Forum on Antivirals for Influenza
Asia-Pacific Alliance for the Control of Influenza APACI
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Higher-dose oseltamivir treatment in adults hospitalized with influenza A and B infections

Prof. Paul KS Chan MD FRCPath
Chairman, Department of Microbiology

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

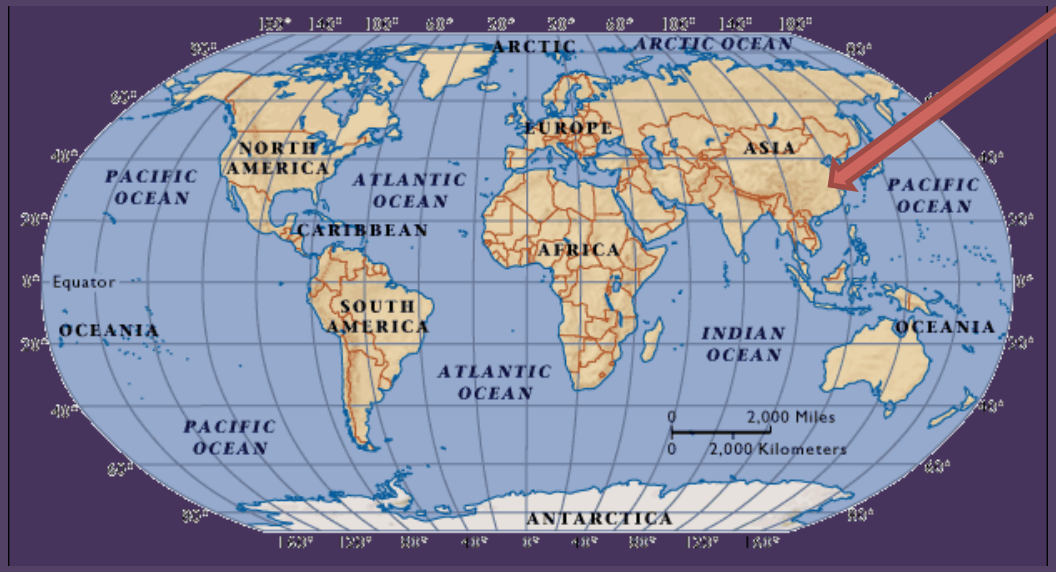
Hong Kong

East Asia

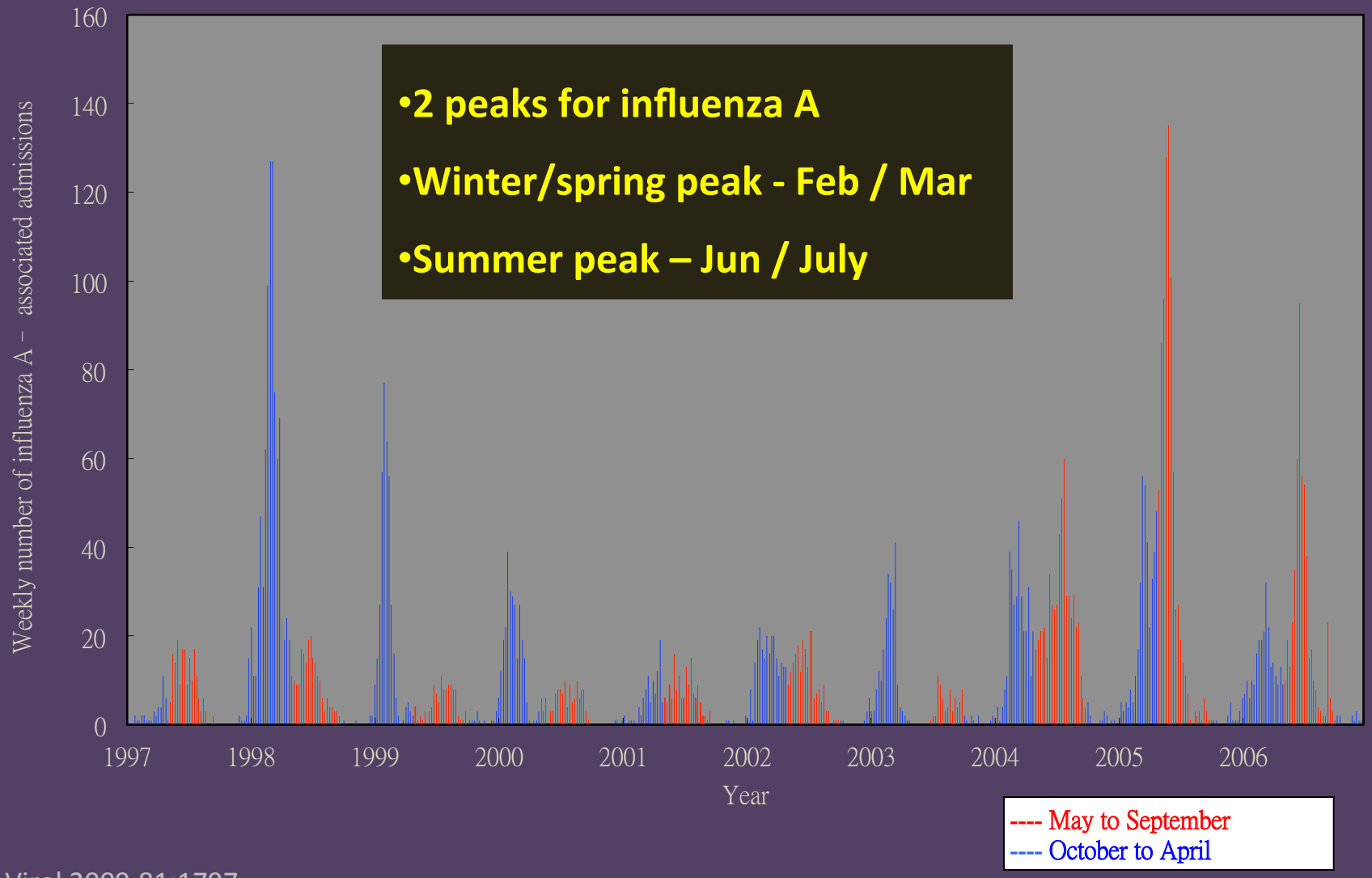
Southern China

1,104 km

Population: 7M

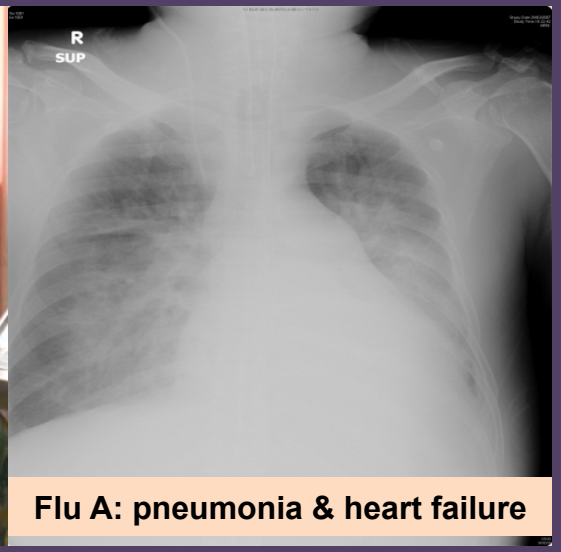


No. of Influenza A admissions per week, 1997-2006

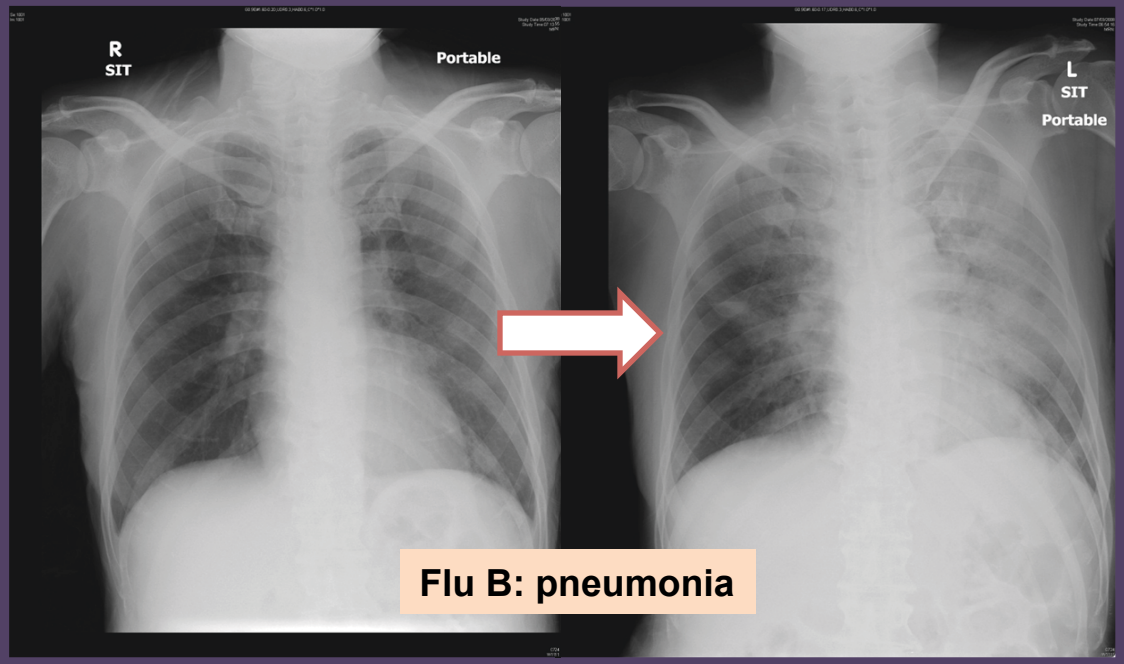


J Med Virol 2009;81:1797

In Hong Kong, ~ 3000 elderly admitted to public hospitals each year



Flu A: pneumonia & heart failure

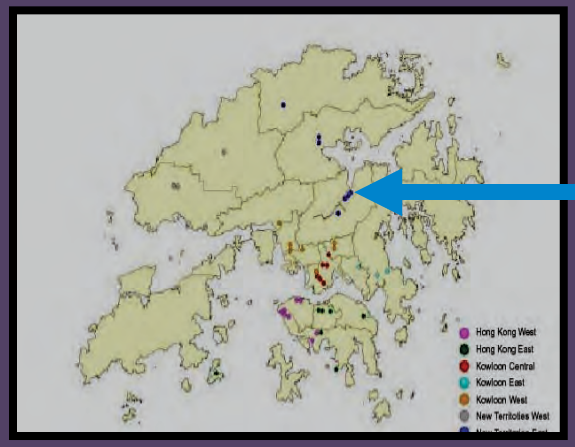


Flu B: pneumonia

ICU admission rate: 5-17%

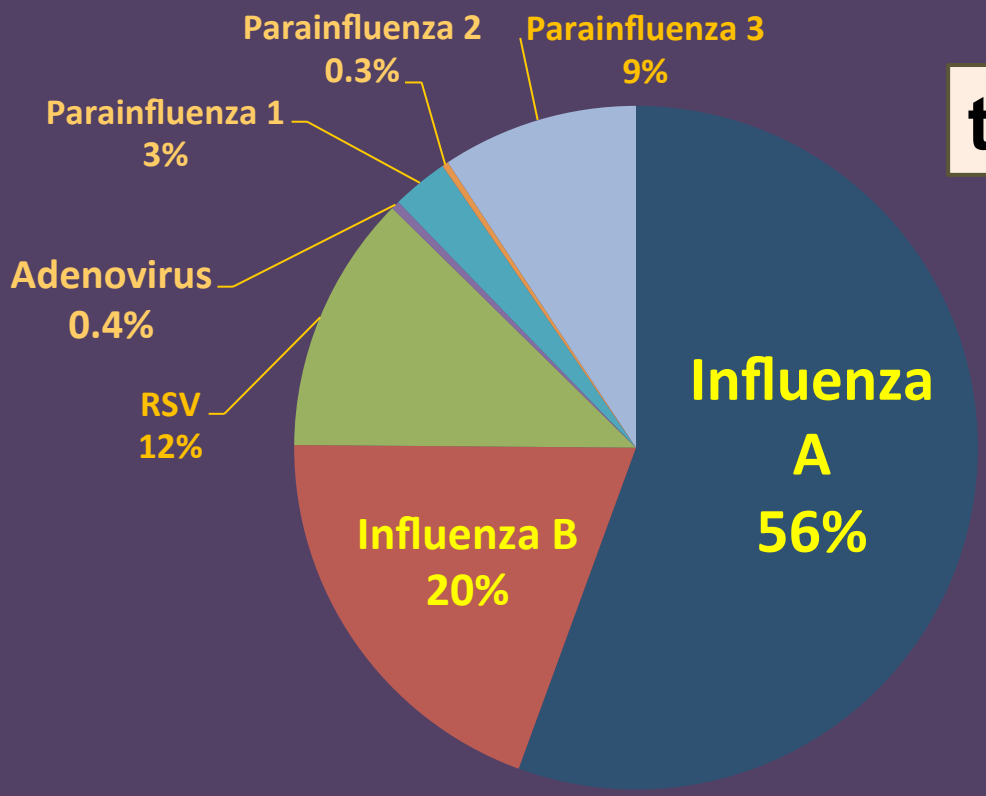
Death rate: 4-8%

Prince of Wales Hospital

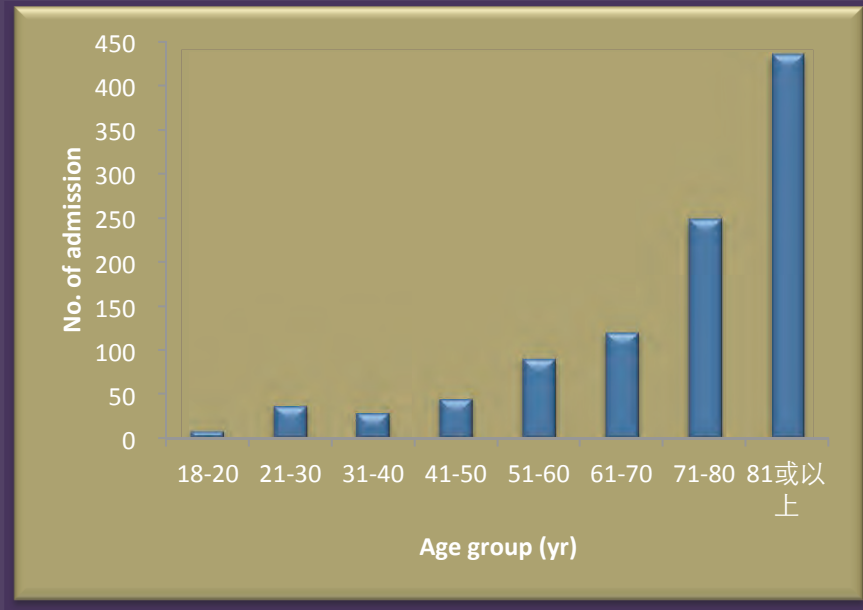


- New Territories East Cluster
- Acute general regional hospital
- ~1,400 bed
- Catchment population: 0.6 M (9% of HK population)
  - 3% children < 5 yr
  - 10% elderly > 65 yr

Adult (>17 yr) admissions associated with respiratory viruses Prince of Wales Hospital, 2012



total:1013



Benefits of antiviral (oseltamivir) treatment for influenza among hospitalized patients (elderly)

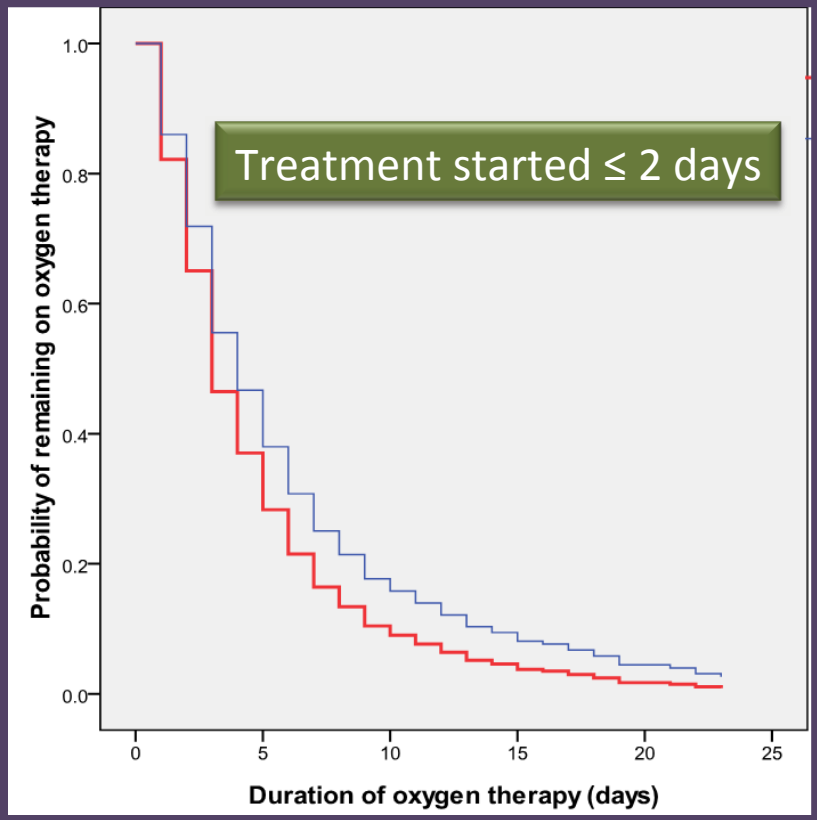
Oxygen therapy

2007-2008
prospective study
754 hospitalized patients

71% Flu A (>75% H3N2)
29% Flu B

Age >70 yr: 60%
Comorbidity: 61%

Received antiviral (oseltamivir): 52%
Developed complications: 77%
Required ventilatory support: 5%
Died: 5%

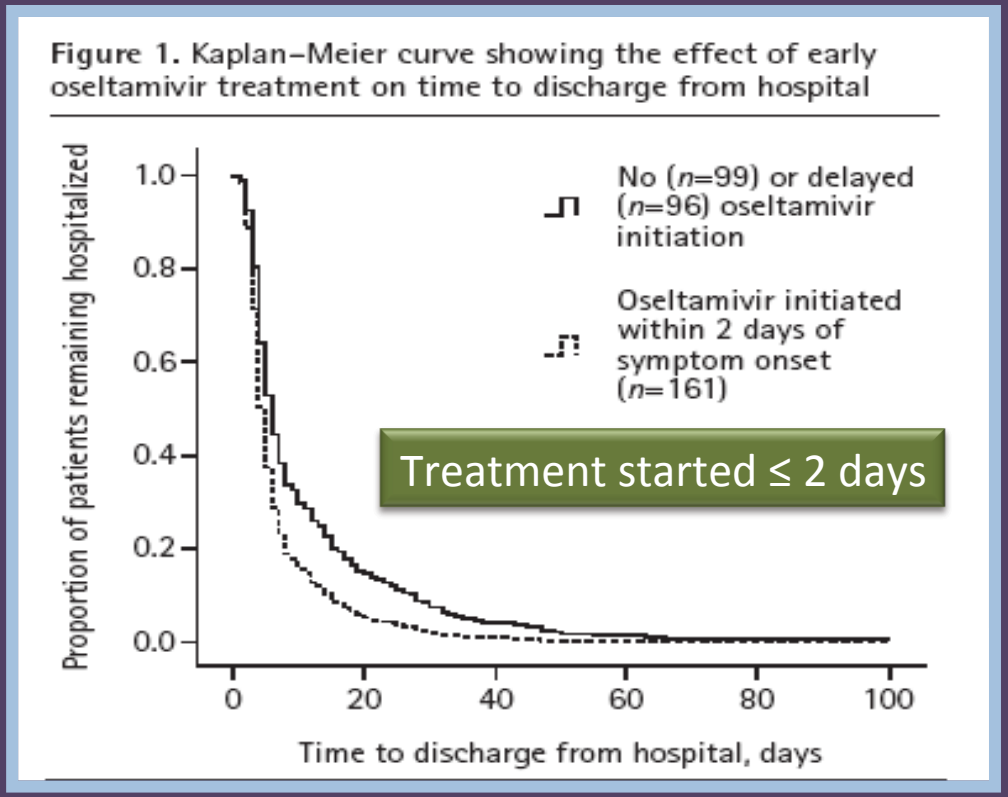


Thorax 2010;65:510.

Length of Hospitalization

2004-2005
Retrospective study
94% Flu A (mainly H3N2), 6% Flu B

356 hospitalized patients
Age >70 yr: 68%
Comorbidity: 69%
Developed complications: 69%
Ventilatory support: 5%
Died: 3%



33% reduction of Length Of Hospitalization

1.5 times more likely to be discharged at any time point) with timely antiviral treatment,

Antivir Ther 2007;12:501

Survival

2007-2008
prospective study
754 hospitalized patients

71% Flu A (>75% H3N2)
29% Flu B

Age >70 yr: 60%
Comorbidity: 61%

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Required ventilatory support: 5%
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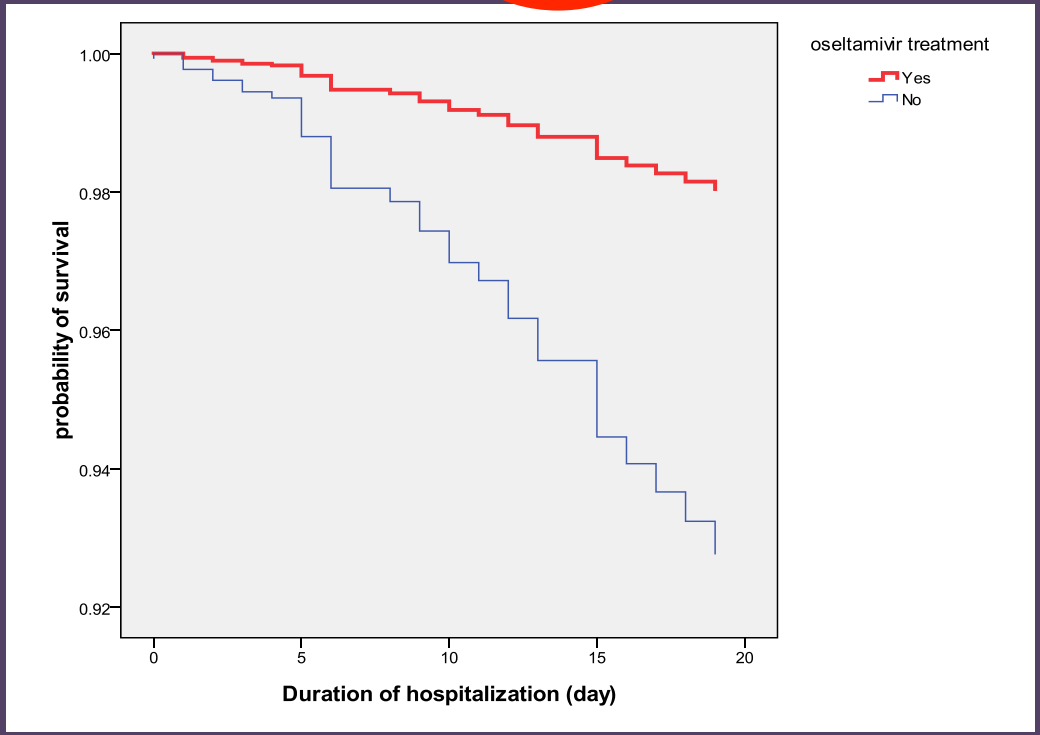
Treatment initiated at any time vs. no treatment



Use of oseltamivir was associated with a higher probability of survival
Adjusted aHR: 0.27 (0.13-0.55), P < 0.001

Thorax 2010;65:510.

Survival

2007-2008
prospective study
754 hospitalized patients

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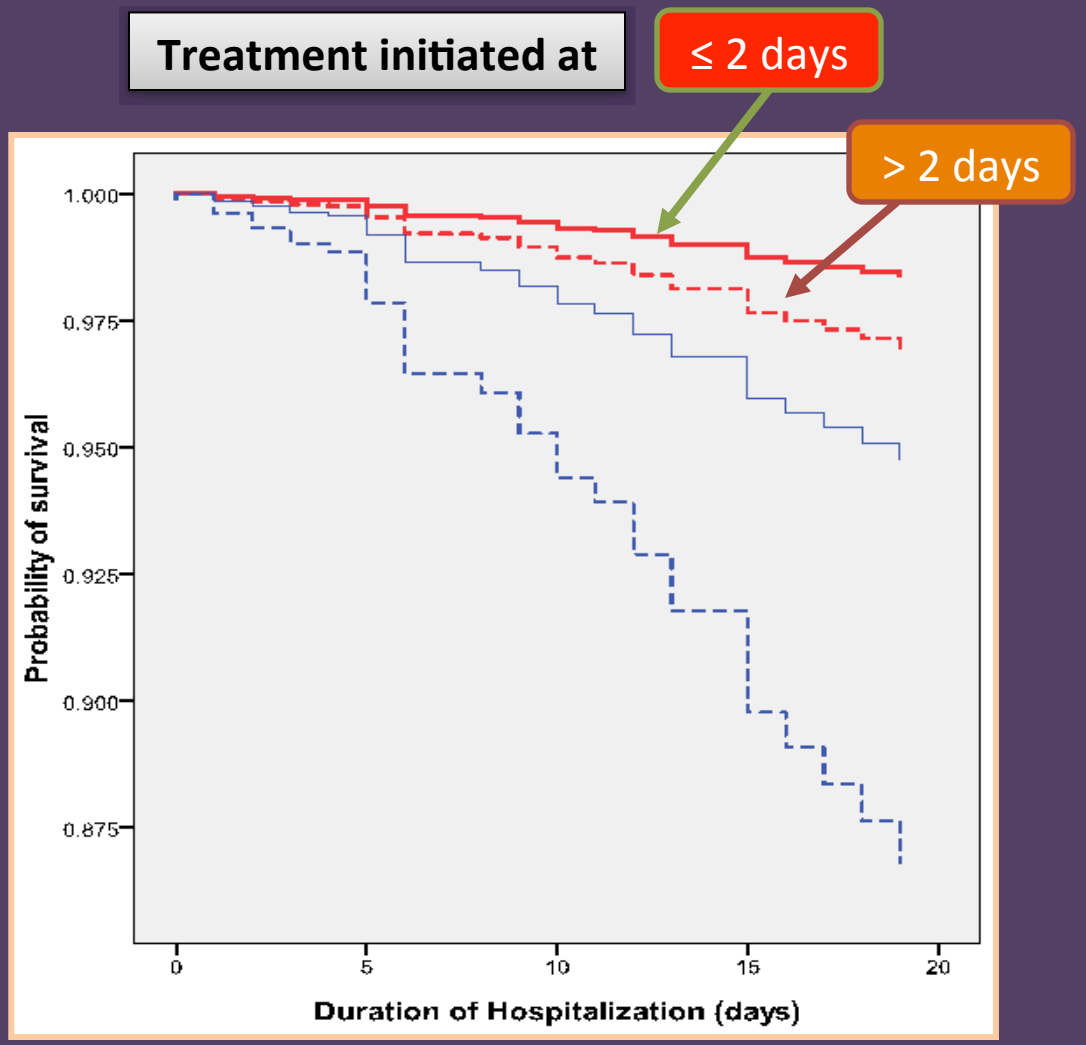


(a) oseltamivir treatment, initiated w ithin 2 days from onset [aHR 1.00]
(b) oseltamivir treatment initiated later than 2 days [aHR 1.87(0.58,6.00); p=0.296]
(c) untreated, lack of rapid virological confirmation [aHR 3.24 (1.14,9.23); p=0.028]
(d) untreated, late presentation [aHR 8.49 (2.19,32.96); p=0.002]

Thorax 2010;65:510.

Survival

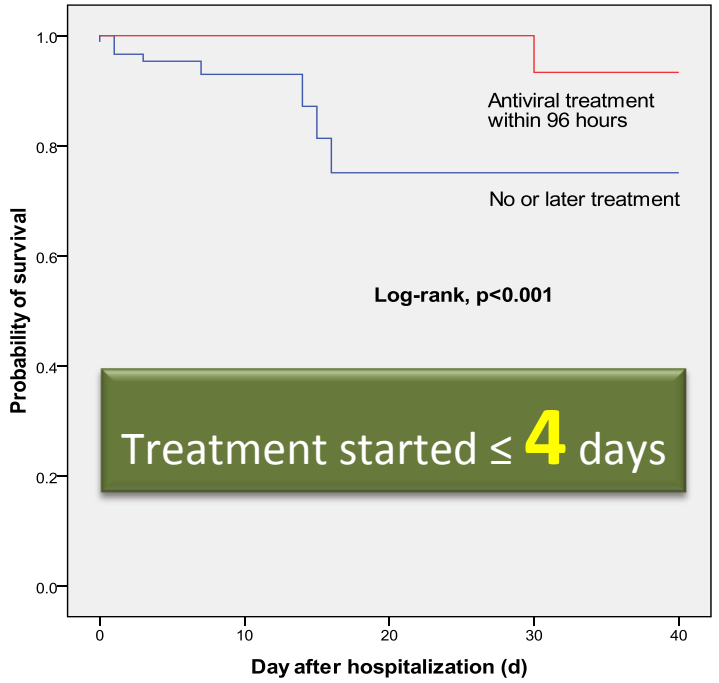
Effective of oseltamivir treatment for 2009 pdmH1N1

Jun 2009 – May 2010

382 adult patients

- Age: 46.5 yr +/- SD: 19.6 yr
- Male: 44.5%
- Comorbidity: 48%
- Developed complications: 68%
- ICU: 7%
- Died: 3%

Figure 1. Kaplan-Meier survival curves of patients hospitalized with pandemic 2009



NOT receiving antiviral treatment within 96 hr was associated with a higher risk of death

OR: 6.85, 95%CI (1.64-28.65), P = 0.008

Oseltamivir is effective,
but some patients do not response !!

Higher dose ??

Safe ??

Extra efficacy ??

Adverse Events in healthy adults 75 mg vs 150 mg oseltamivir

	Placebo N = 466	75 mg bid N = 479	150 mg bid N = 447
Vomiting	15 (3.2%)	57 (11.9%)	53 (11.9%)
Nausea	29 (6.2%)	70 (14.6%)	68 (15.2%)
Insomnia	3 (0.6%)	7 (1.5%)	8 (1.8%)
Dry Mouth	2 (0.4%)	4 (0.8%)	5 (1.1%)
Headache Nos	11 (2.4%)	13 (2.7%)	13 (2.9%)
Vertigo nos	3 (0.6%)	4 (0.8%)	5 (1.1%)
Sore Throat Nos	5 (1.1%)	6 (1.3%)	5 (1.1%)
Abdominal Pain	11 (2.4%)	12 (2.5%)	9 (2.0%)
Epistaxis	4 (0.9%)	3 (0.6%)	3 (0.7%)
Herpes Simplex	5 (1.1%)	4 (0.8%)	5 (1.1%)
Fatigue	7 (1.5%)	6 (1.3%)	7 (1.6%)
Dyspepsia	4 (0.9%)	1 (0.2%)	6 (1.3%)
Cough	10 (2.1%)	7 (1.5%)	9 (2.0%)
Nasal Congestion	10 (2.1%)	5 (1.0%)	6 (1.3%)
Dizziness (exc vertigo)	16 (3.4%)	11 (2.3%)	10 (2.2%)
Diarrhoea	40 (8.6%)	35 (7.3%)	26 (5.8%)

AEs in Adult Phase III Treatment Studies

	Placebo N=1050 No. (%)	**RO 64-0796 75 mg bid N=1057 No. (%)**	**RO 64-0796 150 mg bid N=447 No. (%)**
All Body Systems	427 (40.7)	430 (40.7)	187 (41.8)
Gastrointestinal Disorders	196 (18.7)	244 (23.1)	122 (27.3)
Infections and Infestations	129 (12.3)	106 (10.0)	10 (2.2)
Respiratory, Thoracic & Mediastinal Disorders	63 (6.0)	54 (5.1)	30 (6.7)
General Disorders	58 (5.5)	48 (4.5)	25 (5.6)
Neurological Disorders	41 (3.9)	48 (4.5)	26 (5.8)
Skin & Subcutaneous Tissue Disorders	15 (1.4)	22 (2.1)	11 (2.5)
Disorders of the Ear & Labyrinth	18 (1.7)	15 (1.4)	6 (1.3)
Musculoskeletal, Connective Tissue & Bone Disorders	10 (1.0)	20 (1.9)	4 (0.9)
Disorders of Metabolism & Nutrition	16 (1.5)	12 (1.1)	5 (1.1)
Cardiac Disorders	14 (1.3)	7 (0.7)	3 (0.7)
Disorders of the Eye	11 (1.0)	8 (0.8)	5 (1.1)
Psychiatric Disorders	9 (0.9)	3 (0.3)	9 (2.0)
Vascular Disorders	7 (0.7)	10 (0.9)	4 (0.9)
Renal & Urinary Disorders	5 (0.5)	12 (1.1)	2 (0.4)

Adult Phase III Treatment Studies
Neurologic Disorders

	Placebo n = 1050 [%]	75 mg bid n = 1057 [%]	150 mg bid n = 447 [%]
Headache	16 [1.5]	17 [1.6]	13 [2.9]
Insomnia	10 [1.0]	11 [1.0]	8 [1.8]
Taste disturbance	4 [0.4]	3 [0.3]	3 [0.7]
Weakness	3 [0.3]	1 [0.1]	1 [0.2]
Migraine	--	4 [0.4]	--

Adult Phase III Treatment Studies Psychiatric Disorders

	Placebo n = 1050 [%]	75 mg bid n = 1057 [%]	150 mg bid n = 447 [%]
Depression	3 [0.3]	--	2 [0.4]
Confusion	3 [0.3]	--	--

Summary of Adverse Events by Body System - % Subjects

	Placebo	75 mg	225 mg	450 mg
GI	21.0	13.7	30.9	44.4
Neurologic	20.0	16.8	24.7	24.2
General	11.0	9.5	20.6	16.2
Respiratory	6.0	8.4	11.3	8.1
Muscular	5.0	5.3	3.1	5.1
Skin				2.0
Cardiac	4.0	1.1	2.1	2.0
Injury	2.0	1.1	1.0	1.0

Toxicity is dose-dependent

Most Frequently Reported Events - % Subjects

	Placebo	75 mg	225 mg	450 mg
Nausea	8.0	8.4	25.8	31.3
Headache	20.0	16.8	23.7	23.2
Vomiting	2.0	3.2	7.2	15.2
Dizziness	4.0	2.1	11.3	10.1
Dyspepsia	3.0	-	2.1	9.1
Back Pain				4.0
Abdominal Pain (upper)				3.0
Diarrhea	2.0	-	1.0	3.0
Fatigue	-	1.1	3.1	3.0

Toxicity is dose-dependent

Summary : Safety of higher dose of oseltamivir

- Safety data for doses higher than the 75mg approved dose are **limited**
  - 447 otherwise healthy adults received 150 mg twice daily for 5 days
  - 200 healthy volunteers received either 225mg or 450mg twice daily for 5 days
- Those data available do **not indicate an increased risk** for serious adverse events
  - There was a **dose dependent increase** in nausea, vomiting and dizziness over placebo subjects
- The decision to use doses of Tamiflu higher than the approved dose should be made based upon a **risk-benefit assessment**

Clinical benefits of higher dose of oseltamivir ??

Prospective

4 flu seasons

75 vs 150 mg 2x/D, 5 days

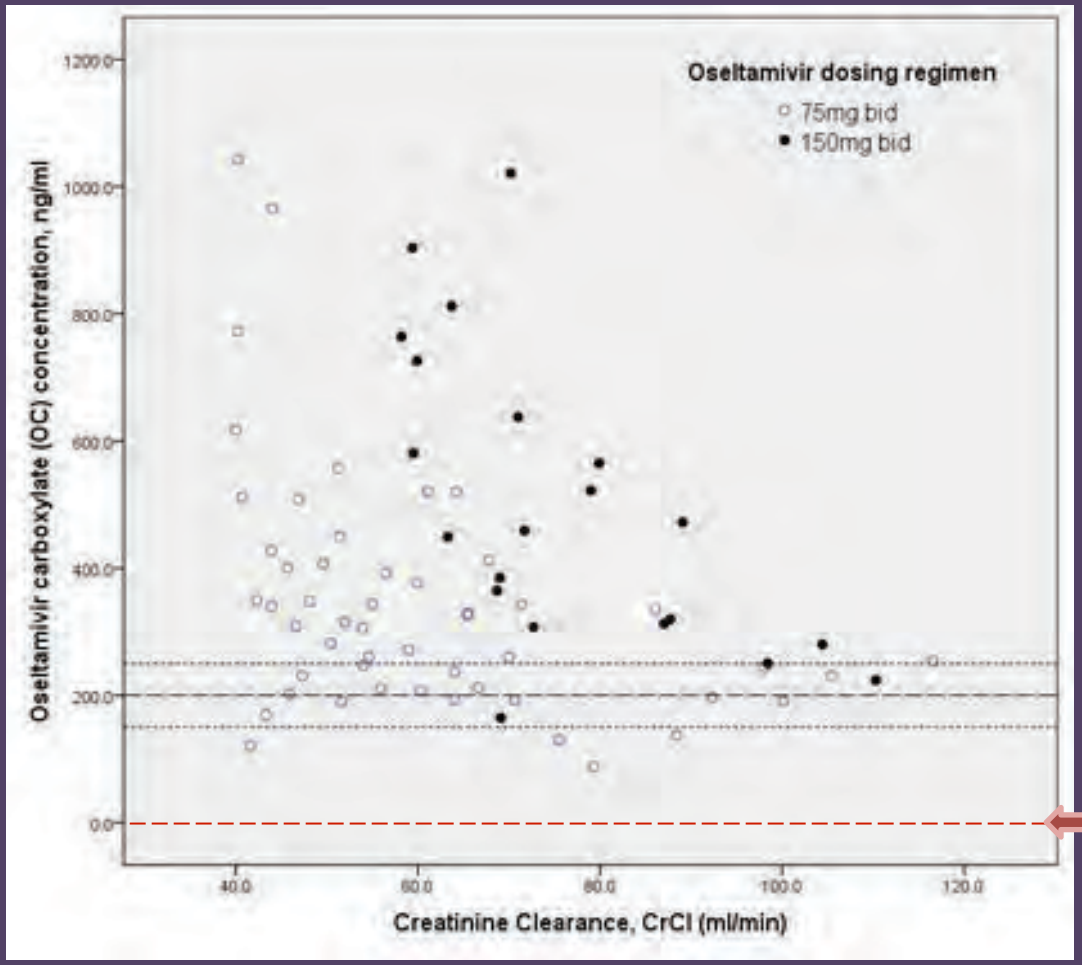
2 hospitals, cross-over

85 A/H3N2, 34 A/H1N1, 36 B

41 subjects: received 150 mg bid

114 subjects received 75 mg bid

Plasma trough oseltamivir concentration



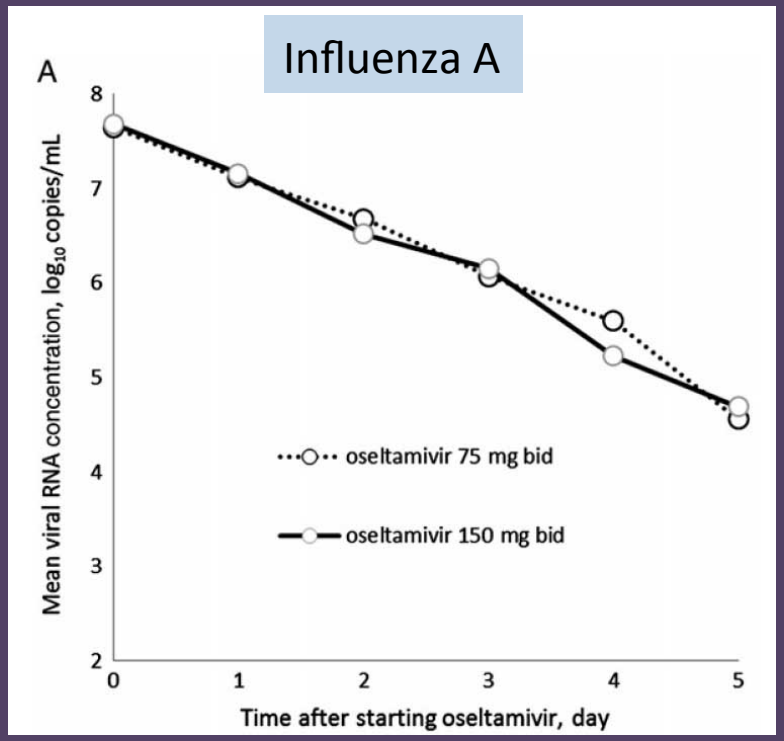
Virological Outcomes

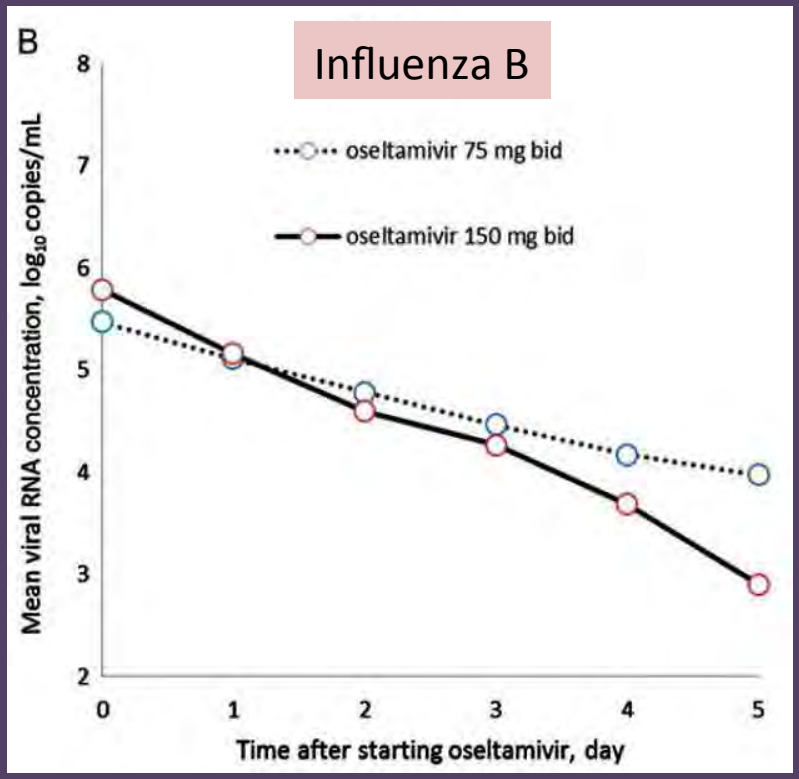
Outcome	Active Arm (n = 70)	Comparator Standard Therapy Arm (n = 87)	*P* Value	150 mg bid Recipients (n = 41)	75 mg bid Recipients (n = 114)	*P* Value	Subgroup 75 mg bid Recipients, CrCl >60 mL/min[a] (n = 49)	*P* Value[a]
Virologic[b]								
PCR negativity at day 5, %	39.7	43.3	.677	44.7	40.2	.634	47.5	.807
Culture negativity at day 3, %	88.2	94.7	.229	90.0	92.2	.739	95.5	.418
Culture negativity at day 5, %	98.6	98.7	>.99	100.0	98.1	>.99	100.0	>.99

Clinical Outcomes

Outcome	Active Comparator Arm (n = 70)	Standard Therapy Arm (n = 87)	*P* Value	150 mg bid Recipients (n = 41)	75 mg bid Recipients (n = 114)	*P* Value	Subgroup 75 mg bid Recipients, CrCl >60 mL/min[a] (n = 49)	*P* Value[a]
Clinical								
Duration of hospitalization, d, median (IQR)	6.0 (3.0–8.0)	4.0 (3.0–6.5)	.138	5.0 (3.0–7.8)	5.0 (3.0–7.0)	.943	4.0 (3.0–6.0)	.300
Duration of oxygen therapy, d, median (IQR)[c]	3.0 (1.3–5.8)	3.0 (1.0–5.0)	.704	3.0 (1.0–6.5)	3.0 (1.0–5.0)	.789	3.5 (3.0–5.0)	.662
Duration of fever >37.5°C, d, median (IQR)[c]	1.5 (0.0–3.0)	1.0 (1.0–2.0)	.982	2.0 (0.0–3.0)	1.0 (1.0–2.0)	.482	2.0 (1.0–2.0)	.785
ICU admission, %	0.0	2.3	.503	0.0	1.8	>.99	2.0	>.99
Death, %	1.4	1.1	>.99	2.4	0.9	.460	2.0	>.99
ICU admission or death, %	1.4	3.4	.629	2.4	2.6	>.99	4.1	>.99

Decline in virus shedding





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A Prospective Intervention Study on Higher-Dose Oseltamivir Treatment in Adults Hospitalized With Influenza A and B Infections

N. Lee,[1,2] D. S. C. Hui,[1,2] Z. Zuo,[3] K. L. K. Ngai,[4] G. C. Y. Lui,[1] S. K. Wo,[3] W. W. S. Tam,[5] M. C. W. Chan,[4] B. C. K. Wong,[1] R. Y. K. Wong,[1] K. W. Choi,[1] W. W. Y. Sin,[1] E. L. Y. Lee,[1] B. Tomlinson,[1] F. G. Hayden,[6] and P. K. S. Chan[2,4]

No advantage of double-dose (150mg bid) oseltamivir over conventional dosage (75mg bid) in influenza A (H3N2, pdm H1N1)

Improves viral clearance in influenza **B**

~40% PCR+ at treatment end
therapy **>5 days** may be necessary for severe cases

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