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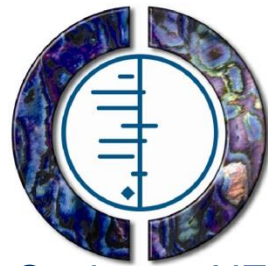
Tamiflu: “A nice little earner”

(BMJ 2014)

Dr Vanessa Jordan PhD

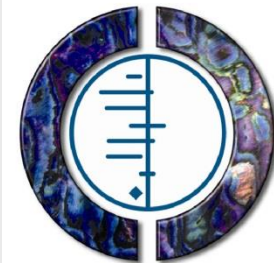
New Zealand Cochrane Fellow

Outline



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- Tamiflu what is it?
- World response to the 2009 Flu pandemic
- Original systematic review findings
- The battle for the secret data
- Tamiflu the final chapter
- All Trials



Tamiflu

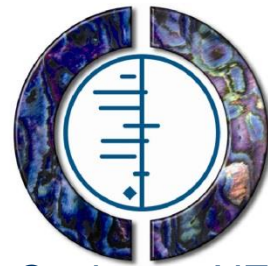
- Neuraminidase Inhibitors
 - licenced by the US Food and Drug Administration (FDA) in 1999
- Zanamivir (Relenza) first released
 - GlaxoWellcome
- Oseltamivir (Tamiflu) dominant brand
 - Roche
- Neuraminidase inhibitors touted
 - “Greatest breakthrough since Penicillin” Independent on Sunday UK
 - “One of the greatest discoveries of the 20th century” Australian politician

Tamiflu® 75

Hartkapsel



2009 pandemic



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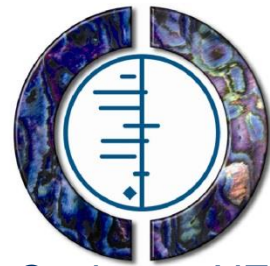
- H1N1 emerged from Mexico
- June 2009 WHO declares pandemic
- 96 countries stock pile enough Tamiflu to treat 350 million people
- Sales in excess of 18 billion USD
- NZ government – One million doses Tamiflu
300,000 doses Relenza value 32 million NZD
- January 2010 “use leftover Tamiflu to grit roads” UK MP suggests

questions



do NIs...

- ...prevent influenza?
- ...ameliorate influenza?
- ...prevent transmission of influenza?
- ...cause adverse events'



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Original review

- First Cochrane review published eight trials
- Review by Kaiser et al 2003 (7 trials)
 - Authored by Roche employees
- 2006 Cochrane review update released
 - Based on 10 trials (incl Kaiser)
 - Published research findings
 - Conclusion: decreased risk of hospital complications and hospital admission

2009 update



- Letter from Keiji Hayashi
 - Could not verify Jefferson's data as 8 out of 10 trials unpublished and not available
- Jefferson and colleagues approached Roche to verify data
- Roche refuses to relinquish data
- Review updated minus un-validated studies
- Conclusion: Drug may work no better than aspirin

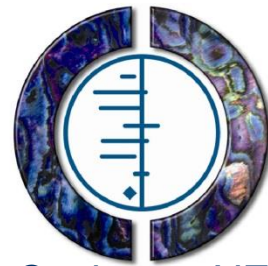
Tug of war for Tamiflu data



- BMJ and Channel 4, UK news enter the fray
- December 2009 Roche announced they would give Cochrane full clinical study reports
- Sept 2010 Roche provided redacted reports for the 10 studies in the Kaiser meta analysis
- Oct 2010 Cochrane requested access to any unpublished studies held by Roche – led to a slew of e-mails with Roche declaring they would release information but were worried about the biased nature of the Cochrane team.



Tug of war for Tamiflu data cont'd



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- 2013 – Roche delivered 160,000 pages of information about Tamiflu containing information about 83 clinical studies

Tamiflu the final chapter



- 2014 – new Cochrane review released

Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children (Review)

Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya IJ, Mahtani KR, Nunan D, Howick J, Heneghan CJ



**THE COCHRANE
COLLABORATION®**

Between April-November 2013 Roche sent us 77 clinical study reports for 83 studies following unanticipated announcement that they would provide redacted complete clinical study reports for all Roche-sponsored trials of oseltamivir

83 oseltamivir studies received from Roche assessed for inclusion

60 studies did not meet the inclusion criteria

Studies identified through the following sources: publicly available documents from FDA, EMA, Japan PMDA; manufacturer trial registry websites; NICE 2000 submission; electronic database searches; and correspondence with manufacturers

121 oseltamivir studies identified (83 delivered by Roche)

61 zanamivir studies identified (30 delivered by GSK)

8 peramivir studies identified (none delivered)

1 laninamivir study identified (ongoing)

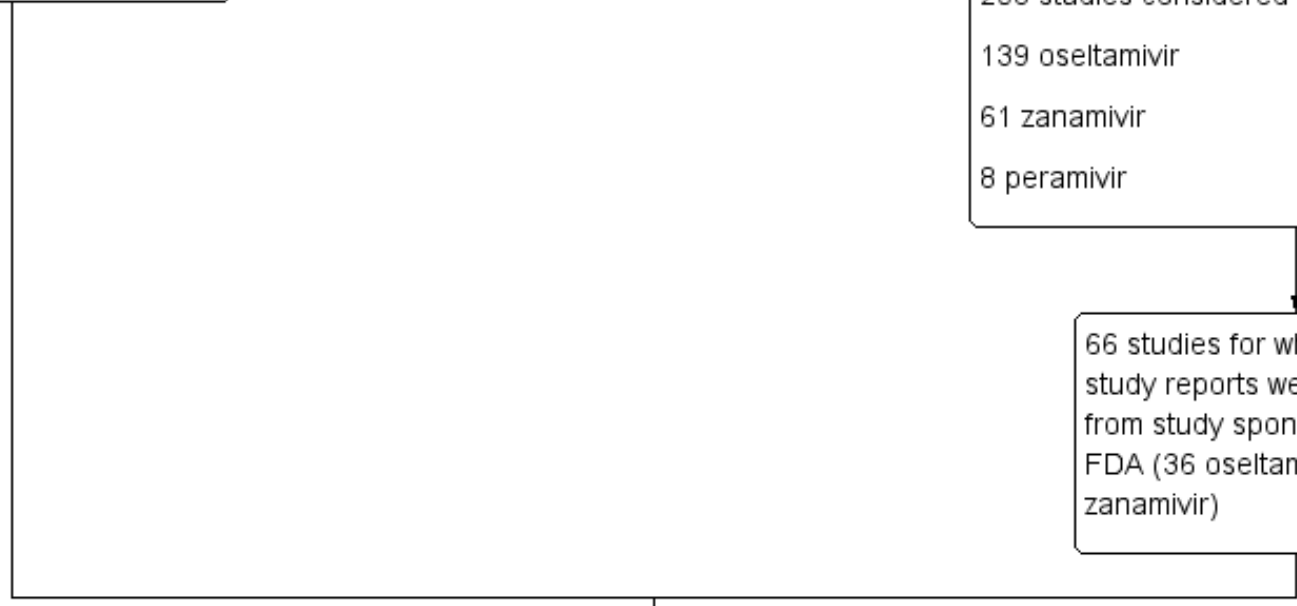
208 studies considered for inclusion

139 oseltamivir

61 zanamivir

8 peramivir

66 studies for which clinical study reports were requested from study sponsors, EMA and FDA (36 oseltamivir, 30 zanamivir)



53 trials meeting review eligibility criteria received from sponsors and EMA (23 oseltamivir trials in 18 clinical study reports; 30 zanamivir trials in 29 clinical study reports)

'Risk of bias' assessments and CONSORT extractions carried out on the basis of clinical study reports of 23 oseltamivir trials and 30 zanamivir trials (stage 1)

20 oseltamivir trials and 26 zanamivir trials progressed to stage 2 of inclusion

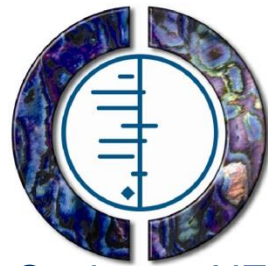
5 trials excluded due to incomplete clinical study report (3 oseltamivir and 2 zanamivir)
2 trials excluded because they did not fit the inclusion criteria (2 zanamivir)

Time to first symptom alleviation



- Oseltamivir
 - Reduced by 16.8 hrs (8.4 – 25.1)
 - 10% reduction from 7 to 6.3 days
- Zanamivir
 - Reduced by 0.6 days (0.39 – 0.81)
 - 10% reduction from 6.6 to 6 days

Hospitalisation



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- Oseltamivir
 - RR 0.92 (0.57 – 1.50)
- Zanamivir
 - Not reported

Serious complications

- Oseltamivir
 - RD = 0.07% (-0.78 to 0.44)
- Zanamivir
 - RD = -0.04% (-0.64 to 0.24)

Adverse effects (Treatment with Oseltamivir)



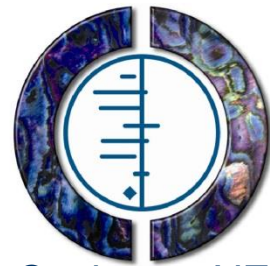
- Nausea vomiting and diarrhoea
 - Nausea RR 1.57(1.14 – 2.15) NNTH 28
 - Vomiting RR 2.43 (1.75 – 3.38) NNTH 22
 - Diarrhoea RR 0.67 (0.46 – 0.98) NNTB = 43
- Cardiac effects
 - Cardiac general events RR 0.49 (0.25 – 0.97) NNTB 148
 - QTc elongation one trial RD 4% (0.71 – 7.30)

Adverse effects (Treatment with Oseltamivir)



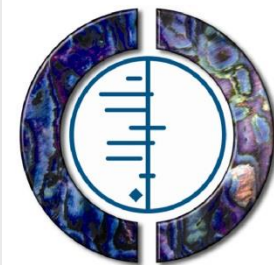
- Psychiatric effects
 - Overall no difference
 - Potential evidence of dose response relationship
 - Trend in 2 trials $p= 0.038$ with likelihood ratio

Placebo	75mg	150mg
1/204	1/206	4/205
2/235	0/242	5/242



Why was the data released?

- An editorial in the BMJ speculated that this has something to do with the fact that Tamiflu will come off patent in 2016
- Original stockpiles have had their shelf life extended to 7 years
- Logical conclusion



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Lessons learnt

- UK public accounts committee “stockpiling antiviral medicine was based on judgement not evidence”
- Tamiflu in the UK the manufacturer provided the licensing body MHRA with only 15 out of 74 trials
- So far there is no comeback on Roche

ALLTrials Campaign

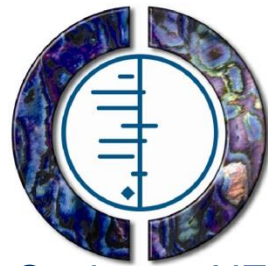
The AllTrials logo, which consists of a red square with a white plus sign and the text '+AllTrials' in white.

+AllTrials

- <http://www.alltrials.net/>

- Initiative started in the UK
- 78,000 individuals & 480 organisations
- European parliament have made it illegal not to publish from clinical trials within one year of the trial finishing effective for trials registered from 2016

Further reading



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- Ben Goldacre “Bad Pharma”
- Peter Gøtzsche “Deadly medicines and organised crime”