adverse events as follows:

363 Oseltamivir is associated with an increased absolute risk of 3.66% for nausea (RR 1.57; CI 1.14–2.15 in the
364 Jefferson et al. analysis and RR 1.60; 95% CI 1.29–1.99 in the Dobson et al. analysis) and 4.56% for vomiting
365 (RR 2.43; 95% CI 1.75–3.38 in the Jefferson et al. analysis, and RR 2.43; 95% CI 1.83–3.23 in the Dobson et al.
366 analysis) among adults in the RCTs [14].
367 Cardiovascular events and gastrointestinal events can occur as both an adverse event from medication but also as
368 complications or symptoms of influenza infection. In the Jefferson et al. analysis, oseltamivir use was associated
369 with a decrease in 'cardiac body system adverse events' (RR 0.49; 95% CI 0.25–0.97) and a decrease in risk of
370 diarrhoea (RR 0.67; 95% CI 0.46–0.98).

However, as shown in 2.1.2.2. **Cochrane review** also reported that renal events, hyperglycemia/worsening of diabetes, pain in extremities and QT prolongation were more reported in oseltamivir group than placebo group. About half of the 'cardiac body system adverse events' were tachycardia or palpitations and these effects may be associated with decreased heart rate observed in the animal toxicity tests. These are also related with inhibition of host's endogenous neuraminidase by oseltamivir and QT prolongation, because QT prolongation was observed closely related with the serum concentration of oseltamivir carboxylate both in animal experiments [14, 61, 62] and in humans (WV16277). During high fever people need high cardiac output, hence less increase of heart rate should be considered as adverse effect as QT prolongation is.

Decreased incidence of diarrhoea (RR 0.67; 95% CI 0.46–0.98) may be the same effect: apparent beneficial effects but may even an adverse effects induced by inhibition of host's endogenous neuraminidase.

	<p>7. [ECDC correction: 5] Efficacy and effectiveness in risk groups ECDC report: 779 Efficacy and effectiveness in risk groups 780 The limited evidence available on the treatment or prophylaxis of risk groups with underlying chronic conditions is 781 discouraging, as these are the groups who are known to develop severe disease and would most need to be 782 protected from severe outcomes of influenza. It is unlikely that more RCTs will be conducted due to the expiry of 783 patents for oseltamivir and zanamivir, and the unavailability of public funding for such studies. It is also unlikely 784 that ethical boards would approve randomised placebo-controlled trials, given the existing evidence for efficacy. 785 Well-designed prospective observational studies among specific risk groups would be a useful addition to the 786 knowledge base. Funding for such observational trials is also an issue and needs more attention. These studies 787 should include longer term follow-up in order to confirm reports on reduced late sequelae (MI, stroke) in 788 oseltamivir-treated persons compared to no treatment.</p> <p>On the list at p32/39 pdf, ECDC recommend as follows: Risk group adults including immunocompromised and pregnant women – 18 years and older: For 'Treatment of patients with medically attended influenza-like illness (ILI)*' and 'Treatment of patients with laboratory-confirmed influenza'. Expert opinion: 'Although limited evidence is available from clinical trials for treatment recommendations of this vulnerable group, treatment during seasonal influenza epidemics should be recommended.'</p> <p>Our comments: High risk group for complicating influenza include elderly, infants, diabetes, renal, hepatic, cardiovascular, respiratory, neurological and immunocompromised patients. However, oseltamivir may worsen these diseases and may be harmful for patients with these conditions. Has ECDC considered this point?</p> <p>6. Conflict of Interest 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. [97] But, only 5 of the 29 studies conducted by scientists who did not receive money had favorable outcomes. It is time we took seriously the effects conflicts of interest have upon the reporting of clinical findings and looked purely beyond the spin to the important outcomes that make a difference to patients.</p> <p>References 97. Dunn AG, Arachi D, Hudgins J, Tsafnat G, Coiera E, Bourgeois FT. Financial conflicts of interest and conclusions about neuraminidase inhibitors for influenza: an analysis of systematic reviews. Ann Intern Med. 2014 Oct 7;161(7):513-8. doi: 10.7326/M14-0933.</p> <p>7. Conclusion As ECDC advice and expert opinion on neuraminidase inhibitor have many limitations including misunderstanding of the most important findings of our systematic review, meta-analysis and discussions. We strongly recommend that our Cochrane review be re-read . Findings from epidemiological studies should be taken into account. Findings from basic sciences are also important to understand the mechanism of efficacy and harm from neuraminidase inhibitors: Inhibition of host's neuraminidase followed by impaired functions of various cell such as immune, metabolic, renal, cardiac and neuronal cells by neuraminidase inhibitors is closely related not only to the symptom relief but also many adverse effects on various organs. Central nervous system depressing and stimulating actions of oseltamivir but not zanamivir may be closely related to abnormal behaviours and sudden death from respiratory failure after oseltamivir use.</p>	<p>5 We acknowledge the concern raised. We have reviewed the limited evidence presented in the reviews and meta-analysis within our scope on potential harms of oseltamivir treatment and consider the potential benefits to patients in these high-risk groups far outweighs the potential risks identified thus far.</p> <p>6 We acknowledge the concern of the commentators. As indicated, most funding sources in studies on NAIs have been transparently declared and subjected to intense public scrutiny.</p> <p>7 This Expert Opinion is produced in line with the explicitly-stated methodology and scope. By no means have all epidemiological studies or basic science relevant to oseltamivir been reviewed, but the findings of the Cochrane review were fully taken into account by the Expert Panel. We believe our Expert Opinion provides a balanced and evidence-based position. This not only acknowledges and endorses many of the findings included in the Cochrane review, but also takes into account the findings of other</p>
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Finally, we find it strange that a public body would dismiss the findings of our Cochrane review and align its conclusions with a pharmaceutically-sponsored meta-analysis for which neither protocol nor assessment of risk of bias seems to exist.

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respected public health and academic researchers in order to formulate a balanced opinion that is relevant to public health and medical practitioners managing seasonal epidemics or pandemics of influenza.

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Number	Name/organisation	Contribution	ECDC assessment
		<p>95. Full prescription information of oseltamivir (revised in April 2010) accessed on 09/06/2015 available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021087s057lbl.pdf</p> <p>96. Moore ML, Chi MH, Zhou W, Goleniewska K, Peebles RS Jr et al (2007) Cutting edge: oseltamivir decreases T cell GM1 expression and inhibits clearance of respiratory syncytial virus: potential role of endogenous sialidase in antiviral immunity. <i>Journal of Immunology</i> 178: 2651-4.</p> <p>97. Dunn AG, Arachi D, Hudgins J, Tsafnat G, Coiera E, Bourgeois FT. Financial conflicts of interest and conclusions about neuraminidase inhibitors for influenza: an analysis of systematic reviews. <i>Ann Intern Med.</i> 2014 Oct 7;161(7):513-8. doi: 10.7326/M14-0933.</p>	