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Flu Warning: Beware the Drug Companies!

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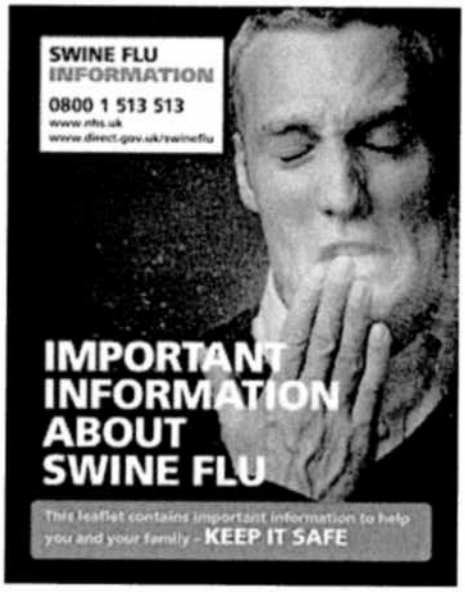

UK Department of Health

A leaflet ready for issue to the public in the UK in response to growing fears of a global pandemic of swine flu, spring 2009

In February 2009, a spike in influenza cases was detected in hospitals around Mexico City. Mexican government officials sent samples of throat cultures from patients to the US Centers for Disease Control (CDC) and the Canadian National Laboratory in Winnipeg, whose scientists found a new version of the H1N1 influenza virus, named for the type of hemagglutinin and neuraminidase molecules on its surface that enable it to spread within the body.

The discovery of what came to be known as "swine flu"—because pigs were the original source of the virus—aroused enormous concern in public health circles. The 1918 flu pandemic that killed tens of millions of people globally was also caused by an apparently new version of H1N1 influenza. Although other H1N1 viruses had been circulating in US populations for more than thirty years,[1] the Mexican virus looked different and at first seemed to be especially aggressive. Soon the World Health Organization (WHO) began raising the alarm. Two billion people—one third of the global population—could contract the disease, the agency warned, and millions might die. World Bank economists suggested that the total cost of such a pandemic—counting lost business and increased health spending—could even reach 4.8 percent of global GDP.[2]

Panic spread throughout the world. In Mexico schools and offices were closed, flights were canceled, and the country lost $2.2 billion within a few weeks.[3] In the UK, the government's swine flu website received 2,600 hits per second and crashed soon after it opened; in New York so many people panicked over any flu-like symptom that hospital emergency rooms were swamped with ten times more patients than normal, worsening care for those who really needed it.[4]

In China and other countries, border nurses quarantined anyone with a fever seeking to enter the country. Even though direct pig-to-human influenza transmission is exceedingly rare, Egypt ordered the slaughter of all the pigs in Cairo, impoverishing thousands of Christian small-scale farmers. And in Afghanistan, the nation's only pig was quarantined.[5]

On June 11, 2009, Margaret Chan, the director-general of the WHO, announced that a "pandemic emergency"—or worldwide epidemic—of H1N1 influenza was officially underway. Governments around the world placed immediate orders for anti-flu drugs and vaccines worth hundreds of millions of dollars, as a new stock index, *RXFLU, tracked company profits. According to J.P. Morgan, up to $10 billion was spent globally on "influenza preparedness" in 2009, including over $4 billion by the US alone.[6]

The predicted dire emergency did not occur. In the 2009–2010 "influenza season" about 18,000 people died from the disease worldwide, fewer than in previous years, and the vast majority of victims had serious underlying conditions such as cancer, lung disease, AIDS, or severe obesity, which can impair breathing.[7] Since one influenza strain usually dominates all others during a typical flu season, H1N1 may actually have saved lives by displacing more aggressive viruses. The WHO maintains that its decisions were based on the best available evidence, but last year European governments, stuck with hundreds of millions of euros' worth of unused medicines and vaccines, began asking questions.

In March 2010, a Council of Europe report[8] concluded that the H1N1 virus was known to be mild well before the WHO issued the pandemic "declaration" and expressed concern about the influence of powerful pharmaceutical companies over decision-making at the agency. A draft of the WHO's response was released in March 2011.[9] It calls for more "transparency" but concludes that "no critic of WHO has produced any direct evidence of commercial influence on decision-making." Unfortunately, the response does not account for the billions of dollars lost in the panic or for the lives that may have been put at risk by the agency's hasty medical recommendations.

Although influenza deaths are relatively rare among those who aren't otherwise ill, since the 1950s experts have periodically warned that a 1918-like pandemic could recur. They became especially alarmed in 1997, when eighteen people in Hong Kong contracted a new influenza virus known as H5N1 from chickens, and six died. This "avian flu" virus didn't spread from person to person, but since it was a thousand times more lethal than ordinary influenza, some experts feared that if it mutated into a virus that could spread more easily, it would kill millions in a very short time.

In 1999, the WHO launched a program to help governments prepare for this terrifying, if unlikely, possibility. The agency produced a document urging governments to draw up plans to alert the public and set up mass vaccination programs in the event that a new "pandemic" virus was found to be spreading. Because such a virus would have been previously unknown, it would take around six months for sufficient quantities of vaccine to be produced. However, the document also contained an annex describing a new class of anti-influenza drugs known as "neuraminidase inhibitors" that might help control the pandemic. [10]

According to the annex, these drugs, by blocking the action of the neuraminidase protein, prevent the influenza viruses from spreading through the body, reducing the severity of symptoms. The drugs would also protect people who had been exposed to the disease, such as health care workers and relatives of patients, from becoming sick, or so the document suggested. In 1999, the manufacturers of these new drugs were still seeking approval from government regulators including the US Food and Drug Administration, but later editions of the WHO's influenza pandemic guidance documents urged governments to "stockpile" them, because in an emergency their manufacturers might not have time to produce enough to meet demand. [11]

When H5N1 "avian flu" broke out again in Asia in 2003, this "stockpiling" recommendation led to a surge in influenza "pandemic preparedness" spending. In 2005–2006, the US and European governments stockpiled nearly $3 billion worth of the most popular neuraminidase inhibitor, known as Tamiflu. [12] At $10–$15 a dose, few developing countries in Africa, Asia, and Latin America would be able to afford Tamiflu, but Margaret Chan, then assistant director-general of the WHO in charge of influenza pandemic coordination, joined by representatives from Hoffman–La Roche, Tamiflu's Swiss manufacturer, urged Western governments to contribute to a Tamiflu stockpile fund for the developing world. [13]

After the 2009 "pandemic emergency declaration," another scramble for the drug was soon underway, and annual Tamiflu sales surged to $2 billion. [14] In Korea, rumors of shortages led HSBC and other powerful banks to compete with hospitals for stocks of the drug. [15] Countries in Asia, Africa, and Latin America placed urgent Tamiflu orders from WHO's stockpile, and some governments even took out loans worth tens of millions of dollars from the World Bank's Avian and Human Influenza Facility to purchase it. [16]

Despite the panic over "avian flu," ordinary influenza was still seen by most people as a mild disease, and most of the Tamiflu purchased in the US and elsewhere was probably "stockpiled" in warehouses and personal medicine cabinets, and not

consumed. But in the early 2000s, Tamiflu was regularly prescribed in Japan, which accounted for over 60 percent of global consumption. [17] It was there that signs of possible trouble with the drug first began to emerge.

Dr. Rokuro Hama runs the Japan Institute of Pharmacovigilance, an Osaka-based nonprofit group that monitors pharmaceutical product safety. In 2002, shortly after Tamiflu was introduced in Japan, he received a number of case reports of children who had begun behaving strangely within hours of taking it. A fourteen-year-old boy wandered out of his family's ninth-floor apartment and jumped over an exterior railing to his death; a seventeen-year-old boy ran out of his house onto a nearby freeway, where he was killed by a speeding truck; a thirty-nine-year-old man and two three-year-old boys died suddenly in their sleep.

Hama wasn't sure that these and the dozens of other similar cases he recorded were necessarily related to Tamiflu. Influenza itself can cause delirium and death in severe cases and the vast majority of those who took the drug suffered no ill effect. But when Hama studied the cases carefully, he realized that the neurological symptoms differed from those sometimes seen in severe influenza cases; rather, they more closely resembled symptoms associated with overdoses of drugs that suppress the central nervous system, such as Valium. [18]

In response to Hama's case reports, the Japanese Ministry of Health, Labor, and Welfare commissioned a research team at Yokohama University to study 2,846 pediatric influenza patients, some of whom had taken Tamiflu. The Yokohama researchers reported that hallucinations and other neuropsychiatric symptoms were no more common among children who had taken the drug than among those who had not. When Hama looked closely at this analysis, he concluded there were a number of errors, most having to do with what epidemiologists call "misclassification"—such as cases in which children with hallucinations were classified as not having taken Tamiflu when they almost certainly had. [19]

Hama reanalyzed the Yokohama data and estimated that Tamiflu resulted in a fourfold increase in the frequency of hallucinations and other neuropsychiatric side effects in children with influenza. [20] A journalist later alerted Hama to the fact that Chugai, the Roche subsidiary that markets Tamiflu in Japan, had provided funds for research to two of the scientists who worked on the Yokohama study. While there is no evidence of wrongdoing, such funding always raises the possibility of a conflict of interest. [21]

Shortly after the WHO "pandemic announcement" in June 2009, Keiji Hayashi, a Japanese pediatrician who was aware of Rokuro Hama's alarming case studies, decided

he wanted more information about the risks and benefits of Tamiflu. After all, if the drug really saved lives, it would be worth prescribing to his patients, despite the slight risk of severe side effects. But when Hayashi turned to the scientific literature, he found very few articles on the subject—and all of the research had been funded by Roche.

The most important paper, whose main author was Laurent Kaiser, a doctor at the Swiss Hôpital Cantonal de Genève, appeared in the *Archives of Internal Medicine* in 2003.[22] This paper, based on a summary of ten studies, concluded that patients who took Tamiflu were 55 percent less likely to experience severe flu complications—such as pneumonia—and 50 percent less likely to need hospitalization than patients who didn't take the drug. Since hospitalization is expensive, Kaiser's finding suggested that the drug not only relieved suffering, it could also save money—an important consideration for governments considering the WHO's advice to stockpile the drug.

While Kaiser's finding seemed powerful, Hayashi was concerned that the drug's entire reputation seemed to rest on this one article and a small number of others. He contacted Tom Jefferson, a British influenza expert with the Cochrane Collaboration, a British government–funded network of epidemiologists that conducts independent reviews of medical research. The Cochrane group had published a favorable review of Tamiflu in 2006, based largely on the same articles that Hayashi had read.[23]

When Jefferson and his colleagues read Hayashi's letter, they too began to wonder whether their initial assessment had been correct. They noticed several ambiguities and errors in Kaiser's article that they hadn't recognized before. For example, the definition of "complications related to influenza" used by the doctors in the study was imprecise, which made it difficult to tell what the study was actually measuring; in addition, the high rate of influenza seen in the clinics where the trials were carried out also seemed odd. Normally, only about 15 percent of what seem like "flu" cases are actually found upon lab testing to be caused by the influenza virus—the others are caused by some other microbe. But in the clinics where the Tamiflu trials were conducted, up to 80 percent of flu-like illnesses were reported to have been caused by influenza itself, raising the possibility that the patients had been selected for some reason that wasn't made clear in the article.[24]

All pharmaceutical drugs are tested by randomly assigning one group of patients (in this case flu sufferers) to take a test drug (in this case Tamiflu) and another to take a placebo that looks the same. It is crucial that neither the patients nor their doctors know who is getting which, because if they did, they might be more inclined—consciously or not—to overrate any improvements in the group receiving the test medicine. However,

Roger Dohmen/Hollandse Hoogte/Redux
A warning about Tamiflu in the Evening Standard, *London, August 23, 2009*

epidemiologists are becoming increasingly aware that even after the patient data has been collected, the statistical analysis of that data can be sensitive to the same wishful thinking. For example, since most trials are conducted at several clinics, a statistician might select for analysis only those clinics, or subgroups of patients, in which outcomes were superior in the test-drug group—even though the results from all the patients and clinics originally enrolled would have shown no such effect. Or the person reporting the statistics might select for publication only those trials showing that the test drug had a positive effect, while suppressing the findings of the others. Data analysis is a subtle art, and some companies even use "data-mining" computer programs to extract positive findings from unpromising data.[25]

In Kaiser's case, one blunder was obvious: the authors had combined the results of several smaller studies to come to the conclusion that Tamiflu reduced complications and hospitalizations. Combining the studies in that way destroyed the "randomization" so the placebo and Tamiflu groups were no longer necessarily similar. For example, if the placebo group now contained more patients with obesity or other risk factors for severe influenza complications, this would give Tamiflu an unfair advantage; if the Tamiflu group now contained more people who took aspirin or other medications, a similar unfair advantage would result. Of course, combining the studies might also result in an underestimate of Tamiflu's effectiveness, but there was no way of knowing one way or the other without seeing the original patient records, which were not described in Kaiser's article.

The Cochrane team soon learned that they weren't the only ones who had doubts about Tamiflu. The US Food and Drug Administration was also circumspect. The active ingredient in Tamiflu was discovered in 1989 by an Australian biotechnology company that licensed it to the British firm GlaxoSmithKline (GSK). The company gave it the trade name Relenza, carried out clinical trials, and submitted the results to the FDA in 1999.[26] The FDA scientific panel that reviewed this evidence was unimpressed; it noted that the drug—a powder for oral inhalation—had little effect on influenza symptoms and seemed to worsen breathing problems in people with asthma. The panel members voted 13–4 against approval, but the agency overruled them and approved the drug anyway. The head of the FDA's antiviral drug program, Heidi Jolson, justified this decision on the grounds that Relenza might be useful for some patients, and even a

weakly effective drug was better than nothing, given the fears then circulating about "avian flu."[27] Relenza was approved the same year. By the end of 2000, a preliminary investigation suggested that Relenza might have been a factor in twenty-two deaths of influenza patients with asthma or other preexisting lung conditions. Yet the drug remains on the market.[28]

Shortly after Relenza's discovery, the hunt was on for a pill version of the drug that would not carry these respiratory risks. In the early 1990s, researchers at Gilead, a US biotech company, developed one and licensed it to Hoffman–La Roche, which gave it the trade name Tamiflu.[29] Because Relenza had already been approved, the FDA gave Tamiflu "fast-track" status, meaning that the clinical evidence was even less stringently reviewed than Relenza's was. According to the FDA's own review documents, the results of the largest Tamiflu trial, involving some 1,500 patients, were never carefully analyzed by the agency, even though its officials knew of the study's existence. According to the documents Roche made available to Jefferson and his team, the company has conducted over one hundred clinical trials of the drug, but the results—let alone the details—of most of these studies have never been thoroughly examined by anyone outside the company, including the FDA.[30] After granting approval, the FDA was cautious and required Tamiflu labels to state that the drug has not been demonstrated to reduce hospitalizations, complications, or deaths from influenza.[31]

When Jefferson became aware of the problems with Kaiser's article and other papers on Tamiflu, he asked the authors for their original raw data so that he and his colleagues could redo the analysis themselves. But Kaiser and the others said that they couldn't find the data, and suggested that he contact the company.[32] After a delay of several months, Roche officials sent the Cochrane group a set of "research summaries" that essentially restated the results presented in the articles he was concerned about.

According to the Cochrane group's rules, the researchers were obliged to respond to Hayashi's question in print within six months. The UK and Australian governments were also pressuring the group to update their 2006 Tamiflu review, so in December 2009 the researchers published an article in the *British Medical Journal* (*BMJ*) indicating that it was impossible to say whether Tamiflu reduced severe complications from influenza or not.[33] In a letter accompanying this article, a Roche official stated that the company would make "full study reports" available to independent researchers in the very near future.[34]

Just after New Year's Day 2010, Roche made additional data available to the Cochrane group and to the Harvard epidemiologist Marc Lipsitch. In a December 2010 conference presentation, Lipsitch presented a reanalysis of the ten "Kaiser studies"

showing that in each case Tamiflu reduced what he called "lower respiratory tract complications" by about 40 percent.[35] Although this resolved the problems created when Kaiser lumped the studies together, it didn't address the other problems the Cochrane team had identified, including the ambiguous definition of "lower respiratory tract complications" and the mysteriously high rate of influenza among the patients in the trials. These remaining problems raise questions about Lipsitch's conclusions.

Meanwhile, the Cochrane team, which had by then grown to seven members,[36] spent much of 2010 sifting through the heap of documents—some 3,200 pages in all—that Roche made available to them. They also assembled a dossier of information on Tamiflu from various other sources, including the FDA and other national drug regulators. In doing so, they noticed yet more discrepancies between the articles that had appeared in scientific journals and Roche's internal documents, many concerning the drug's safety. According to published articles, no potentially drug-related serious side effects—or "serious adverse events" as they are called—were reported in the papers describing two Roche-sponsored clinical trials in which 908 people took Tamiflu; but according to Roche's unpublished documents, three "serious adverse events" that were possibly related to Tamiflu occurred in these trials.[37]

In 2008, an article in the journal *Drug Safety*, signed by a group of Roche authors, claimed that rats and mice, both given a very high dose of Tamiflu, showed no ill effect.[38] But according to documents submitted to the Japanese Ministry of Health, Labor, and Welfare by Chugai, the Japanese Roche subsidiary, the exact same dose of Tamiflu killed more than half of the animals.[39] As they died, the rats exhibited many of the same central nervous system symptoms that Hama had described in his case series on the Japanese children.[40]

The Cochrane group found, moreover, that cases of hallucination and weird accidents have been fairly commonly reported in Roche's post- marketing surveillance of Tamiflu.[41] An article in *The International Journal of Clinical Practice* claimed that these symptoms were just as common in influenza patients who did not take Tamiflu.[42] However, the data on which that observation is based have not been made public.

How common are such discrepancies in the published medical literature? Six years ago, John Ioannidis, a professor of epidemiology at the University of Ioannina School of Medicine in Greece, found that nearly half of published articles in scientific journals contained findings that were false, in the sense that independent researchers couldn't replicate them.[43] The problem is particularly widespread in medical research, where peer-reviewed articles in medical journals can be crucial in influencing multimillion-

and sometimes multibillion-dollar spending decisions. It would be surprising if conflicts of interest did not sometimes compromise editorial neutrality, and in the case of medical research, the sources of bias are obvious. Most medical journals receive half or more of their income from pharmaceutical company advertising and reprint orders, and dozens of others are owned by companies like Wolters Kluwer, a medical publisher that also provides marketing services to the pharmaceutical industry. [44]

Some of the Tamiflu articles were composed by "ghostwriters" associated with Adis, a Wolters Kluwer subsidiary that specializes in producing brochures and professional-looking articles for pharmaceutical company clients. This may help explain why some of the authors of the Tamiflu articles told Jefferson that they didn't have the original clinical trial data upon which those articles were based: some of them may never have seen it. The Tamiflu ghostwriters told Deborah Cohen, a *BMJ* reporter, that neither they nor the named authors on the articles had handled the Tamiflu data themselves—they had just been given the tables and figures by Roche officials and instructed to emphasize both the dangers of influenza and the benefits of Tamiflu in the articles. [45]

Eventually the Cochrane researchers realized that although there was much of interest in the documents Roche had sent them, they were still unable to draw any conclusions about whether or not Tamiflu was safe and effective against influenza complications such as pneumonia. Detailed descriptions of the original methods used in the trials were missing from the files they had received, making it impossible to reconstruct how the research had been planned from the start, and whether that plan had been modified along the way. Nor did the company provide them with any of the detailed case histories of patients who had experienced adverse events in the trials. Throughout 2010 and early 2011, Jefferson and his colleagues wrote to Roche on numerous occasions requesting the missing information. Despite the company's promise to make "full study reports" available to independent researchers, this request was never granted, so the Cochrane group continued to publish articles that were critical of Tamiflu.

All Roche had to do to silence these Tamiflu skeptics was to release the information they requested. I began to wonder why Roche didn't do this, and so I wrote to the company directly in February 2011. A Roche representative replied that Jefferson's Cochrane group had all the material it needed to do a proper analysis of Tamiflu's effectiveness. Since I knew from detailed discussions with Jefferson and his colleagues that they did not consider this to be true, I tried a different approach. Among the documents the Cochrane group received from Roche was a table of contents listing four or five chapters or "modules" for each of the Kaiser studies. Module 1 was a summary of the trial results. But according to the table of contents, Modules 2 through 5

contained the information Jefferson and his colleagues had been seeking, including the randomization protocol and its modifications, detailed patient histories, and reports of adverse events. But while Roche had sent them Module 1, it had not sent the others.

"Do the 'full study reports'" containing all five modules exist?" I asked my correspondent at Roche. "A simple 'yes' or 'no' answer will do." In reply, she did not say "yes" or "no," but repeated her claim that the Cochrane group had all the information it needed to analyze the Tamiflu studies.

The many contradictions in the evidence concerning Tamiflu and Relenza raise questions about the WHO's decision to declare an influenza "pandemic emergency" in 2009 and promote these drugs to fight it. In May 2009, a month before the pandemic declaration was issued, Roy Anderson, a prominent British epidemiologist and adviser to both the WHO and the UK government, gravely warned a BBC radio audience that only Relenza and Tamiflu would prevent a catastrophe on the scale of the 1918 influenza pandemic.[46] At the time, Anderson was receiving £116,000 per year from GlaxoSmithKline, manufacturer of Relenza. Calls for Anderson to resign from the UK government's Scientific Advisory Group for Emergencies soon followed.[47] A few months later, Anderson, citing a desire to concentrate on research, stepped down from his post as rector of Imperial College London, but he remains an adviser to both the UK government and the WHO.[48]

During the ten years leading up to the pandemic declaration of 2009, scientists associated with the companies that were to profit from the WHO's "pandemic preparedness" programs, including Roche and GlaxoSmithKline, were involved at virtually every stage of the development of those programs. The companies funded the documents giving guidance on preparing for the influenza pandemic, in which the WHO recommended the stockpiling of Tamiflu and Relenza. Consultants drafted parts of these documents and joined WHO officials in fund-raising for the Tamiflu stockpile. Industry-supported scientists were also on the committee that issued the "pandemic emergency declaration."[49] That announcement caused developing countries to request assistance from the WHO's Tamiflu stockpile fund, and these requests contributed to a tripling of the drug's sales in 2009.[50] By declaring a pandemic and linking the response to Tamiflu stockpiling, the WHO could not have done a better job of promoting Roche's interests. Until Roche shares more information on Tamiflu with independent researchers, we won't know whether the agency did so at the expense of the rest of us.

Conflicts of interest plague American public health agencies too. One member of the WHO's Emergency Committee was Nancy Cox, head of the Influenza Division at the

US Centers for Disease Control, whose lab receives grants from the International Federation of Pharmaceutical Manufacturers Association, of which Roche and GSK are members. I was surprised to learn that a US government agency, which issues policy recommendations to state, federal, and international health authorities, could receive money from an organization supported by industries that stood to profit from those recommendations.[51] A recent CDC guidance document issued by the Influenza Division, listing Cox as director on the first page, ignores the Cochrane group's concerns, claiming that clinical trials show Tamiflu is effective against severe influenza complications and is not associated with neuropsychiatric side effects.[52]

The FDA also relies increasingly upon fees and other payments from the pharmaceutical companies whose products the agency is supposed to regulate.[53] This could contribute to the growing number of scandals in which the dangers of widely prescribed drugs have been discovered too late. Last year, GlaxoSmithKline's diabetes drug Avandia was linked to thousands of heart attacks, and earlier in the decade, the company's antidepressant Paxil was discovered to exacerbate the risk of suicide in young people. Merck's painkiller Vioxx was also linked to thousands of heart disease deaths. In each case, the scientific literature gave little hint of these dangers. The companies have agreed to pay settlements in class action lawsuits amounting to far less than the profits the drugs earned on the market.[54] These precedents could be creating incentives for reduced vigilance concerning the side effects of prescription drugs in general.

The billions wasted on the H1N1 pandemic by the US government alone exceed the entire $3.2 billion annual budget of the FDA. Strengthening this agency, and creating new laws to ensure its independence from the drug industry, could potentially save our cash-strapped government money, and it could also save lives. Forcing drug companies to make all their original data available to all independent researchers would achieve much the same thing, and cost absolutely nothing. Legislators and the public should demand both of these reforms without delay.

—April 14, 2011

LETTERS

Take Your Tamiflu! July 14, 2011

Who Died From Flu? June 23, 2011

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