# Debate Regarding Oseltamivir Use for Seasonal and Pandemic Influenza

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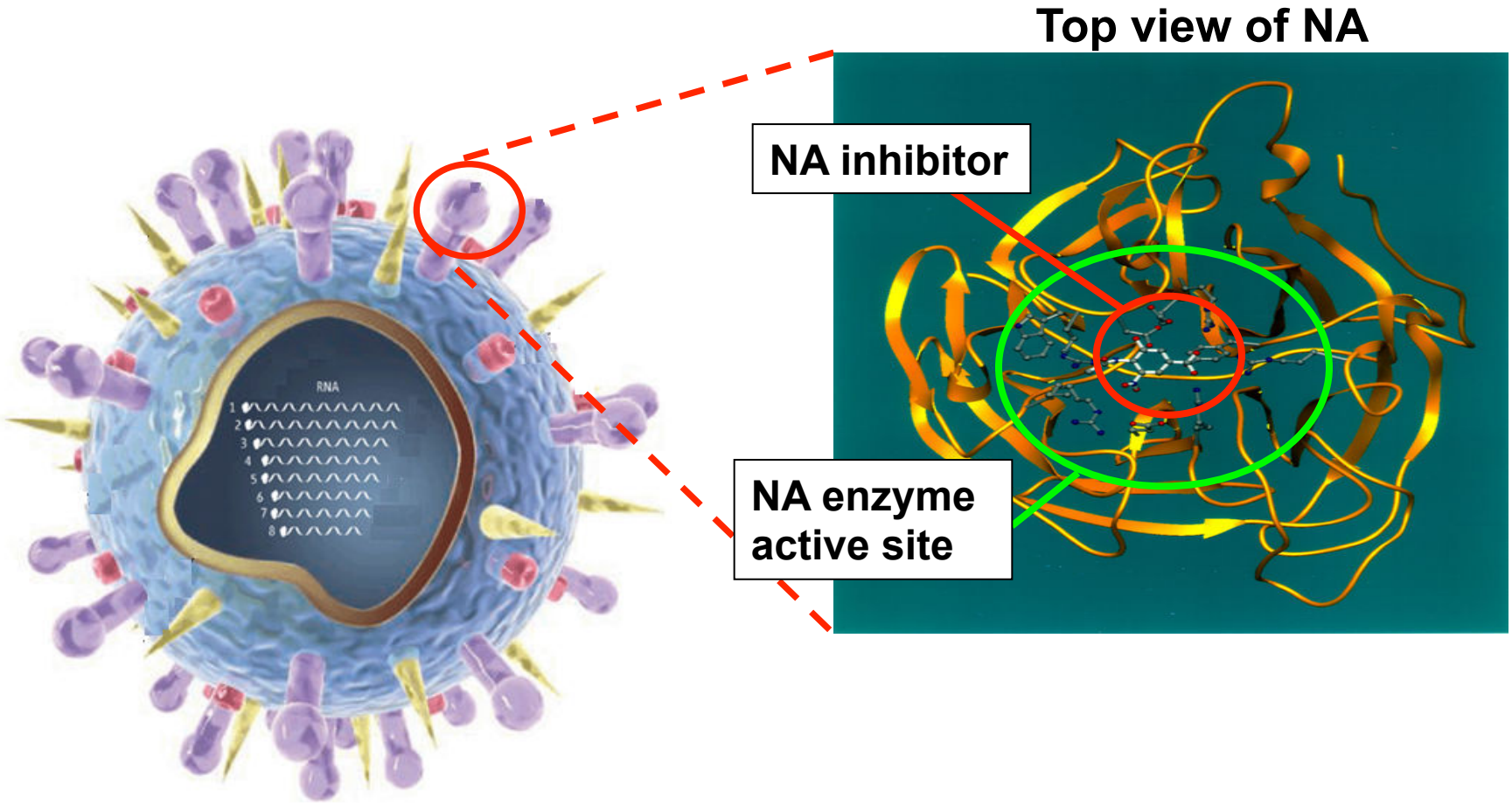
VIDRL

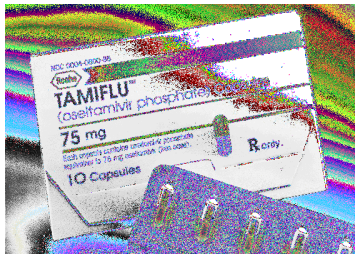
# NA inhibitor antiviral drugs



# The NA inhibitors

## Oseltamivir

- Oral, IV(?)
- Global




## Zanamivir

- Inhaled, IV(?)
- Global


## Peramivir

- IV
- Japan, S.Korea, China, US

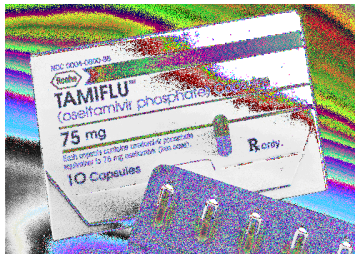

## Laninamivir

- Inhaled (single)
- Japan

# The NA inhibitors

## Oseltamivir

- Oral, IV(?)
- Global




## Zanamivir

- Inhaled, IV(?)
- Global


- Came on the market in many countries in 2000 after clinical studies had been conducted among influenza virus–infected patients with uncomplicated illness.

- Oseltamivir is market leader ……due to ease of oral administration
  - Use for seasonal influenza mainly in Japan and US

- With human infections of highly pathogenic influenza A(H5N1) virus from 2003 with a high case-fatality risks of >50%, governments began to consider antiviral drug administration as a key component of their pandemic response
  - suitable vaccines would not be available

# Stockpiling for a pandemic

- Oseltamivir was simpler (oral) administration than zanamivir (inhalation) and because of systemic effect of oseltamivir was expected to be appropriate for treatment of highly pathogenic viruses

- Oseltamivir was suddenly in high demand!

- Roche had warned that need to stockpile to guarantee availability

- Since 2005, governments of middle-income and high-income countries around the world have spent billions of dollars (estimated) stockpiling oseltamivir (*US Gov. Accounting Office*).

# 2009 A(H1N1)pdm09 pandemic

- The first pandemic of the 21st century occurred unexpectedly in 2009 after the global spread of a novel virus—influenza A(H1N1)pdm09—of swine (rather than avian) origin.

- In response, many countries activated their stockpiles of antiviral agents or accessed existing community supplies.

- This was the first time that specific antiviral drugs were available in a pandemic.

- In the United States during 2009, 8.7 million oseltamivir prescriptions (28.4 prescriptions/1,000 persons) were dispensed from community pharmacies, not from the stockpile, at a cost of US  $905 million.

# 2009 A(H1N1)pdm09 pandemic

- provided an opportunity to review the effectiveness of oseltamivir in the pandemic setting and to determine the benefit of oseltamivir for patients who were hospitalized with confirmed influenza A(H1N1)pdm09 virus infection.

- Such observational data were valuable to ascertain the effect of oseltamivir in severely ill or hospitalized patients given the continued absence of data from placebo-controlled, randomized controlled trials.

- Questioning whether oseltamivir is useful for treating serious illness and whether it should be stockpiled extended the debate on the effectiveness of oseltamivir that was already ongoing

**Oseltamivir Treatment of Seasonal Influenza**

**Oseltamivir Treatment of Severe Influenza**

**The disconnect between the mild vs severe influenza data**

**Implications for Stockpiling**

**Summary and the way forward**

# Oseltamivir Treatment of Seasonal Influenza

The Cochrane group, after partially successful efforts to retrieve unpublished data from Roche, conducted a meta-analysis of the effectiveness of oseltamivir in treating uncomplicated community-acquired influenza.

- focused on an intention-to-treat (ITT) analysis
  - patients with influenza-like illness who did not have laboratory-confirmed influenza
- oseltamivir reduced symptom duration in the ITT group by <24 hours
- oseltamivir had no specific influenza antiviral effect, even though the drug had been specifically designed to achieve exactly that

*(Jefferson et al, 2006; Jefferson et al, 2010; Jefferson et al, 2014)*

A subsequent meta-analysis (funded by an unrestricted grant from Roche) also confirmed a ≈1-day reduction in symptoms

- among adults and adolescents who had laboratory-confirmed influenza and were treated within 48 hours of symptom onset (intention-to-treat-infected groups – ITTI)
- no benefit was found for ITT group
- concluded that the effect of oseltamivir was due to its effect on the influenza virus, rather than a nonspecific antiviral effect

*(Dobson et al, 2015)*

# Oseltamivir Treatment of Seasonal Influenza

**Secondary analyses from the Dobson et al meta-analysis suggested the following:**

- Oseltamivir treatment resulted in a 63% (95% CI 19%–83%) decreased risk in hospitalization for any cause, based on 9/1,591 (0.6%) oseltamivir treated vs 22/1,302 (1.7%) placebo-treated patients;

- Oseltamivir treatment resulted in a 44% (95% CI 25%–58%) decreased risk of antibiotic prescription for lower respiratory disease in patients with laboratory-confirmed influenza, based on 65/1,544 (4.2%) oseltamivir-treated vs 110/1,263 (8.7%) placebo-treated patients.

- However, hospital admissions were all cause and not confined to those that may have been associated with influenza infection and no formal diagnostic criteria existed for lower respiratory tract infection
    - these secondary analyses less convincing than the analyses of primary endpoints.

- Even though these findings were largely in agreement with those of the Cochrane group, and the arm's length funding mechanism from Roche, the meta-analysis has been criticized as being influenced by the manufacturer

# Oseltamivir Treatment of Severe Influenza

**No randomized control trials (RCTs) exist assessing the effect of oseltamivir on severe outcomes of laboratory-confirmed influenza**

- The Cochrane group chooses only to conduct meta-analyses of RCTs

- Evidence is instead derived from observational studies on the use of oseltamivir to treat complications of influenza virus infection, as in hospitalized patients or in those who died.
  - subject to uncontrolled bias
  - E.g. sicker patients may be more (or less) likely to be treated, thus attenuating (or exaggerating) the effect of the intervention.
  - a serious outcome may occur soon after the treatment was initiated in a severely ill patient, so that the treatment has not had a chance to succeed. Similarly, patients who receive early treatment are more likely to benefit from treatment than patients who receive late treatment.

- To minimize bias, researchers have attempted to adjust for time from disease onset to treatment and time from treatment to outcome. Some observational studies have also adjusted for propensity to be treated as well as patient coexisting conditions and disease severity, which may affect treatment decisions and outcomes.

# Oseltamivir Treatment of Severe Influenza

**Among studies that have attempted to control for these biases, a decreased risk for death after oseltamivir treatment has been reported, and early treatment appears to be critical (*Muthuri et al, 2014; Lee et al, 2010; Hiba et al, 2011*).**

- Observational study controlled for propensity to treat and patient coexisting conditions and demonstrated the odds of death increased by 2.2 times (95% CI 1.4–3.5 times) if treatment was started late (>48 hours after symptoms) (*Hiba et al, 2011*).

- In an attempt to overcome the criticisms of design and analysis of the observational studies, Roche chose to fund a patient level meta-analysis of individual data from 78 different observational studies, which included >29,000 patients (*Muthuri et al, 2014)*

- By adjusting for time, propensity to treat, and patient coexisting conditions, early treatment versus no treatment was also associated with a reduction in mortality (adjusted OR 0·50; 95% CI 0·37–0·67; p<0·0001).

- These associations with reduced mortality risk were less pronounced and not significant in children.

- However, even this carefully designed study has been criticized by the Cochrane group on methodologic grounds and

# Oseltamivir Treatment of Severe Influenza

- Heneghan et al (Cochrane group), published a systematic review and a meta-analysis in 2016, which included summary data on 30 studies, with 11,013 patients, and 1301 deaths (12%). Individual patient data was obtained from four studies with 3071 patients and 242 (8%) deaths. Analysis showed insufficient evidence that oseltamivir reduced the risk of mortality [hazard ratio (HR) 1.03, 95% CI 0.64 to 1.65].

- So why the different outcomes?

    - Different data
        - But descriptive data shows quite similar results
        - Of the 78 studies included in Muthuri et al, 27 studies: all patients received NAIs; 16 studies: had no mortality.
            - Studies with no events or without a control group are often not include in an analysis
    - Statistical model used is different
        - Generalized linear mixed vs time-dependent cox regression models !!!
        - See link below (or a cleverer person than me) for an explanation
    - Confounding by indication
        - Both attempted to adjust for potential confounders , but residual confounding may remain.

Mark Jones: http://www.cebm.net/oseltamivir-mortality-muthuri-et-al-2014-conclusions-differ-heneghan-et-al-2016/

# Oseltamivir Treatment of Severe Influenza

- There is scant other evidence for the benefit of oseltamivir on reducing the risk for death apart from a few potentially informative observational studies that support the conclusion that oseltamivir use has a beneficial effect on reducing the risk for death:
    - oseltamivir treatment decreased the risk for death from influenza A(H5N1) virus by 49% (95% CI 23%–66%) (258 patients; 7 countries) (*Adisasmito et al. 2010*)
    - a study from Hong Kong, which enrolled mostly elderly, hospitalized patients with co-existing conditions during 2007–2008, found oseltamivir treatment reduced risk for death (adjusted hazard ratio 0.27, 95% CI 0.13–0.55; $p<0.001$), with a further reduction associated with earlier treatment (*Lee et al., 2010*).
    - a small prospective observational study of patients hospitalized with laboratory-confirmed influenza in the 2005–06 season in Ontario, Canada, found the adjusted odds ratio of death among oseltamivir-treated patients was 0.21 (95% CI 0.06–0.80; $p = 0.03$), based on 22 (10%) of 219 deaths in the untreated group compared with 4 of 103 deaths in the treated group (*McGeer et al, 2007*).
- No data on oseltamivir effectiveness for treating infections with avian influenza A(H7N9) virus in China

# The disconnect between the mild vs severe influenza data

- The evidence from RCTs is that oseltamivir treatment decreases the duration of symptoms by up to 1 day in adolescent and adult patients with laboratory-confirmed seasonal influenza

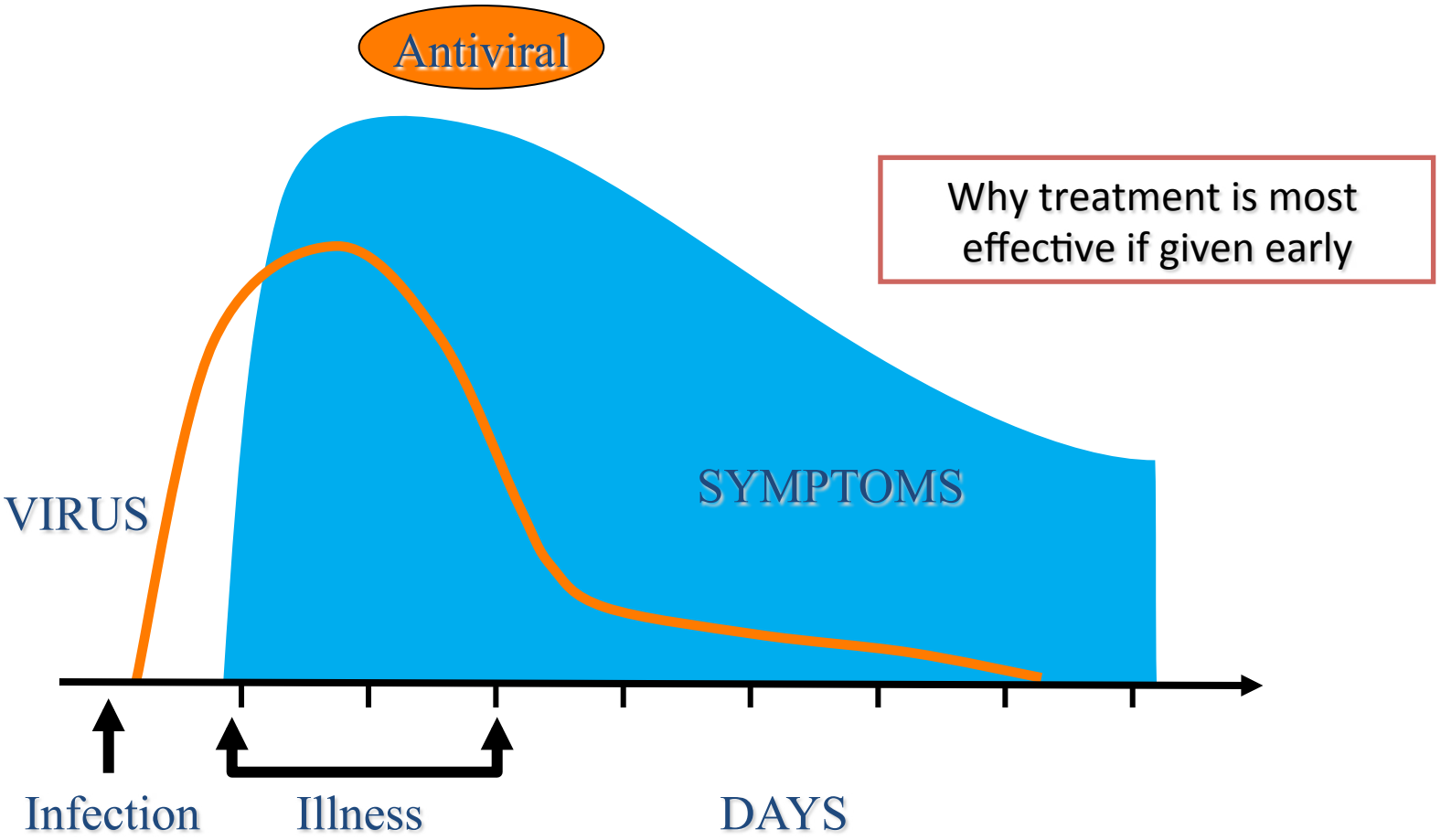
- Reviews of observational data regarding patients hospitalized with influenza A(H1N1)pdm09 or influenza A(H5N1) infections found that risk for death is cut in half if treatment is initiated within 48 hours of symptom onset.

- Small prepandemic observational studies, although they generally have controlled less for potential biases, also support the conclusion that risk for death is decreased with oseltamivir treatment.

- These 2 lines of evidence may appear inconsistent. How would an intervention that has a modest effect on symptom duration in patients whose uncomplicated influenza was treated after a visit to a general practitioner be able to cut in half the risk for death among hospitalized patients?

# The disconnect between the mild vs severe influenza data

Not surprising that treatment for uncomplicated influenza will only produce a modest effect……



# The disconnect between the mild vs severe influenza data

- It is therefore plausible that community-based randomized controlled trials are not capturing critical information about the mode of action of oseltamivir that is beneficial to severely ill patients.

- It is possible that benefit to severely ill patients may be related to the increased duration of viral shedding and higher viral loads found in this group of patients.

- may relate to decreasing the adverse outcome associated with a cytokine storm, which would not be expected in patients with mild disease.

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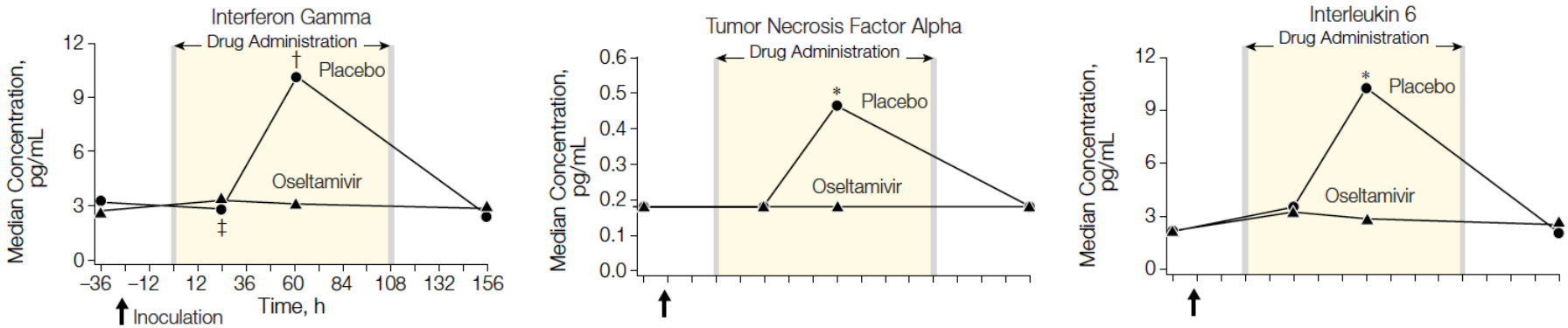
- A RCT of 117 healthy adults experimentally infected with seasonal influenza virus A(H1N1) reported that oseltamivir treatment significantly reduced interleukin-6, interferon-γ, and tumor necrosis factor-α cytokine responses in patients compared with responses in placebo-treated patients (*Hayden et al., 1999*).



# Implications for Stockpiling

- RCT data from patients with mild influenza and observational data from severely ill patients demonstrate the clear benefits of initiating treatment as early as possible

- NAI use in Japan is so widespread that almost every confirmed influenza case is treated, led to the extensive and rapid delivery of the drugs in the 2009 pandemic

- >98% (984/1,000) Japanese children hospitalized with influenza A(H1N1)pdm09 were treated with an NAI, 89% received NAIs within 48 hours and 70% within 24 hours. Only 1% of the hospitalized children ultimately required mechanical ventilation, and 1 death was recorded (*Sugaya et al., 2011*).

- Similar ecologic data were observed among pregnant women in Japan, who were at increased risk for hospitalization and death when infected with A(H1N1)pdm09.

- Pregnant Japanese women were treated prophylactically after close contact with an infected person, and if infected and hospitalized, >90% were given NAIs within 48 hours of symptom onset. In comparison to the high mortality rates among pregnant women in many countries around the world (*Burioni et al., 2009*), no maternal deaths occurred in Japan during the pandemic (*Nakai et al., 2012*).

# Implications for Stockpiling

- Data from Japan suggest that rapid access to stockpiled NAIs in a pandemic is necessary to achieve the greatest benefit from their use.

- Rapid access during the 2009 pandemic in Japan was possible because rapid access represented routine care for seasonal influenza.

- In other countries, the 2009 pandemic confirmed that centralized stockpiles did not facilitate rapid distribution (*Gutiérrez-Mendoza et al., 2012*) and that decentralized stockpiles would be more efficient.

- Stockpiles in hospitals, for example, would facilitate rapid treatment of ill patients in a pandemic but might also allow the periodic use of some material for the treatment of interpandemic seasonal influenza to avoid wastage due to an expiring stockpile (*Gutiérrez-Mendoza et al., 2012*).

- Over-the-counter administration, as has been approved in NZ, is a great example of how the drug may be able to be accessed quickly….assuming it is dispersed rapidly to pharmacies!

# Summary and the way forward

Use for Seasonal Influenza

- General agreement that oseltamivir reduces symptoms in healthy adults and adolescents with influenza by up to 1 day.
- Disagreement on the mechanism - the Cochrane group maintains that there is a nonspecific effect of oseltamivir
- There have been no RCTs that can be meta-analyzed to summarize the effect of oseltamivir on severe outcomes of influenza virus infection.

# Summary and the way forward

Use for Seasonal Influenza

- Evidence from observational studies consistently suggests that oseltamivir reduces the risk for death in severely ill patients with influenza infection. Although recent Cochrane group paper does not support this.
- The apparent discrepancy between a modest drug effect for healthy persons and an effect on number of deaths remains unexplained.
- Oseltamivir should be used for treatment of hospitalized patients with laboratory-confirmed seasonal influenza

# Summary and the way forward

Use for Pandemic Influenza

- Oseltamivir should be stockpiled for the treatment of patients with severe laboratory-confirmed pandemic influenza, whether hospitalized or not.
- These stockpiles should be widely distributed to facilitate rapid use when needed.
- Without a mechanism for rapid distribution of the drug in an emergency, any potential benefit of such large-scale stockpiling will not be realized.

# Summary and the way forward

Use for Pandemic Influenza

- Rapid distribution in an emergency is only likely if a mechanism exists for routine rapid distribution.
- In countries where such a mechanism does not exist, stockpiling oseltamivir for widespread community use during a pandemic is unlikely to be effective

# Summary and the way forward

The way forward

- It is unlikely that conventional RCT-level evidence to support antiviral treatment of severe laboratory-confirmed influenza in hospitalized patients will appear within the next decade

- Due to the ethical constraints of evaluating oseltamivir vs placebo, when oseltamivir is the current standard of care for the treatment of severe influenza infection.

- New studies should be high-quality prospective multisite observational studies and employ methods to minimize bias to the greatest extent possible.

# Summary and the way forward

The way forward

- Studies designed for assessing interventions for seasonal influenza should be readily adaptable to studies of pandemic influenza on very short notice.

- Because of the ethical and design constraints of RCTs, prospective observational studies are more feasible than RCTs in an emergency response situation.

- In addition to data on outcome, such as risk of ICU admission and death among adults, or length of stay among children, these observational studies should also record time from disease onset to treatment and time from treatment to outcome to minimize bias. Sequential data on markers of immune function in at least a subset of recruited patients would also be valuable.

# Acknowledgements:

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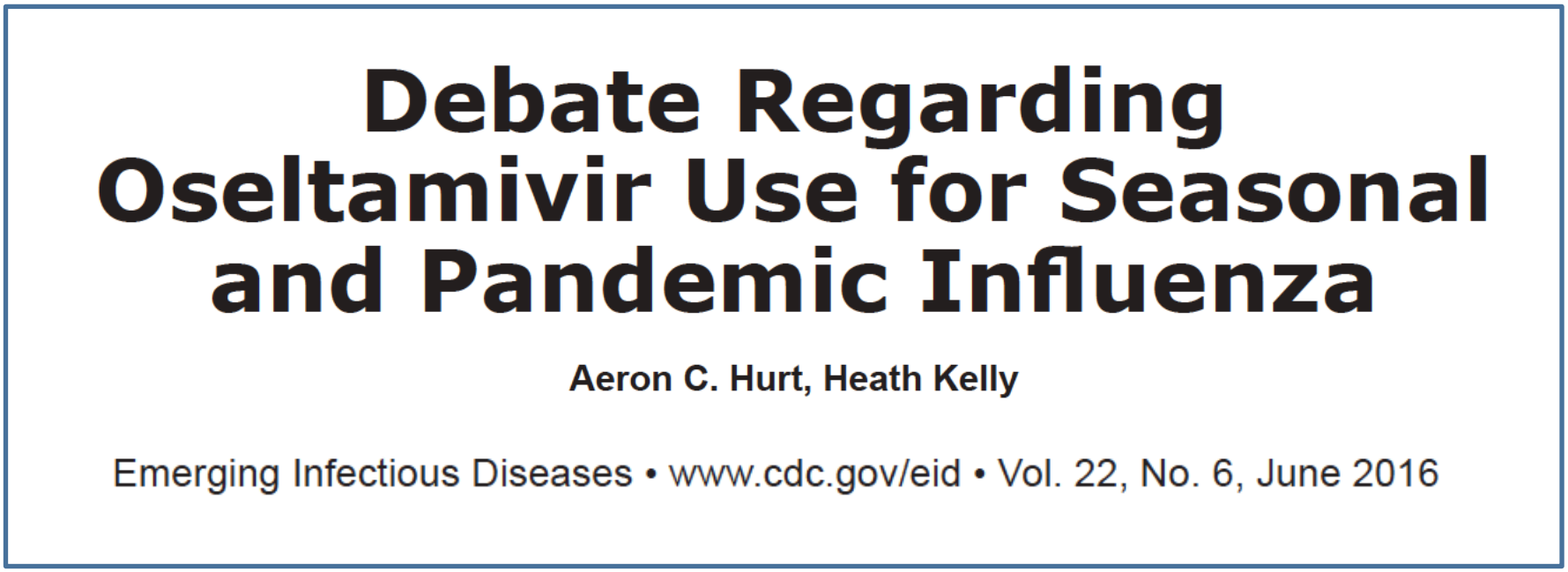
Former Head, epidemiology at the Victorian Infectious Diseases Reference Laboratory

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