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Tamiflu: the battle for secret drug data

Influenza drug oseltamivir has made billions of pounds for Roche, but why won't the company give patients and doctors access to the full clinical data? As part of the *BMJ*'s open data campaign, we this week launch a new site dedicated to the cause. **David Payne** reports

This week the *BMJ*, as part of its ongoing open data campaign, has launched a website aimed at persuading Roche to give doctors and patients access to the full data on oseltamivir (Tamiflu).

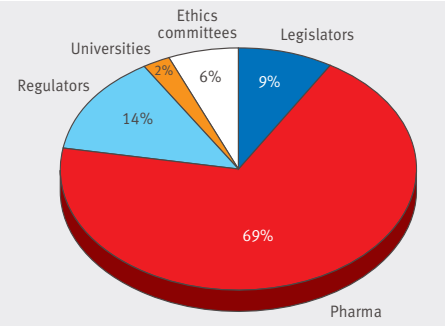
The new site, www.bmj.com/tamiflu, displays emails and letters dating back to September 2009, when researcher Tom Jefferson first asked the company for the unpublished dataset used in a Roche supported analysis, published in 2003.[1]

Jefferson needed the data by the following month to update the Cochrane Collaboration's review on neuraminidase inhibitors in healthy adults. At first the company asked him to sign a confidentiality agreement promising that he would not publish the data in full.[2]

Then it declined to supply it on the grounds that it had been approached by an independent expert influenza group undertaking a similar meta-analysis and wanted to avoid a conflict. Roche added that its study reports had also been shared with the regulatory authorities.

Jefferson told the company in an email: "I recognise that more people than me are interested in reviewing the trials of interventions for influenza at the moment.

"But I don't understand why this should lead to exclusivity, or why you would believe that there would be a conflict between our plans to update our Cochrane review and the plans of the other research groups you mention."



Results of a poll on bmj.com last week, 569 votes cast, which asked "who is mainly at fault for denying access to negative clinical trial results?"

Jefferson's October deadline passed. Two months later the Cochrane review, published in the *BMJ*,[3] said that because eight of the 10 randomised controlled trials on which effectiveness claims were based were never published, the evidence could not be relied on. Also, the two published studies were funded by Roche and authored by Roche employees and external experts paid by Roche.

The review concluded: "Paucity of good data has undermined previous findings for oseltamivir's prevention of complications from influenza. Independent randomised trials to resolve these uncertainties are needed."

An accompanying *BMJ* investigation and analysis article described how Cochrane's attempt to reproduce an analysis underpinning the use of oseltamivir in pandemic flu hit a brick wall.[4 5]

In December 2009 Roche promised to make full study reports on the 10 trials available to doctors and scientists.[6] Butlast month *BMJ* editor in chief Fiona Godlee reminded the company, in a letter to board member John Bell, that Roche had still not made the full clinical study reports available.[2]

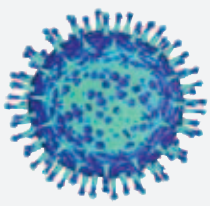
She told him: "Tamiflu has been a huge commercial success for Roche. Billions of pounds of public money have been spent on it, and yet the evidence on its effectiveness and safety remains hidden from appropriate and necessary independent scrutiny.

"I am appealing to you as an internationally respected scientist and clinician and a leader of clinical research in the UK to bring your influence to bear on your colleagues on Roche's board."

Roche has yet to respond formally, but the email exchanges are now in the public domain at www.bmj.com/tamiflu for all to see.

All emails are loaded as jpeg images using the *BMJ*'s rapid response system and as pdfs. They are displayed in chronological order, and readers can join the debate by submitting comments, which will then be considered for publication. There is also an interactive timeline reminding

TAMIFLU TIMELINE



October 1997
The US Food and Drug Administration approves oseltamivir for the treatment of influenza in adults

May 2002
WHO, with partners, develops a new global agenda on influenza surveillance and control. Part of the guidance includes country level stockpiling of antiviral drugs to treat influenza

July 2005
Kaiser and colleagues publish their meta-analysis of the effect of oseltamivir on flu related lower respiratory tract complications.[1] The review contained unpublished data from the manufacturer, Roche

July 2006
The Cochrane Collaboration carries out its first review—including data from the Kaiser meta-analysis—into the use of neuraminidase inhibitors (NIs) for preventing and treating influenza in healthy adults. They conclude that "In a serious epidemic or pandemic, NIs should be used with other public health measures"

March 2009
H1N1 influenza ("swine flu") emerges in Mexico and spreads globally

June 2009
WHO declares a flu pandemic. Following WHO guidelines, governments worldwide start to stockpile oseltamivir, spending $6.9bn (2009 value)

readers of key developments in the oseltamivir story going back to the early days of the H1N1 influenza pandemic in 2009.

Accountability

www.bmj.com/tamiflu allows readers to witness attempts to compel greater accountability and responsibility in public health decision making and policy. The *BMJ* plans to launch other campaigns linked to its investigations in the future.

Jefferson's colleague Peter Doshi, a postdoctoral fellow at Johns Hopkins University, Baltimore, describes bmj.com/tamiflu as the online equivalent of an open letter.

He said: "I'm not aware of anything that does more than just a simple open letter. The reader can see the correspondence almost as a stage play. One can see how the actors are actually acting, especially when one is pushing for accountability but the other party refuses to engage. If you make that kind of behaviour visible, perhaps you can actually achieve progress."

"For decades industry and regulators have worked largely under agreement—sometimes forced by law and other times just tacit agreements—that the data that would be shared between them would be confidential and treated as a trade secret.

"Now we're realising there is a number of enormously harmful consequences from those policies in which arguably drug disasters like Vioxx [rofecoxib] or Celebrex [celecoxib] or Avandia [rosiglitazone] could have been detected much earlier had the data been available."

Also listed is the Cochrane group's correspondence with the World Health Organization[7] and the US Centers for Disease Control and Prevention (CDC).[8]

The WHO correspondence begins with an email from Jefferson in February 2012. He asks WHO scientists how its review process had led to it including oseltamivir in its March 2011 "essential medicines" list.

Arguably drug disasters like Vioxx or Celebrex or Avandia could have been detected much earlier had the data been available

Had it asked the manufacturers of neuraminidase inhibitors for the unpublished trial data? Also, what had WHO scientists made of Cochrane's conclusion "that there is no evidence that oseltamivir can limit the spread of influenza."

WHO told Jefferson that it was currently developing a standard guideline on clinical management of influenza virus infection.

It had also commissioned several evidence reviews, including one on oseltamivir that was set to appear soon in a peer reviewed medical journal. It promised to alert Jefferson when the review appeared.

The email exchange with the CDC asked for written answers to six detailed questions in response to an article posted on its website on 7 February 2012, *CDC Recommendations for Influenza Antiviral Medications Remain Unchanged*.[9]

Why, for example, did the CDC not consider unpublished data? Had it asked Roche for any? Did it have any evidence that oseltamivir could stop the spread of influenza?

The CDC article maintained that reviews of randomised controlled trials might not fully inform the question of whether antiviral treatment reduces severe complications of influenza.

But is also maintained that "reviews of RCTs . . . have found consistent clinical benefit of early oseltamivir treatment in reducing the risk of lower respiratory tract complications."

Neither Jefferson nor Doshi was impressed with the CDC's response, which they challenged in five follow-up emails.

Jefferson told the *BMJ* last week that the US Food and Drug Administration had described Tamiflu's effects as modest. "Despite this, WHO and CDC have been extensively promoting the drug. WHO has made Tamiflu one of the essential drugs, so it sits next door to aspirin and penicillin, cortisone," he said.

"The CDC has extensively recommended the use of Tamiflu, and, as you know, governments worldwide have stockpiled it on the advice, essentially, of WHO.

"We were trying to find out exactly what evidence these decisions were made on. So we asked questions, and we also asked WHO and CDC whether they'd seen our review and what their thoughts were.

"Readers will see the kind of stonewalling that we got. Indeed, my correspondence with WHO shows that they didn't answer a single one of my questions.

"Politicians have ignored the problem and have not demanded accountability from their own decision makers, from regulators, and from industry."

This could be about to change, in the UK at least. Last week Sarah Wollaston, a general practitioner and Conservative member of parliament, raised the issue of missing data in parliament. Health minister Norman Lamb has agreed to meet experts to discuss what he referred to as "the really important issue" of access to data from clinical trials.[10]

In an email telling Jefferson about the planned meeting, Wollaston said: "It will surely be a turning point in the campaign for open data if we can show that £1 in every £200 of the total NHS budget for 2009 was spent stockpiling a drug for which a drug company had knowingly concealed data either showing it had no real benefits . . . or worse . . . caused real harm."

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References are in the version on bmj.com.
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NEWS, p 2; EDITORIAL, p 7; OBSERVATIONS, p 35

July 2009
Japanese paediatrician Keiji Hayashi contacts the Cochrane Collaboration with questions about the Kaiser meta-analysis. He points out that the review was based on unpublished, unpeer reviewed data from Roche given in confidence to the authors

October 2009
Tom Jefferson, from the Cochrane Collaboration, requests data from Roche. It offers the data, but on the proviso that an agreement is made of confidentiality not only of the data but of the agreement itself. Cochrane declines

December 2009
BMJ missing data cluster. The *BMJ* calls for Roche to make all its data available for scientific scrutiny. The Cochrane team re-analyses the data from its previous meta-analysis, excluding the data shared with Kaiser by Roche. The team find no evidence to suggest that oseltamivir reduces complications in cases of influenza

January 2011
Cochrane Collaboration approaches the European Medicines Agency to obtain the data it used as the basis of the approval of oseltamivir

April 2011
The European Medicines Agency sends 25 453 pages of clinical study reports to the Cochrane Collaboration

October 2012
Data from Roche are still undisclosed, despite assurances that the company would open them up to scientific scrutiny

BRIGHT LIGHTS AND BIG CITY HEALTH PROBLEMS

Nigel Hawkes reports on the magnified problems that modern cities present and how public health is responding to the challenges

bmj.com

News: UK drug service is ill equipped to deal with new "legal highs" taken by clubbers, conference is told (*BMJ* 2012;345:e7162)

FRANCOIS LOCHON/GAMMA RAPHO/GETTY IMAGES

Homeless in Paris: everyday ills are magnified in the cities, where 70% will live by 2050

Cities are places of extremes where problems come in only large or super size: everyday ills are magnified, poverty is concentrated, and personal freedom readily turns into licence. For public health, they are the miner's canary. Where cities lead, the rest of society follows.

Cities are also increasingly where most people live. As David Wilson of the World Bank reminded the inaugural City Health conference last week, in 1950 only 30% of the world's population lived in urban areas. By 2050 it will have risen to 70%. The urban milieu that most of them will inhabit, he said, will be crowded, polluted, and unsafe—an environment that discourages exercise and exacerbates behaviours such as unhealthy eating, smoking, and alcohol and drug misuse. Fortunately, cities are also the engines of opportunity where new ideas emerge, where cooperative action is more easily established, and where wealth is generated.

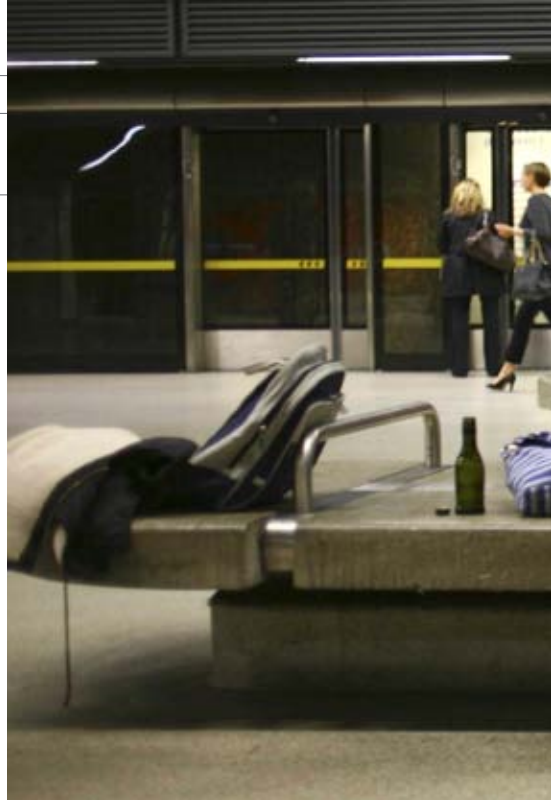
The City Health conference, held in the Guildhall in the City of London on 22-23 October, aimed to identify public health threats through the concentrating lens of city life. Organised by the London Drug and Alcohol Policy Forum, it was the first of a series, with Glasgow already lined up to host next year's event. The conference coincides with a fundamental change in the organisation of public health in England that will make local authorities responsible for its delivery under the guidance of a new body, Public Health England.

Like so many institutions in England, Public Health England will be run by a Scot, Duncan Selbie, who may have more to say in Glasgow than he did in London. The organisation is barely on its feet so he was light on specifics. But he did say that entrusting public health to local authorities had been "a stroke of genius" and that from the conversations he had already had, local authorities were "absolutely up for it." His organisation, he promised, would be professionally led and evidence based—"what I want is public health professionals in the room helping local government"—and he attempted to allay concerns that it would lack the resources needed.

"It's not about £2bn or £4bn, it's about the £101bn the NHS had got and the billions the local authorities have got," he said. "If people think public health will be like it was, they're going to be surprised—and if they think it's going to be worse, they're going to be even more surprised." He promised, anyway, that the 2013-14 spend would be maintained at existing levels.

Problems of modernity

While Victorian London transformed public health by modernising its sewers and water supplies, today's public health problems are not the result of a failure to modernise but of modernity



itself, argued Phil Hanlon, professor of public health at Glasgow University. Modernity had created a society dominated by consumption, where personal freedom had degenerated into selfish individualism. And while evidence was important, it was not the only value: the true, the good, and the beautiful needed to be integrated. While people still sought to achieve this platonic ideal in their own lives, in government and organisations a narrower reductionist version had taken hold, dominated by economism and an exaggerated belief in the power of science—"scientism." "The application of guidelines is not enough," he said. "We've been doing that for ages." It was "delusional" to believe they could solve today's public health problems.

If so, it was a delusion still shared by most of those who spoke at the conference. Plenty of guidelines were put forward: guidelines for licensing clubs and pubs, for training bouncers how to deal with people under the influence of drugs, for helping strippers avoid the pitfalls of their trade, for transforming blighted neighbourhoods.

Some guidelines really worked, such as the painstaking preparations by the Department of Health for health cover during the 2012 London Olympics. So well prepared was London that the impact of the games on health provision for Londoners was "minimal," said Lily Makurah of the Department of Health. Everything worked, she said, attributing the success to organisations having worked across traditional boundaries and having a single point of contact for advance planning in each organisation involved.

Others were less successful. Professor Mark Bellis of the Centre for Public Health at Liverpool John Moores University said that better licensing, staff training, targeted policing, CCTV, and the provision of late night transport designed to

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tackle public drunkenness had had the perverse effect of creating "the safest possible environment for people to get drunk in." Pub Watch and antisocial behaviour orders, which exclude violent offenders from licensed premises or from entire night life areas, had pushed violence out but had not addressed the underlying issue.

He summarised the problem: "50% of all violence in England is alcohol related—one million incidents a year. 20% of violence occurs in or around pubs and clubs, 80% of emergency department assault patients have been drinking, and 50% of adults avoid town and city centres at night. Safer drinking messages are irrelevant to nights out—the late night economy operates on selling alcohol to drunk people."

Safer drinking messages are irrelevant to nights out—the late night economy operates on selling alcohol to drunk people

He provided his own checklist of what might be done, starting with proper attempts to enforce the law that serving those already drunk is illegal. At present, there are only a handful of such prosecutions each year. The public should be told of the often hidden consequences of heavy drinking sessions, which include rape, child abuse, and domestic violence. Early life interventions had been shown to help, and minimum alcohol pricing would reduce harms. "Cities can flourish on a reputation for a safe, exciting night life—what reputation does UK night life currently have?" he asked.

But James Nichols of Alcohol Research UK warned that imposing public health obligations on licensing authorities was tricky. In Scotland, where protecting and improving public health were part of the licensing obligations, the authorities had struggled to understand and impose this public health objective. In April this year, on the first occasion a Scottish health board has been able to influence licensing decisions, Edinburgh refused Sainsbury Local and two other stores an alcohol licence in an area of the city, South Bridge, that it deemed already over-provided. Sainsbury's has launched a court challenge.

"Will the policy stand up in court?" he asked. The problem was that two conflicting views were seeking reconciliation: "Public health sees the population; licensing sees the street. Licensing sees crime and disorder, trade regulation, and the economy, while public health sees greater availability of alcohol leading to greater harms."

Rehabilitation of cities

Two speakers from Vancouver, Senator Larry Campbell and Lindsey Richardson, a postdoctoral fellow at the British Colombia Centre of Excellence in HIV/AIDS, gave accounts of the attempts to rehabilitate an entire area of the city, Downtown Eastside. In the 1990s, Campbell said, it had been a public health disaster, riddled with poverty, homelessness, and drug addiction, with residents preying on each other. "If you were elderly or mentally ill, you were definitely at risk there," he said.

The task of turning it round was not for the faint of heart, he said, and required political battles that went on night after night. "If you stay with it, a consensus will start to build. When we started we were in a minority; when we finished we were in the majority." A particular battle centred on the Insite supervised injection site for addicts, which survived court challenges and is credited with greatly reducing infections and cutting death rates. Downtown Eastside today is showing signs of recovery, with greater life expectancy, fewer drug related deaths, and reduced homelessness.

In London, warned Owen Bowden-Jones, a consultant psychiatrist from Central North West London NHS Foundation Trust, while the numbers seeking help for heroin or cocaine addiction were declining, a new drug threat was emerging. Bowden-Jones is a founder of the Club Drug Clinic at Chelsea and Westminster Hospital, which opened 18 months ago and is now overwhelmed with people seeking help for their addiction to a bewildering range of new "legal highs."

Club drugs needed no clandestine dealers, he said. They could be bought openly on the internet from nearly 700 different sites and delivered next day through your letterbox like a package from Amazon. Last year 49 different drugs were detected, a total he expected to rise to 60 this year. Some were far from innocuous. Ketamine causes a thickening of the bladder wall, leading to painful ulcerative cystitis; the clinic has found that three quarters of those who used ketamine were in pain from bladder damage. Clients using mephedrone reported depression and psychosis, while users of GBL (gamma butyrolactone) experienced high levels of dependence and difficult withdrawal symptoms.

Yet data from the National Drug Treatment Monitoring System show only a small increase in the number of people taking club drugs who are presenting for treatment. "What we are dealing with here is a new drug demographic that the treatment system has not kept pace with," he said. "Since we opened the doors of the Club Drug Clinic we have demonstrated that club drug users who are put off by traditional heroin and crack services will engage with a service specifically oriented to their needs."

Cities, urged Wilson in his closing address, must capitalise on their greatest advantage, concentrated intelligence, to drive and apply the innovations needed to solve these problems. Finding a positive note on which to close, he said: "I doubt that most of our forebears gathered in this Guildhall—even at their most ebullient—would believe the progress we have made.

"So much of urban health—the fight against mental illness, addictions, and diseases such as AIDS—shines a light on the worst and best in us. When we respond with prejudice we are at our worst. When we respond with science, compassion, and the conviction that each individual matters, we are at our best. When we measure ourselves against these principles it is clear how much progress we have made. For all the challenges we face, there has never been a better time to be alive."

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