# The intriguing story of a highly unsystematic Cochrane review

*by Adam Jacobs*

A strange story hit the mainstream news in early December about a systematic review of the role of neuraminidase inhibitors (such as oseltamivir [Tamiflu]) in treating flu [1]. This made the lead story on 8 December on Britain's prestigious TV news programme Channel 4 News [2]. The story involved the Cochrane Collaboration, the *British Medical Journal*, and Roche (makers of Tamiflu), and I don't believe any of them emerged from the story with much credit.

A previous Cochrane review [3] had concluded that oseltamivir was effective in preventing the complications of flu, based on a meta-analysis of 10 studies [4] that found a 59% reduction in hospitalisations. However, that meta-analysis, despite having been published in the prestigious *Archives of Internal Medicine*, contained a schoolboy error in its statistical analysis. This is surprising, given that Roche has some very smart statisticians and that one would hope that a journal such as the *Archives* would have some good peer-reviewers. However, it's not earth-shatteringly astonishing. Mistakes like that get through more often than we'd like to think.

So what was the error? What they had done was to add up all the hospitalisations in the oseltamivir and placebo groups in all 10 trials, and to treat the totals as if they had come from a single trial. That is not a statistically valid method, because it means that the analysis is not based on a randomised comparison. The trials had different inclusion criteria and therefore different risks of hospitalisation, and not all trials had equal numbers of oseltamivir and placebo patients. The effect of the drug was therefore confounded by the type of trial[1]. A correct way to do the analysis would either be by logistic regression[2], controlling for the trial, or by a meta-analysis of the results of all trials. Pooling the data and ignoring which trial they came from, however, which is what was actually done, is seriously flawed.

When the Cochrane reviewers came to update their meta-analysis, they realised that the review on which their previous conclusions had been based was flawed, so they needed more details on the 10 trials included in the meta-analysis. Sadly, only 2 of them had been published. Although that is disappointing by today's standards of clinical trial transparency and reporting, it would be wrong to be too hard on Roche for that: the trials completed about 10 years ago, and at the time it was quite common for many trials to remain unpublished. So the sensible thing for the Cochrane reviewers to do would be to ask Roche to supply the data.

However, rather than asking Roche directly for the data, they discussed the problem with Channel 4 News, who then approached Roche to ask for the data. It is unclear why they chose to approach Roche through an intermediary from the media rather than doing so directly. As Roche said in their response on the *BMJ* website [5], this was "a move that questioned whether the motives for inquiries were truly for clarity and scientific validation". Indeed.

However, although Roche had a great opportunity at that point to occupy the moral high ground, they spectacularly missed that opportunity by not making the data available in full. They were prepared to supply the data to the Cochrane reviewers if they signed a confidentiality agreement, but the reviewers were not prepared to sign such an agreement. This makes both sides look pretty bad to me. I don't see why Roche can't make the data available in full, and I don't see why the Cochrane reviewers should refuse to sign a confidentiality agreement. Maybe Roche believed that there were some valid reasons to keep the data confidential, although personally I struggle to imagine what those reasons could be, let alone how they could trump the absolutely pressing public relations reasons for making all the data available. It's also hard to imagine why the Cochrane reviewers felt unable to sign the agreement, even if they did have every right to feel a bit miffed at being asked to do so. Their failure to sign the agreement looks like they were simply trying to make a point, and is totally inconsistent with a desire for honest scientific enquiry.

Nonetheless, some data were supplied, and although they were not sufficiently detailed to answer all the Cochrane reviewers' questions, progress was being made, dialogue had been established, and it might be reasonable to think that ongoing dialogue would result in the necessary data being supplied before too long. However, the Cochrane reviewers were too impatient for this. They decided to go ahead and publish their review anyway.

1 Shameless plug: anyone who has trouble following this statistical argument about confounding is highly recommended to attend the EMWA workshop "Critical appraisal of medical literature" (unfortunately not on offer in Lisbon), where confounding is explained in detail.

2 Further shameless plug: anyone who is not familiar with logistic regression is highly recommended to attend the EMWA workshop "Statistical analysis of binary data" (available in Lisbon: book early to avoid disappointment), where logistic regression is explained in detail.

This seems extraordinary to me. The whole point of Cochrane reviews is that they are supposed to be systematic, in other words to include all the available data. To knowingly publish a review that excludes 8 relevant studies because they weren't willing to wait until they had got hold of the data seems irresponsible.

The Cochrane reviewers could easily have waited until they got the data before publishing their review. Roche could easily have published the study reports, in full, on their website. However, as it is, neither side did the things that they could easily have done to give us a reliable answer to the question of whether oseltamivir prevents complications of flu. So the rest of us still don't know whether or not it does.

All in all, a bad day for science.

**Adam Jacobs**
*Dianthus Medical Limited*
*ajacobs@dianthus.co.uk,*
*www.dianthus.co.uk*

This article is an edited version of a blog that was previously published on my website.

**References:**

1. Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ* 2009;339:b5106.
2. Channel 4 News. New doubts over Tamiflu. http://tinyurl.com/ykd9aev
3. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database Syst Rev* 2006;3:CD001265.
4. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med* 2003;163:1667–1672.
5. Smith J. Roche replies to the authors of the Cochrane Review on oseltamivir. *BMJ* 2009;339:b5364.

## Word macros: A free resource

Macros are a useful aid for editing files in Word. After spending 20-odd years writing, editing and publishing using Macs and Acorns, **Paul Beverley** (paul@archivepub.co.uk) thought that other writers and editors might like to benefit from his development work. He has written a book about using Word macros which is downloadable without charge from his (advert-free) website at: http://www.archivepub.co.uk/TheBook. The book is an invaluable resource even if you are not a technical whiz kid. It explains the basics under the headings: What is a (Word) macro? Why use a macro? How do I run a macro? What jobs can macros do? Installing a macro.

But if you are a technical whiz kid he suggests that you skip these sections and go straight to "My Ten Best Macros".

Definitions box

## Potency

The term potency is one of the most misunderstood and misused words in medicine. It clearly has something to do with the power of a drug, and the International Union of Pharmacology (IUPHAR) defines potency as: 'An expression of the activity of a drug, either in terms of the concentration or amount needed to produce a defined effect, or, less acceptably, with regard to the maximal effect attainable. An imprecise term that should always be further defined.'[1] A potent drug is therefore a drug that is effective at a low dose or low concentration (high dilution).

There are a number of ways of expressing potency numerically. The commonest is as the reciprocal of the dose (or concentration) that produces a defined effect, usually half the maximal effect. The dose (concentration) that produces half the maximal effect is the $ED_{50}$ ($EC_{50}$), so that the potency is $1/ED_{50}$ (or $1/EC_{50}$). The units are those of a dilution ($mol^{-1}$ for a dose or $L..mol^{-1}$ for a concentration). A more precise term is the $pD_2$—an exponent system (like pH) defined as the negative logarithm (to the base 10) of the dissociation equilibrium constant or $K_A$. (The $K_A$ is defined as the molar concentration of the drug that causes 50% of the receptors to be occupied at equilibrium). For example, if the $K_A$ of a drug is $10^{-9}$ $mol.L^{-1}$ (i.e. 1 $nmol.L^{-1}$), its $pD_2$ is 9.0. The more potent a drug is, therefore, the higher will its $pD_2$ be.

Interestingly, in homeopathy, the term potency is used to define how dilute a particular preparation is. Starting from the Mother Tincture (an alcoholic solution or extract of the original material), serial 100-fold dilutions are made with distilled water. Each of these dilutions is referred to as a potency. Thus, a preparation at the tenth potency has been diluted 1 in 100 ten times. For example, starting from a Mother Tincture at a concentration of (say) 1 $g.mL^{-1}$, our preparation at the tenth potency would have a concentration of $10^{-20}$ $g.mL^{-1}$. Homeopathic remedies are commonly used at the thirtieth potency, which, starting from our 1 $g.mL^{-1}$ Mother Tincture, would be $10^{-60}$ $g.mL^{-1}$. Homeopathic remedies are therefore the safest medicines available as they are, by their very nature, completely incapable of producing any adverse effects.

**John Carpenter**
*John.carpenter.medcom@btinternet.com*

1 *Pharmacol Rev* 995;47:255–266