

Influenza Antivirals: Efficacy and Logistical Considerations

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Antiviral Agents for Influenza

Agent	Route	Spectrum	Therapy*	Prophylaxis*
M2 Inhibitors⁺				
Amantadine	Oral	A only	≥ 1 yr	≥ 1 yr
Rimantadine	Oral	A only	≥ 13 yr	≥ 1 yr
Neuraminidase inhibitors				
Zanamivir	Inhaled	A and B	≥ 7 yr	≥ 5 yr
Oseltamivir	Oral	A and B	≥ 1 yr	≥ 1 yr

⁺Currently not recommended for use due to high frequency of resistance in H3N2 infections

*Current FDA-approved age range

Antivirals in Pandemic Influenza: *Introduction*

- **Most of the treatment and prophylaxis data are derived from studies in seasonal influenza.**
 - **Limited data from sporadic H5N1 infections and use of M2 inhibitors in pandemic-like event (1968, 1977)**
- **Use of pediatric experience as surrogate for expected effects in pandemic disease.**
 - **More prolonged and higher level viral replication**
- **Focus on use of NAIs for prophylaxis and treatment in outpatient adults and children**

M2 Inhibitor Prophylaxis During Pandemic Influenza

Protective efficacy

Pandemic	Influenza A illness	Seroconversion
1968 H3N2	59-100%	28-52%
1977 H1N1	31-71%	19-39%

Hayden. J Infect Dis 176:S56, 1997

Chemoprophylaxis of Epidemic Influenza

Efficacy (vs placebo or no drug)

Strategy

M2I

ZNV

OSEL

Seasonal (4-6 weeks)

Non-immunized adults

85-91%

67-84%

76-84%

Immunized at-risk/elderly

58-75%

83%

92%

Post-contact/post-exposure

Households

3-100%

82%

67-89%

Nursing homes

Variable

Yes*

Yes

? = No controlled study or not reported

*Efficacy 61% better than rimantadine in comparative study

Influenza Prevention In Household Contacts

Antiviral (Study)	Days of dosing	Total no. contacts (age)	Reduction in 2° influenza illness (95% CI) ⁺	Reduction in influenza infection ⁺
Oseltamivir (Welliver et al, 2000)	7	955 (13+ yr)	89% (67-97%)	63% (40-80%)
Oseltamivir* (Hayden et al, 2004)	10	792 (1+ yr)	68% (35-84%)	35% (9-54%)
Zanamivir* (Hayden et al, 2000)	10	837 (5+ yr)	80%	57%
Zanamivir (Monto et al, 2002)	10	1,291 (5+ yr)	79% (57-89%)	55% (37-68%)

*Index case given treatment

⁺Index influenza +

Tolerability of NA Prophylaxis In Households

Antiviral (Study)	Days of dosing	No. exposed (age)	Comment
Oseltamivir (Welliver et al, 2000)	7	493 (13+ yr)	AE withdrawal 1%; nausea 5.5%
Oseltamivir (Hayden et al, 2004)	10	410 (1+ yr)	Nausea 8%; emesis 4.5%
Zanamivir (Hayden et al, 2000)	10	568* (5+ yr)	Early cessation 1%; 1 pneumonia in index (day 4)
Zanamivir (Monto et al, 2002)	10	661 (5+ yr)	Early withdrawal 1%

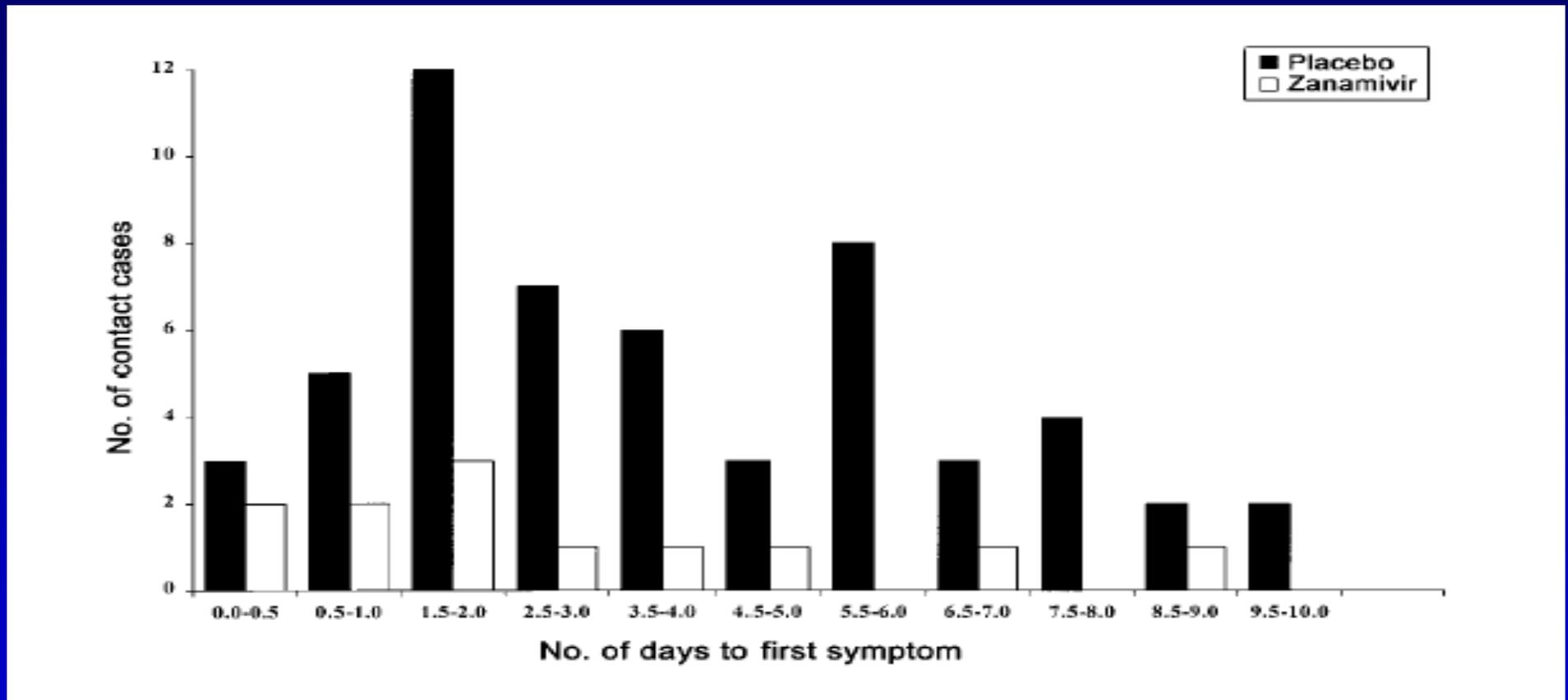
*Number includes index cases

Influenza in Index Cases In Households

Antiviral (Study)	Primary recruitment strategy	No. (%) influenza + index cases	No. (%) influenza + contacts*
Osetamivir (Welliver et al, 2000)	Clinic-based	163 (43%)	12 (1.3%)
Osetamivir (Hayden et al, 2004)	Clinic-based + prospective	184 (62%)	26 (3.2%)
Zanamivir (Hayden et al, 2000)	Prospective	157 (49%)	Not tested
Zanamivir (Monto et al, 2002)	Clinic-based + prospective	282 (58%)	Not tested

*Before initiation of prophylaxis

Interval from PEP Initiation to Illness Onset in Household Contacts (N = 1,291)



Note: zanamivir PEP started \leq 36 hr of index illness onset

Monto et al. JID 186:1582, 2002

Oseltamivir PEP In Households: *Reductions in Influenza Illness, 2000-01*

Contact age (yr)	No.	Observation	Osel PEP	Efficacy (95% CI)
13+	373	8%	2%	74%
1-12	129	24%	11%	55% (-13%, 82%)
1-5	20	36%	22%	39% (-211%, 88%)

Note: All index cases influenza-positive and treated with oseltamivir (ITTI)

Hayden et al. JID 189:440, 2004

Influenza Post-exposure Prophylaxis (PEP) with Neuraminidase Inhibitors: *Comments*

- **Socially targeted PEP with NAIs is effective and generally well-tolerated in protecting household contacts during seasonal influenza.**
 - **Secondary cases occur early, often in first few days after index case recognition.**
- **Use in young children warrants further study.**
 - **Oseltamivir efficacy may be lower than in adolescents.**
 - **Inhaled zanamivir with current device is not applicable in young children.**

Treatment of Acute Influenza

Outcome	M2I	ZNV	OSEL
Symptom relief	Yes	Yes	Yes
Complications reduction	?	Yes	Yes
Decrease antibiotic use	?	20-28%	24-40%
Decrease hospitalization	?	?	~50%
Treatment of viral complications	?	?	Yes
Reduction in transmission	~30%	?	?Yes

Kaiser et al. Arch Intern Med 160:3234, 2000 and 163:1667, 2003; Whitley et al. Ped IDJ 20:127, 2001; Hedrick et al. Ped IDJ 19-410, 2000

Zanamivir in Adults: *Effect of Time to Treatment*

VARIABLE	PLACEBO			INHALED ZANAMIVIR			COMPARISON OF INHALED ZANAMIVIR AND PLACEBO†	
	MEAN	NO. OF	SUBJECTS	MEAN	NO. OF	SUBJECTS	DIFFERENCE (95% CI)	P VALUE
	±SD	MEDIAN		±SD	MEDIAN			
	day			day				
All subjects (intention-to-treat analysis)	5	6.0±2.9	144	5	5.3±2.6	132	-0.7 (-1.4 to 0)	0.04
Confirmed influenza infection	5	6.3±2.9	89	4	5.4±2.7	85	-0.8 (-1.7 to 0)	0.05
Fever at enrollment (temperature, ≥37.8°C)	7	6.8±2.8	54	4	5.3±2.6	46	-1.4 (-2.5 to -0.4)	0.01
No fever at enrollment	4	5.5±3.0	35	4	5.5±2.9	39	0.1 (-1.3 to 1.4)	0.93
Initiation of treatment								
≤30 hr after onset of symptoms	7	7.0±2.7	45	4	5.1±2.2	43	-1.9 (-2.9 to -0.8)	0.001
>30 hr after onset of symptoms	4	5.5±3.0	44	5	5.8±3.1	42	0.3 (-1.0 to 1.5)	0.68

Hayden et al. N Engl J Med 337:874, 1997

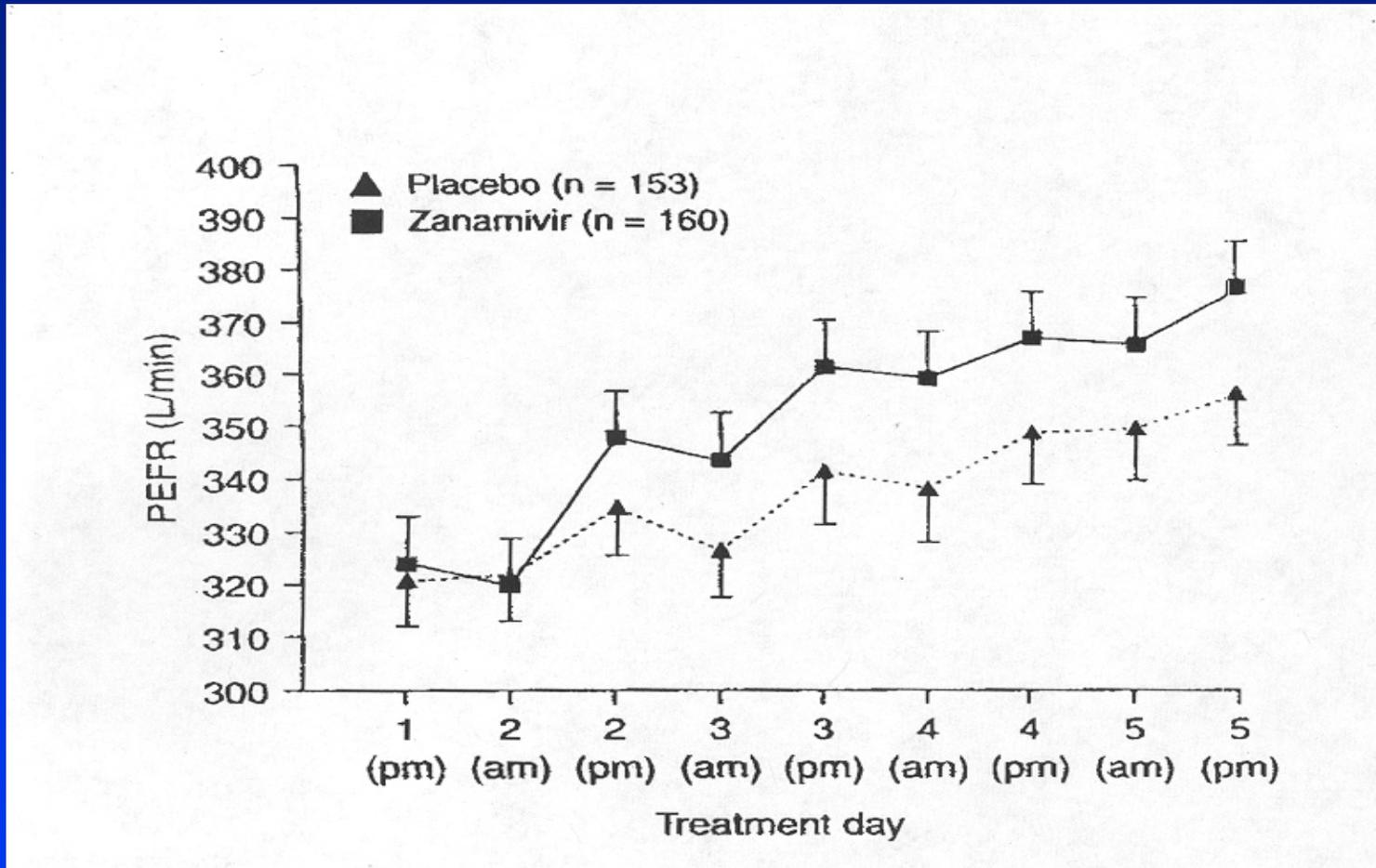
Inhaled Zanamivir Treatment: *Complications and Antibiotic Use*

Respiratory events leading to antibiotics	Placebo (n=765)	Zanamivir (n=807)	Risk Reduction
Any event	18%	13%	28%*
Upper respiratory	8%	7%	10%
Lower respiratory	9%	5%	40%*
Acute bronchitis	7%	5%	
Pneumonia	2%	1%	

Zanamivir Treatment in Asthma/COPD Patients

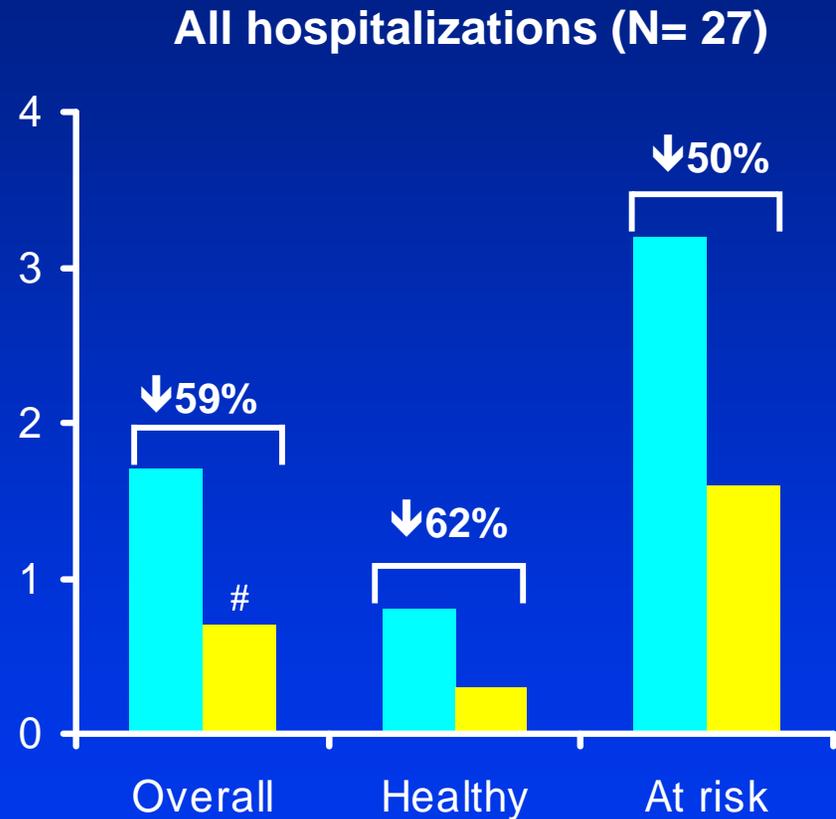
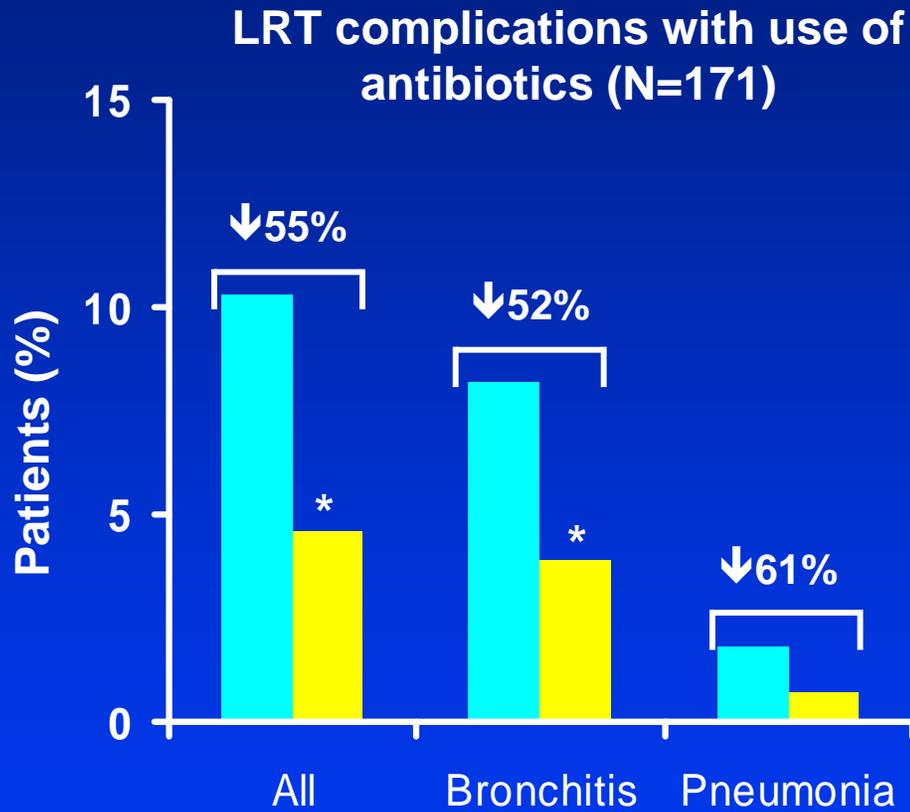
- **525 ambulatory patients \geq 12 yr (82% asthma)**
 - 60% influenza-infected, 23% immunized
- **Time to alleviation + no relief medications: 7.5 vs 10 days (p = 0.024)**
- **Good overall tolerance (ZNV vs placebo):**
 - Fewer lower respiratory AEs (14% vs 20%)
 - Low discontinuation rate (<1% vs 2%)
 - Hospitalizations (1% vs 2%)
 - No differences in spirometry (FEV₁) on days 6, 28

Zanamivir Treatment in Asthma/COPD Patients: *Effect on PEFRs*



Murphy et al. Clin Drug Invest 20: 337, 2000

Oral Oseltamivir for Influenza (N=2,413): Effect on Antibiotic Use and Hospitalizations



* $P < .001$ vs placebo

■ Placebo

■ Oseltamivir

$P = .02$ vs placebo

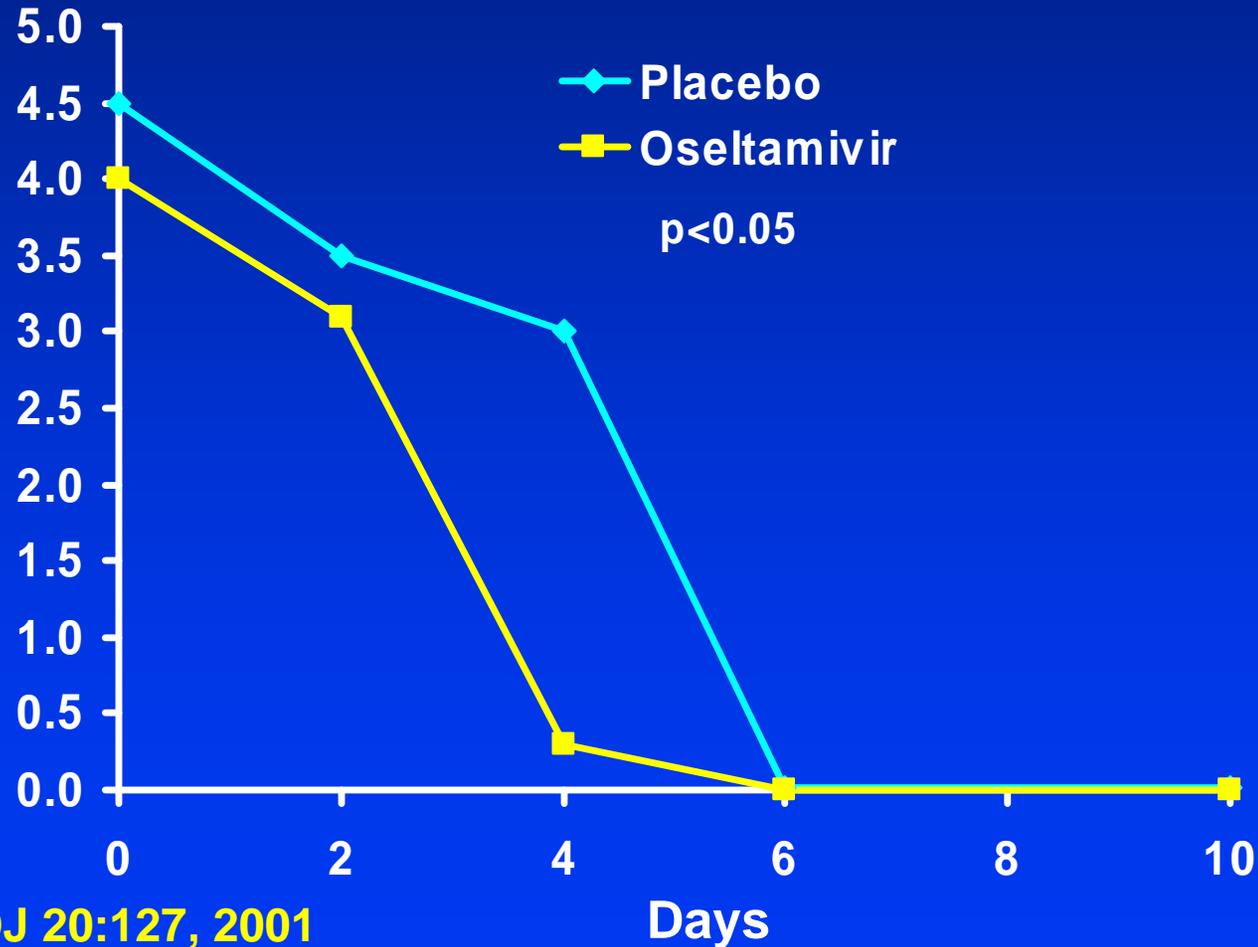
Oseltamivir Treatment in Children

- 698 children 1-12 years with ILI \leq 48 hrs
 - 65% influenza positive
 - Oseltamivir 2 mg/kg bid or placebo for 5 days
- 1.5 days \downarrow duration of illness by (\downarrow 26%)
- Fewer complications (placebo vs oseltamivir):
 - Less antibiotic use (41% vs 31%, \downarrow 24%)
 - Fewer new AOM diagnoses (21% vs 12%, \downarrow 44%)
- Excess emesis with oseltamivir (8.5% vs 14.3%)
- Few withdrawals due to AEs (1.1% vs 1.8%)

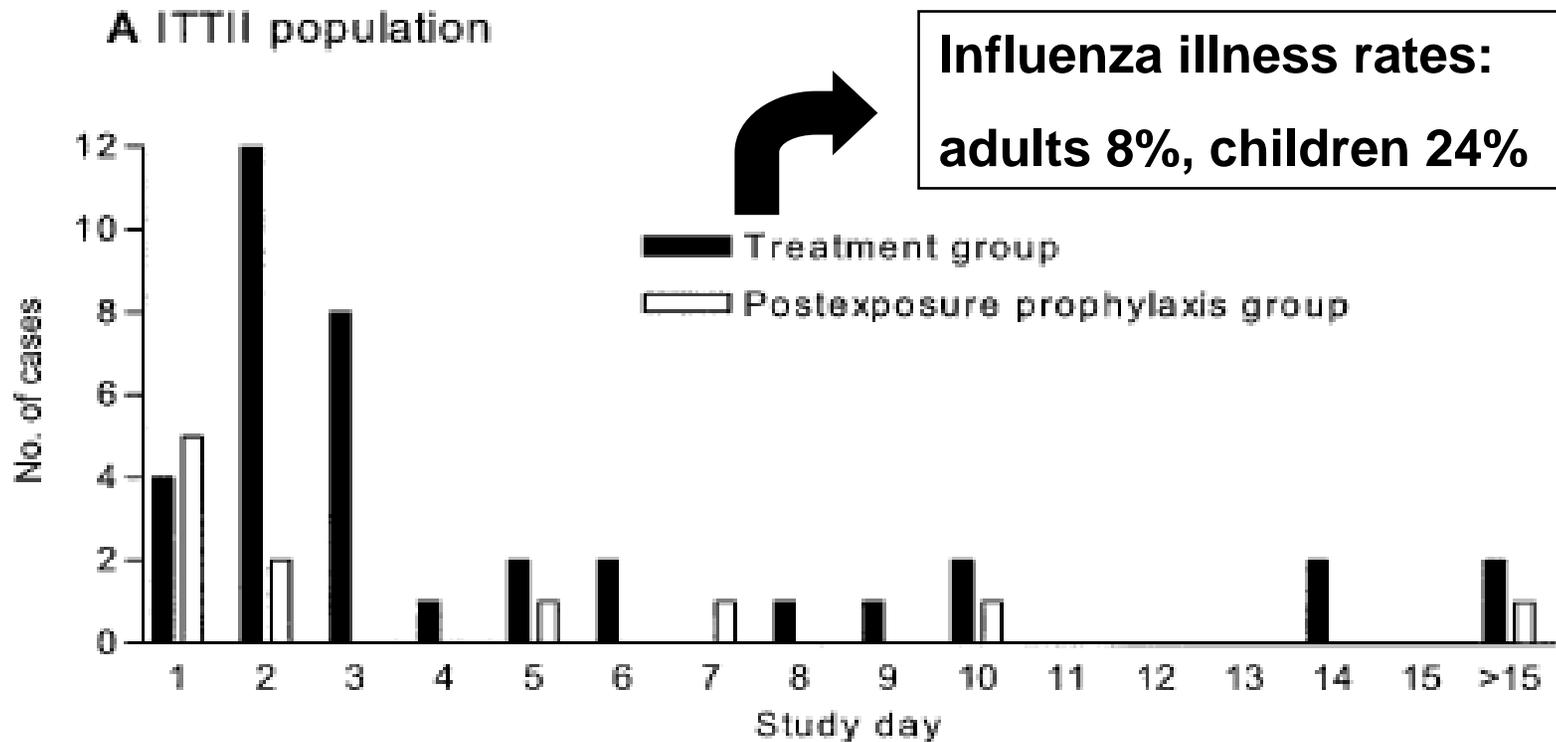
Whitley et al. *Pediatr Infect Dis J* 20:127, 2001

Oseltamivir Treatment In Children: *Antiviral Effect (Nose and Throat Swabs)*

Viral titer \log_{10} TCID₅₀/mL



Intervals from Influenza-Positive Index Case to Secondary Illnesses in Households (N = 502)



Note: oseltamivir PEP or observation ≤ 2 days after index onset; all index cases ≥ 1 year treated with oseltamivir (Hayden et al. JID 189:440, 2004)

Oseltamivir Observational Studies: *Major Outcomes*

- **Reductions in complications/hospitalizations /mortality in treated nursing home residents (Bowles et al. J Am Geriatr Soc. 2002;50:608-616)**
- **Lower mortality in leukemia or HSCT patients (Chemaly et al. CID 2007; 44:964–7; Nichols et al. CID 2004; 39:1300–6)**
- **26% (95% CI, 10%, 39%) reduction in hospitalization in outpatients \geq 1 yr old with ILI treated with oseltamivir (Nordstrom et al. Curr Med Res Opin. 2005;21:761-768)**

Oseltamivir Observational Studies: *Major Outcomes*

- 52% (95% CI, 28%, 67%) reduction in pneumonia in children 1-12 yrs with clinical influenza Dx treated ≤ 1 day (Barr et al. *Curr Med Res Opin* 23:523, 2007)
- 22% (95% CI, 9%, 33%) fewer all-cause hospitalizations ≤ 14 days in previously healthy ≥ 13 yrs with clinical influenza Dx treated ≤ 1 day (Blumentals and Schulman. *Curr Med Res Opin* 23:2961, 2007)
- 30% (95% CI, 6%, 48%) fewer all-cause hospitalizations ≤ 14 days in diabetics ≥ 18 yrs with clinical influenza Dx treated ≤ 1 day (Orzeck et al. *Clinical Therapeutics* 29:2246, 2007)

Hospitalized Adults: *Toronto Invasive Bacterial Diseases Network 1*

- **Prospective cohort study of 327 adults hospitalized with community-acquired influenza in Ontario, 2004-2006**
 - **Laboratory-based surveillance; non-randomized**
 - **103 (32%) treated with oseltamivir**
 - **88% rapid antigen positive**
 - **Time to treatment > 48 hr in 71%, > 72 hr in 49%**
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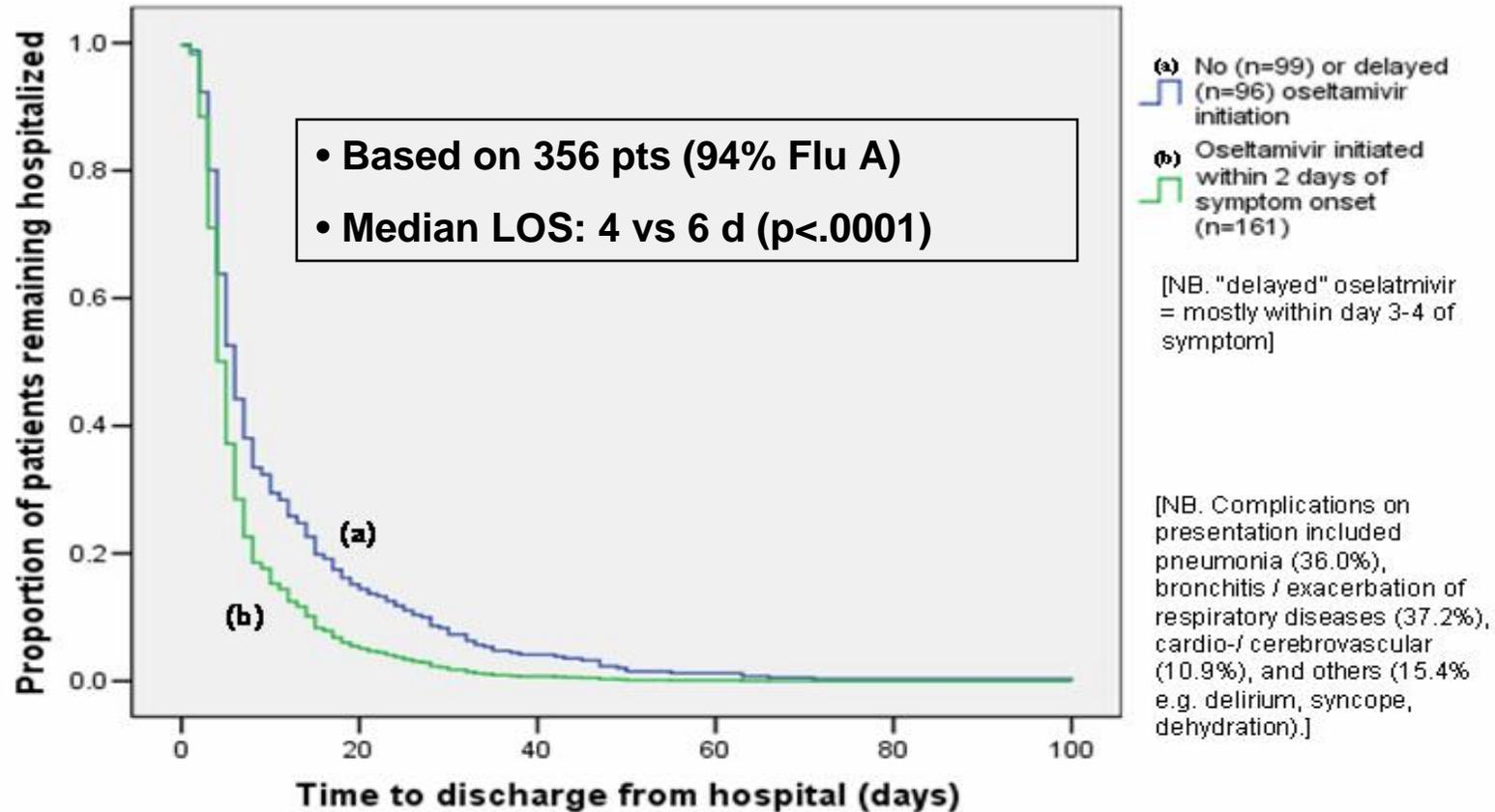
Table 4. Multivariable analysis of the impact of antiviral therapy on mortality associated with laboratory-confirmed influenza requiring hospitalization, Toronto Invasive Bacterial Diseases Network surveillance, 2005–2006.

Variable	OR (95% CI)	P
Oseltamivir therapy	0.21 (0.06–0.80)	.02
Intensive care unit admission	10.5 (3.9–27)	<.001
Charlson comorbidity score (per point)	1.3 (1.0–1.6)	.03
Time from onset of symptoms to emergency department presentation (per 24-h period)	0.51 (0.31–0.87)	.01

NOTE. ORs <1 indicate that the variable is associated with reduced mortality. Variables that were considered in multivariable analysis are listed in the final paragraph of Methods.

- **15-day mortality 3.9% (oseltamivir) vs 10.0% (no Rx)**
- **Even delayed antiviral therapy in hospitalized adults appears to be beneficial.**

Figure 1. Kaplan-Meier curve showing the effect of early oseltamivir treatment on time to discharge from hospital

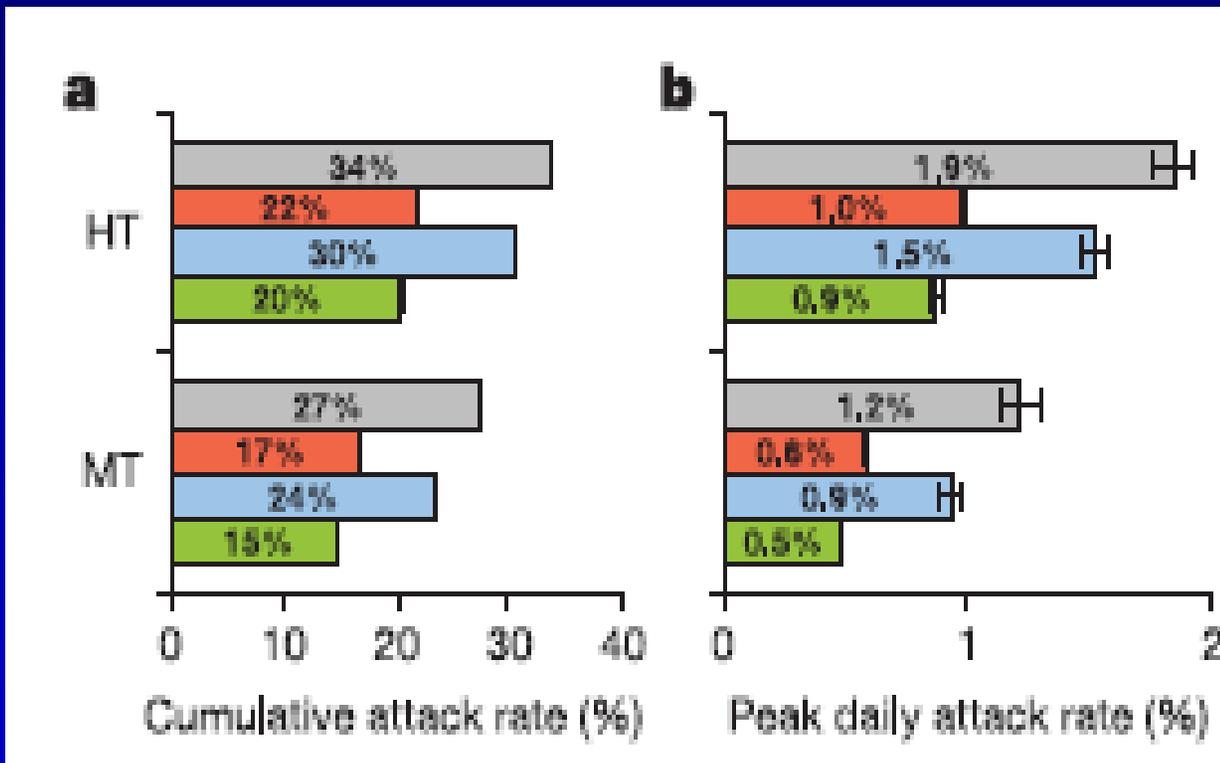


Oseltamivir Treatment Effects in A(H5N1) Infection

Virus	Survivors/ Treated (%)	Survivors/ Untreated (%)	P-value
Presumed clade 1	45/82 (55%)	6/26 (23%)	0.006
Presumed clade 2	43/106 (41%)	1/30 (3%)	< 0.001
Total	88/188 (47%)	7/56 (12%)	< 0.001

Adapted from Writing Committee of Second WHO Consultation on Human H5 Infections. N Engl J Med 358: 261, 2008

Antiviral Prophylaxis and Household Quarantine during Pandemic Influenza

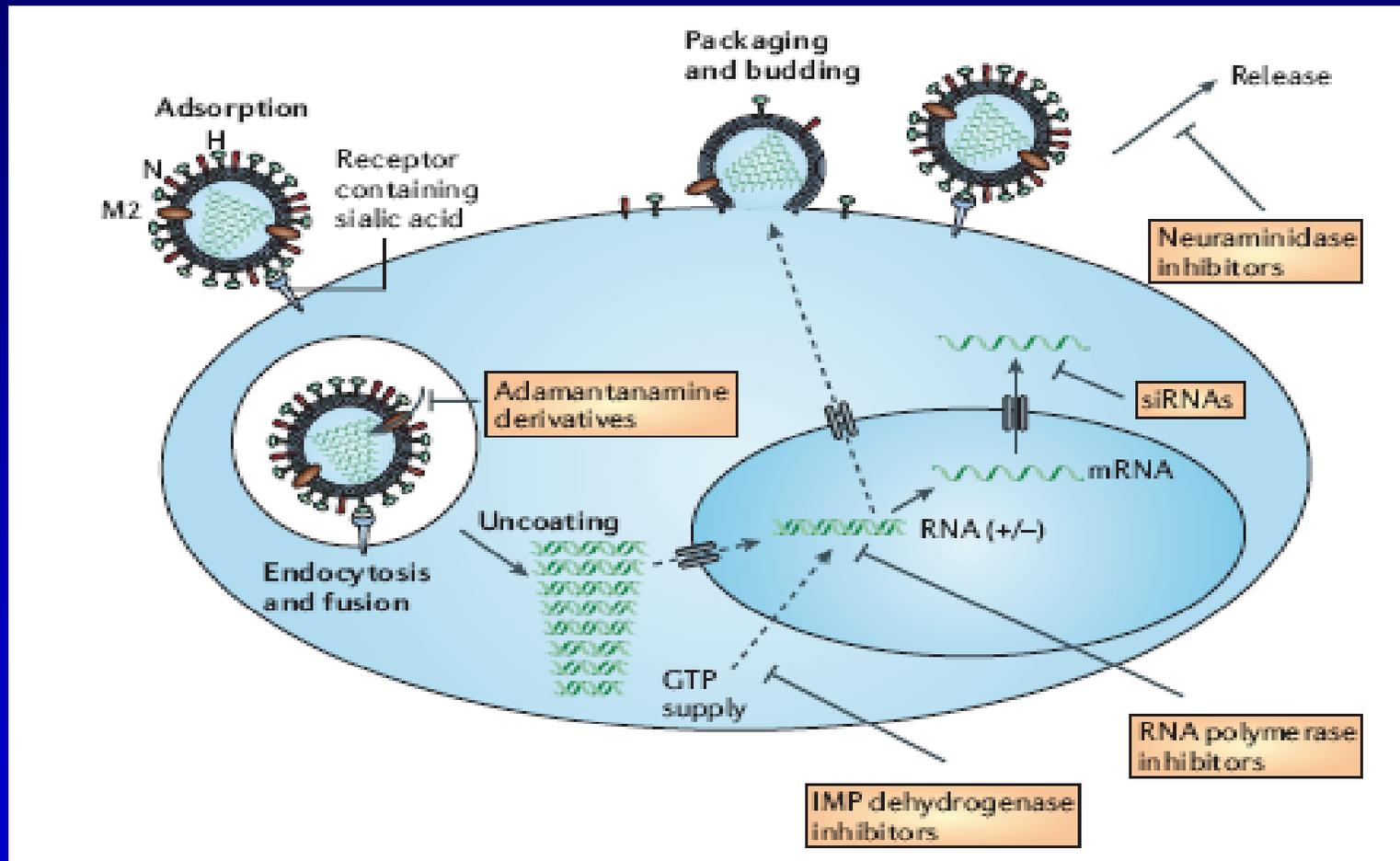


- Grey = no intervention
- Red = treatment of 90% \leq 1d + 90% PEP
- Blue = voluntary quarantine x 14d
- Green = combination

Influenza NAI Treatment: *Comments*

- **Early NAI treatment reduces illness duration and LRT complications in seasonal influenza.**
 - **Oseltamivir treatment appears to reduce all-cause hospitalizations and perhaps severity in hospitalized.**
- **Oseltamivir appears to benefit some H5N1 patients.**
 - **Time to treatment and resistance emergence are important variables.**
 - **Inhaled zanamivir is unstudied to date.**
- **Modeling studies predict substantial reductions in pandemic influenza impact if high levels of household-based treatment and PEP.**

Influenza Virus Replication and Sites for Antiviral Inhibition



Investigational Anti-Influenza Agents in Clinical Development

Agent	Target	Sponsor	Route	Development phase
Zanamivir	NA	GSK	IV	Phase 1, 2a
Peramivir	NA	Biocryst	IV, IM	Phase 2
CS8958	NA	Sankyo, Biota	Topical	Phase 2 →3
T-705	Polymerase	Toyama	Oral	Phase 2
DAS181	HA receptor	Nexbio	Topical	Phase 1
Poly-ICLC	IFN induction	NIH/Oncovir	Topical	Phase 1

BACK-UP SLIDES

Oseltamivir and the Risk for Abnormal Behavior in Children Aged < 18 Years

- Study by Japan Ministry of Health, Labour and Welfare found no increased risk for abnormal behavior in children with influenza aged < 18 years during 2006-2007 season
 - 12% event rate among 7487 children who took oseltamivir
 - 13% event rate among 2228 children who did not take oseltamivir

Matsuyama, K., Bloomberg News, 14 July 2008

Abnormal Behaviours during Influenza, Japan, 2006-7

Age (yr)	Oseltamivir treatment	Total no.	No. (%) abnormal behaviour	P-value
< 18	Yes	7,181	700 (9.7%)	<0.0001
	No	2,477	546 (22.0%)	
10-17	Yes	2,256	132 (5.9%)	<0.0001
	No	984	106 (10.8%)	

- Working Group for Clinical Evaluation of Oseltamivir Phosphate
- Serious abnormal behaviour in 0.3% of oseltamivir recipients vs 0.8% of non-recipients

Pharma Japan vol. 2073, p 17-18, 14 January 2008

INFLUENZA TREATMENT IN NURSING HOME ELDERLY, *Ontario, 1999 - 2000*

Outcome	Percent of patients			
	No therapy (N = 23)	Amantadine + (N = 19)	Oseltamivir ⁺ (N = 50)	Oseltamivir late (N = 23)
Antibiotics	65	37	20	70
Complication	48	16	6	35
Hospitalization	22	11	0	17
Death	22	11	2	4

⁺Treatment \leq 2 days after Sx onset

Bowles et al. *J Amer Geriatric Society* 50:608-616, 2002

Neuraminidase Inhibitor Treatment: *Effects on Transmission*

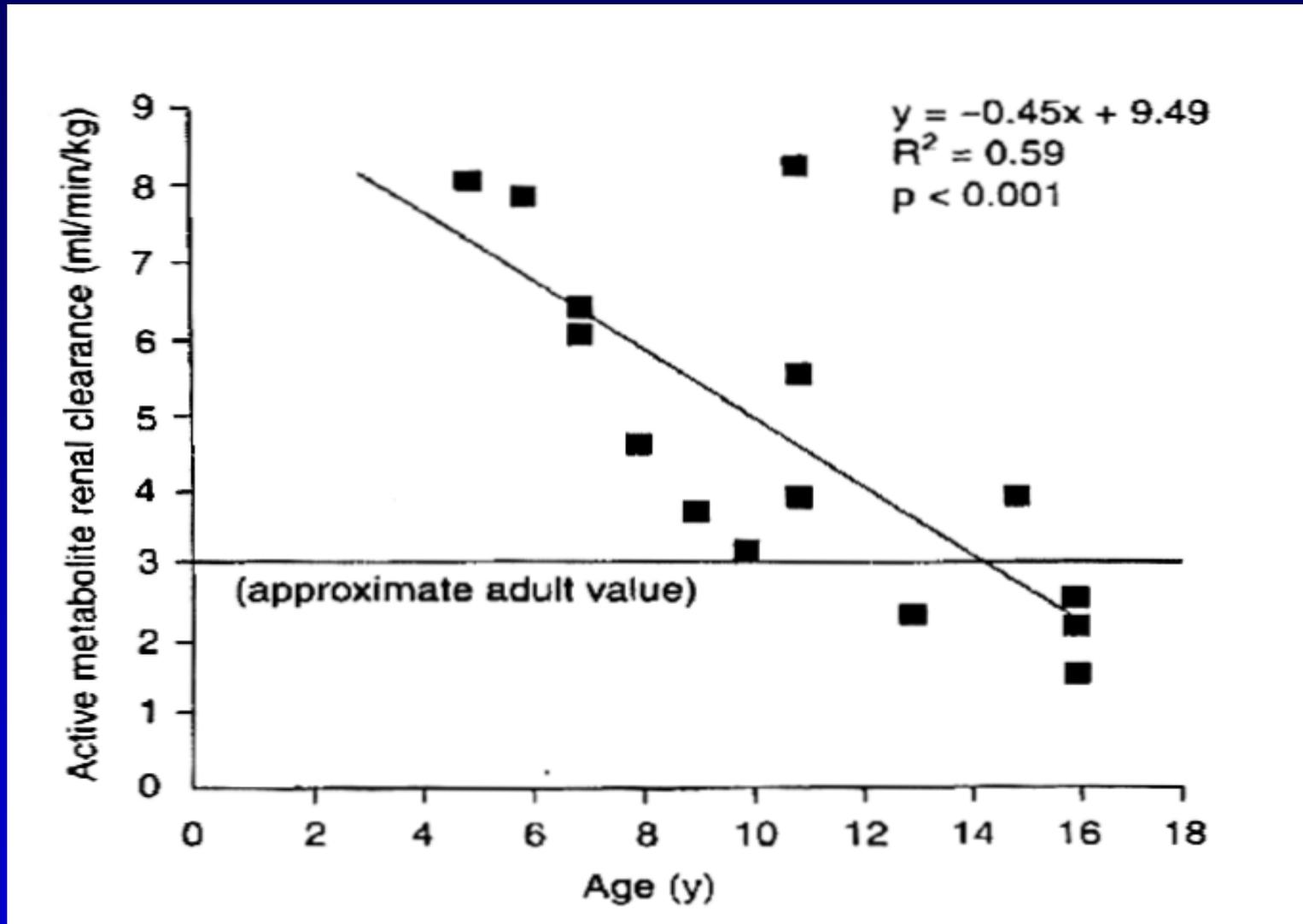
- 4 randomized, household-based studies of PEP
 - 2 zanamivir, 2 oseltamivir
 - 2 with and 2 without index case treatment
- Estimated effectiveness of treatment on reducing infectiousness of index case:
 - Endpoint = 2^o illness in contacts on days 1-7
 - 2% (95% CI, -141%, 60%) for zanamivir
 - 81% (95% CI, 45%, 93%) for oseltamivir
 - Endpoint = 2^o infection in contacts on days 1-7
 - 16% (-62%, 57%) for zanamivir
 - 16% (95% CI, -33%, 46%) for oseltamivir

Oseltamivir Is Adequately Absorbed Following Nasogastric Administration to Adult Patients with Severe H5N1 Influenza

Walter R. J. Taylor^{1,2*}, Bui Nghia Thinh³, Giang Thuc Anh³, Peter Horby^{1,2}, Heiman Wertheim^{1,2}, Niklas Lindegardh^{2,4}, Menno D. de Jong^{2,5}, Kasia Stepniewska^{2,4}, Tran Thuy Hanh³, Nguyen Duc Hien⁶, Ngo Minh Bien³, Ngo Quy Chau³, Annette Fox^{1,2}, Nghiem My Ngoc⁵, Martin Crusat⁵, Jeremy J. Farrar^{2,5}, Nicholas J. White^{2,4}, Nguyen Hong Ha⁶, Trinh Thi Lien⁶, Nguyen Vu Trung⁶, Nicholas Day^{2,4}, Nguyen Gia Binh³

- **Nasogastrically administered oseltamivir 150 mg bid in 3 ventilated pts (2 H5N1, 1 H3N2)**
 - Two sampled on CVVH (45 ml/kg/h); 1 pregnant
- **Steady-state trough OC concentrations (376, 575 and 2730 ng/ml) were higher than previously reported in healthy subjects (~300 ng/ml)**

Oseltamivir Exposure in Children (2 mg/kg)



Treatment of Influenza in Immunocompromised

Population (Study)	Drug	No. episodes	Outcomes
BMT, leukemia (Englund, 1998)	M2 inhibitor	15	Resistant virus in 33% Influenza deaths in 2 (13%)
HSCT, leukemia (LaRosa, 2001)	M2 inhibitor	55 (total)	Progression to pneumonia in 35% vs 76% without Rx (P <0.01)
HSCT (Nichols, 2004)	Rimantadine	8	Progression to pneumonia 13% vs 18% without Rx (n=34)
	Oseltamivir	9	No progression to pneumonia
BMT (Machado, 2004)	Oseltamivir	38 (15 A, 23 B)	Progression to pneumonia 5% No mortality Ag positivity \geq 7 days in 8%

Efficiency of Pandemic Antiviral Use

No. persons	Antiviral strategy	Percent on drug	Duration (days)	Total doses needed
1,000	Prophylaxis	100%	56	56,000
1,000	Treatment	35%	5	3,500

16-fold Δ

Oseltamivir: *Effect of Time to Treatment*

