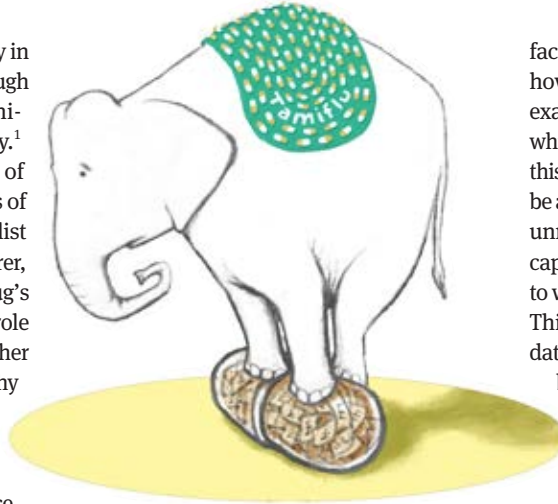# Oseltamivir: the real world data

To coincide with the publication of an updated systematic review by the Cochrane group the *BMJ* invited **Nick Freemantle and colleagues** to consider the current status of observational studies of oseltamivir and their influence on policy and practice

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Oseltamivir has become a mainstay in the treatment of influenza, although there is no evidence from clinical trials that it reduces mortality.[1] In 2009 we published a review of observational studies examining the effects of oseltamivir in influenza. It was based on a list of studies provided by Roche, the manufacturer, that it claimed provided evidence of the drug's "real life" value.[2] The evidence supported a role for oseltamivir in reducing pneumonia and other complications of influenza in otherwise healthy adults. But we found no evidence that it was associated with mortality, little information on safety, and none on pregnancy related outcomes. We have now updated our evidence by doing a systematic search of published observational studies. Here we explain the advantages and drawbacks of observational data and what they tell us about oseltamivir.

Worldwide influenza is a major public health concern. During an epidemic about 5-15% of the global population develop an upper respiratory tract infection, 3 to 5 million people contract severe disease, and there are between 250 000 and 500 000 influenza related deaths.[3] Vaccination is the leading public health control measure to prevent disease and reduce the effect of epidemics, but neuraminidase inhibitors (oseltamivir or zanamivir) or M2 ion channel blockers (amantadine or rimatidine) may be prescribed to reduce the duration of symptoms and improve clinical outcomes. The use of neuraminidase inhibitors increased substantially during the 2009 pandemic of influenza A/H1N1, partly because there was no effective vaccine but also because of concerns over increasing drug resistance to amantadine and rimatidine.[3]

Why randomised trials aren't the be all and end all

Randomised controlled trials are the gold standard in research and have a central role in drug evaluation and health policy. Randomisation ensures that participants differ only by the play of chance and treatment allocation. This means that in a well designed randomised trial, the only explanations for a difference in outcome are the effect of the experimental treatment or chance, and if chance is not a plausible explanation (for example, because of a small P value) then the experimental treatment must be the explanation. However, even impeccably designed randomised controlled trials have limitations. For example, trials often include participants who are relatively healthy, young, male, lacking comorbidities, or more motivated and adherent to treatment than patients seen in clinical practice, so the results may be not be able to be generalised to a wider population. Furthermore, trials of relatively short duration in selected participants without other risk factors may not provide evidence of real world safety.

What do observational data have to offer?

Observational studies have some advantages over randomised trials. They can be conducted in actual populations receiving treatment and can be conducted rapidly with accruing data, avoiding the long lead times and substantial costs associated with randomised trials. They can also be conducted when it is considered unethical to randomise patients between treatment conditions, such as in pregnancy.[4] Observational studies may also provide information on the safety of interventions because they can include more participants and follow them up over a longer period.

The challenge for observational studies is that treatment is not allocated by the play of chance (randomisation) so they are subject to substantial bias.[4] Observational studies should adopt approaches to reduce bias and potential confounders, but they can account only for known factors or confounders and are at the mercy of how accurately these factors are recorded. For example clinicians use their judgment to decide which treatment participants should receive, and this will be influenced by whom they recognise to be at higher risk. Their judgment therefore forms unrecorded information on risk that cannot be captured in a statistical model,[4] which gives rise to what is known as confounding by indication. This confounding is relevant to observational data on influenza patients because doctors may be more likely to treat patients who are sicker. Similarly, treatment may be given only to those who survive long enough to receive it, or remained ill for longer, termed survivorship bias.

Survivorship bias may play out in different ways in observational studies of oseltamivir. Jain and colleagues describe a multivariable analysis where receiving antiviral therapy within two days after the onset of illness was associated with reduced mortality, but their analysis was open to survivorship bias and confounding by indication.[5] It is likely that a patient who presented atypically and did not received early antivirals but recovered well might be spared oseltamivir and perhaps not included in the study or data set. On the other hand a sicker or deteriorating patient might be treated even though late treatment was not recommended. When a sicker group of patients is treated late, or when subjects who die early (before the opportunity to receive antiviral treatment) are included in an analysis as "untreated," survivorship bias will make treatment appear more efficacious.

A recent study used a statistical approach that claimed to overcome survivorship bias by including treatment with antivirals as a time dependent explanatory variable.[6] This approach can address the survivorship bias associated with early deaths, but the method does nothing to recover information about patients missing from the analysis.

Statistical techniques are available to address other types of confounding in observational studies, including multivariable statistical modelling and propensity scores.[4] Propensity scores, which use patient characteristics to estimate the likelihood they received a certain treatment, can be used to match groups or included in a multivari-

able model to adjust for or weight different propensities to receiving the treatments.[7] Propensity scores are not as robust as randomisation, as they incorporate only available risk information and often in a somewhat crude way. In the observational studies of oseltamivir, propensity scores adjusting for patient risk may not account for other factors such as patient entitlement to care, staffing levels, or high dependency care facilities, which can partly explain the outcomes measured.

Taking stock of the evidence

Following the 2009 H1N1 pandemic the World Health Organization commissioned Hsu and colleagues to review the observational evidence for oseltamivir, including studies up to November 2010.[8] They found some evidence that oseltamivir might reduce mortality in high risk populations (odds ratio=0.23, 95% confidence interval 0.13 to 0.43) but they included low quality studies in which the investigators did not use best methods to address bias. This makes the finding of these studies unreliable, a point recognised by the authors, leaving it unclear whether the pooled results are reliable.

We performed a systematic search of published observational studies to find new evidence published after 2012 and review this together with older studies under stricter inclusion and quality criteria. We included only those studies that prespecified a statistical method for dealing with bias (box). We focused on the effects of oseltamivir in patients with influenza and its association with mortality. We collated and reviewed narratively those studies found to have used potentially adequate methods to address confounding. In addition, we identified studies that examined the effect of oseltamivir in pregnancy and on neuropsychiatric events. Below, we summarise the evidence.

Mortality

Only three modestly sized studies met our inclusion criteria and provided estimates of the effect of oseltamivir on mortality.[9] [18] [19] Even though the studies met our inclusion criteria they were all open to bias because of inadequacies in design, analysis, and reporting. Each study points towards oseltamivir reducing mortality (fig 1),[9] [18] [19] and there was no evidence of heterogeneity between study results (P=0.77). Thus the studies included provided reasonably consistent evidence, which points towards a benefit for oseltamivir in this setting.

Adisasmito and colleagues' (2010) study of people who were and were not treated with oseltamivir included 221 people with confirmed influenza A/H5N1, of whom 140 died, drawn from a registry of 12 countries sponsored by Roche.[9]

Identification of observational studies

Search methods

We designed a sensitive search to retrieve observational studies from electronic bibliographic databases. In order to retrieve non-randomised studies, we used no study design filter. No date limitation or language restriction was applied.

We identified 7523 items from the following databases on 25 February 2014

MEDLINE via OVID (1946 to 25 February 2013)

EMBASE via OVID (1947 to 24 Feb 2013)

Cochrane Library via Wiley (Issue 2 of 12, 2014) including the Database of Reviews of Effects (DARE), Health Technology Assessment (HTA), and Economic Evaluations Database (EED) to scan the reference lists of relevant systematic reviews

PUBMED via NLM 'Related Articles' search in PUBMED using the previous review of observational studies (Freemantle, 2009) as a seed paper[2]

The search strategy was devised on OVID MEDLINE and then adapted for the other databases. The search strategies are available in appendix 1 on bmj.com. Screening of the search was limited to studies published from January 2010 to update the searches conducted by Hsu et al.[8] In addition we screened the 51 studies included in Hsu et al to see whether they would indeed meet our more stringent criteria.

Inclusion and exclusion criteria

We included studies published in English that compared outcomes for patients prescribed oseltamivir versus patients prescribed no drug. Patients of all ages with or without comorbidities were eligible for inclusion. Randomised trials were excluded, as were observational studies without a "no treatment" comparator population. We excluded studies that did not use multivariable models or other appropriate methods to condition for observed confounders. Thus, studies that use propensity score matching or adjustment were included, but studies that adjusted for a single confounding factor (age), or undertook no adjustment, were excluded.

Study assessment and review methods

DK and LS screened the titles and abstracts of publications identified in the search for potential inclusion. MC, NF, and LS screened full text articles. Where there was uncertainty about the inclusion of a study this was resolved through discussion. The major design characteristics of included studies were tabulated. Studies that included mortality outcomes, harms (neuropsychiatric outcomes), or that were conducted in pregnancy were summarised in narrative review.

We identified 18 potentially adequately designed observational studies (table 1, appendix on bmj.com).[9-26] These studies fell naturally into two types: those based on large scale medical records or insurance claims based databases[10-13] [16] [17] [21] [25] and those based on tailored disease registries,[9] [14] [15] [18] [19] [22-24] [26] with the largest study including more than 80 000 subjects and the smallest studies including fewer than 300 subjects.

Five studies used propensity score based methods to address observed sources of confounding,[9] [12-14] [16] with the remainder using multivariable regression models. Four studies included an assessment of the effects of oseltamivir on mortality.[9] [14] [18] [19] Three studies examined pregnant women,[11] [24] [25] five studies included only children and adolescents,[10] [14] [21-23] nine included adults and children,[9] [12] [15-20] [26] and two included only adults.[11] [13] Four studies included only patients admitted to hospital with influenza virus.[14] [18] [19] [26]

Liem and colleagues (2009) included 67 (72%) of 93 cases of influenza A/H5N1 infection diagnosed in Vietnam from a retrospective notes review of laboratory confirmed cases between January 2004 and December 2006.[18] There were 26 deaths among the 67 included cases (18 deaths among the 55 patients treated with oseltamivir). Given the small number of deaths the multivariable regression models are likely to be overfitted and may have provided unstable results. Overfitting is a problem associated with multiple testing where including too many explanatory variables means that a positive result can be expected simply on the basis of chance. Harrell and colleagues suggested that as a rule of thumb for survival models the maximum number of explanatory variables should be one tenth the number of observed deaths.[27] The big problem with overfitted models is that they can appear to fit the data well but will fail to

predict the outcome in new data sets. Coupled with publication bias (only studies with positive results being published) overfitting causes major problems because it may lead to exaggerated estimates of treatment effect in some studies.

McGeer and colleagues studied 322 adults admitted to Toronto Invasive Bacterial Diseases Network hospitals with laboratory confirmed influenza from 1 January 2005 to 31 May 2006.[19] Again, given the number of deaths (27 deaths by 15 days), the parameter estimates may be biased by overfitting.

A fourth study, by Coffin and colleagues, also examined risk of death but did not report overall results. The authors studied 252 children admitted to one of 41 participating US hospitals with influenza and treated with oseltamivir within 24 hours of admission; these were matched with children who were not treated with oseltamivir using a propensity score.[14] They found no

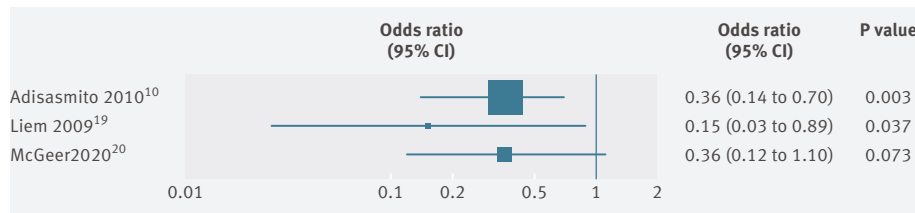| Odds ratio (95% CI)		Odds ratio (95% CI)	P value
Adisasmito 2010[10]		0.36 (0.14 to 0.70)	0.003
Liem 2009[19]		0.15 (0.03 to 0.89)	0.037
McGeer2020[20]		0.36 (0.12 to 1.10)	0.073

Fig 1 | Estimated effects of oseltamivir in reducing mortality. (Odds ratio for Adisasmito[9] derived from the reported hazard ratio and control exposure event rate)
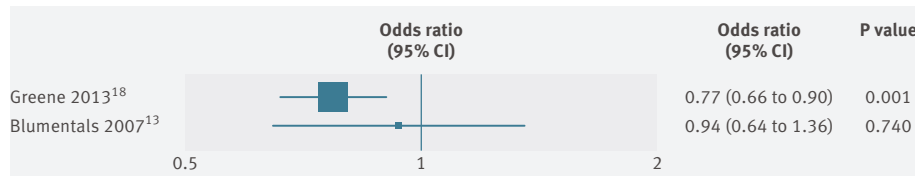
Odds ratio (95% CI)		Odds ratio (95% CI)	P value
Greene 2013[18]		0.77 (0.66 to 0.90)	0.001
Blumentals 2007[13]		0.94 (0.64 to 1.36)	0.740

Fig 2 | Estimated effects of oseltamivir in reducing psychiatric events

difference in the rate of death between these two groups and did not provide a summary estimate of risk or the actual numbers of deaths in the matched cohorts. Somewhat oddly they did report the predicted risk of death, and it seems likely that there were no more than two deaths in each group. Their failure to publish the overall results is evidence of publication bias.

Pregnancy

Since 2009 three observational studies have been published that focus on the association between treatment with oseltamivir during pregnancy and maternal infant outcomes.[11 24 25] No significant associations between adverse pregnancy outcomes and the use of oseltamivir were observed, but the confidence intervals are wide and do not preclude harm. One study indicated higher rates of transient hypoglycaemia in exposed infants, but again the confidence intervals were wide (odds ratio=4.0, 95% confidence interval 1.23 to 12.76).[24] We could not ascertain whether pregnant women were included in the published observational studies evaluating the effects of oseltamivir on mortality.[9 18 19]

Neuropsychiatric events

Three studies report rates of neuropsychiatric events (psychiatric or neurological events such as depression or seizures) with oseltamivir.[12 16 17] Funch and colleagues (2012) found no significant difference in reported adverse events between treated and untreated adults but found a modest increase among treated adolescents (relative risk=3.14, 1.05 to 9.67; P=0.046).[16] However, subgroup analyses such as this are well known to be potentially misleading.[28] The studies by Blumentals and colleagues (2007) and Greene and colleagues (2013) both point towards oseltamivir reducing neuropsychiatric events, although only Blumentals is statistically significant (fig 2). Blumentals studied staff

employed by Roche and Thompson Healthcare, and the work of Greene and colleagues was sponsored by America's Health Insurance Plans (AHIP) under contract from the Centers for Disease Control and Prevention (CDC).

What is needed?

We have summarised the better designed observational evidence on the effects of oseltamivir in the treatment of influenza. The effects on new psychiatric and neurological conditions and evidence on the harms of treatment in pregnancy remain unclear.

The health of pregnant women is difficult to examine in randomised trials but data are important because pregnant women may be at higher risk of illness and complications associated with influenza.[29-32] Pregnant women could be included in future randomised trials investigating oseltamivir to provide more robust estimates of efficacy and safety with "a plan for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child."[33]

How persuasive should we find the results of mortality studies described here? The studies seem to show that oseltamivir reduces mortality. However, they are based on relatively small numbers of participants, use designs that are known to be open to substantial biases,[4] and were not optimally designed or conducted. We consider the findings interesting but inconclusive.

Recently, a large observational study funded by Roche examined the effects of neuraminidase inhibitors on mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection, based on individual patient data (and pooling many previous studies).[6] This study provides data that support a reduction in mortality and the advantages of early treatment over late treatment and in pregnancy. However, the propensity score method used was weak

(classifying patients into quintiles of the propensity score), and the time dependent covariate survival approach used may not adequately deal with likely survivorship bias. The authors did not describe whether there was an interaction between the propensity score and outcome, which as we have previously described is a useful check on how well the method addresses bias.[4]

Those hoping to be informed by the observational studies might question why randomised trials in higher risk populations, specifically those with comorbidities, have not been conducted. As health systems have been happy to purchase substantial stockpiles of antiviral agents against the perceived risk of an influenza pandemic, it has not been in the interests of manufacturers to undertake such trials, and others with a research funding interest have not taken up the challenge to support trials in this area despite the clear importance of such trials.

We might also wonder why drug regulators have not taken the licensing of antiviral drugs more seriously, requiring high quality evidence of effect in a range of populations as they do for other conditions, particularly among those at high risk because of comorbidities.

Influenza is a predictable threat that occurs every year, and people with comorbidities face potentially serious consequences as a result. Requiring or facilitating adequately designed research would be in the public interest, and public funding mechanisms have failed in their duty of care towards patients.

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