Review of Antiviral Treatment of Mild and Severe Influenza Infections in Children

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Influenza in Children

How important of children with influenza infection ?

1. Children (esp. younger age) are highly susceptible to influenza infection
2. Children with influenza are usually the source of spreading among family
3. Prevention of influenza among children confer "Herd effect" to elderly in family
4. Children with influenza had higher complication rate

Natural Attack Rate of Influenza in Unvaccinated Children and Adult: a meta-regression analysis

- 34 RCTs contributing 47 influenza seasons; 1970-2009
- Attack rate of Flu A & Flu B in unvaccinated peoples

	Flu in Adult	Flu in Children
• Influenza A	2.3%	12.27%
• Influenza B	0.59%	5.5%
• All type of Influenza	3.5%	15.3%

★ Overall flu in children is 4 times more than adult

★ Overall flu B in children is 9 times more than adult

(BMC Infect Dis 2014;14:670)

Seasonal Influenza Burden in Children <5 yrs.

- Annual incidence is highest in children <5 yrs.
- Co-circulates and infected with other respiratory viruses eg. RSV
- Complication most common in youngest children <2 yrs.
- Secondary bacterial infect are common (eg. *S.aureus, S.pneumoniae, H.influenzae*)
- Increased severity in children with underlying chronic medical conditions

(Systemic Review by CHERG.)

Clinical Outcome of Influenza in Children

1. Influenza :- Asymptomatic (20-30%)

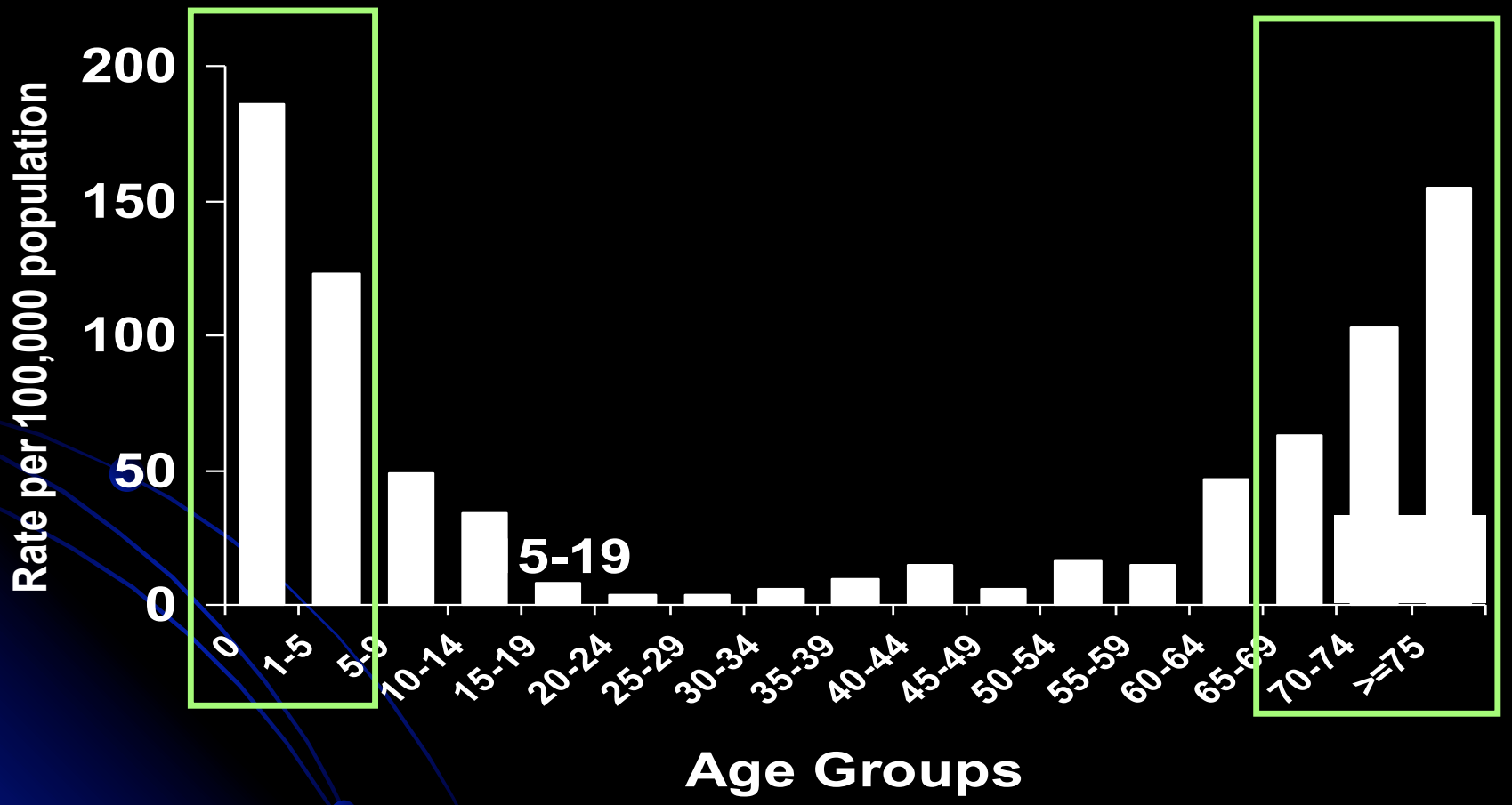
   :- Symptomatic- outpatient (70-80%)

2. Severe influenza- hospitalized (1-5%)

3. Death from influenza (0.01-0.1%)

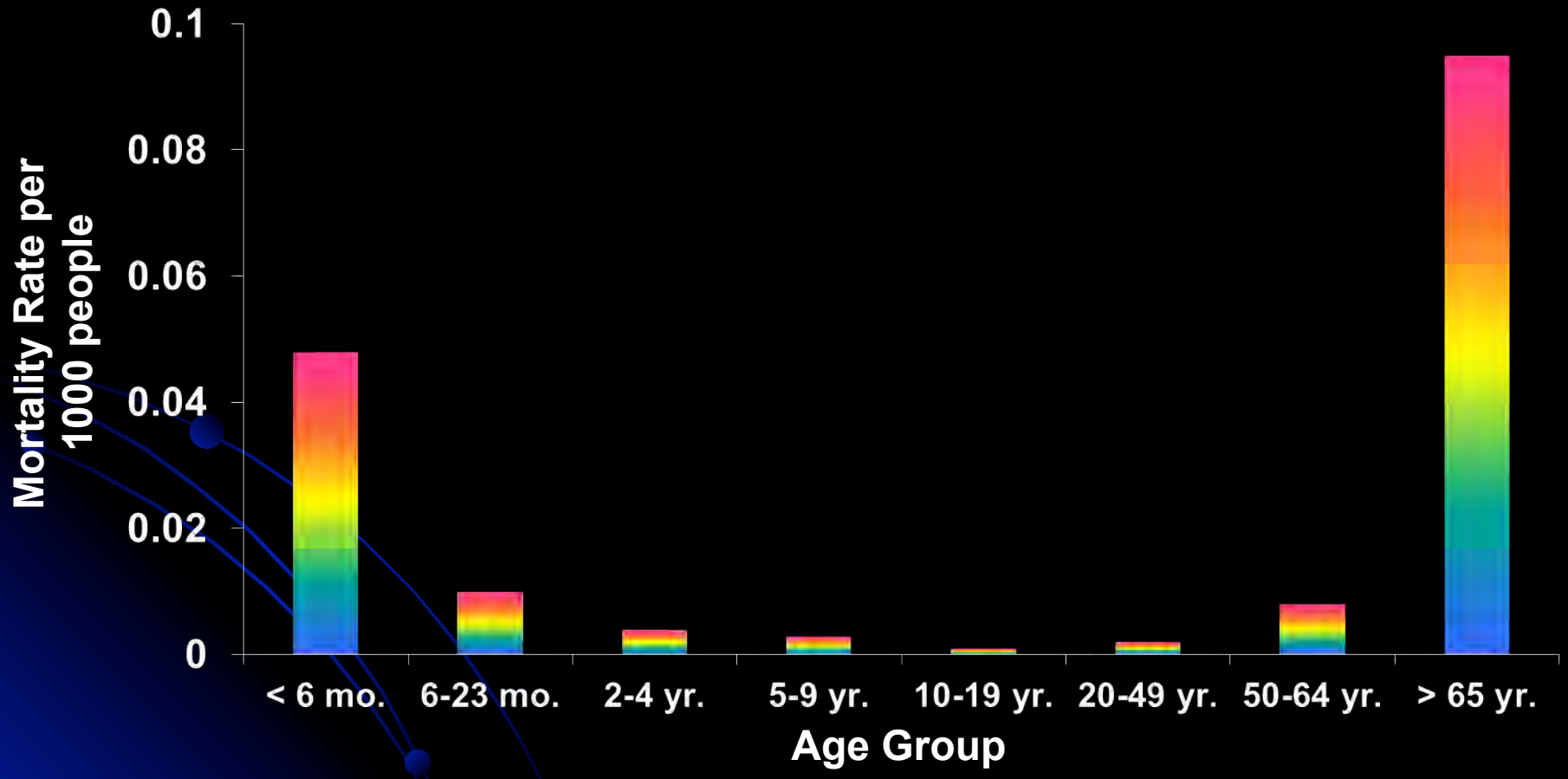
High risk to Influenza associated complications

Annualized Incidence of Influenza Pneumonia SaKaeo and NakhonPhanom:2005-2006(n=661)



Mortality Rates Due to Influenza and Pneumonia

Age-associated rates of influenza-related deaths, data from British Columbia, 1998-2004 influenza season



(Sebastian R, et al. Vaccine 2008; 26: 1397-403.)

Mortality Rates from Influenza and Pneumonia :- 2007, US

Age :- younger than 1 year, mortality rate 5.2 / 100,000 pop.

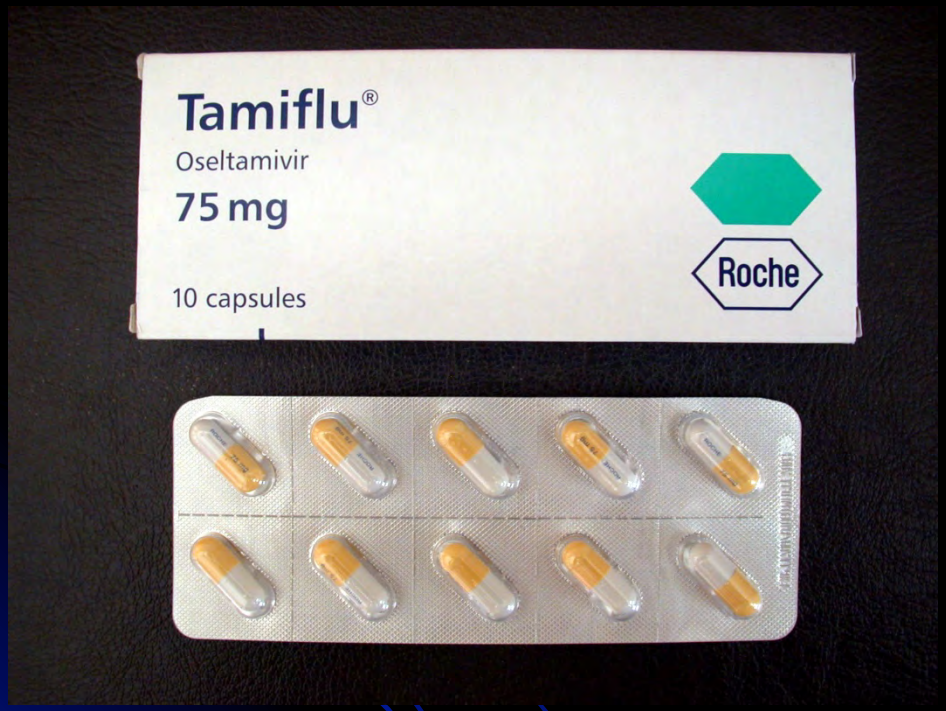
:- age 1-4 years, mortality rate 0.7 / 100,000 pop.

:- age 5-14 years, mortality rate 0.3 / 100,000 pop.

Total 20,000 deaths in children each year in US

(Xu J .www.cdc.gov/NCHS/data/nvsr58/nosr58_19.pdf.)

Antiviral for Influenza in Children

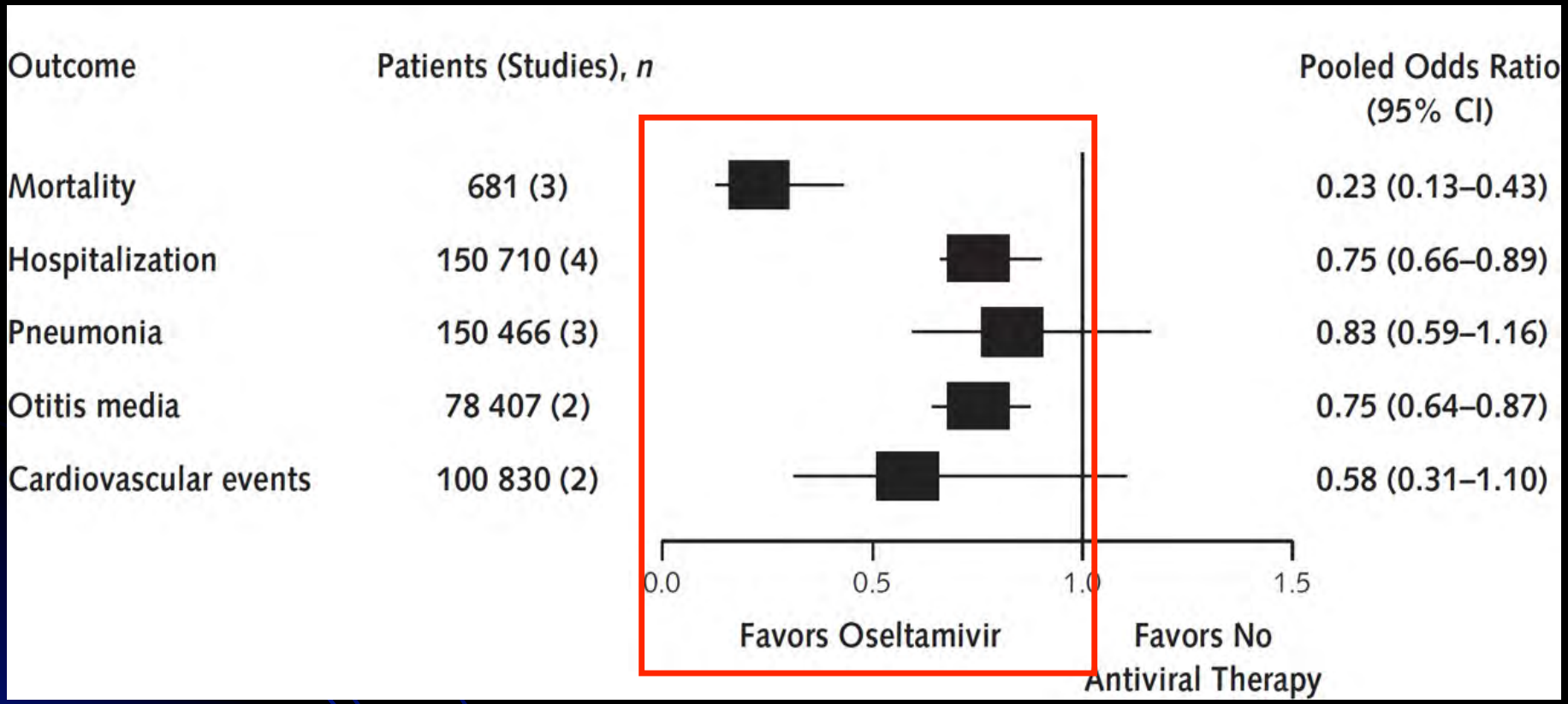


Recommendation of Antivirals for Seasonal Flu in Thailand

1. Treatment

2. ~~Chemoprophylaxis~~

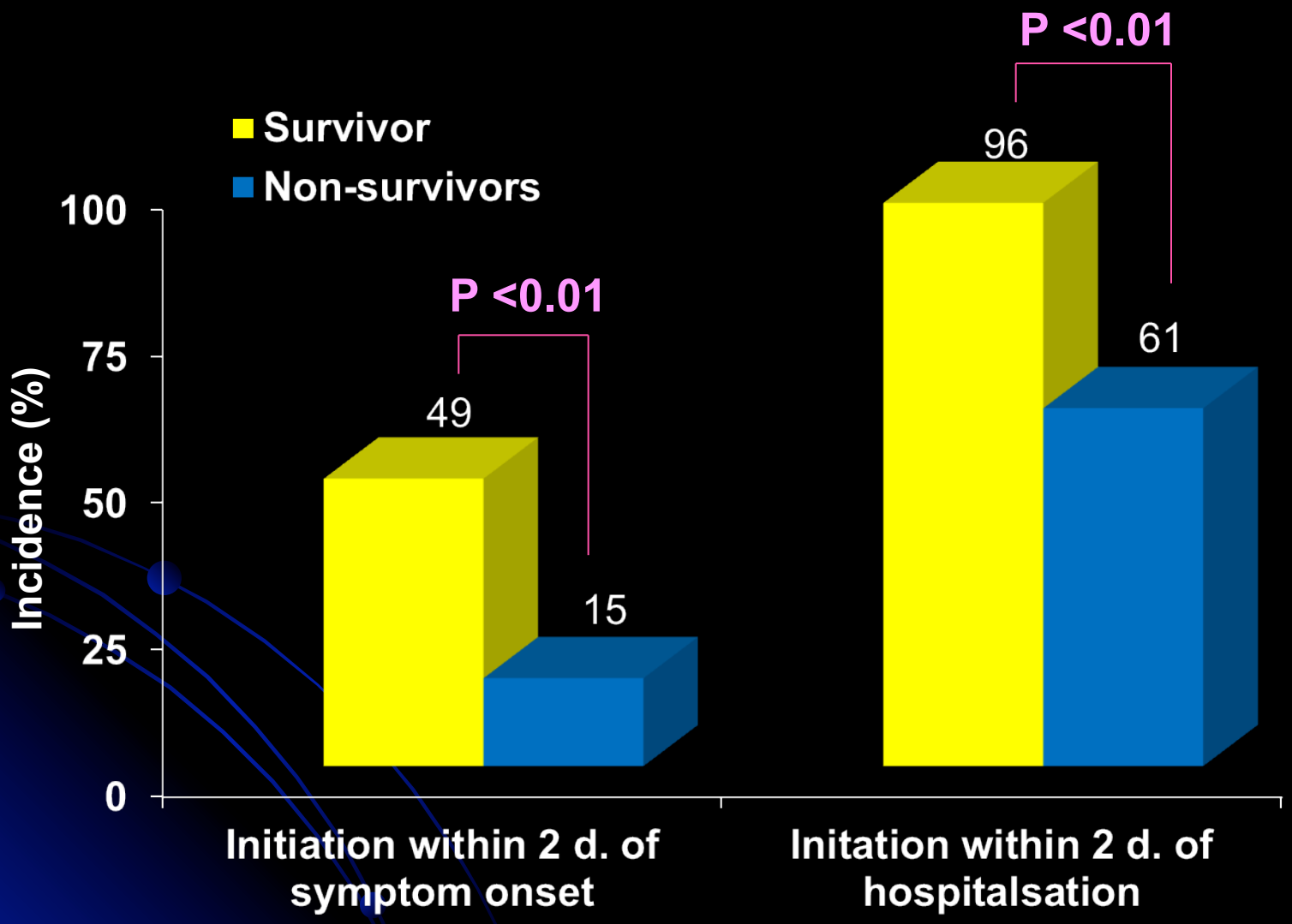
Random-effects meta-analysis of oral oseltamivir versus no antiviral therapy based on studies that provided adjusted effect measures.



Hsu J et al. Ann Intern Med doi: 10.1059/0003-4819-156-7-201204030-00411

Annals of Internal Medicine

Hospitalized patients with pH1N1 2009 who survived were more likely to have oseltamivir early



(Lec et al. CID 2010; 50: 1498-504.)

Oral Oseltamivir Treatment of Influenza in Children (1)

- N= 695 children (placebo 235, oseltamivir 217)
  1. reduce mean duration of illness by 36 h (P< 0.0001)
     - Placebo 137 hr. (95% CI 125-150)
     - Oseltamivir 101 hr. (95%CI 89-118)
  2. reduce cough , coryza and duration of fever
  3. reduce AOM by 44% (12% VS 21%)
  4. reduce antibiotic prescription in flu-infected oseltamivir Rx (31% VS 41%) P=0.03

(Whitley RJ, et al . PIDJ 2001;20:127-33.)

Oral Oseltamivir Treatment of Influenza in Children (2)

- N= 695 children (placebo 235, oseltamivir 217)

  5. excess vomiting 5.8%

  6. Oseltamivir treatment did not affect influenza- specific antibody response

  Summary :- Oral Oseltamivir is efficacious and well tolerated when given within 48 hr. of illness

(Whitley RJ, et al . PIDJ 2001;20:127-33.)

Efficacy of Oseltamivir treatment started within 5 days of symptom onset reduce influenza illness duration and virus shedding in an urban setting in Bangladesh :- A randomized placebo controlled trial

- Oseltamivir provide best benefit when used within 48 h. of onset
- Urban Bangladesh :– N=1163 subjects with RIDT positive
- Age >1 y. – <5 yr.= 51%, all of them symptom ≤5 d.
- Symptom <48 hr. (67% of cohort); >48 hr. (33% of cohort)
- Result :- reduced major symptoms was significantly shorter in
- Oseltamivir VS placebo group. (3 VS 4 d.)

:- in onset >48 hr. group was significantly reduced viral shedding on days 2 and 4 but not d.7

:- vomiting was more common in Osel. group (5.9% VS 3.2%)

(Fry AM, et al. Lancet Infect Dis 2013; Nov 22.)

Oseltamivir for Influenza in Adult and Children: Systematic Review and regulatory comments

- **Conclusion**

  :- Treatment trial found modestly reduces time to first alleviation of symptoms

  :- Causes nausea and vomiting and increases risk of headache, renal and psychiatric syndromes

  :- Limited evidences of clinically significant on complications and viral transmission

  :- Prophylactic studies, it reduces prospection of symptomatic flu

*** Summary:- Benefit and harm should be concerned to use oseltamivir for treatment, prophylaxes and stockpiling.**

(Jefferson T, et al. BMJ 2014; 348: g2545.)

Antiviral for Influenza in Children

- Oseltamivir is drug of choice

  - double-dose regimen was believed to provide better outcome in severe hospitalized influenza

  - but SEAICRN Group had study RCT found no benefit of double-dose over standard dose

- Inhaled Zanamivir is alternative but is more difficult to use (age less than 7 yr.) but some benefit for influenza strain resistant

Limitation of Oseltamivir and Zanamivir Treatment in Influenza (during pH1N1-2009)

Especially in young children

- Syrup formulation :- not widely available ,expensive and can not divided for other patient
- Contraindicated for less than 1 year (off label-common)
- Indication for treatment or prophylaxis based on stockpile of individual country
- Inhale Zanamivir is very difficult use in young children, ventilated patient and asthmatic patient
- Parenteral antivirals are not available in most countries

Antiviral Treatment Indication and Decision

- Clinical judgment based on underlying conditions, disease severity, and time since symptom onset are also important factors in treatment decisions.
- Antiviral treatment is recommended as soon as possible for all persons with suspected or confirmed influenza requiring hospitalization or who have progressive, severe or complicated illness regardless of previous health or vaccination status.

1 = CDC : 2009. www.cdc.gov/H1N1 flu / recommendations html.
2 = NEJM 2010; 362 : 1708-19.
3 = CID 2009; 48: 1003-32.

When will pediatrician use Oseltamivir in ILI patient?

- Clinical judgment on the basis of
  - underlying disease
  - disease severity
  - time since symptom onset
  - local influenza activity
- Decisions on treatment can be made easily if RIDT positive,

  But if RIDT negative; treatment should not be withheld in high risk patient or base on clinical judgement.

(AAP recommendation, 2014-2015. Pediatrics November 2014, Vol 134, No5.)

Update on Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza :- ACIP 2011 (1)

1. Early antiviral Rx. in suspected or confirmed patient with severe influenza eg.
    - severe illness eg. pneumonia, sepsis, encephalitis etc.
    - complicated eg. pneumonia
    - progressive illness eg. Pneumonia, severe fever , vomiting
    - required hospitalization

(MMWR. January 21, 2011/ Vol 60 / No.1.)

2 yo. Girl had fever for 4 days ,

cough and dyspnea for 1 d.

History of URI in family members.

Lung - crepitation both

CXR:- RUL infiltration and Perihilar

infiltration both lung

Rapid test for flu A & B = Negative

.

Will you give antibiotics?

Will you give Oseltamivir?

Recommendation of treatment of Community-Acquired Pneumonia (CAP) in Thai children and adult :-2009-15

- 3rd generation cephalosporin eg

  Cefotaxime ,Ceftriaxone

  +

  Macrolides eg. Azithromycin, Erythromycin

Since 2009-15 (consider to added if suspected flu) +

Antiviral agent eg. Oseltamivir

Estimated Burden of Influenza :- Southeast Asia

- Estimated 11-26% of outpatient illness[1]
- Estimated 6-14% of hospitalized pneumonia cases[1]
- Thailand :- active surveillance found 10.4% of pneumonia caused by influenza in 2 provinces, high risk are young age (<5 y.) and elderly (≥65 y.)[2]

1 = Influenza Other Respi Viruses. May 2008; 2(3) : 81-92.
2 = Vaccine 2004; 23(2) : 182-7.

Boy 4 ½ yr. had high fever (39-40 C),cough, runny nose for 1 day .There were 7 roommate friends had same illness and 5 of them confirmed had Flu B.

Will you test RIDT ?

Will you give Oseltamivir?

Update on Antiviral Agents for the Treatment and chemoprophylaxis of Influenza :- ACIP 2011 (2)

2. Early antiviral Rx in suspected or confirmed patient with higher risk for severe or complicated influenza eg.
   - chronic medical conditions
   - children < 2 yo.
   - pregnancy and < 2 wk postpartum, obesity with BMI $\geq$ 40 , (Thailand $\geq$ 100 kg.) etc.

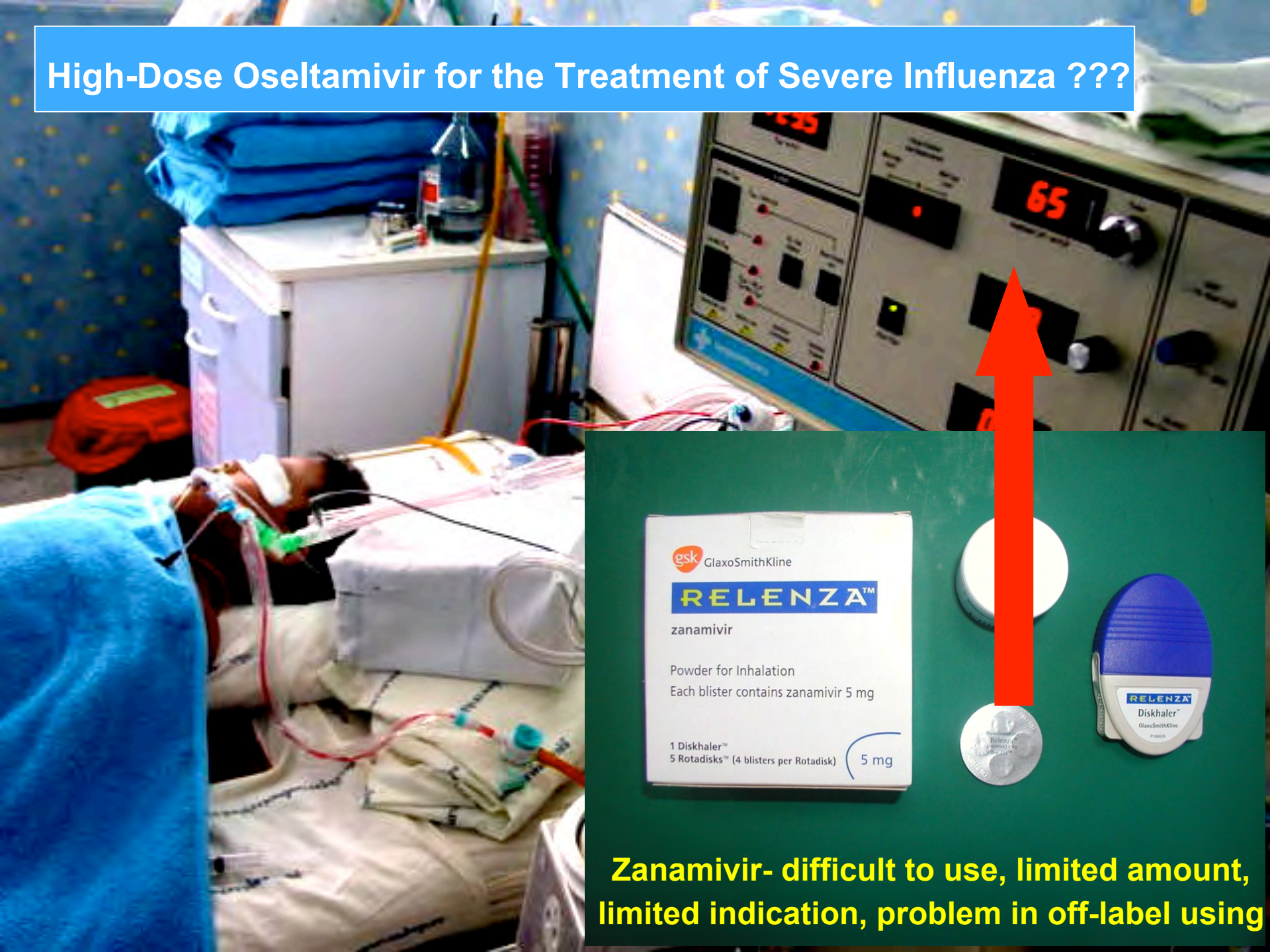
3. Either Oseltamivir or Zanamivir for pH1N1 2009, H3N2, B or Flu A unknown subtype (H5)

(MMWR. January 21, 2011/ Vol 60 / No.1.)

The other twin was still healthy, no any symptom. If second twin starting to have fever and same illness, Will you give oseltamivir??

Granddad 66 yo , had diabetes under control. If have fever and ILI. Will you give oseltamivir ??

High-Dose Oseltamivir for the Treatment of Severe Influenza ???



High-Dose VS Standard-Dose Oseltamivir for the Treatment of Severe Influenza: double blind RCT

- Apr 2007 – Feb 2010, Vietnam, Thailand, Singapore, Indonesia
- N = 326 ; 313 evaluable data at day 5 of Rx (viral shedding)
- 246 (75.5%) children, 80 adults
- Negative PCR at D5 :-

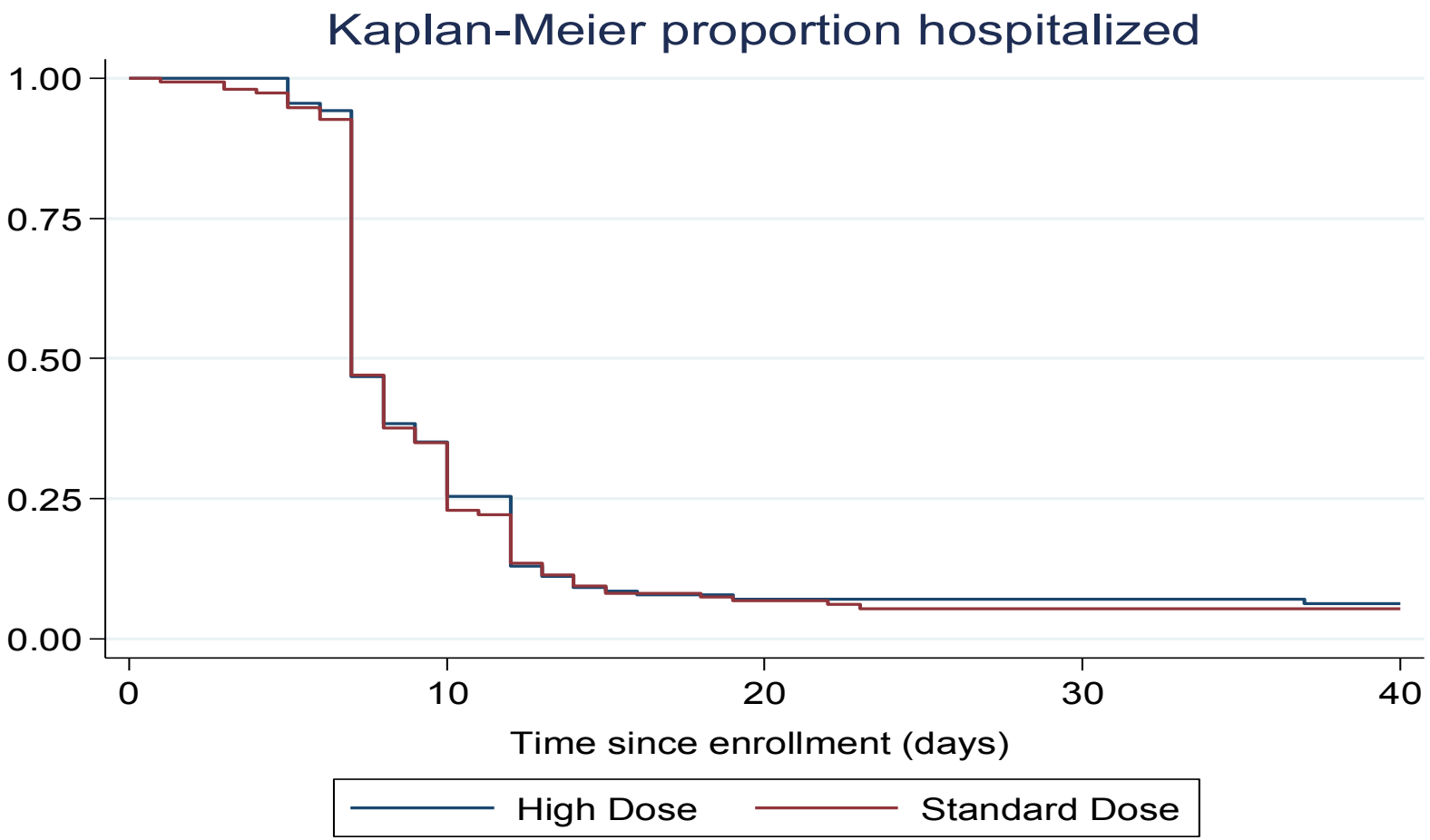
  : 115/159 (72.3%;95%CI 64.9-78.7%) in Double Dose group

  : 105/154 (68.2%;95%CI 60.5-70.0%) in Standard Dose group

" There were NO virologic or clinical advantages with double-dose oseltamivir compared with standard dose in patients with severe influenza admitted to hospital. "

(SEAICRN. BMJ2013;346:f3039 doi:10.1136/bmj.f3039.)

Duration of Hospitalization



(SEAICRN. BMJ2013;346:f3039 doi:10.1136/bmj.f3039.)

Summary :- Antiviral for Influenza in Children

1. Children are the source and reservoir of influenza virus
2. Burden of morbidity and mortality usually underrecognised
3. Disease attack and hospitalization are highest in age < 5 yr.
4. Highly vulnerable to serious influenza-associated complications especially pneumonia in young children
5. Antiviral treatment has been demonstrated to be cost effective in influenza illness
6. Antiviral therapy usually safe and well tolerated in children with low side effect

Thank you.