ECDC Public consultation

Expert Opinion on neuraminidase inhibitors for prevention and treatment of influenza – review of recent systematic reviews and meta-analyses

Deadline for comments: Wednesday 16 March 2016 sent to influenza_public_consultation@ecdc.europa.eu.

☒ I am submitting the comments contained in this document on behalf of **myself.** (All fields mandatory)

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Disclosure of conflict of interest.

RH, TJ and CH are co-recipients of a UK National Institute for Health Research grant for the systematic review discussed in this article (HTA – 10/80/01 Update and amalgamation of two Cochrane Reviews: neuraminidase inhibitors for preventing and treating influenza in healthy adults and children— http://www.nets.nihr.ac.uk/projects/hta/108001). This review focused on oseltamivir, manufactured by Roche, and zanamivir, manufactured by GSK.

TJ and CH are co-recipients of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews.

In addition:

RH wrote two books published in 2008 about the harm of oseltamivir and antipyretics. RH provided scientific opinions and expert testimony on 14 adverse reaction cases related to oseltamivir for the applications by their families for adverse reaction relief by PMDA (Pharmaceuticals and Medical Devices Agency) and in the lawsuits for revocation of the PMDA's decision concerning with these reactions. Most of the cases were reported in: IJRSM 2008:20:5-36.

TJ is co-recipient of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. TJ receives royalties from his books. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011-13, TJ acted as an expert witness in a litigation case related to oseltamivir and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013) and in 2014 was retained as a scientific adviser to a legal team acting on oseltamivir. In 2014-15 TJ was a member of two advisory boards for Boerhinger. He is a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial.

CH receives payment for running educational courses at the University of Oxford and University of Oxford ISIS consulting services for external teaching and training. He also receives royalties for books (Evidence Based Toolkit series by Blackwell BMJ Books).

Comments on document under public consultation:

Introduction

As ECDC advice has many limitations, we would like to comment on it as the following contents shows:

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Note: we cite the reference number, same as in the ECDC report if the document is cited in the ECDC report. We cited 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 the 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
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
308 4. These meta-analyses included 11 RCT's 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**.

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 hospitalizations; rather than the availability of individual patient data (IPD).

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

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.

1.2.3. All hospitalizations

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]

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 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 randomized 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**]

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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 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" (p542).

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]).

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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 hospitalization.

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.

2.1.2.1. Antibody production

Oseltamivir 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.

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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, I^2 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.

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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 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.

Figure1:　Japanese RCT for influenza prophylaxis (adults: 75 mg o.d, 42 days)
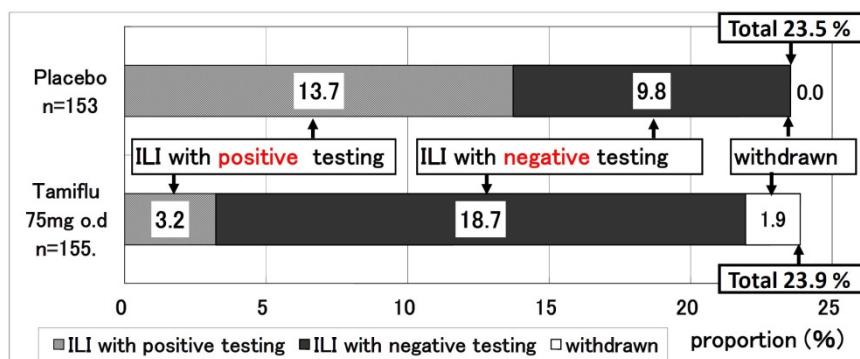
Total percent of persons with flu symptoms who had positive testing and negative testing and those withdrawn were 23.5 % for placebo group and 23.9 % for the Tamiflu 75mg o.d. group (for 42 days): no difference between both groups.
#1: ILI (Influenza-like illness): if one or more of the following symptoms were seen
　　1）fever 37.5℃ 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
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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:
359 The Expert Group concluded that on the basis of their review of the evidence presented, oseltamivir or zanamivir
360 use was not associated with an increase in serious adverse events or events leading to withdrawal from treatment
361 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?

We reported in the Cochran systematic review that

"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, I^2 statistic = 0%; RD 1.06%, 95%CI 0.07 to 2.76; NNTH = 94, 95% CI 36 to 1538). Initial analysis of patients with psychiatric adverse events in the on-treatment period showed a borderline statistically significant result (P = 0.06), hence we conducted sensitivity analysis using Peto's method (P = 0.05) as well as the analysis reported in Figure 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)."

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

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.

However, we found that :

"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."

Is it appropriate to state that there were   "no serious adverse effects"?

2.2.2.2. Injury and poisoning

Although, oseltamivir increased "injury and poisoning" in the treatment trials, we discuss here, because it may be related to the psychiatric reactions.

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 the Dobson's paper [17]) .

By our own analysis excluding Japanese trial, we have similar results:

Pooped 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:

Pooled odds ratio (by Fixed effects, conditional maximum likelihood) = 6.54 (95% CI = 1.51 to 59.34, P = 0.0051),

Pooled odds ratio (by Peto's method) = 4.08 (95% CI = 1.55 to 10.71, P = 0.0043).

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.

2.2.2.3. Other adverse reactions

*Other than psychiatric events, w*e 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.

2.2.2.3.1. Renal impairment

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 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, I^2= 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
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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
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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
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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
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76. http://rxisk.org/drugs-a-z/   accessed on March 9 2016

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
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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 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/5257410g24403m68/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:
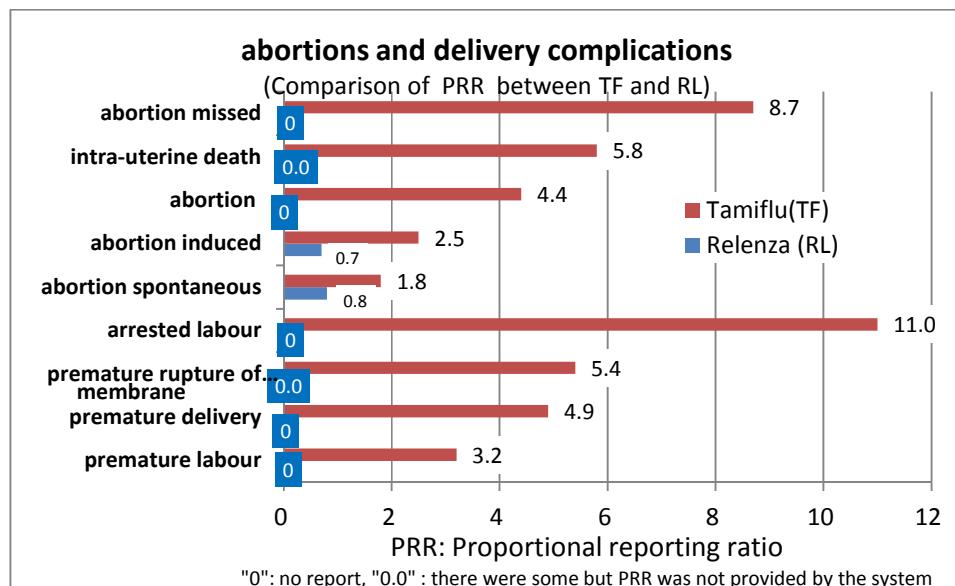
548 **Severe outcomes in pregnant women**
549 Pregnancy is a known risk factor for severe influenza disease, as also noted for the 2009 influenza A(H1N1)pdm09
550 pandemic, and a systematic review published by Mosby et al in 2011 was drawn to the attention of the group by
551 one of the experts [24]. 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
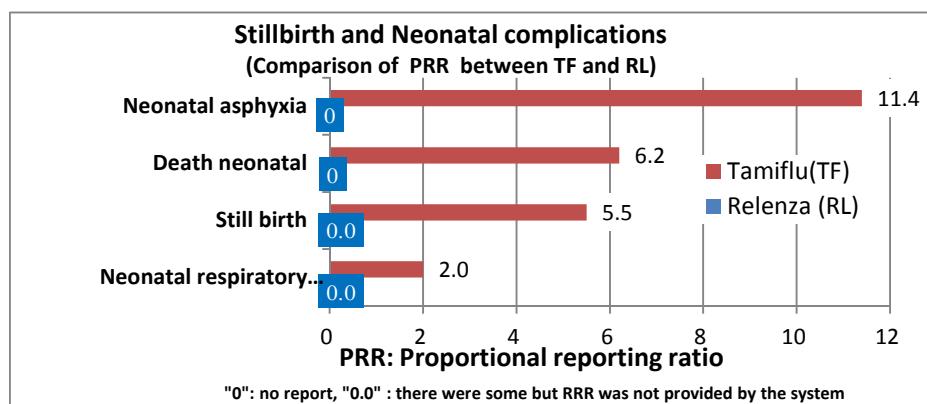
abortion related reactions (especially of **abortion missed**), intra-uterine fetal death and complicated delivery (**Figure 2)**, **still birth and neonatal death or asphyxia** (**Figure 3**) related to Tamiflu but not to Relenza. Note that a proportional reporting ratio of 2 or more indicates at least 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.

Figure 2: abortions and delivery complications (Analysis of FDA's spontaneous ADR reports)

abortions and delivery complications
(Comparison of PRR between TF and RL)

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)

Stillbirth and Neonatal complications
(Comparison of PRR between TF and RL)

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].**

Figure 4:   Dose of oseltamivir and mortality trend in juvenile (7-day-old) rats
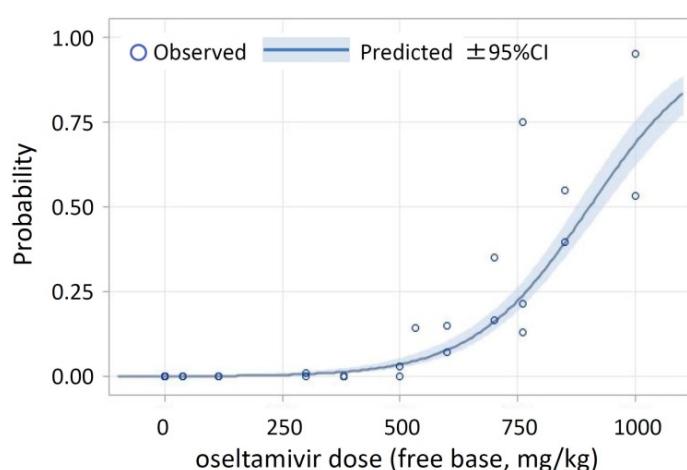
Data from ref **[80-84].**
In the TK tests, the proportion of deaths is underestimated because rats were withdrawn for determination of plasma and brain concentration. The results show that for each additional dose of 100 mg/kg, the odds of death more than double (OR = 2.26, 95% CI: 2.01 - 2.54, P<0.0001).

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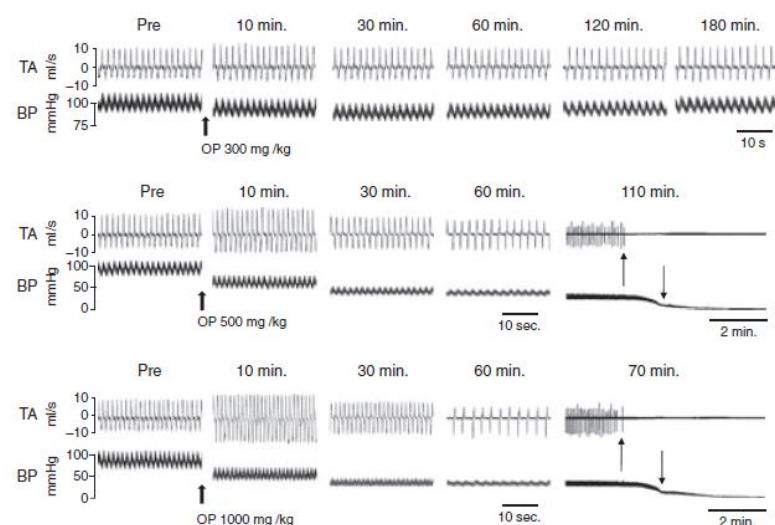

Figure 3 (of ref **[85]**): intraduodenal injection of oseltamivir phosphate (OP) at higher doses (500–1000 mg/kg) provoked ventilatory arrest followed by cardiac arrest in spontaneously breathing anaesthetized rats. Traces of tracheal airflow (TA) and blood pressure (BP) were taken before (pre) and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

References
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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].

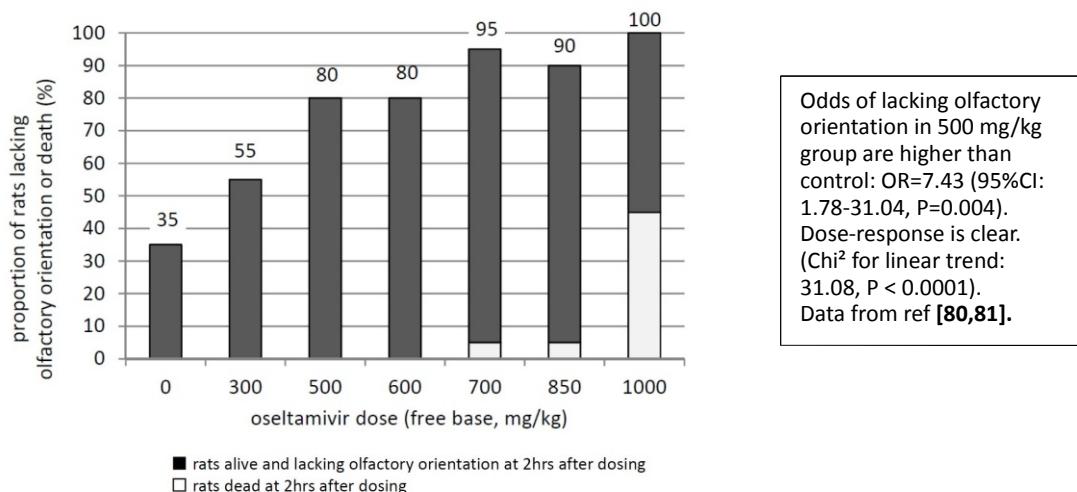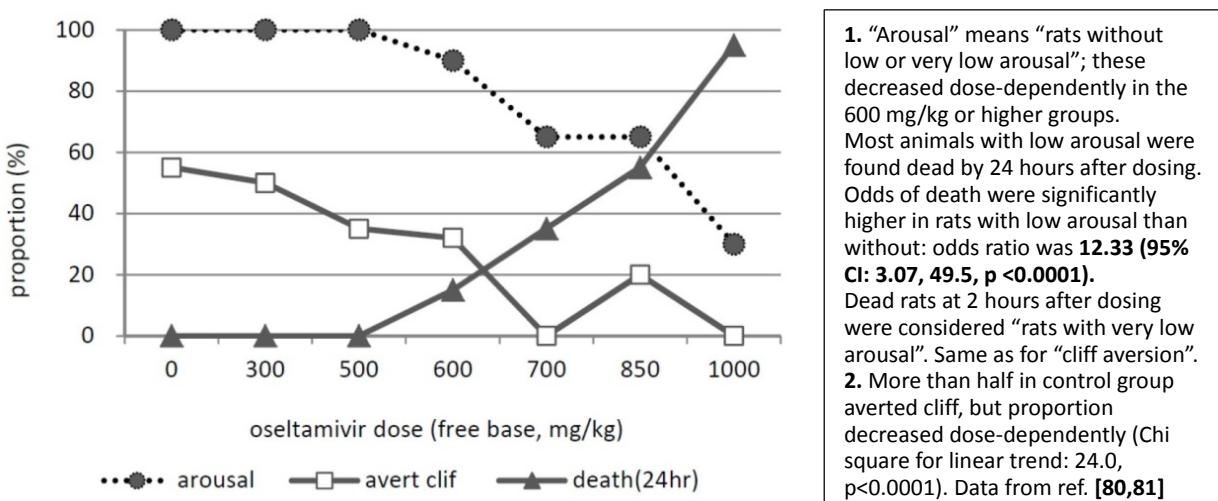**Figure 6: Proportion of rats lacking olfactory orientation at 2 hours after dosing oseltamivir**

Odds of lacking olfactory orientation in 500 mg/kg group are higher than control: OR=7.43 (95%CI: 1.78-31.04, P=0.004). Dose-response is clear. (Chi² for linear trend: 31.08, P < 0.0001). Data from ref **[80,81].**

■ rats alive and lacking olfactory orientation at 2hrs after dosing
☐ rats dead at 2hrs after dosing

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

1. "Arousal" means "rats without low or very low arousal"; these decreased dose-dependently in the 600 mg/kg or higher groups. Most animals with low arousal were found dead by 24 hours after dosing. Odds of death were significantly higher in rats with low arousal than without: odds ratio was **12.33 (95% CI: 3.07, 49.5, p <0.0001).** Dead rats at 2 hours after dosing were considered "rats with very low arousal". Same as for "cliff aversion". **2.** More than half in control group averted cliff, but proportion decreased dose-dependently (Chi square for linear trend: 24.0, p<0.0001). Data from ref. **[80,81]**

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 Cochran 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 (TNF-α) and interferon gamma (IFN-γ), were completely suppressed by oseltamivir administered 28hours 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-1β, IL-6, granulocyte–macrophage colony-stimulating factor (GM-CSF), keratinocyte-derived chemokine (KC), Macrophage inflammatory protein-1α (MIP-1α), and Monocyte chemotactic 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.

7. 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.

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 is "Although limited evidence is available from clinical trials for treatment recommendations of this vulnerable group, treatment during seasonal influenza epidemics should be recommended."

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?**

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.

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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.

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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