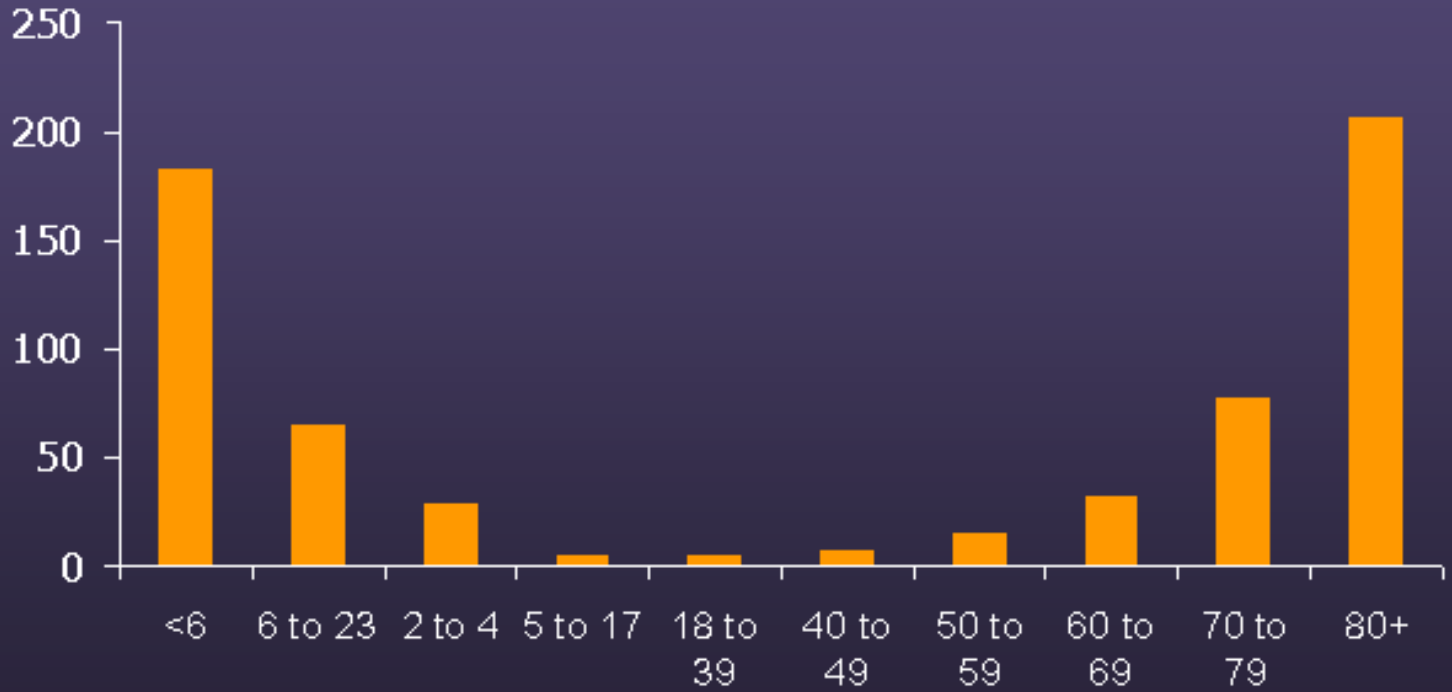


## Possible Roles of Antivirals in Seasonal Flu

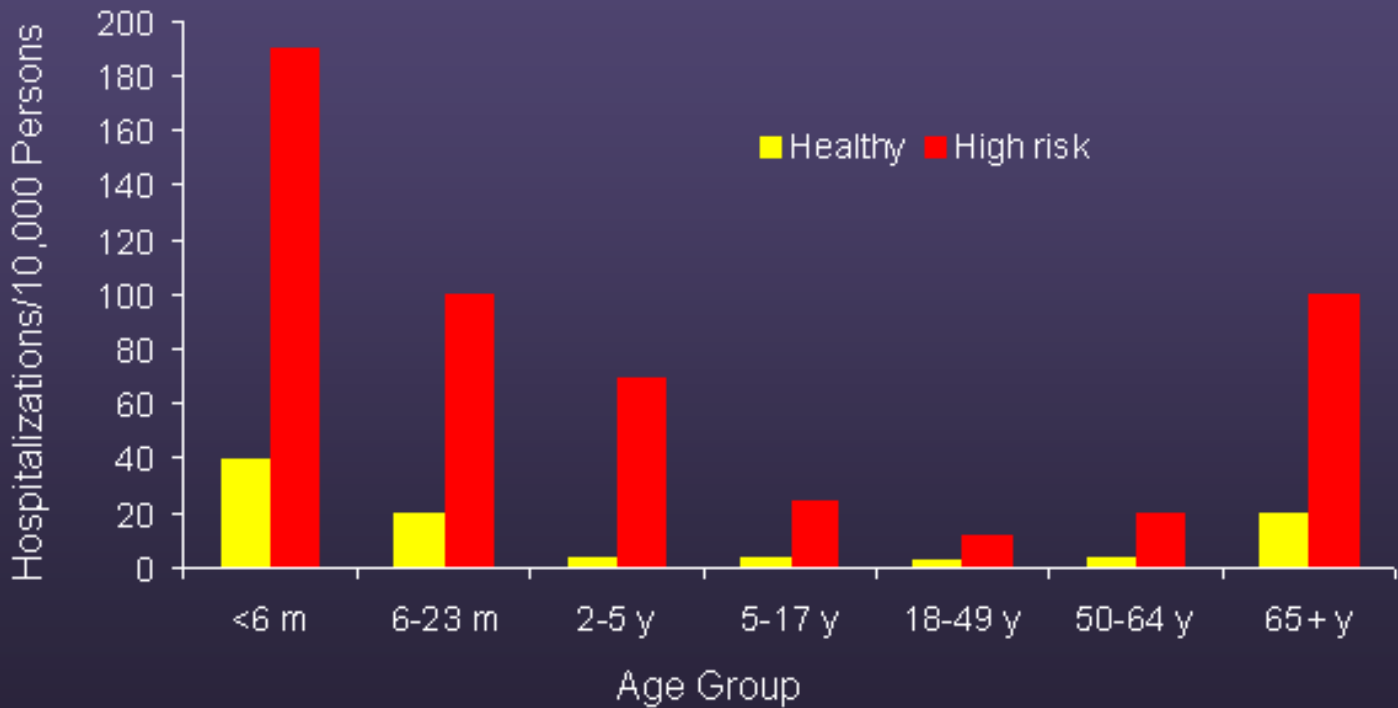
- Postexposure prophylaxis
- Seasonal prophylaxis
- Decrease symptoms
- Decrease transmission
- Decrease disability and time out from work
- Decrease morbidity
- Decrease mortality

## Rate Per 100,000 of Laboratory-Confirmed Influenza-Associated Hospitalizations, Colorado, 2004-2005



CDC *MMWR*. 2005; 54: 535-537.

## Influenza-Associated Hospitalizations per 10,000 Healthy and High-Risk Persons by Age Group



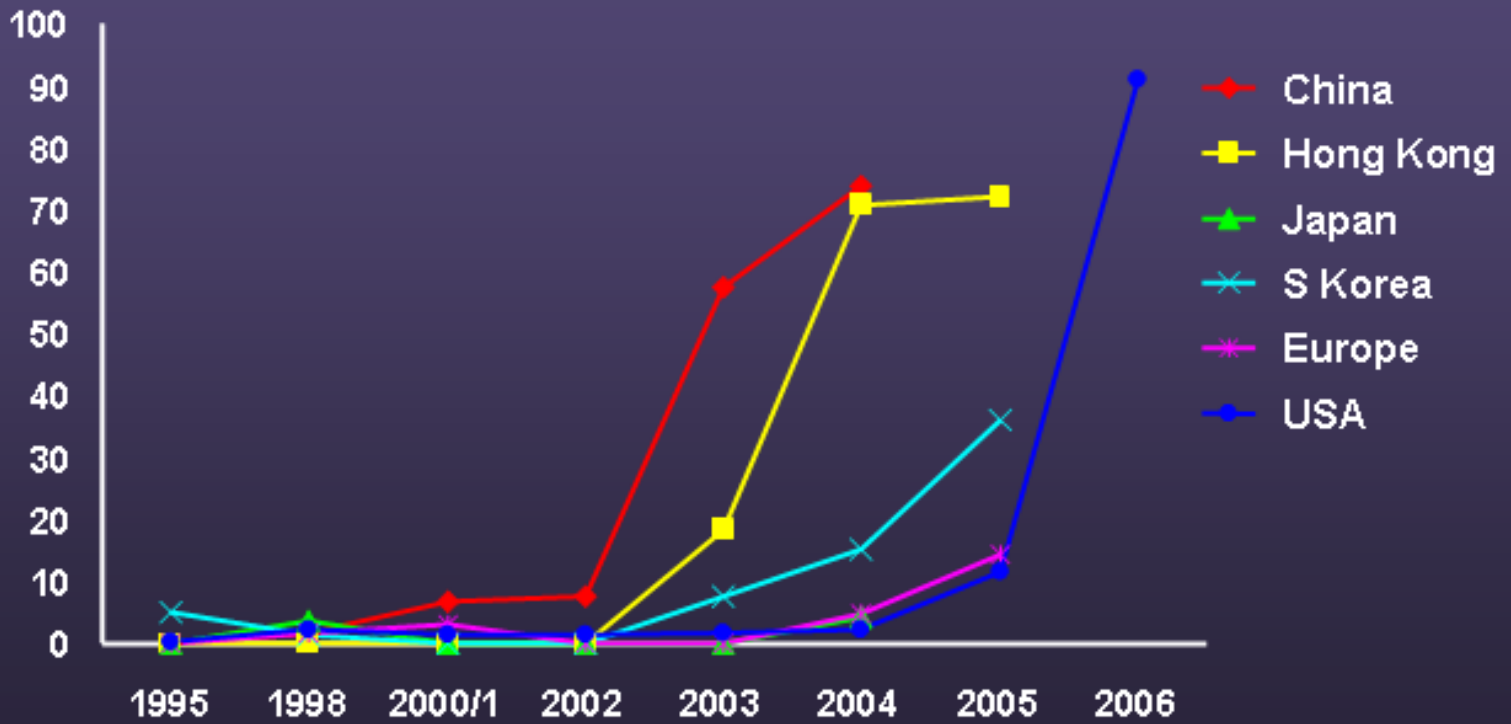
Neuzil K et al. *N Engl J Med.* 2000;342:225-231.

Glezen WP. *Am Rev Respir Dis.* 1987;136:550-555

# Approved Antivirals for Influenza

	Route	Approved Treatment	Approved Prophylaxis
<b>M2 Ion Channel Inhibitors</b>			
Amantadine	PO	≥1 year	>1 year
Rimantadine	PO	>13 years	>1 year
<b>Neuraminidase Inhibitors</b>			
Zanamivir	Inhaled	≥5 years	>7 years
Oseltamivir	PO	≥1 year	>1 year

# Antiviral Resistance to M2 Inhibitors in Community Isolates of A/H3N2 1995-2005



Bright R et al. *Lancet*. 2005;366:1175-1181.  
Bright R et al. *JAMA*. 2006;295:891-894.

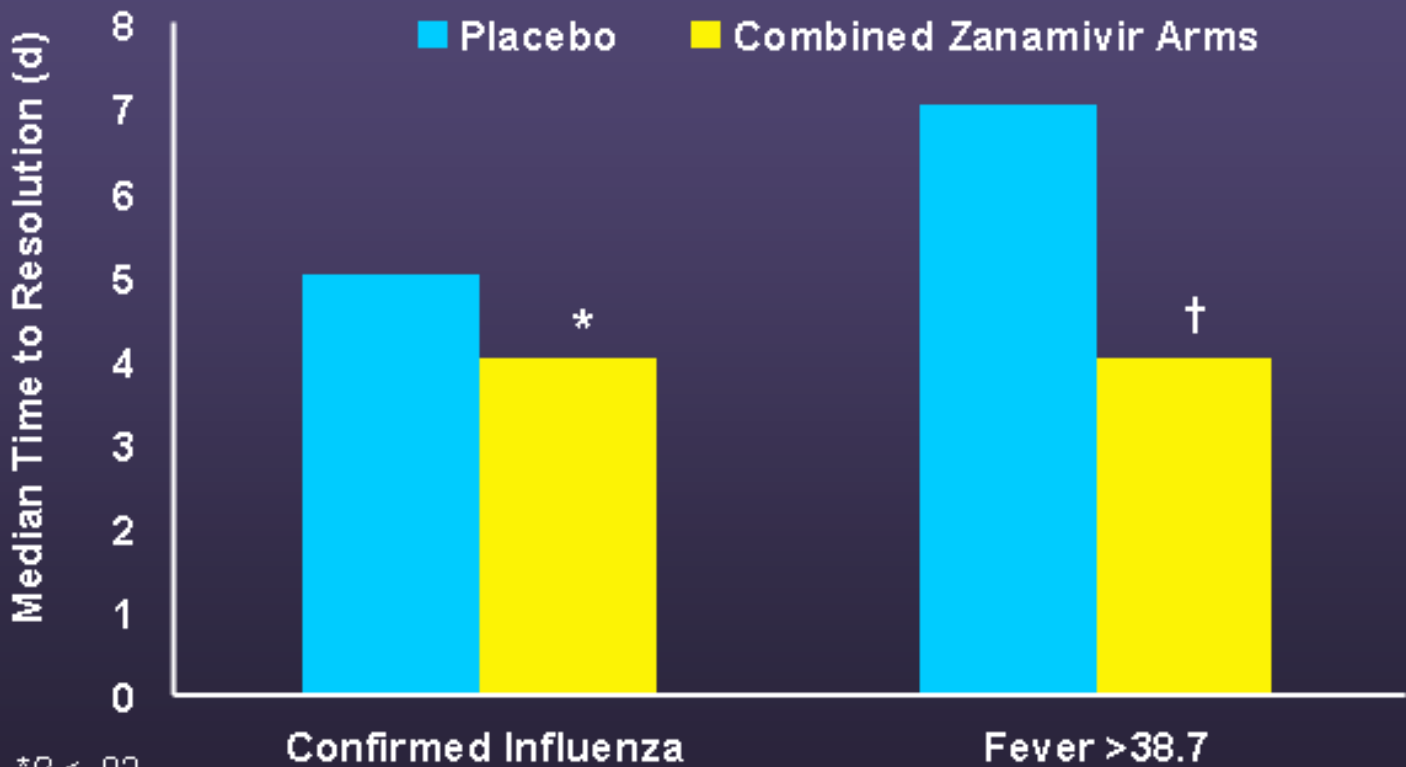
# Antiviral Chemoprophylaxis of Influenza

Strategy	AM/RM	Zanamivir	Oseltamivir
<b>Seasonal</b>			
Nonimmunized adults	85%-91%	84%	84%
Immunized NH elderly	58%-75%	?	92%
<b>Postcontact/Postexposure</b>			
Households	3%-100%	82%	67%-89%
Nursing homes	Variable	71%	Yes

Hayden FG et al. *NEJM*. 1989;321:1696; Monto AS et al. *JAMA*. 1999;282:31; Hayden FG et al. *NEJM*. 1999; 341:1336; Hayden FG et al. *NEJM*. 2000;343:1282; Peters PH Jr et al. *J Am Geriatr Soc*. 2001;404:1025. Welliver R. *JAMA*. 2001;285:748; Hayden FG et al. *J Infect Dis*. 2004;189:440.

# Effects of Zanamivir

## Time to Resolution of All Flu Symptoms



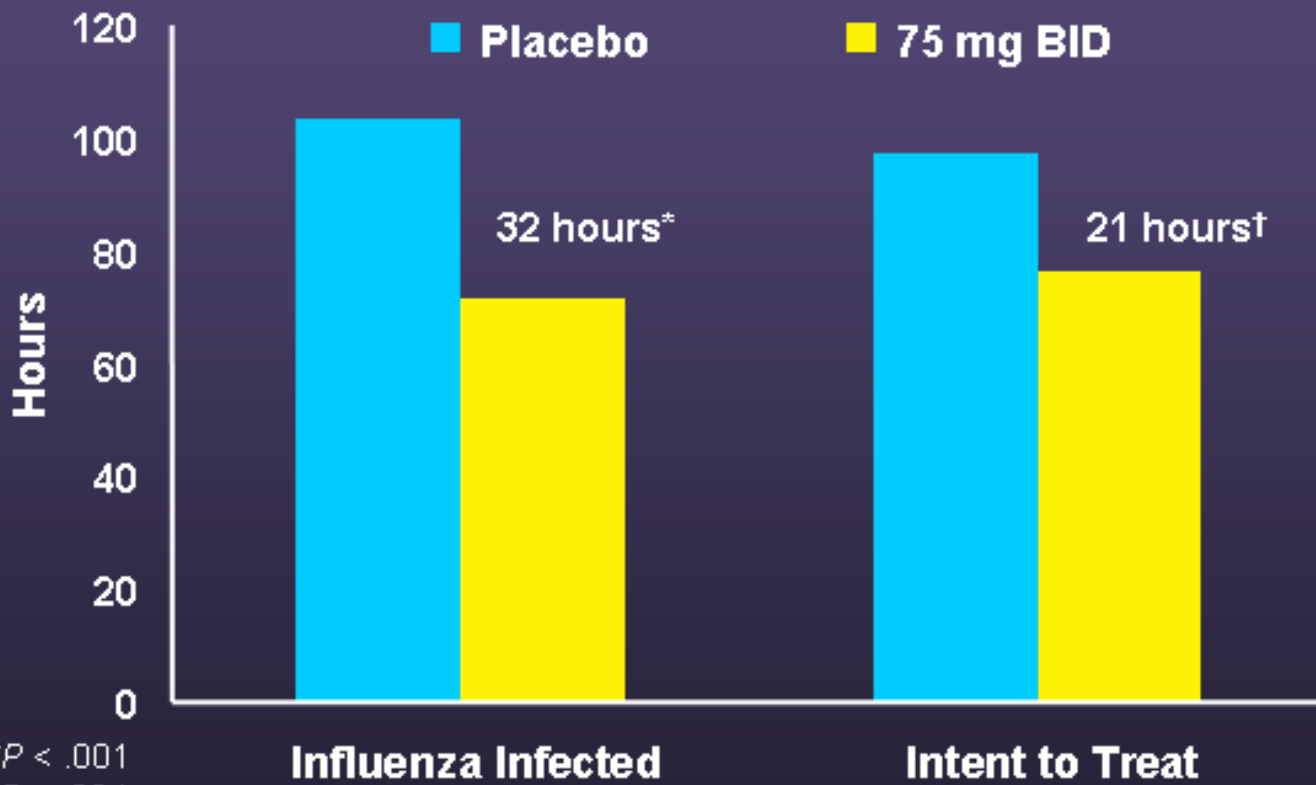
\* $P < .02$

† $P = .001$

Hayden F et al. *N Engl J Med.* 1997;337:874-880.

# Effects of Oseltamivir

## Time to Resolution of All Flu Symptoms



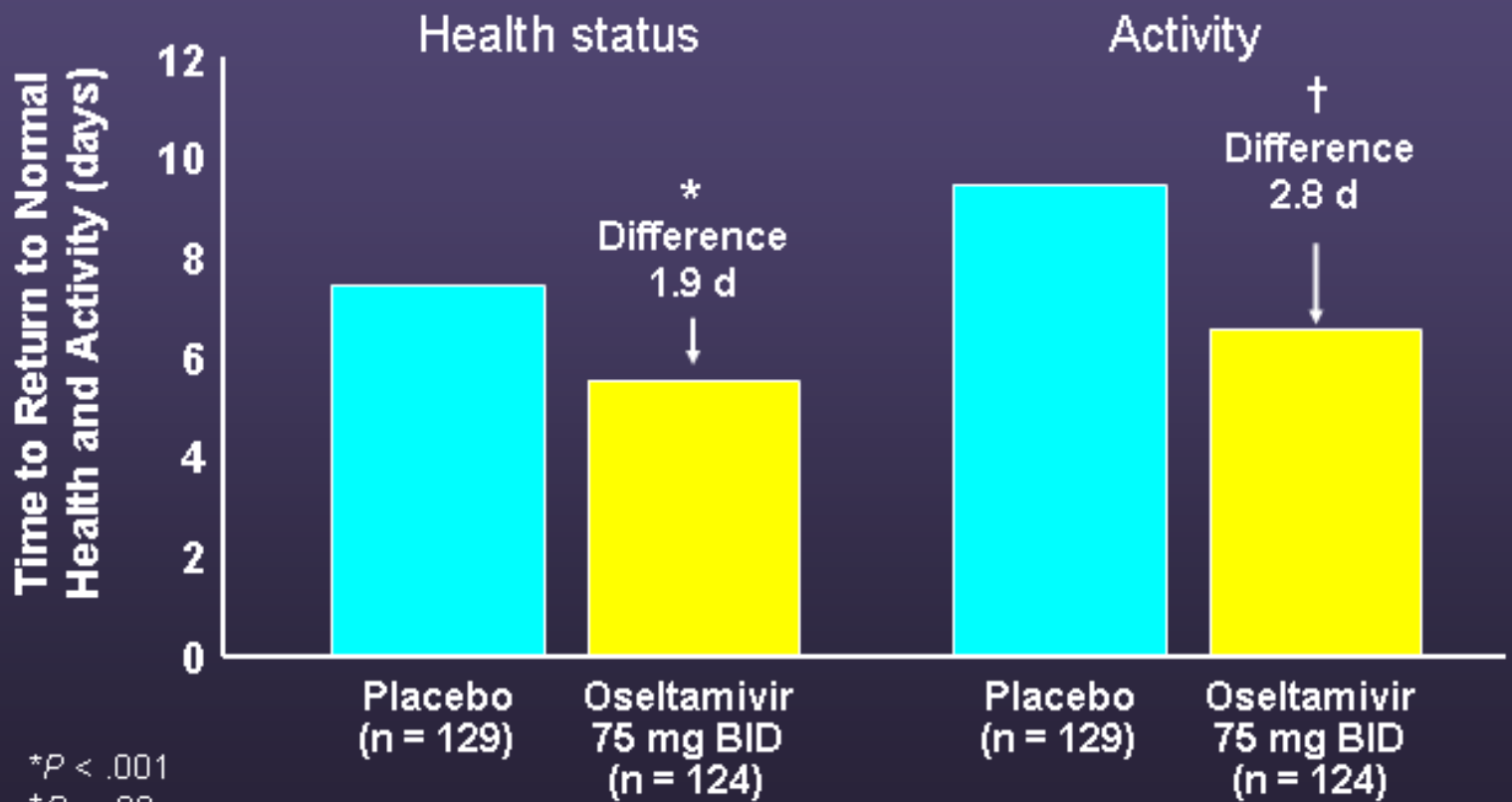
\* $P < .001$

† $P = .004$

Treanor J et al. *JAMA*. 2000;283:1057-1059.

# Effects of Oseltamivir

## Return to Normal Activities



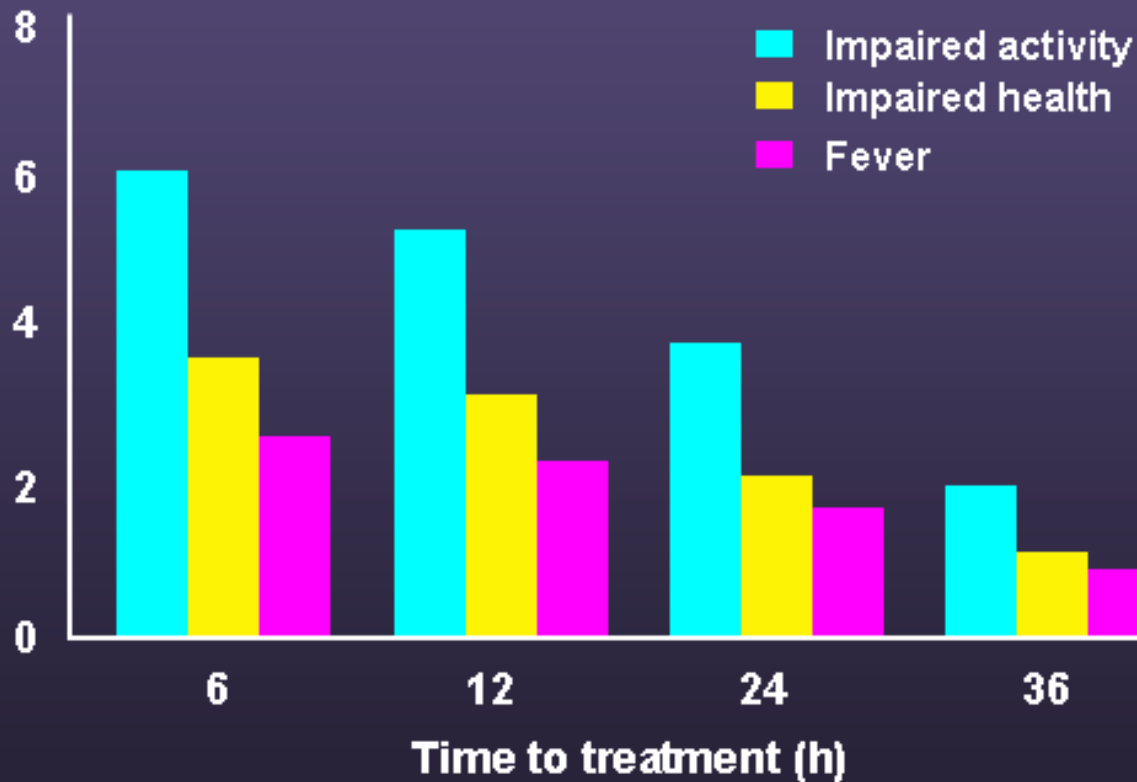
\* $P < .001$

† $P = .02$

Treanor J et al. *JAMA*. 2000;283:1057-1059.

# Oseltamivir

## Effect of Time to Treatment



Aoki F et al. *J Antimicrob Chemother.* 2003;51:123-129.

# Oseltamivir Treatment Meta-analysis of RCTs

## Effect on Complications

	Placebo	Oseltamivir	Risk Reduction
LRTI requiring ABX	10.3%	4.6%	55%*
Pneumonia	1.8%	0.7%	61%
Any ABX use	19%	14%	26%*
Hospitalization (Healthy adults)	0.8%	0.3%	60%
Hospitalization (High-risk elderly)	3.2%	1.6%	50%*
Hospitalization (Total)	1.7%	0.7%	59%*

Kaiser L et al. *Arch Intern Med.* 2003;163:1667-1672.

\* $P < .01$

# Toronto Invasive Bacterial Disease Network (TIBDN) Study

- South central Ontario (population 4 million; 23 hospitals)
- 2004/5 and 2005/6 influenza seasons
- Eligible patients:
  - ▶ hospitalized
  - ▶ positive laboratory test for influenza
- Primary outcome variable: Death
- 512 of 541 (95%) identified cases enrolled
  - ▶ 185 children <15 years
  - ▶ 86 adults 15-64 years
  - ▶ 241 adults ≥ 65 years

## TIBDN Study: Risk Factors Associated With Death Multivariate Analysis

<b>Characteristic</b>	<b>Odds ratio (95% CL)</b>	<b>P value</b>
Nursing home residence	2.9 (1.0, 8.1)	.04
Duration of symptoms prior to admission (per 24 hours)	.56 (0.15, 0.93)	.02
ICU admission	9.9 (3.8, 26)	<.001
Neuraminidase therapy	.29 (.09, .99)	.05

McGeer A et al. 46th ICAAC; 2006; Abstr V-1696. San Francisco

# Antiviral Resistance

# Oseltamivir Resistance

## Emergence During Treatment

Setting	Resistance Reported/ Number Patients	Rate of Emergence
Adult trials	1/350	<<1%
US pediatric trial	5/147	4%
Japanese children	7/43	16%
Japanese children	9/50	18%

Kaiser L et al. *Arch Intern Med.* 2003;163:1667-1672.  
Whitley R et al. *Pediatr Infect Dis J.* 2001;20:127-133.  
Kiso M et al. *Lancet.* 2004;364:759-765.

## Oseltamivir Resistance, Japan, 2003-2004

- Single season survey of NAI resistance
  - ▶ 6 million treatment courses (or ~5% of population)
  - ▶ Outpatient isolates from 74 public health labs
  - ▶ Phenotypic susceptibility by NAI assay
- 3/1,180 (0.3%) of influenza A (H3N2) isolates resistant
  - ▶ 2 E119V, 1 A292K
- Very low frequency of resistance in community isolates despite substantial oseltamivir use

Neuraminidase Inhibitor Susceptibility Network.  
*WHO Weekly Epi Record*. April 29, 2005.

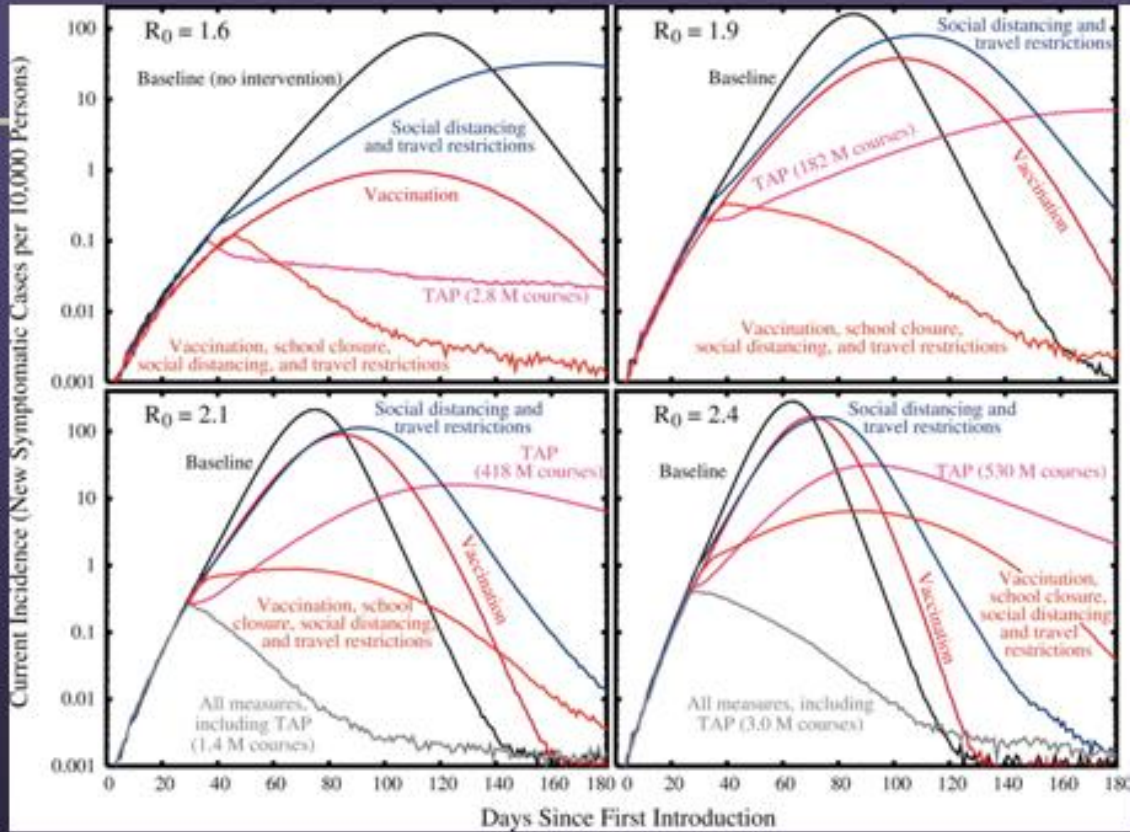
# Pandemic Influenza and H5N1 Virus

# Potential Uses of Antivirals: Pandemic Influenza

- Ring prophylaxis to contain a small outbreak
- Prophylaxis
  - ▶ Health care workers (HCWs), first responders
  - ▶ Outbreaks and clusters
  - ▶ Families
  - ▶ Postexposure prophylaxis in families and work groups
  - ▶ General public
- Secondary decrease in transmission via reduced shedding
- Treatment
  - ▶ HCWs, essential personnel
  - ▶ Patients at high risk of complication

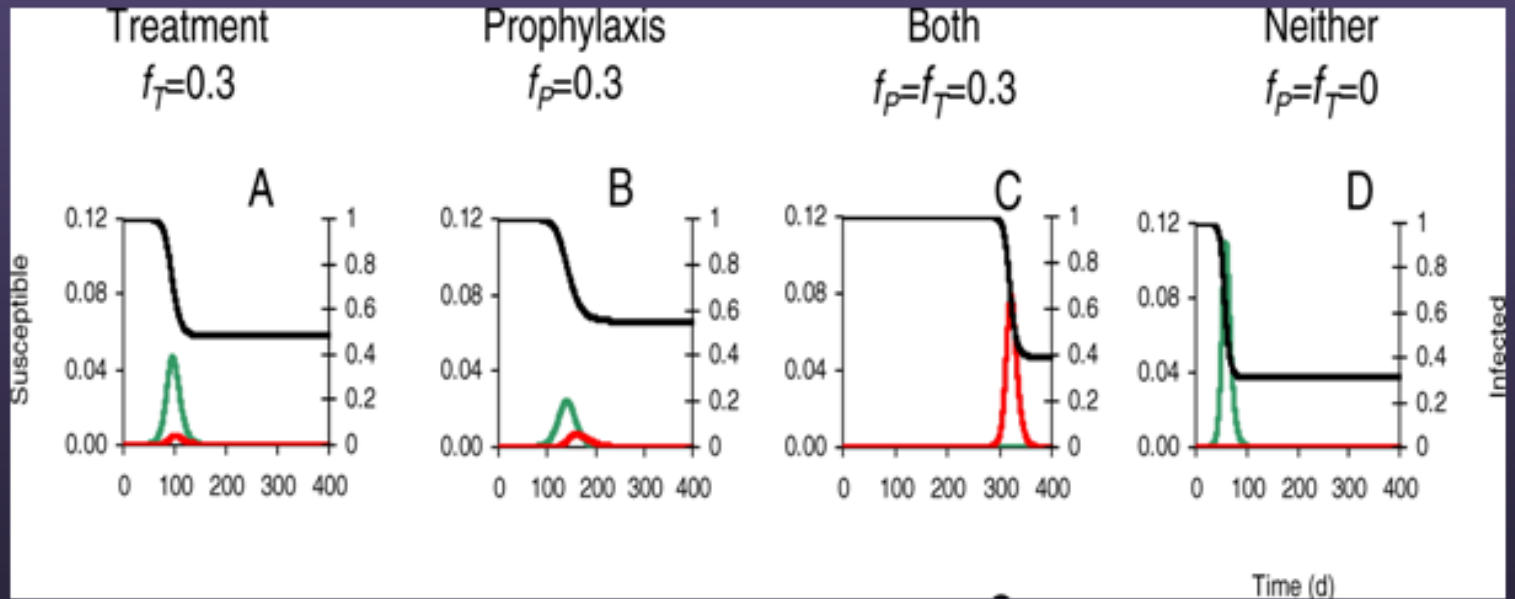
Ferguson N et al. *Nature*. 2005;437:209-214.

Fig. 2. Epidemic curves (note the logarithmic scale) demonstrating the effectiveness of several different mitigation strategies, as compared to the baseline scenario without any intervention, for different values of  $R_0$



Germann TC et al. 2006; *Proc Natl Acad Sci USA*. 103, 5935-5940

# Modeled Effect of Antiviral Treatment, Prophylaxis, Both, or Neither on Infections With Sensitive or Resistant Virus



Lipsitch M et al. *PLoS Med.* 2007;4(1): e15.

# WHO Guidance for Antiviral Chemoprophylaxis for H5N1

- In high risk exposure groups , including pregnant women, oseltamivir should be administered for 7–10 days after the last exposure; zanamivir could be used as alternative (strong recommendation).
- In moderate risk exposure groups, oseltamivir might be administered for 7-10 days after the last exposure; zanamivir might be used (weak recommendation).
- In low risk exposure groups oseltamivir or zanamivir should probably not be administered for chemoprophylaxis (weak recommendation).
- Pregnant women in the low risk group should not receive oseltamivir or zanamivir for chemoprophylaxis (strong recommendation).
- Amantadine or rimantadine should not be administered as chemoprophylaxis (strong recommendation).

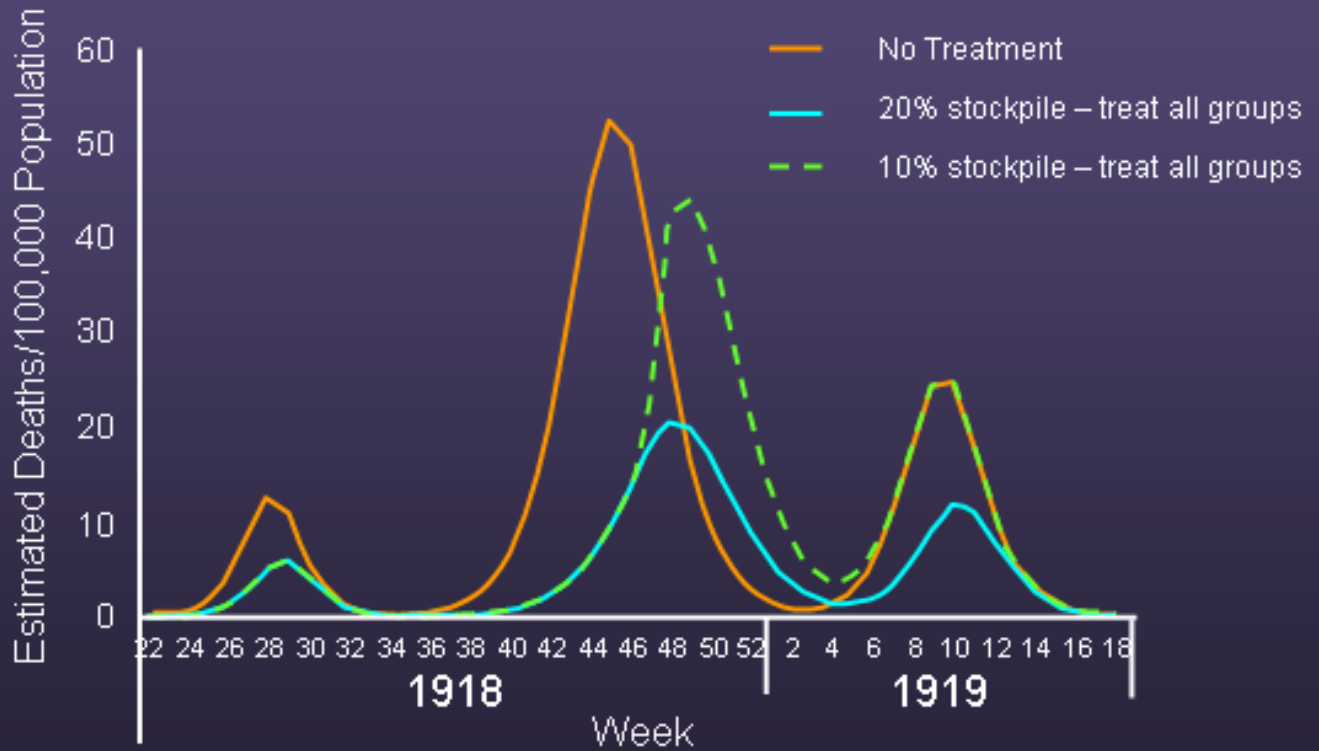
WHO. *Rapid advice guidelines for pharmacological management of H5N1*. 2006.

## Antiviral Effects on Viral Transmission and Pathogenicity: Observations From Household Trials

	Zanamavir	95% CI	Oseltamivir	95% CI
Prophylactic efficacy	75%	54-86	81%	35-94
Efficacy at preventing infectiousness	19%	-160-75	80%	43-94
Efficacy at decreasing pathogenicity	52-56%		56-79%	

Halloran ME et al. *Am J Epidemiol.* 2007;162:212-221.

# Estimated Pandemic Mortality 1918-1919



Gani R et al. *Emerg Infect Dis.* 2005;11:1355-1362.

# WHO Guidance for Antiviral Treatment for H5N1

- Oseltamivir remains treatment of choice (strong recommendation); zanamivir might be used as an alternative (weak recommendation)
- Do not use amantadine or rimantadine alone as a first-line treatment (strong recommendation)
- Consideration can be given to double-dose oseltamivir or combination of neuraminidase inhibitor and an M2 inhibitor (weak recommendation), but this should only be done in the context of prospective data collection
- Do not use high-dose steroids or prophylactic antibiotics

WHO. *Rapid advice guidelines for pharmacological management of H5N1*. Updated 2007. [http://www.who.int/csr/disease/influenza/meeting2007\\_03\\_19/en/index.html](http://www.who.int/csr/disease/influenza/meeting2007_03_19/en/index.html)

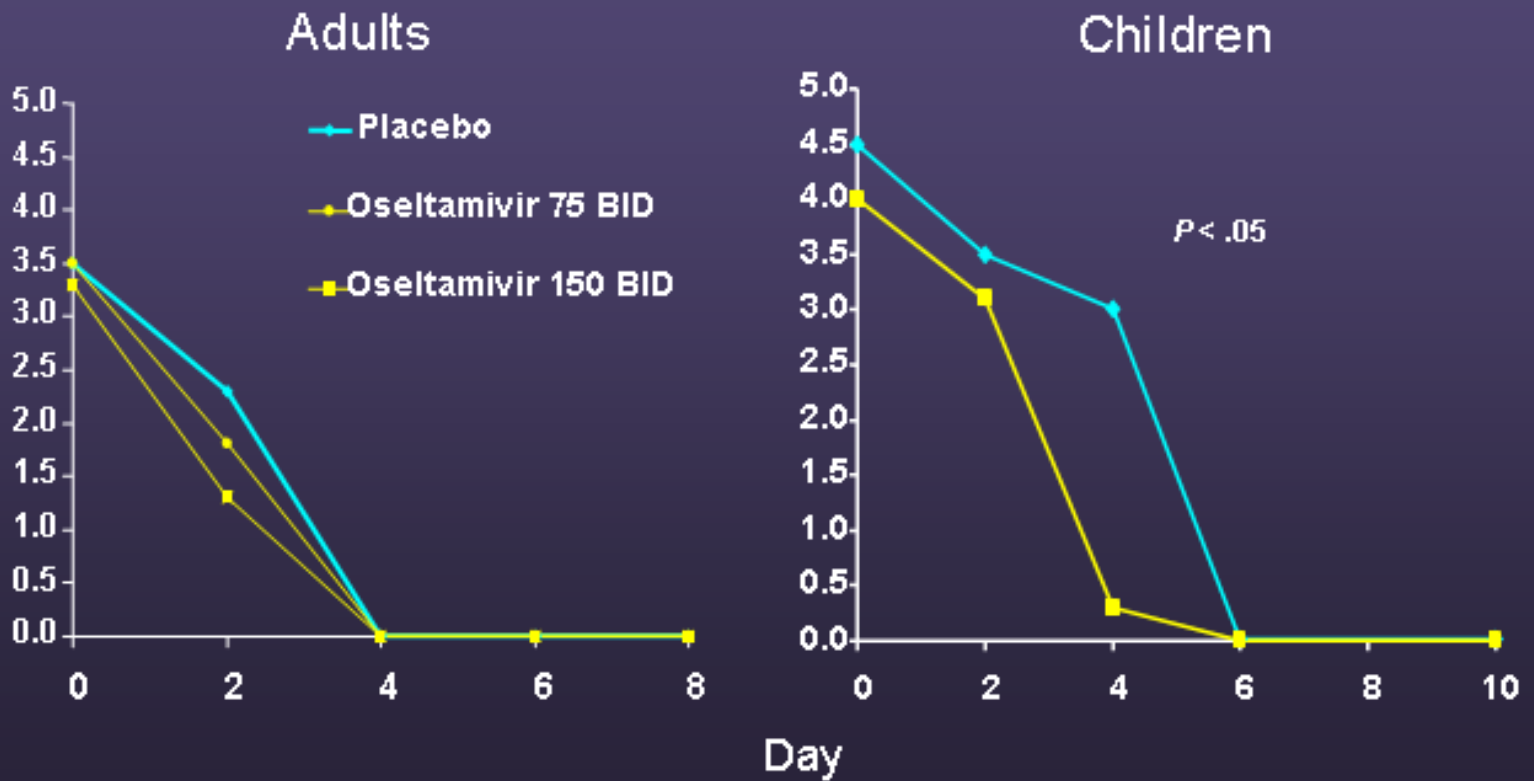
## Detection of Virus RNA in H5N1 vs H3N2

	<u>H5N1 fatal</u>	<u>H5N1 nonfatal</u>	<u>H3/H1</u>
VL nose	5.8 log	4.5 log	4.8 log
VL throat	7.5 log	5.9 log	4.8 log
Rectum	5/7	na	na
Blood	9/11	0/5	0/6

De Jong MD et al. *Nature Medicine*. 2006;12:1203-1207.

# Oseltamivir Treatment

## Antiviral Effect



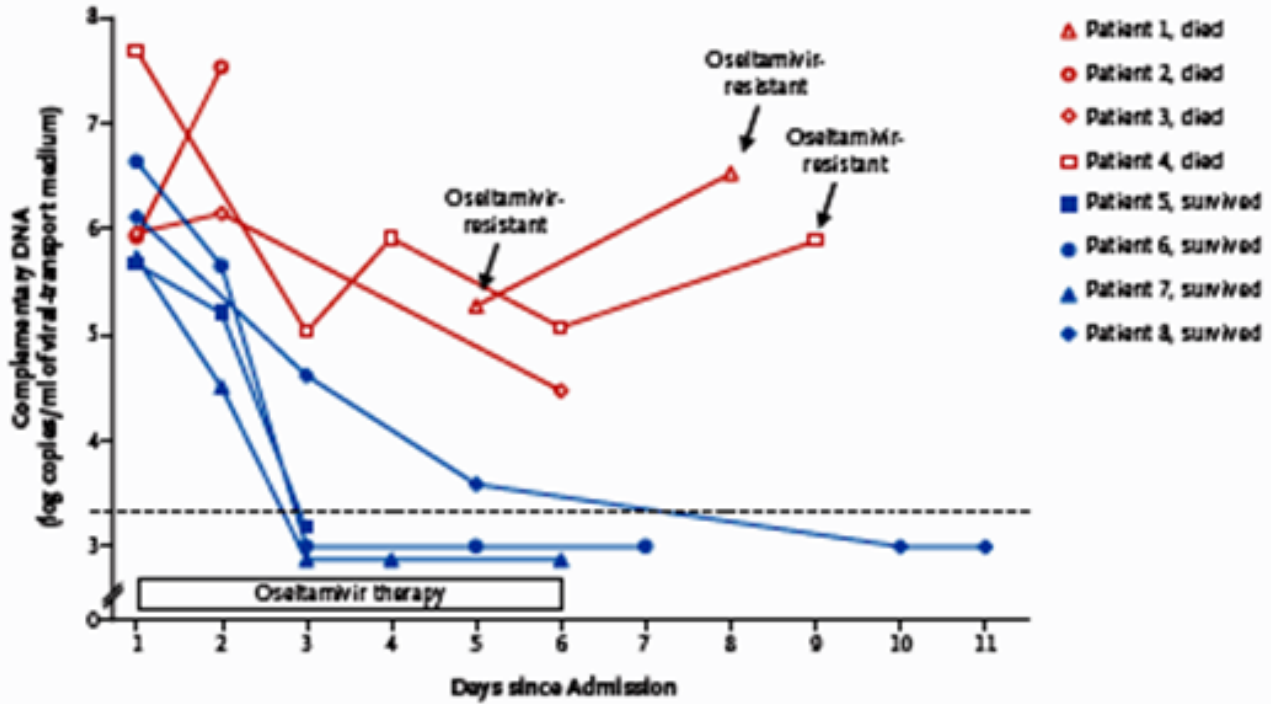
Treanor J et al. *JAMA*. 2000;283:1016-1024.

Whitley R et al. *Pediatr Infect Dis J*. 2001;20:127-133.

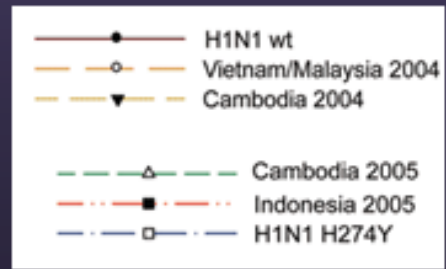
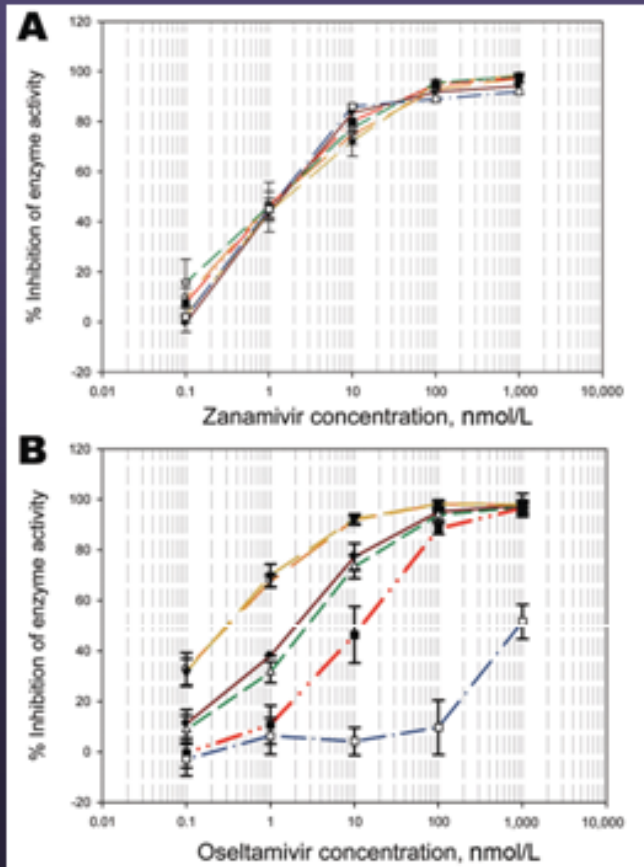
BRIEF REPORT

### Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection

Menno D. de Jong, M.D., Ph.D., Tran Tan Thanh, M.Sc.,  
 Truong Huu Khanh, M.D., Vo Minh Hien, M.D., Gavin J.D. Smith, Ph.D.,  
 Nguyen Vinh Chau, M.D., Bach Van Cam, M.D., Phan Tu Qui, M.D.,  
 Do Quang Ha, M.D., Ph.D., Yi Guan, M.D., Ph.D., J.S. Malik Peiris, D.Phil, M.D.,  
 Tran Tinh Hien, M.D., Ph.D., and Jeremy Farrar, D.Phil., F.R.C.P.



# Reduced Sensitivity to Oseltamivir in H5N1 Clade 2 Isolates



McKimm-Breschkin J. *EID*. 2007; Sept epub.

# Investigational Agents in Clinical Development

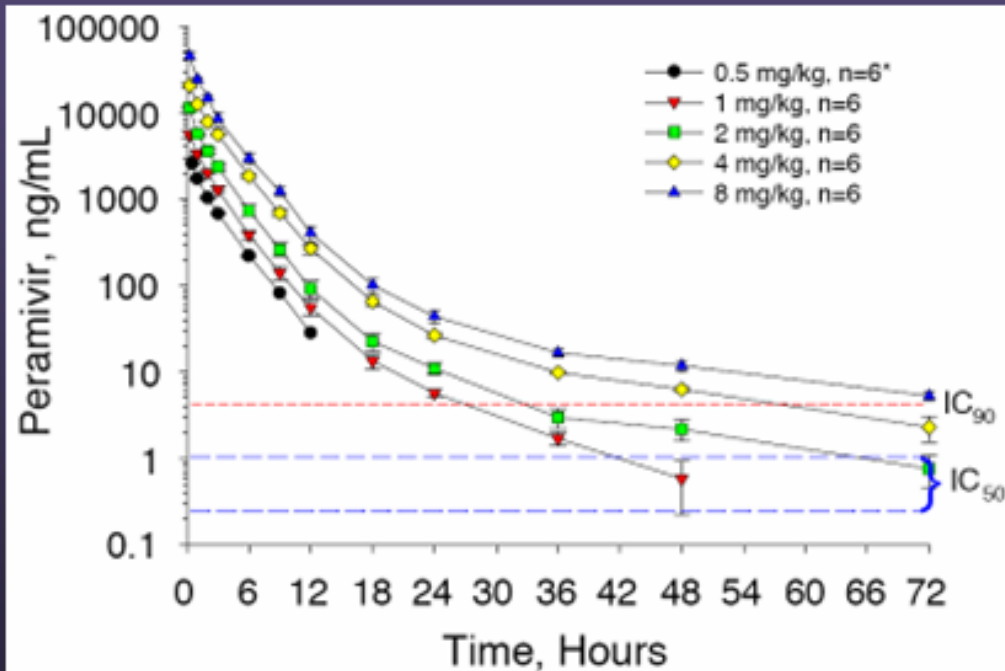
Agent	Target	Sponsor	Route	Development Phase
Zanamivir	NA	GSK	IV	Phase 1, 2a
Peramivir	NA	BioCryst	IV, IM	Phase 1
CS8958	NA	Sankyo, Biota	Topical	Phase 1
T-705	Polymerase	Toyama	Oral	Pending
DAS181	HA receptor	NexBio	Topical	Pending

# Other Antiviral Approaches to Treatment of Influenza

Agent	Target
Zanamivir dimer	NA
Cyanovirin-N	HA
Sialylglycopolymer	HA
Ribavirin	Polymerase
Viramidine	Polymerase
SiRNA	Polymerase
Monoclonal and polyclonal Ab	HA, NA
Combination therapy	NA and M2 channel

# Peramivir

Phase I human PK data



Well tolerated  
T<sub>1/2</sub> = 20 hours.

Phase I data unpublished: Collaboration between NIAID and Biocryst. Courtesy John Beigel