Osel tamivir (Tamiflu) was approved by the US Food and Drug Administration in 1999 for the treatment of uncomplicated influenza within 48 hours of the onset of symptoms. The manufacturer’s press release stated that the drug was studied in two randomised trials enrolling a total of 849 patients with influenza and reported a 1.3 day mean reduction in the duration of symptoms.1 The drug was described as safe, with less than 1% of patients discontinuing it because of adverse effects. It was approved by the European Medicines Agency in 2002.2

On the basis of these limited (and ultimately revealed as incomplete) data, governments acted. Concerned about a possible outbreak of avian influenza, as well as the H1N1 pandemic in 2009, the UK government stockpiled oseltamivir at a cost of over £600m (€680m; $770m) from 2006 to 2014. Similarly, the US government has spent over $1.5bn stockpiling the drug, based on recommendations from the Centers for Disease Control and Prevention (CDC).3 And in 2010, in the wake of the worldwide pandemic of H1N1 influenza, oseltamivir was added to the World Health Organization’s list of essential medications.4 This list is intended to guide decisions on national formularies and should include only “the most efficacious, safe, and cost effective medicines for priority conditions.” As a result, oseltamivir has been described as “a nice little earner,” generating over $18bn in sales worldwide, half of it from governments stockpiling the drug.5

As recently as 2014, the director of the CDC stated that oseltamivir can “prevent serious complications; if you have influenza and get the medicine early, you may not need to be admitted to a hospital .... Antiviral flu medicines save lives, but they’re unfortunately underutilized.”6 He even encouraged use in patients more than two days after the onset of symptoms. Yet, the FDA had long concluded that there was no evidence that oseltamivir reduced complications, hospital admissions, or mortality and actually prevented the manufacturer from making such claims in their promotional materials.

So, what is the truth? An editorial in The BMJ described a “multisystem failure,”7 which is an apt description for the series of decisions based on flawed evidence made by the EMA, CDC, and WHO. These include the failure to publish all available evidence, to make the data available at the individual patient level, and to recognise the limitations of observational data. Among the factors in play in these failures were Roche’s desire for profit, public fear of pandemic influenza, and politicians wanting to be seen as “doing something” to protect their constituents.

Published data
To date, only three trials of oseltamivir in adults have been published in the medical literature.8-10 These trials emphasised the per protocol analyses, which included only patients with a confirmed diagnosis of influenza, and reported a mean reduction of 30 hours in the duration of symptoms. Of course, what really matters is how the drug works for patients with influenza-like illness since near patient tests for influenza lack sensitivity,11 and are little used in most European countries.12 After publication of their 2009 Cochrane review,13 Jefferson’s team was alerted to the existence of several unpublished trials.14 Following requests from The BMJ, the clinical trial reports were eventually made available to researchers. A meta-analysis published in 2013 found only a 20 hour mean reduction in symptoms and no evidence of a reduction in the likelihood of pneumonia, hospital admission, or complications requiring an antibiotic.15 Jefferson’s Cochrane review, using an even larger set of unpublished studies, confirmed these findings and provided additional evidence of the drug’s harms, such as nausea (number needed to harm=28), vomiting (NNH=22), and psychiatric events (NNH=94).16 Individual patient data have still not been made available to researchers. Withholding these data was a serious breach of research ethics by Roche: suppressing information obtained from patients enrolled in trials of a then experimental drug, who thought that they were contributing to the medical knowledge base.

Observational studies
The CDC based its recommendation to stockpile oseltamivir largely on data from observational studies that showed a reduction in mortality for very sick hospital inpatients but are subject to confounding by indication, selection bias, and survivorship bias. The author of a recent systematic review of observational studies concluded that the findings were interesting but inconclusive because of the small sample size and flawed study designs.17

WHO downgrades status of oseltamivir
Important lessons from the Tamiflu story

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The manufacturer may not push back against the WHO decision, since the first generic version of oseltamivir was recently approved. Nevertheless, the story has several important lessons. Firstly, it is vital that all trials be published, and that individual patient data be made available for independent reanalysis. Efforts are under way (http://www.alltrials.net/) and deserve our support. Secondly, money spent stockpiling drugs that are minimally effective is money not spent on other public health priorities. Because diverting these funds causes direct harm to the public, we must demand better evidence to inform these decisions. Thirdly, belief in the efficacy of oseltamivir may have led to less research to find truly effective drugs for influenza, again harming the public.

It is appropriate that WHO downgraded the status of this drug based on the concerted efforts of The BMJ, Jefferson and his team, and many others. A House of Commons report provides an excellent summary: “This longstanding regulatory and cultural failure impacts on all of medicine, and undermines the ability of clinicians, researchers, and patients to make informed decisions about which treatment is best.” Removal of oseltamivir from the essential medicines list is better late than never, but still comes far too late.

Competing interests: I have read and understood BMJ policy on declaration of interests and declare that I received funding from Roche Diagnostics for a study of the impact of a point of care polymerase chain reaction test for influenza on clinical decision making and inappropriate use of antibiotics and oseltamivir. Roche had no role in study design, analysis, writing, interpretation, or decision to publish.

Provenance and peer review: Commissioned, not externally peer reviewed.

1 Roche receives FDA approval of Tamiflu, first pill to treat the most common strains of influenza-ab.


3 Abdoul K. The missing data that cost 2bn. BMJ 2014;358:g2695. doi:10.1136/bmj.g2695.


5 Jack A. Tamiflu: “a nice little earner.” BMJ 2014;358:g2524. doi:10.1136/bmj.g2524. 24811410.


16 EFPIA. Position paper minimally effective is money not spent on other public health priorities. Because diverting these funds causes direct harm to the public, we must demand better evidence to inform these decisions. Thirdly, belief in the efficacy of oseltamivir may have led to less research to find truly effective drugs for influenza, again harming the public.

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