Health Intervention and Technology Assessment Program

In memory of our beloved Ajarn Tada Yipintsoi

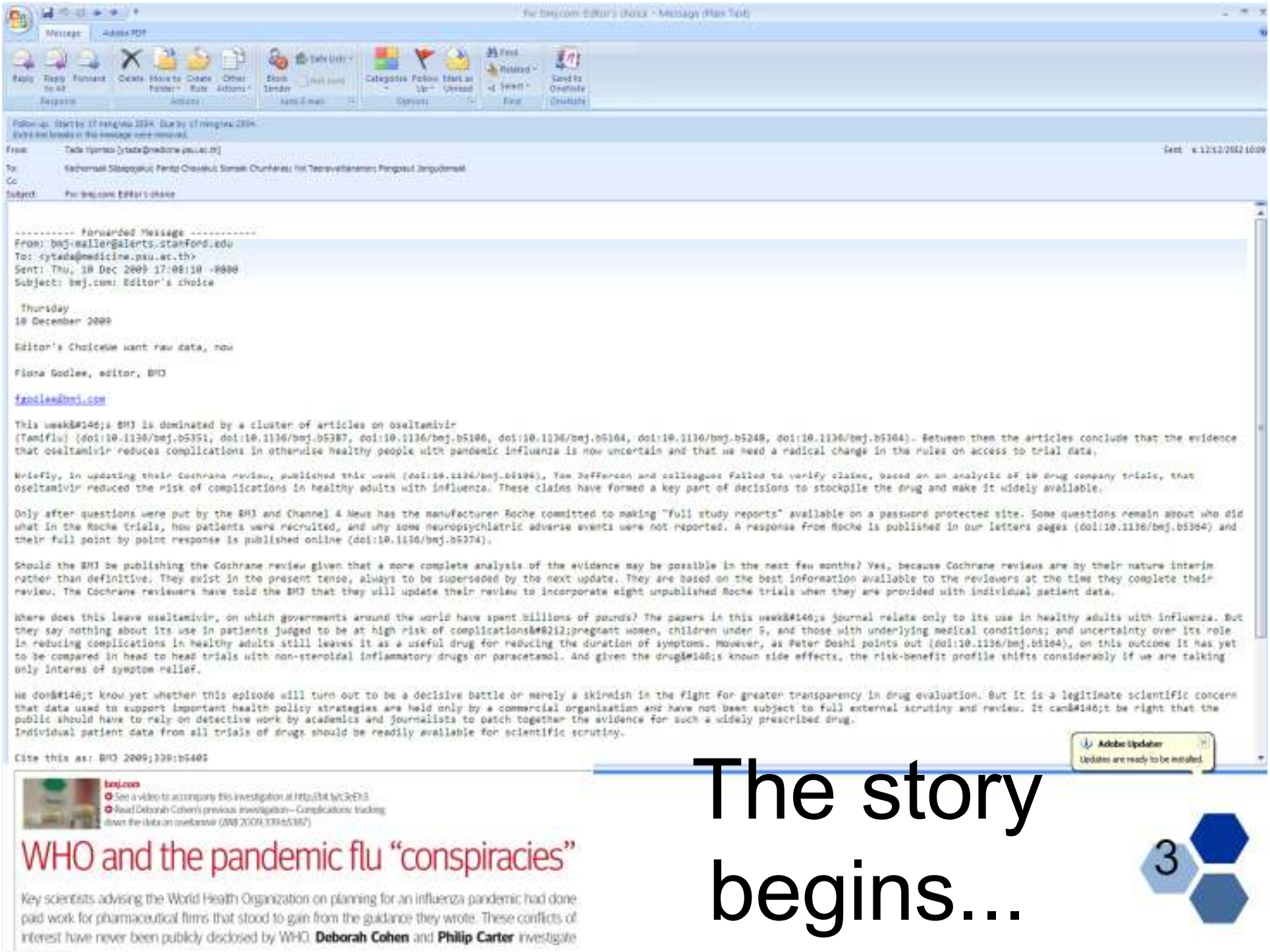
Yot Teerawattananon, M.D., Ph.D.
Health Intervention and Technology Assessment (HITAP)

R2R conference
20 July 2011

Health Intervention and Technology Assessment Program

Health Intervention and Technology Assessment Program (HITAP) www.hitap.net

- A non-profit organisation established in Jan 2007
- An associate organisation with Bureau of Health Policy and Strategy, MoPH
- Appraising a wide range of health interventions and technologies in order to provide HTA information to inform policy decision and educate relevant stakeholders and the publics
- Ajarn Tada was the chair of the Steering Committee and HITAF since their inception



---------- Forwarded Message ----------
From: bmj-mailer@alerts.stanford.edu
To: <ytada@medicine.psu.ac.th>
Sent: Thu, 10 Dec 2009 17:08:10 -0800
Subject: bmj.com: Editor's choice

Thursday
10 December 2009

Editor's Choicewe want raw data, now

Fiona Godlee, editor, BMJ

fgodlee@bmj.com

This week’s BMJ is dominated by a cluster of articles on oseltamivir (Tamiflu) (doi:10.1136/bmj.b5351, doi:10.1136/bmj.b5387, doi:10.1136/bmj.b5106, doi:10.1136/bmj.b5164, doi:10.1136/bmj.b5248, doi:10.1136/bmj.b5364). Between them the articles conclude that the evidence that oseltamivir reduces complications in otherwise healthy people with pandemic influenza is now uncertain and that we need a radical change in the rules on access to trial data.

Briefly, in updating their Cochrane review, published this week (doi:10.1136/bmj.b5106), Tom Jefferson and colleagues failed to verify claims, based on an analysis of 10 drug company trials, that oseltamivir reduced the risk of complications in healthy adults with influenza. These claims have formed a key part of decisions to stockpile the drug and make it widely available.

Only after questions were put by the BMJ and Channel 4 News has the manufacturer Roche committed to making "full study reports" available on a password protected site. Some questions remain about who did what in the Roche trials, how patients were recruited, and why some neuropsychiatric adverse events were not reported. A response from Roche is published in our letters pages (doi:10.1136/bmj.b5364) and their full point by point response is published online (doi:10.1136/bmj.b5374).

Should the BMJ be publishing the Cochrane review given that a more complete analysis of the evidence may be possible in the next few months? Yes, because Cochrane reviews are by their nature interim rather than definitive. They exist in the present tense, always to be superseded by the next update. They are based on the best information available to the reviewers at the time they complete their review. The Cochrane reviewers have told the BMJ that they will update their review to incorporate eight unpublished Roche trials when they are provided with individual patient data.

Where does this leave oseltamivir, on which governments around the world have spent billions of pounds? The papers in this week’s journal relate only to its use in healthy adults with influenza. But they say nothing about its use in patients judged to be at high risk of complications—pregnant women, children under 5, and those with underlying medical conditions; and uncertainty over its role in reducing complications in healthy adults still leaves it as a useful drug for reducing the duration of symptoms. However, as Peter Doshi points out (doi:10.1136/bmj.b5164), on this outcome it has yet to be compared in head to head trials with non-steroidal inflammatory drugs or paracetamol. And given the drug’s known side effects, the risk-benefit profile shifts considerably if we are talking only interms of symptom relief.

We don’t know yet whether this episode will turn out to be a decisive battle or merely a skirmish in the fight for greater transparency in drug evaluation. But it is a legitimate scientific concern that data used to support important health policy strategies are held only by a commercial organisation and have not been subject to full external scrutiny and review. It can’t be right that the public should have to rely on detective work by academics and journalists to patch together the evidence for such a widely prescribed drug.
Individual patient data from all trials of drugs should be readily available for scientific scrutiny.

Cite this as: BMJ 2009;339:b5401

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bmj.com
See a video to accompany this investigation at http://bit.ly/c3eEh3
Read Deborah Cohen's previous investigation—Complications: tracking down the data on oseltamivir (BMJ 2009;339:b5387)

WHO and the pandemic flu "conspiracies"

Key scientists advising the World Health Organization on planning for an influenza pandemic had done paid work for pharmaceutical firms that stood to gain from the guidance they wrote. These conflicts of interest have never been publicly disclosed by WHO. **Deborah Cohen** and **Philip Carter** investigate

The story begins...

Statement to the press by WHO Director-General Dr Margaret Chan
11 June 2009

Ladies and gentlemen,……..

I have conferred with leading influenza experts, virologists, and public health officials. In line with procedures set out in the International Health Regulations, I have sought guidance and advice from an Emergency Committee established for this purpose.

On the basis of available evidence, and these expert assessments of the evidence, the scientific criteria for an influenza pandemic have been met.

I have therefore decided to raise the level of influenza pandemic alert from phase 5 to phase 6.

The world is now at the start of the 2009 influenza pandemic.

http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html

Oseltamivir (Tamiflu) in healthy adults

World Health Organization

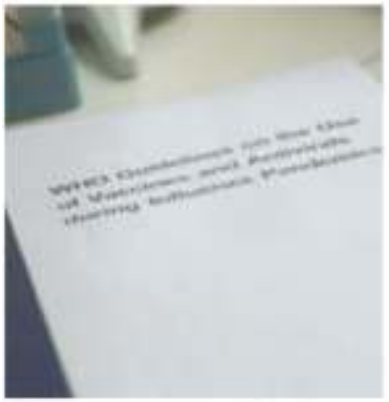
17 March 2006

ADVICE ON USE OF OSELTAMIVIR

Oseltamivir (Tamiflu®) is recommended for use for both treatment and prophylaxis of influenza. The currently recommended doses are:

http://www.who.int/csr/disease/avian_influenza/guidelines/useofoseltamivir2006_03_17.pdf

The story continues…..



The 2004 WHO pandemic guidelines advised governments to stockpile antivirals. No conflict of interest statements were published

Billions of dollars' worth of antivirals, such as oseltamivir and zanamivir, have been stockpiled on WHO's recommendation

THE COCHRANE COLLABORATION®

Letter from Dr. Keiji Hayashi to the Cochrane Collaboration questioning about unpublished data and potential COI of published data used in

Antivirals for influenza in healthy adults: systematic review

T Jefferson, V Demicheli, D Rivetti, M Jones, C Di Pietrantonj, A Rivetti

Summary

Background Use of antivirals is recommended for the control of seasonal and pandemic influenza. Our aim was to review the evidence of efficacy, effectiveness, and safety of registered antivirals against naturally occurring influenza in healthy adults.

Lancet 2006; 367: 303–13
Published Online January 19, 2006
DOI: 10.1016/S0140-6736(06)

Oseltamivir use in healthy adults

- Reduce hospital admission by 61%
- Reduce secondary complication by 67%
- Reduce lower respiratory tract infections requiring antibiotics by 55%
- This information depends very much on the analysis of Kaiser et al 2003

ORIGINAL INVESTIGATION

Impact of Oseltamivir Treatment on Influenza-Related Lower Respiratory Tract Complications and Hospitalizations

Laurent Kaiser, MD; Cynthia Wat, MBBS, MRCP; Tracy Mills, MSc; Paul Mahoney, MSc; Penelope Ward, MBBS; Frederick Hayden, MD

Background: Influenza causes lower respiratory tract complications (LRTCs), particularly bronchitis and pneumonia, in both otherwise healthy adults and those with underlying conditions. The aim of this study was to assess the effect of oseltamivir treatment on the incidence of LRTCs leading to antibiotic treatment and hospitalizations following influenza illness.

Methods: We analyzed prospectively collected data on LRTCs and antibiotic use from 3564 subjects (age range, 13-97 years) with influenzalike illness enrolled in 10 placebo-controlled, double-blind trials of oseltamivir treatment.

Results: In adults and adolescents with a proven influenza illness, oseltamivir treatment reduced overall antibiotic use for any reason by 26.7% (14.0% vs 19.1% with placebo; $P<.001$) and the incidence of influenza-related LRTCs resulting in antibiotic therapy by 55% (4.6% vs 10.3% with placebo; $P<.001$). In those subjects considered at increased risk of complications, 74 (18.5%) of 401 placebo recipients developed an LRTC leading to antibiotic use compared with 45 (12.2%) of 368 oseltamivir recipients (34.0% reduction; $P=.02$). Hospitalization for any cause occurred in 18 (1.7%) of 1063 placebo recipients compared with 9 (0.7%) of 1350 oseltamivir-treated patients (59% reduction; $P=.02$). In contrast, among subjects with an influenzalike illness but without a confirmed influenza infection, the incidence of LRTCs (6.7% vs 5.3%), overall antibiotic use (19.7% vs 19.3%), or hospitalizations (1.7% vs 1.9%) was similar between placebo and oseltamivir recipients, respectively.

Conclusion: Oseltamivir treatment of influenza illness reduces LRTCs, antibiotic use, and hospitalization in both healthy and "at-risk" adults.

Arch Intern Med. 2003;163:1667-1672

In search for raw data

- 8/10 RTCs were unpublished
- Prof.Hayden— “cannot find the original files…”
- Roche— “provide little new information and would therefore be unlikely to be accepted for publication….”
- Referred to unpublished study M76001 (the biggest trial) by Prof.Treanor– “I don’t have anything in my files of old studies that’s identified as M76001…”

“Ghost write”

- Different names appeared on regulartoty documents and published papers

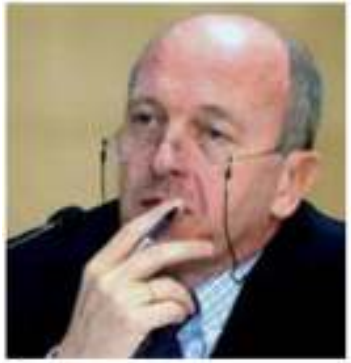
The former employees at Adis said medical writers were under pressure regarding the content of the articles. They said that they liaised directly with Roche’s marketing department: “We were under pressure to get messages out. The Tamiflu accounts had a list of key messages that you had to get in. It was run by the marketing department and you were answerable to them. In the introduction for Tamiflu, I had to say what a big problem influenza is. I’d also have to come to the conclusion that Tamiflu was the answer,” they said.

Complications: tracking down the data on oseltamivir Deborah Cohen
BMJ 2009;339:doi:10.1136/bmj.b5387 (Published 8 December 2009)

The conspiracies at WHO

The European Scientific Working Group on Influenza is an industry funded society. It claims links to WHO and the ECDC. It also lobbies governments

Fred Hayden, from the University of Virginia, was the author of the key 2004 WHO document arguing for antiviral stockpiling. He was a Roche consultant at the time



Rene Snacken, a Belgian public health official, appeared at Roche promotional events. He helped draft the first WHO pandemic plan and gave evidence to the EMEA about oseltamivir

Albert Osterhaus, from Erasmus University, appeared in a Tamiflu sponsored symposium while working for WHO. He says he has always been transparent about his industry links

Swedish state epidemiologist, Annika Linde, has had financial connections to Roche. She gave evidence to the EMEA while linked to Roche. She says she didn't keep any money.

Arnold Monto, from Michigan University, had declared a financial relationship with Roche, GSK, and ViroPharma. This was not made public by WHO when he wrote its vaccine guidelines

Karl Nicholson, from Leicester University, had declared a financial relationship with various drug companies. This was not made clear by WHO when he wrote the Pandemic Influenza annexe

Oseltamivir use in healthy adults (again!)

BMJ 2009; 339:b5106

BMJ

RESEARCH

Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis

Tom Jefferson, researcher,[1] Mark Jones, statistician,[2] Peter Doshi, doctoral student,[3] Chris Del Mar, dean; coordinating editor of Cochrane Acute Respiratory Infections Group[4]

- prevent symptoms and shorten the duration of illness by about **one day** if taken within 48 hours of the onset of symptoms
- reduce the chance of people exposed to influenza developing **laboratory confirmed influenza** but **not influenza-like illness**
- Evidence for or against their benefit for **preventing complications** of influenza is **insufficient**
- Toxicity and the effects on complications have been debated

Impacts

- A distortion of public health priority all over the world and a waste of substantial public money
- Damage to public trust over WHO and medical community - WHO redefined "pandemic" a month before the pandemic was declared
- Margaret Chan--"At no time, not for one second, did commercial interests enter my decision making." Response: WHO Director-General replies to the BMJ Margaret Chan BMJ 2010;340:doi:10.1136/bmj.c3463 (Published 29 June 2010)
- Jefferson & Doshi-- "this self evaluation is irrelevant and misses the point: that transparent declarations of interest are crucial to allow others to decide for themselves"

Time to face up to the locums scandal Fiona Godlee BMJ 2010;340:doi:10.1136/bmj.c3519 (Published 29 June 2010)

Lessons taught by Ajarn Tada

Academics

- Putting academic integrity at the highest priority
- Be honest and transparent, away from the potential COI

Practitioners

- Misinformation and manipulation through marketing strategies are common—neurontin, statins, vaccines etc.
- Using R2R to prove and help define ‘the fact’

"It takes two to speak the truth--
one to speak and another to hear"

Henry Thoreau