# Current knowledge on neuraminidase inhibitor effectiveness

David Smith

Clinical Virologist and Director of National Influenza Centre, PathWest Laboratory Medicine WA

Clinical Professor, University of Western Australia

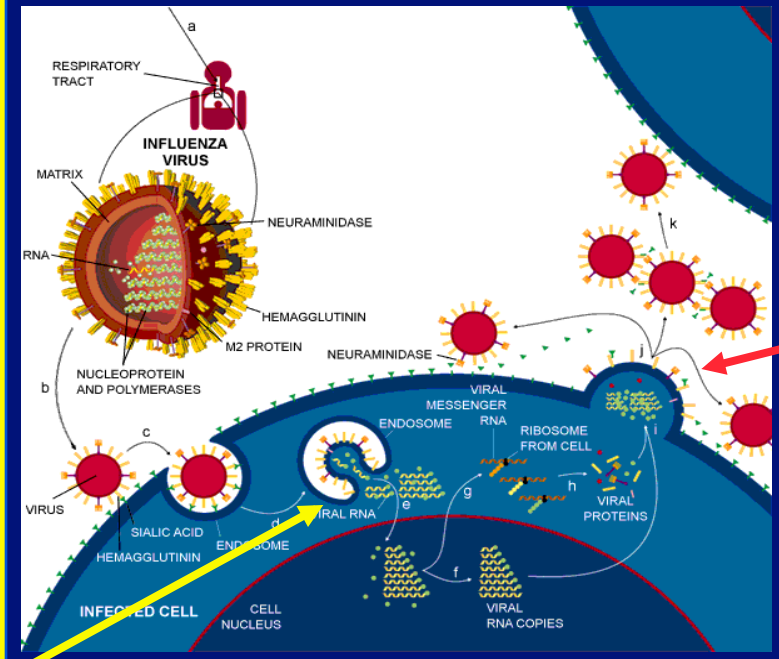
# Antiviral agents for influenza

- Adamantanes (M2 ion channel blockers)
  - Amantadine, rimantadine
- Neuraminidase inhibitors
  - Oseltamivir (oral and intravenous)
  - Zanamivir (inhaled and intravenous)
  - Peramivir (intravenous)
  - Laninamivir (inhaled)
- Other drugs in development
  - Antiviral agents
  - Immunomodulators
- (Hayden FG. (2012) Newer Influenza Antivirals, Biotherapeutics and Combinations. Influenza and Other Respiratory Viruses 7(Suppl. 1), 63–75.)

# Antiviral agents for influenza

**M2 ion channel blockers**

- Block M2 protein and prevent virus uncoating
- Only for influenza A
- High levels of resistance, including A/ H1N1 2009




**Neuraminidase inhibitors**

- Active against all known strains of human and animal influenza
- Block release of virus from infected cells

Matrix protein inhibitors no longer recommended for the treatment or prophylaxis of influenza

# Cochrane report 2006

*(Jefferson et al. Lancet 2006;367:303-313.)*

- "We do not see a role for the use of neuraminidase inhibitors in seasonal influenza, since the evidence shows that they are ineffective against influenza-like illness."
  - *In fact they failed to show a statistically significant effect against ILI, but did work against confirmed influenza*
- "Because of their low effectiveness, neuraminidase inhibitors should not be used in seasonal influenza control and should only be used in a serious epidemic or pandemic alongside other public-health measures."

# Effectiveness of neuraminidase inhibitors for treatment of influenza

(*Cochrane review:Jefferson et al. Lancet 2006;367:303-313.)*

| | Zanamavir | Oseltamivir |
|---|---|---|
| Prevention of infection | 50-70% | 50-70% |
| Prevention of influenza illness | 80-90% | 80-90% |
| Shorten illness | 1-3 days | 1-3 days |
| Reduce fever | 1-2 days | 0.5-2 days |
| Reduce complications | 60-70% | 60-70% |
| Reduce pneumonia | No data | 80-90% |
| Reduce viral shedding | 40-60% | 50-70% |

# Cochrane review 2007

## Neuraminidase inhibitors for preventing and treating influenza in children

*Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD002744. DOI:* 10.1002/14651858.CD002744.pub2

- Three trials involving 1500 children with ILI /influenza , 977 had laboratory-confirmed influenza.
- For laboratory-confirmed influenza in healthy children
  - Oseltamivir ↓ duration of illness by 26%(36 hours) (P <0.0001)
  - Zanamivir ↓ duration of illness by 24% (1.25 days) (P <0.001)
  - Oseltamivir significantly ↓ complications of influenza (particularly otitis media) - trend to benefit for zanamivir
- Oseltamivir reduced lab-confirmed influenza by 7.7% (10 hours) in asthmatic children (NS)
- Prophylactic oseltamivir – 55% protective efficacy (NS)
- Adverse events profile of zanamivir same as placebo, vomiting was more common in children treated with oseltamivir.

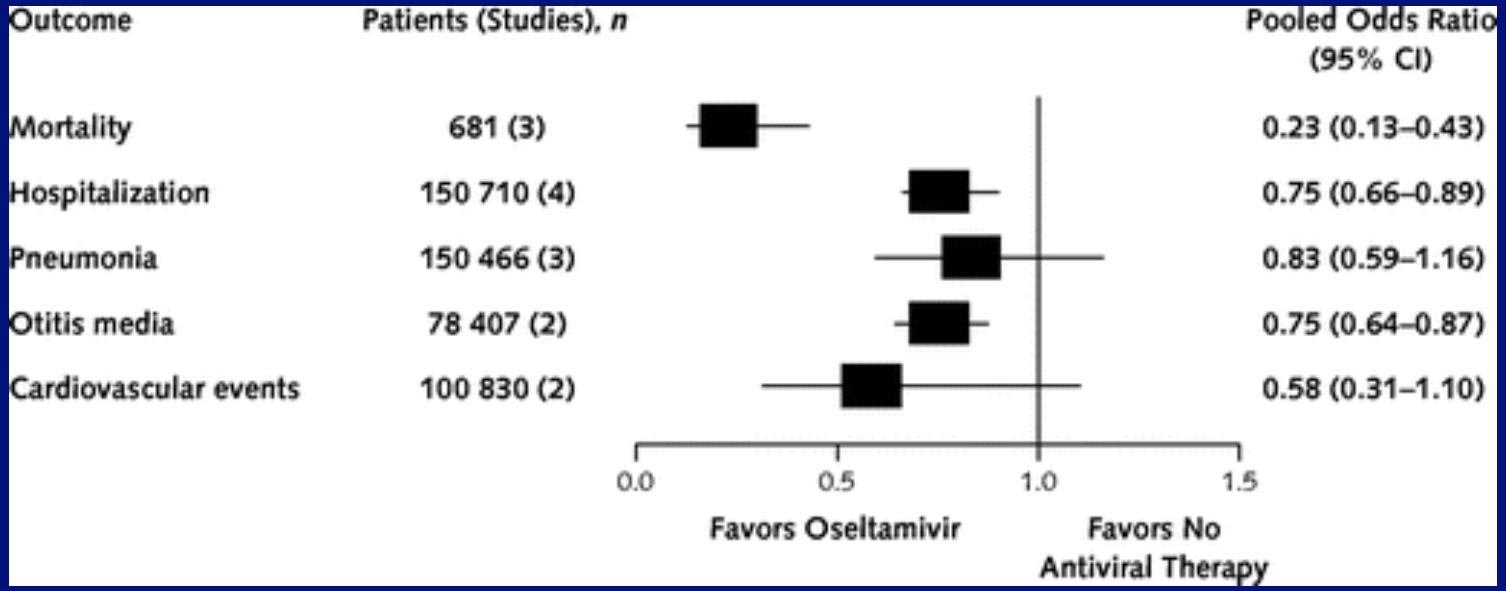
# Oseltamivir for pandemic influenza

- Early therapy
  - Decreases viral shedding
  - Reduces progression to pneumonia and death in immunocompetent and immunocompromised patients
- Therapy commenced >48 hours after onset still reduces mortality in hospitalised patients
- Oral/NG absorption adequate in most patients
- Prophylaxis reduces transmission and secondary cases

# NAIs for influenza: observational data

*Hsu et al: Antivirals for treatment of infleunza: A systematic review and meta-analysis of observational studies Ann Intern Med.* 2012;156:512-524

Meta-analysis of oral oseltamivir versus no antiviral therapy.




Oral oseltamivir and inhaled zanamivir have significant benefits in the treatment of influenza, though the confidence limits for the extent of that benefit are wide

# Antiviral drugs for the treatment of influenza

*(Burch et al. Health Technology Assessment 2009; Vol. 13: No. 58)*

- Oseltamivir and zanamivir both reduced symptom duration a little
- Effect on symptom duration were larger and more clinically significant in at risk patients
- "both zanamivir and oseltamivir resulting in statistically significant reductions in antibiotic use"
- "In general, the estimates from the cost-effectiveness model were more favourable in at-risk populations compared with otherwise healthy populations."
- "Despite some concerns, the use of NIs in at-risk populations appeared to be a cost-effective approach for the treatment of influenza."

# Effectiveness and safety of neuraminidase inhibitors in reducing influenza complications

*Falagas et al. J Antimicrob Chemother 2010; 65: 1330–1346*

- Eleven RCTs (10 double-blind) were included
- Total influenza-related complications were significantly less likely in treated patients with confirmed influenza infection
  - otherwise healthy patients : RR 0.74, (95% CI 0.58–0.95]
  - high-risk patients : RR 0.37, (95% CI 0.24–0.59)
- Trends suggested it reduced the individual complications, with acute otitis media significantly less likely (RR 0.50, 95% CI 0.30–0.85).
- No deaths were observed in trials that reported on mortality.
- No differences were found in the comparisons regarding the safety outcomes.

# Cochrane re-do 2014

- Included unpublished data
- Oseltamivir reduced time to alleviation of symptoms by 16.8 hrs in adults and 29 hrs in healthy children; zanamivir by 0.6 hrs in adults
- No significant effect on hospitalisations in adults
- No significant effects on serious complications or those leading to study withdrawal.

Jefferson T et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. (review). *Cochrane Dabase Syst Rev.* 2014 Apr 10;4:CD008965

# Cochrane review 2014

- Oseltamivir significantly reduced self-reported, investigator-mediated, unverified pneumonia, no significant effect in the trials that had diagnostic criteria for pneumonia. No effect for OST in children or zanamivir in adults or children.
- Zanamivir significantly reduced bronchitis in adults. OST no effect. Neither reduced OM or sinusitis
- Harms: Increased nausea and vomiting, less diarrhoea and cardiovascular events. Less seroconversion in children. Psychiatric events more common, especially at higher dose (300mg per day)

Jefferson T et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. (review). *Cochrane Dabase Syst Rev.*_2014 Apr 10;4:CD008965

# Cochrane 2014

- Oseltamivir and zanamivir have small non-specific effects on time to alleviation of influenza symptoms.
- Trials inconclusive about effect on complications due to lack of diagnostic definitions
- "The influenza virus-specific mechanism of action proposed by the producers does not fit the clinical evidence" (i.e. OST relieves symptoms only)

Jefferson T et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. (review). *Cochrane Dabase Syst Rev.* 2014 Apr 10;4:CD008965

# A differing opinion *(Dunning J. BMJ 2014;348)*

- "The clear discrepancy between the Cochrane group's conclusions and global experience of antivirals suggests that something is amiss."
- "abundant evidence from the 2009-10 pandemic …… after adjusting for confounding, antiviral therapy was associated with significant reductions in mortality in adults, most notably a 50% reduction with early treatment"
- "By accepting only the narrowest definitions of acceptable evidence, we would deny patients effective treatments and endanger public health."

*Freemantle N. Oseltamivir: the real world data. BMJ* 2014;348:g2371

- Randomised trial do not usually represent a real-life population in terms of outcomes and safety
- Observational studies:
  - Can use more representative patient populations
  - Easier to conduct and data can be accrued over longer periods of time giving more data on effectiveness and safety
  - Can be done if a placebo group is unethical
  - But confounders may not be identified and decisions about treatment may be influenced by clinical factors.

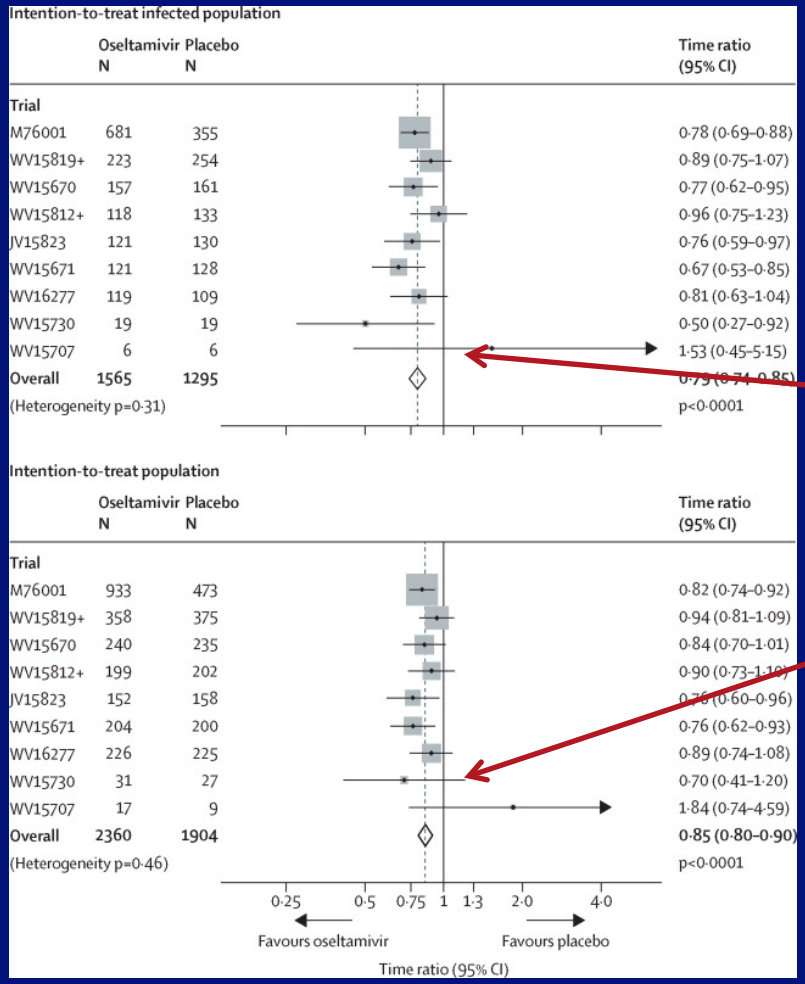
# Doing RCT meta-analysis a better way: Individual patient data?

- Why individual patient data?
- Allows combination of data across trials, which improves
  - Analysis of overall outcomes
  - Analysis of outcomes in patient subgroups
  - Ability to check data quality
  - Sensitivity analyses on key outcomes

Dobson J et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet. 2015; (online Jan 30)

- Individual patient data; published and unpublished trials; data quality audited by the FDA; trials that were included were almost identical to those used in the Cochrane analysis
- Included intention to treat, and intention to treat restricted to those with documented influenza
- Assessed 5 days treatment, with 21days total observation
- Primary outcome was time to alleviation of all symptoms.
- Main complication measured was lower respiratory tract infection requiring antibiotics occurring >48 hours after starting treatment.
- Hospitalisation for any cause an additional outcome.

# Effect of oseltamivir on the time to alleviation of all respiratory symptoms

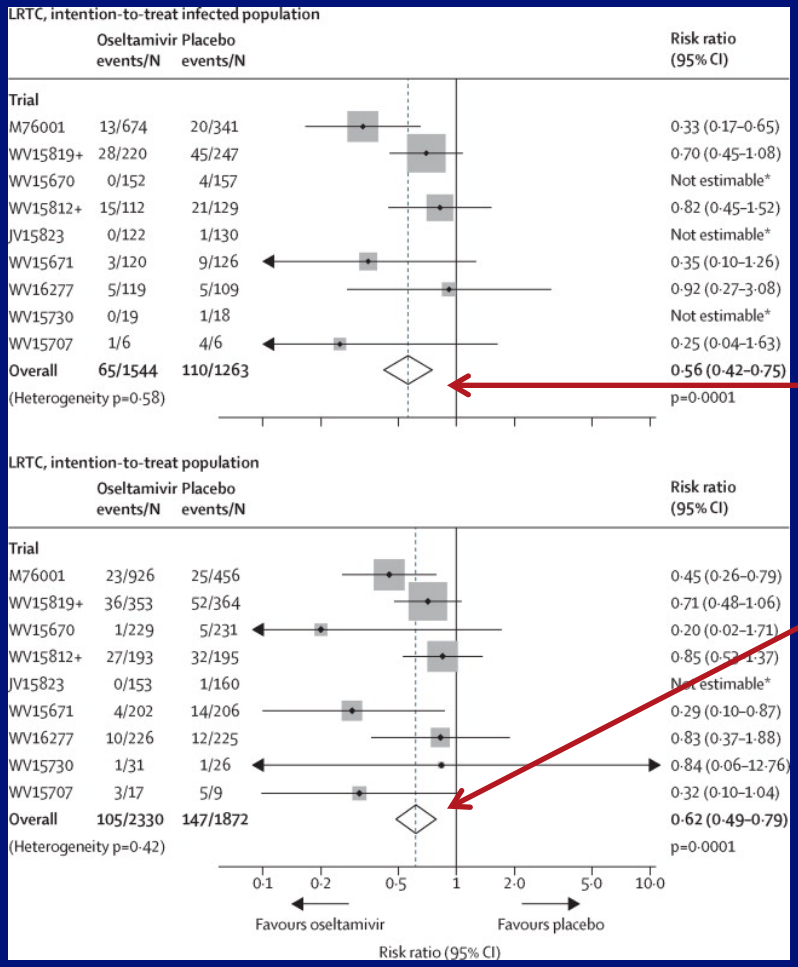



Oseltamivir treatment shortened the time to alleviation of all respiratory symptoms by:

- 25.2hrs in the ITT infected population
- 17.8 hrs in the ITT population

Dobson J et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet. 2015; (online Jan 30)

# Effect of oseltamivir on lower respiratory tract complications

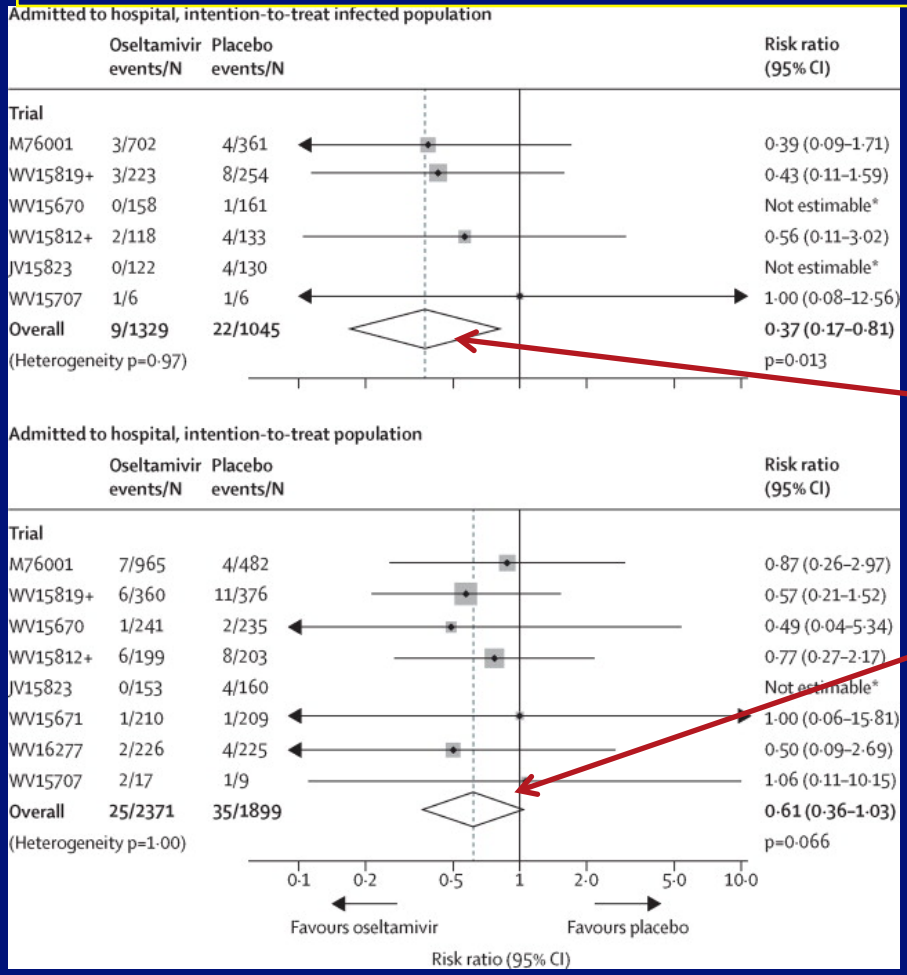



Oseltamivir treatment reduced lower respiratory tract complications by:

- 44% in the ITT infected population
- 38% in the ITT population

Dobson J et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet. 2015; (online Jan 30)

# Effect of oseltamivir on all hospital admissions




Oseltamivir treatment reduced hospital admissions by:

- 63% in the ITT infected population
- 39% (NS) in the ITT population

Dobson J et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet. 2015; (online Jan 30)

# Summary

- Conclusion was that oseltamivir reduces duration of symptoms, and reduces the risk of lower respiratory tract and hospitalisation.
- Oseltamivir increased the risk of nausea by 3.7%. and vomiting by 4.7%. There was no evidence of neurological or psychiatric effects, or of serious adverse events.
- Whether the benefits outweigh the increased nausea and vomiting is a clinical decision.
- Findings broadly compatible with those of observational studies and the Cochrane analysis.

Dobson J et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet. 2015; (online Jan 30)

# What more do we need?

- Better and widely-accessible tests for the rapid diagnosis of influenza
- Better and widely-accessible information on influenza activity within regions and areas
- More good quality evidence based data for all neuraminidases, both RCTs and observational studies, including data in high-risk populations

# Conclusions

- The evidence available indicates that neuraminidase inhibitors are effective in treating and preventing influenza infection, reducing complications and preventing hospital admission due to influenza
- Use of these should be clinical decision based on the likelihood of the patient being exposed to influenza and/ or having influenza, the benefit that may be attained by treating or preventing it and how that is balanced against likely side effects