Tamiflu: A Colossal Waste of Money

A pharmaceutical giant exposed for pushing an ineffective and costly drug shows us how Big Pharma can exploit fear for profit

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Independent review raises big question mark

There are many different types of the influenza virus. Most of them will give a healthy person only a few uncomfortable days, but some can make you seriously ill. The most famous is the Spanish flu that appeared in 1918; by the time it had run its course, it had infected over 500 000 000 people and killed at least 50 000 000 [1]. The Asian flu of 1957-8 and the Hong Kong flu of 1968-9 are each estimated to have killed over a million people.

The most serious recent outbreak was due to the H5N1 avian flu virus that appeared in the mid-2000s. It can have a mortality rate in humans as high as 60%, but because it does not usually pass from human to human, not many people were infected and by 2013 just 375 deaths had been recorded [2, 3].

When neuraminidase inhibitors - antiviral drugs claimed to combat influenza - appeared on the market, many governments decided to stockpile the drugs in case a new virus appeared that was as deadly as H5N1 but more easily transmitted among humans. They spent large amounts of money, £500 million in the UK and $1.3 billion in the US [4, 5], much of it on oseltamivir developed by Roche and marketed under the trade name Tamiflu.

Even at the time, not everyone was convinced this was the right decision. There have always been doubts about the effectiveness of Tamiflu or indeed any

antiviral drug, as a means of preventing or combatting either seasonal or pandemic influenza (see [6] How to Stop Bird Flu Instead, *SiS* 35, and [7]).

The Cochrane Collaboration, a global not-for-profit organisation whose aim is "to produce accessible health information free from commercial sponsorship and other conflicts of interest," were not convinced by the case for Tamiflu. They pointed out that all the evidence was based on trials sponsored by the industry and they found discrepancies in the data and signs of reporting and publishing bias: of the many trials carried out across the world only a few had been published. Cochrane tried to conduct their own analyses but were refused access to the rest of the data, and had to resort to a Freedom of Information suit.

When this eventually succeeded, Cochrane did a thorough review based on 46 randomised controlled trials (RCTs, see Box) carried out by pharmaceutical companies as part of the licensing procedure [8, 9]. They found the benefits of Tamiflu and other neuraminidase inhibitors to be much smaller than had been claimed, and noted that the US Food and Drug Administration (FDA) had concluded that the overall effect of oseltamivir and zanamivir (another neuraminidase inhibitor) was "modest."

Cochrane's Review concludes that the hundreds of millions of dollars paid to Roche and other pharmaceutical companies has been largely a waste of money that could have been much better spent on other health measures.

Randomised controlled trials (RCTs)

The way to see whether a drug works is to give it to some people and see what happens. The problem is that most of the time only some of the people treated will get better; and for all you know they might have got better anyway, without taking the drug.

You can improve the experiment by having two groups of people, one who are given the drug, and another, the control group, who are not. If the proportion of the treated patients who recover is significantly higher than the proportion in the control group, that is more convincing than if there were nothing to compare the treatment with.

That still isn't really enough, because you really want to be sure that the only difference between the groups was that the patients in one were treated and those in the other were not. So there are a lot of questions you have to deal with before you can be confident of your result.

How were patients assigned to the groups? If they were offered the chance to try the new drug, were those who volunteered different in some way from those who did not? Did doctors only offer the new drug to people they judged had a good chance of profiting from it, or to people who were the most seriously ill? Were those who were taking the drug treated differently in other ways from those who were not? Was there a placebo effect, i.e. did it make a difference to patients simply to know that they were being given a new drug? Were there more dropouts from one group than the other and why, and how might that have affected the outcome? If your records are from hospitals, how accurate are they, bearing in mind that doctors are primarily interested in helping people recover, rather than filling in forms for your research. Or did you rely on forms filled in by the patients, which are even less likely to be accurate? And so on.

These objections can be largely overcome by conducting a randomised controlled trial (RCT). In RCT, some of the volunteers are chosen at random to be given the drug. The remainder, the control group, are given a placebo, a pill that is meant to have no effect so that they do not know they are not taking the drug. Ideally, the trial is "double blinded" in that the researchers collecting the data also do not know who is being given the drug. This prevents them from unconsciously treating the two groups differently or allowing the volunteers to deduce which group they are in.

RCTs are regarded by many as the 'gold standard' of drugs trials. There are, however, some drawbacks. Even if the treatment and control groups are closely matched, the whole sample may not be typical of all the people for whom the drug is intended. RCTs are typically expensive to run, and in many situations it is impracticable, unethical or even impossible to organise. They can only be used when it is acceptable to leave the choice of treatment to chance rather than the preference of the patient or the judgement of the medical team.

Observational or anecdotal evidence is bound to remain important in the development of evidence-based health care and indeed in other fields as well. At the same time, we have to be conscious of the shortcomings of such evidence, which are precisely what RCTs are designed to overcome.

Counter-review claims Tamiflu saves lives

Naturally, there was an immediate response from Roche who had made so much profit from Tamiflu, from governments who had spent so much of the

taxpayers' money; and from the scientists and health workers who had devoted so much time and effort to the project. They still maintain that Tamiflu is effective, that it alleviates the symptoms of influenza and saves lives, and they claim that treatment with Tamiflu reduced the risk of death by 19% compared with no treatment [10, 11]. Roche's counter-review was based not on the RCTs but on observational evidence from 78 studies of patients admitted to hospital between January 2009 and March 2011. Roche claim that this "real-world" data are more relevant to judging the efficacy of the drug than results from an RCT. The Cochrane Collaboration chose not to use the observational data because they found it to be flawed; they discuss this in detail in their review [8]. (See also the correspondence published by the BMJ [12].)

An independent 'Multiparty Group for Advice in Science' to the rescue

Roche's counter-review raises numerous questions. Is Tamiflu actually effective in the real world, whatever the RCTs found, or was that an artefact of the way the observational data were collected, analysed and selected for publication? If it is more effective, why does that not show up in the RCTs? Why was Tamiflu licensed and so much money spent on it when an analysis of the data available at the time (naturally the observational data came *after* Tamiflu was licensed) now seem to show so little benefit? Why have the manufacturers been so determined not to allow Cochrane access to the vast amount of unpublished data [12]?

In 2013, Roche announced that in the interests of transparency it would supply any data requested by what it described as a "third party group", the Multiparty Group for Advice in Science (MUGAS) [10].

In fact, while the name might lead you to imagine an independent body bringing together representatives of a number of organisations to consider a range of issues (rather like All-Party Groups in the UK Parliament), MUGAS is funded by Roche and is led by four scientists, three of whom are advisers to Roche. It appears to have been set up specifically as part of the attempt to counter the Cochrane's criticisms [13].

Another organisation involved is European Scientists Working on Influenza (ESWI). On their websites, MUGAS and ESWI give as their point of contact the same mobile telephone number in Belgium [13, 14]. The name MUGAS is a registered trademark of Semiotics, a company that describes its mission as

"translating science to the world," but whose actual activity seems mostly to be concerned with influenza and in particular oseltamivir [15].

If Tamiflu and other neuraminidase inhibitors are nowhere near as effective as their manufacturers claim, building up huge stockpiles has been a colossal waste of money. It has also led our governments to believe that we are ready for the next serious outbreak of influenza when we are not. Governments must not ignore the Cochrane analysis, and they cannot rely on the misleadingly named MUGAS to resolve the issue for them. If they are not willing to trust Cochrane, they will have to find other independent experts to explain the discrepancies.

The lesson for the future is that all the data from drug trials including Phase 4 (studies of licensed drugs after they are on the market and being used by clinicians) must be made available to independent researchers, not restricted only to those with a vested interest in promoting the drug in question. The pharmaceutical industry might find this inconvenient, but it would not be as inconvenient as they would have us believe, especially if it were clear from the outset that this would have to be done and the trials were designed and the results recorded with that in mind. Companies have found they can live with registering Phase 1 trials, something they opposed for many years [16, 17]. We pay a lot of money for drugs and our health depends on their being both effective and safe. We have the right to demand that everything is done to make sure that they are.

Postscript

This story has its ironic side. Roche are insisting that what they call "real-world" evidence is more relevant than carefully analysed results from RCTs. Yet for years the biotech industry has steadfastly refused even to look at real-world evidence of the harm caused to humans, animals and the environment in the case of genetically modified organisms (GMOs), dismissing it as "anecdotal" and therefore not worthy of consideration.

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