

[Back](#) ▶

WHO H1N1 Flu Controversy - Investigation Raises Questions About WHO's Handling of Pandemic

By Todd Neale, Staff Writer, MedPage Today

Published: June 04, 2010

Experts advising the World Health Organization on pandemic influenza and writing some of its guidance did not disclose their financial ties to the pharmaceutical industry, according to an investigative report in the BMJ.

Some of the paid relationships involved companies that made antivirals and vaccines and were positioned to benefit financially from preparations for a flu pandemic, reported Deborah Cohen, features editor of BMJ, and Philip Carter, a journalist with the Bureau of Investigative Journalism in London.

The conflicts of interest were never publicly disclosed by WHO, according to the report, which was featured under the headline, "Did the drug industry influence WHO's decisions about the swine flu pandemic?"

The investigation "has uncovered evidence that raises troubling questions about how WHO managed conflicts of interest among the scientists who advised its pandemic planning, and about the transparency of the science underlying its advice to governments," Cohen and Carter wrote.

Although they said that "experts need to work with industry to develop the best possible drugs for illnesses," they argued that "questions remain about what level of involvement experts with industry ties should have in the formulation of public health policy."

The U.S. Department of Health and Human Services came to WHO's defense, issuing the following statement:

"The WHO handled the outbreak in a very measured and appropriate manner. Their decisions were driven by the existing and evolving conditions at the time and what the best scientific information was telling us. It's very easy to look back through a 20-20 lens and essentially be an armchair quarterback."

Addressing the possibility of industry influence on WHO's decisions, the HHS spokesman said, "The WHO based its decisions on strong public health considerations, and I don't think there was any indication from our perspective that their decisions were influenced by industry in any way."

The H1N1 pandemic, which will mark its one year anniversary on June 11, "could, of course, have been far worse," Cohen and Carter wrote. "Planning for the worst while hoping for the best remains a sensible approach. But our investigation has revealed damaging issues. If these are not addressed, H1N1 may yet claim its biggest victim -- the credibility of the WHO and the trust in the global public health system."

Second Report Adds to Controversy

A report from the Council of Europe Parliamentary Assembly published on the same day the BMJ report was released called into question WHO's handling of the H1N1 pandemic. That inquiry was led by Paul Flynn, a British member of parliament.

A provisional version of the report stated, "The Parliamentary Assembly is alarmed about the

way in which the H1N1 influenza pandemic has been handled, not only by the World Health Organization (WHO), but also by the competent health authorities at the level of the European Union and at the national level."

"It is particularly troubled by some of the consequences of decisions taken and advice given leading to distortion of priorities of public health services across Europe, waste of large sums of public money, and also unjustified scares and fears about health risks faced by the European public at large," it stated.

The report also addressed the transparency issues raised by Cohen and Carter, "which have generated concerns about the possible influence of the pharmaceutical industry on some of the major decisions relating to the pandemic."

Experts Dispute Charges

Experts contacted about the BMJ report disputed the insinuation that researchers' financial ties to industry influenced WHO's decision-making surrounding pandemic influenza in general and the H1N1 pandemic specifically.

"I do find these investigations troubling, when the only way WHO could be exonerated is if there had been tens of millions dead," said John Barry, a distinguished scholar at Tulane University and author of *The Great Influenza*. "And then we'd have investigations about how ineffective they were."

"While I agree WHO should have disclosed any relationship between advisers and industry," he continued, "based on what WHO actually did, I find it absurd to accuse them of having been influenced by the drug industry. Antivirals, though hardly a magic bullet, are the only drug option. And a recommendation to stockpile them was the only option."

Addressing concerns that the pandemic was declared to profit pharmaceutical companies, Barry said that "if anything, WHO was slow to make that call. And if you know anything about the history of the influenza virus, again it had no option. 1918 saw a very mild spring wave, quite comparable to what we experienced in 2009. It turned virulent months later."

John Treanor, MD, a vaccine expert at the University of Rochester Medical Center, in Rochester, N.Y., agreed that WHO's preparations were justified.

"I think even the authors [of the BMJ report] would have to agree that there really was no choice here but to prepare for a pandemic," he said. "If there had been a severe pandemic and there had been no preparations, the outcome (and the outcry) would have been far worse."

Although some of the WHO's advisers received compensation from manufacturers of the same antivirals and vaccines recommended for use during the H1N1 pandemic, Treanor noted that there are few options available for combating influenza.

"You can tweak the plans -- how much antivirals, what kinds, where is the vaccine coming from, who should be vaccinated first, should you close schools, etc. -- but the basic elements are going to be the same," he said. "So I don't see the argument here as whether WHO made the right recommendation at the time, regardless of who was advising them -- they clearly did."

One researcher, Henry Miller, MD, criticized WHO for mistakes made, including the declaration of a pandemic for H1N1 influenza in the first place. However, "the stockpiling of anti-flu medicines and the production of vaccine weren't among them," said Miller, a biotechnology expert at Stanford University's Hoover Institution.

"Much of the criticism of WHO as having been unduly influenced by industry seems to be coming from anti-industry NGOs [nongovernmental organizations]," Miller said.

Planning Began in 1999

Cohen and Carter detailed WHO's pandemic influenza preparation starting in 1999, when a preparedness plan was drafted by six researchers in collaboration with the European Scientific Working Group on Influenza (ESWI). Over the next decade, according to their investigation, WHO failed to disclose industry ties among researchers advising the organization.

The document drafted in 1999 did not include information on conflicts of interest. Cohen and Carter pointed out that ESWI is funded entirely by Roche, which makes oseltamivir (Tamiflu), and that two of the authors of the document had participated in Roche-sponsored events in the previous year. Both were also involved in a randomized controlled trial of oseltamivir supported by the company.

In 2002, WHO called together flu experts to craft guidelines for the use of vaccines and antivirals during an influenza pandemic. The panel included representatives of Roche and Aventis Pasteur (now Sanofi-Pasteur), which makes flu vaccine, and three experts who had been named in marketing material for oseltamivir.

The resulting report, which advised stockpiling antivirals, was published in 2004, and the main author, Frederick Hayden, MD, of the University of Virginia in Charlottesville, confirmed that he was being paid by Roche for lectures and consulting when the report was produced and published.

Conflicts Not Disclosed

Several additions to the report did not include information about conflicts of interest, according to Cohen and Carter.

"WHO has failed to provide any details about whether such conflicts were declared by the relevant experts and what, if anything, was done about them," they wrote.

"Leaving aside the question of what declarations experts made to WHO, one simple fact remains: WHO itself did not publicly disclose any of these conflicts of interest when it published the 2004 guidance," Cohen and Carter wrote. "It is not known whether information about these conflicts of interest was relayed privately to governments around the world when they were considering the advice contained in the guidelines."

Conflicts of interest were similarly not disclosed in updated plans made in the following years, they said.

"No public declarations of interest have been made and to date no details have been provided by WHO in response to our requests," Cohen and Carter wrote.

Compounding this lack of transparency is the fact that the 16 members of the emergency committee that has been advising WHO during the H1N1 pandemic have remained anonymous, at least officially. The chair is known to be John MacKenzie of Curtin University in Perth, Australia.

The BMJ investigation turned up another three members, including Arnold Monto, MD, of the University of Michigan School of Public Health; John Wood, PhD, of the National Institute for Biological Standards and Control in the U.K.; and Masato Tashiro, MD, PhD, director of the WHO collaborating center for surveillance and research on influenza in Tokyo.

Wood and Tashiro said they have no conflicts of interest, but Monto has received speakers' fees from GlaxoSmithKline, maker of zanamivir (Relenza).

Anonymity Stance Questioned

In a statement, WHO's secretary-general Margaret Chan, MD, MPH, said the purpose of keeping the committee members anonymous "is to protect the integrity and independence of the members while doing this critical work -- but also to ensure transparency by publicly providing the names of the members as well as information about any interest declared by them at the

appropriate time."

"This is a troubling stance," Fiona Godlee, MBBChir, editor-in-chief of the BMJ, wrote in an accompanying editorial. "It suggests that WHO considers other advisory groups whose members are not anonymous -- such as the Strategic Advisory Group of Experts on Immunization -- to be potentially subject to outside influences, and it allows no scrutiny of the scientists selected to advise WHO and global governments on a major public health emergency."

"Given the scale of public cost and private profit, it would seem important to know that WHO's key decisions were free from commercial influence," Godlee said. The investigation "finds that this was far from the case."

She said the recovery of the WHO's damaged credibility "will be fastest if it publishes its own report without delay or defensive comment, makes public the membership and conflicts of interest of its emergency committee, and develops, commits to, and monitors stricter rules of engagement with industry that keep commercial influence away from its decision-making."

Balancing Act Called For

According to the University of Rochester's Treanor, the important issue to consider is not whether WHO made the right decisions about the H1N1 pandemic -- because he believes they made the right recommendations at the time -- but "the much more tricky and generic question about how to appropriately separate the interests of the pharmaceutical industry from the interests of public health, while at the same time being able to take advantage of existing expertise on the issues, the bulk of which resides in individuals with some kind of ties to industry."

"In our current system of healthcare," Treanor said, "the responsibility for demonstrating that these interventions are safe and effective lies with the manufacturer. Hence, individuals with the greatest experience and insight into these interventions will almost always either be employees of industry or individuals paid by industry to conduct studies."

When evaluating advice from a panel of experts, he said it's important to consider the fact that researcher's will always view the products they do work on in a positive light, even if they weren't paid by industry.

"After all," Treanor said, "it's much more fun to be involved in the development of an effective product than one that doesn't work."

According to John Bartlett, MD, founding director of the Center for Civilian Biodefense Strategies at Johns Hopkins, the fact that conflicts of interest are prevalent among influenza experts "is not at all surprising to me since the people in medicine who know most about flu are often conflicted because they also are advisers to pharma and often do the big trials that are funded by pharma."

He said he is not an authority on influenza, but that "the colleagues I know who do this work often/usually have these connections, but that is usually good for better pharma and good for better WHO advice."

Harvey V. Fineberg, MD, PhD, president of the Institute of Medicine, chairs the WHO committee to review management of the H1N1 pandemic and functioning of the International Health Regulations. Today, following publication of the reports by BMJ and the Parliamentary Assembly of the Council of Europe, Dr. Fineberg released the following statement:

"Our review committee welcomes the opportunity to learn from reports published today by the British Medical Journal and released by the Social, Health and Family Affairs Committee of the Parliamentary Assembly of the Council of Europe (PACE). These reports raise questions about potential, inappropriate influences on WHO decision-making in the assessment and response to the 2009 H1N1 pandemic and, more generally, question practices employed by WHO to guard against conflict of interest among its expert advisers. These topics are among those that will be

fully considered by our review committee. At our upcoming meeting in Geneva (30 June to 2 July 2010) we anticipate hearing from critics of WHO as well as from those who were involved from the public and private sectors, at national and international levels, and in policy and decision-making related to the H1N1 pandemic."

Carter reported no conflicts of interest. Cohen reported being paid expenses by WHO for giving talks at two conferences.

Godlee reported writing articles on the challenges faced by WHO and on the influence of the drug industry. She reported being in favor of a more assertive approach to conflict of interest and supporting efforts to control the influence of the drug industry on medical research, medical education, and health policy.

Treanor made the following disclosure: "I am very significantly funded by industry to perform studies of experimental vaccines. This funding is in the form of contracts to my institution for my lab to conduct lab assays or for my clinical staff to enroll subjects and follow them in a variety of clinical studies. The sponsors of these studies currently include Protein Sciences Corporation, Bavarian Nordic, GlaxoSmithKline, Pfizer, Sanofi-Pasteur, Vaxinnate, Mercia Pharma, Paxvax, and Ligocyte. I am also considering attending a scientific advisory board for Novartis, for which I would receive an honorarium, and I am on the scientific advisory board for Immune Targeting Systems (ITS) and also received an honorarium last year from Abbott for an advisory meeting. We also conduct clinical trials of experimental live vaccines through a contract with NIH, but the vaccines are supplied by MedImmune through a cooperative research and development agreement (CRADA) with NIAID."

Barry reported giving a talk, hosted by Gilead, which developed oseltamivir, four years ago to public health leaders and individuals from the biotechnology industry. He received an honorarium. "I'm sure Gilead paid some and possibly all of that fee. I never had any relationship with them," Barry said.

Bartlett said he is not connected to any pharmaceutical company with an interest in influenza.

Miller reported no conflicts of interest.



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