Dear Dr Sylvie Briand,

We read with interest your response to our request that oseltamivir be deleted from the WHO Essential Medicines list. Thank you for including both on the WHO website (WHO 2013).

We have seven questions for you:–

A. **Your (false) claim that RCTs did not address important public health outcomes.** You wrote: “it remains the case that few such studies exist on influenza antivirals that address the important public health outcomes of severe disease and mortality”.

   1. On what basis does WHO know this to be true?

   2. Has WHO requested full clinical study reports from Roche, which pledged in Dec 2009 to make them available (Smith 2009)?

We have received over 25,000 pages from clinical study reports of randomized trials of oseltamivir as part of our Cochrane review (Jefferson et al. 2012). Outcomes assessed include hospitalization, and pneumonia, and other secondary complications of influenza were recorded in around a dozen randomized controlled trials oseltamivir such as M76001, ML16369, WV15670, WV15671, WV15707, WV15730, WV15812, WV15819, WV15872, WV15876, WV15978, and WV16277. These trials are only a small proportion of the total number of trials of oseltamivir, as we are aware of the existence of over 120 trials. Complete data for the majority of these remains out of reach to independent investigators, and likely even some or most regulators.

   3. Did WHO’s guideline development process miss the existence of these RCTs?
B. **Harms of oseltamivir.** You state that WHO antiviral guidelines “took into account the available evidence for efficacy and safety” but nowhere in your response to our comment is there a discussion about harms. Prospective cohort studies such as Fujita et al. have shown increased neuropsychiatric adverse events such as delirium and unconsciousness, and a proportional mortality study by Hama et al. has shown that Tamiflu use could induce sudden deterioration leading to death especially within 12 hours, consistent with sudden deaths observed in a series of animal toxicity studies, several reported case series and the results of prospective cohort studies. Prospective cohort studies or proportional mortality studies have better controls than the retrospective cohort studies and surveillance case analysis that Hsu et al. analyzed.

4. Did WHO’s guideline development process miss the existence of these studies?

5. How is WHO responding to the current investigation Roche is under for alleged non-compliance with pharmacovigilance obligations for 19 medicines, including oseltamivir?

C. **Biased interpretation of observational studies.** You wrote that “a systematic review of observational studies ... concluded that oseltamivir may reduce duration of symptoms, hospitalization, and mortality ... (Hsu et al. 2012).” You did not however mention the limitations of this study -- mentioned in the paper’s abstract. The authors concluded that the evidence for these outcomes was “very low-quality evidence” to “low-quality evidence”, and the authors concluded “as with the randomized trials, the confidence in the estimates of the effects for decision making is low to very low.”

6. Why has WHO made decisions based on papers which themselves say should not be the basis for decision making?
It remains a fact that CDC, ECDC, WHO and other agencies have not vetted Roche's original oseltamivir clinical trial data. The one agency that has—the US FDA—concluded that the drug reduces the time to first alleviation of symptoms by about a day, and reduces the chance of developing symptomatic influenza. The FDA-approved Tamiflu labeling itself states that “Tamiflu has not been shown to prevent such complications” such as pneumonia (Hoffman-La Roche 2012).

7. Is WHO willing to keep a drug on the essential medicines list if its only benefit is symptom reduction, perhaps similar to what we might expect from a drug like aspirin?

We look forward to receiving your response.

We request that you make this letter available under the “Oseltamivir (Deletion) -- Adults and Children” section of your website. We will post a copy at http://bmj.com/tamiflu/who

Yours sincerely,
Chris Del Mar, Peter Doshi, Rokuro Hama, Carl Heneghan, Tom Jefferson, Mark Jones, Matthew Thompson
Cochrane Neuraminidase Inhibitors Review Team

References

https://www.jstage.jst.go.jp/article/jjpe/15/2/15_2_73/_article
[http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf](http://iospress.metapress.com/content/5257410g24403m68/fulltext.pdf)

[http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf)


[http://www.bmj.com/content/339/bmj.b5374](http://www.bmj.com/content/339/bmj.b5374)

WHO. Oseltamivir (Deletion) -- Adults and Children. 2013. 