

# **Challenge in Management of Influenza**

**By**

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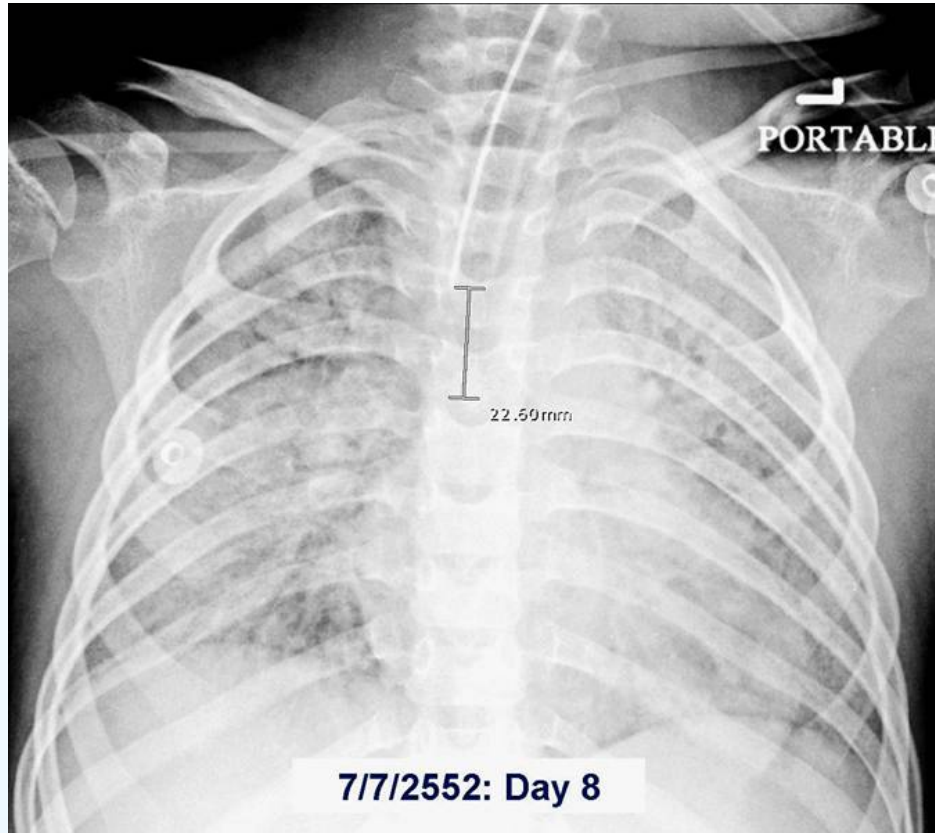
**Mahidol University**

*For JITMM Nov 2010*

# **What Are the Challenges in Treating Patients with Influenza?**

- **Making prompt and accurate diagnosis**
- **Identifying patients at risk for severe diseases**
- **Treatment in severe cases**

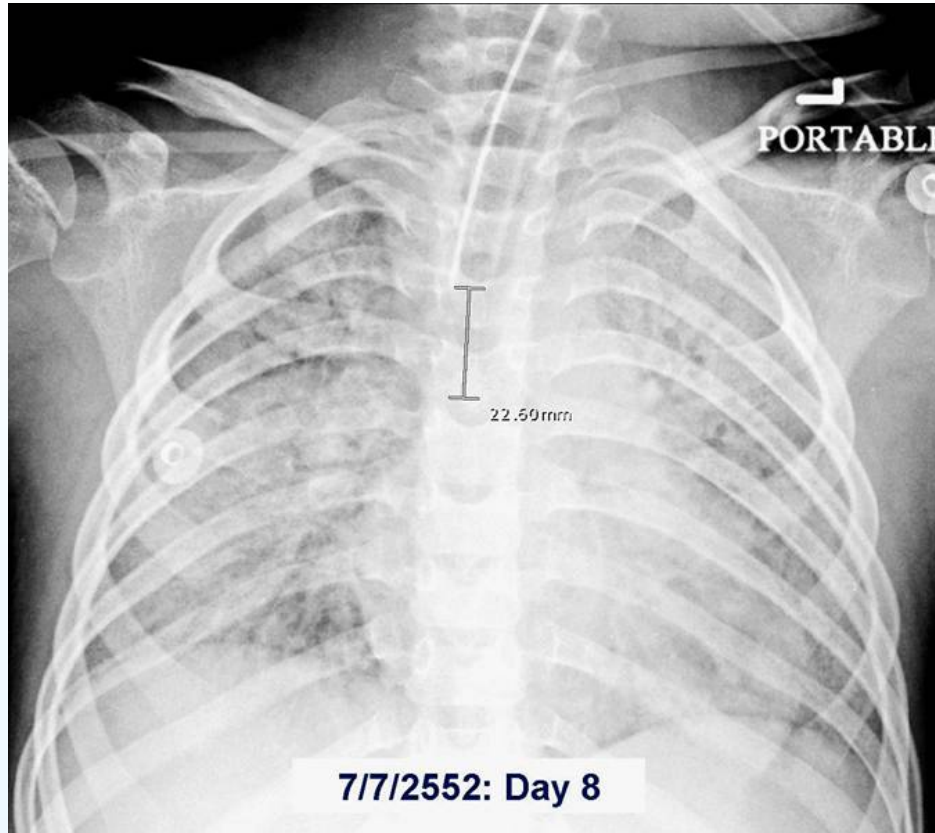
# A 6 Years old girl known case of epilepsy, delayed development, presented with high fever and diarrhea



- 2 days after, she developed shock, received iv fluid resuscitation. Soon after, she had shortness of breath.
  - PE: Drowsy. T=39.5C, RR=60 /min, HR 120/min, BP 90/60,
  - SpO2 = 85%, in room air >> intubated.
- Lungs-fine crepitation bilaterally  
Mild liver enlargement.
- DDX: Dengue shock  
Severe pneumonia  
Encephalitis

***Throat swab: Negative for rapid test***

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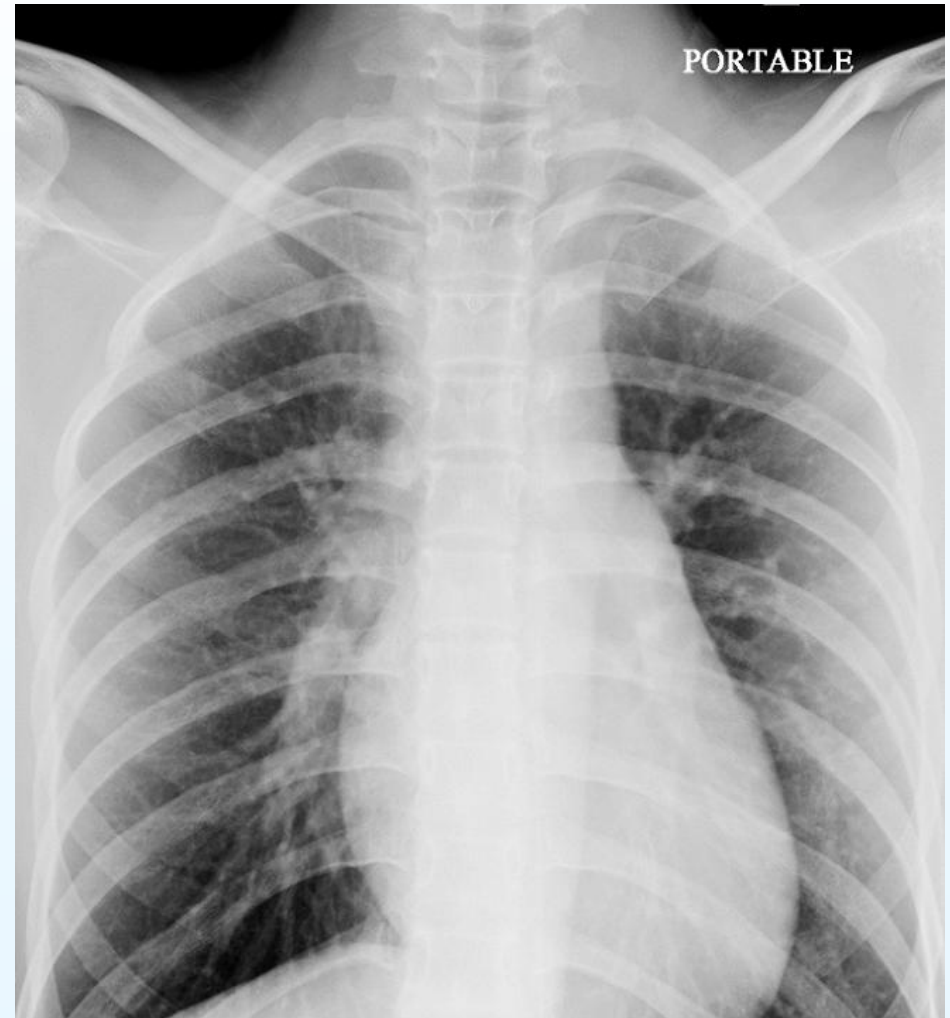


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Encephalitis

***Throat swab: Negative for rapid test.  
NP wash for -PCR: positive influenza A pH1N1***

# A 13 year-old girl with alteration of consciousness

- 3 days history of high grade fever, headache, sore throat, myalgia and drowsiness.
- T 39.3°C, P 100/min, RR 24/min, BP 115/80 mmHg, SpO2 97% (room air)
  - GA : Drowsy, lethargic
  - RS : clear
  - Neuro : Stiff neck and Kernig sign: positive
    - : Reflex 2+ all, BBK – normal
- CSF: WBC 30 (PMN 1, L 29 ), RBC 40 Protein 38 mg%, sugar 66 mg% (BS 113 ).
- Dx: Encephalitis





**CT brain – leptomenigeal enhancement, no mass  
CSF PCR for HSV and enterovirus: negative**



**CT brain – leptomeningeal enhancement, no mass  
CSF PCR for HSV and enterovirus: negative**

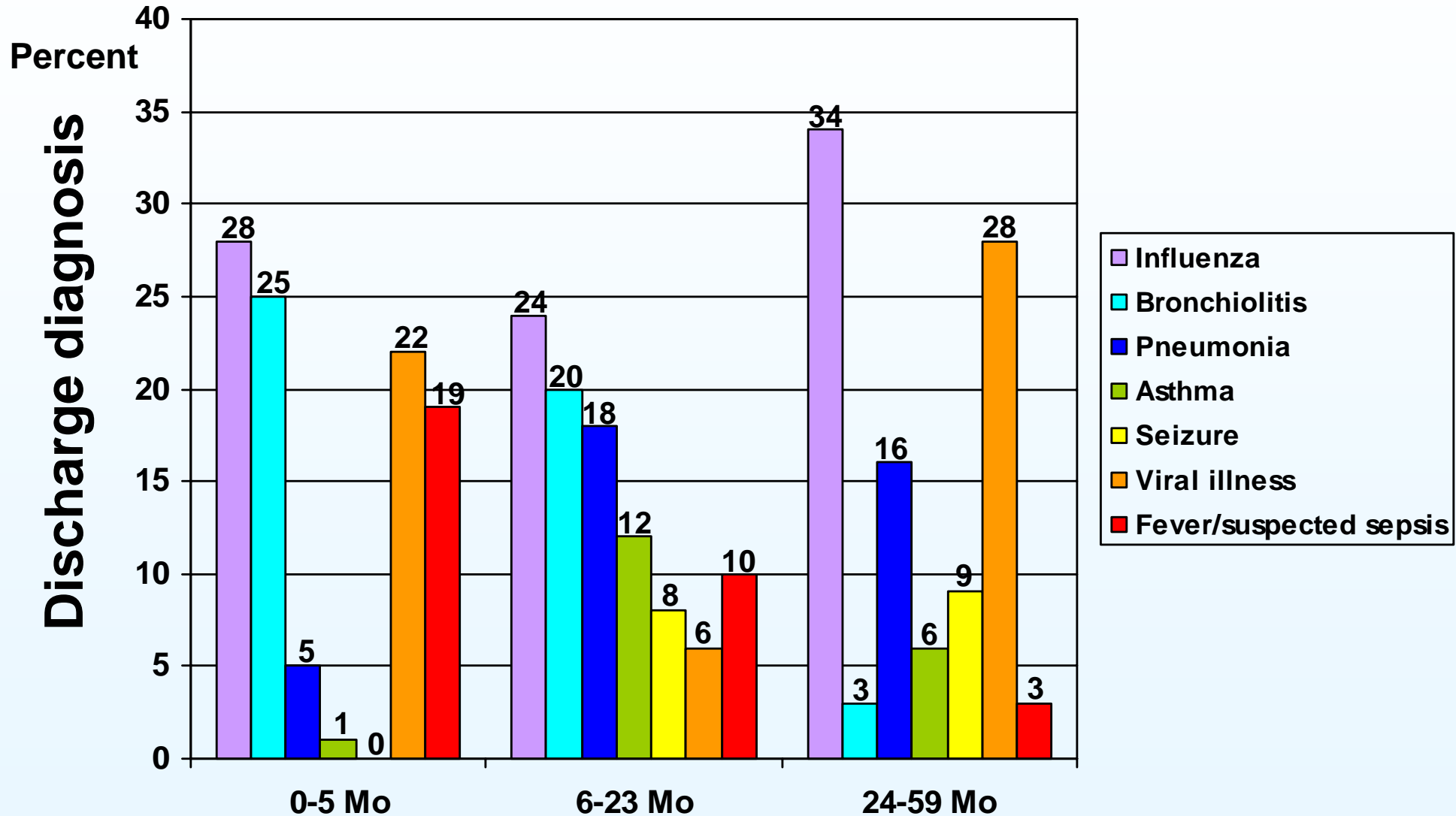
***NP wash for -PCR: positive influenza B***

# The Challenges of Making Diagnosis

- **Definite diagnosis cannot be made by clinical manifestation**
  - **Of all the patients with ILI, only 5-10% had influenza.**
  - **Diagnostic tests available are not perfect**
    - **Rapid test is not sensitive**
    - **PCR is expensive, longer turn-around time, not widely available**
  - **Over-diagnosis >> overuse of antiviral drugs**
  - **Under-diagnosis >> delayed antiviral treatment and may result in serious diseases**

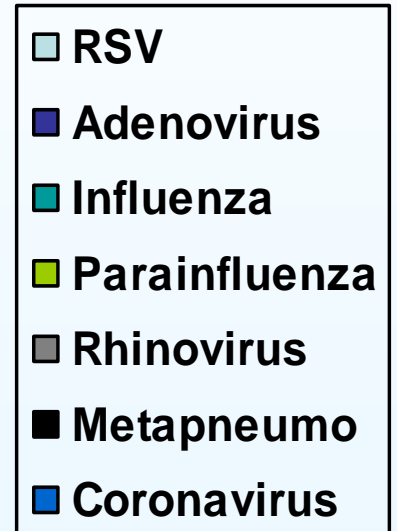
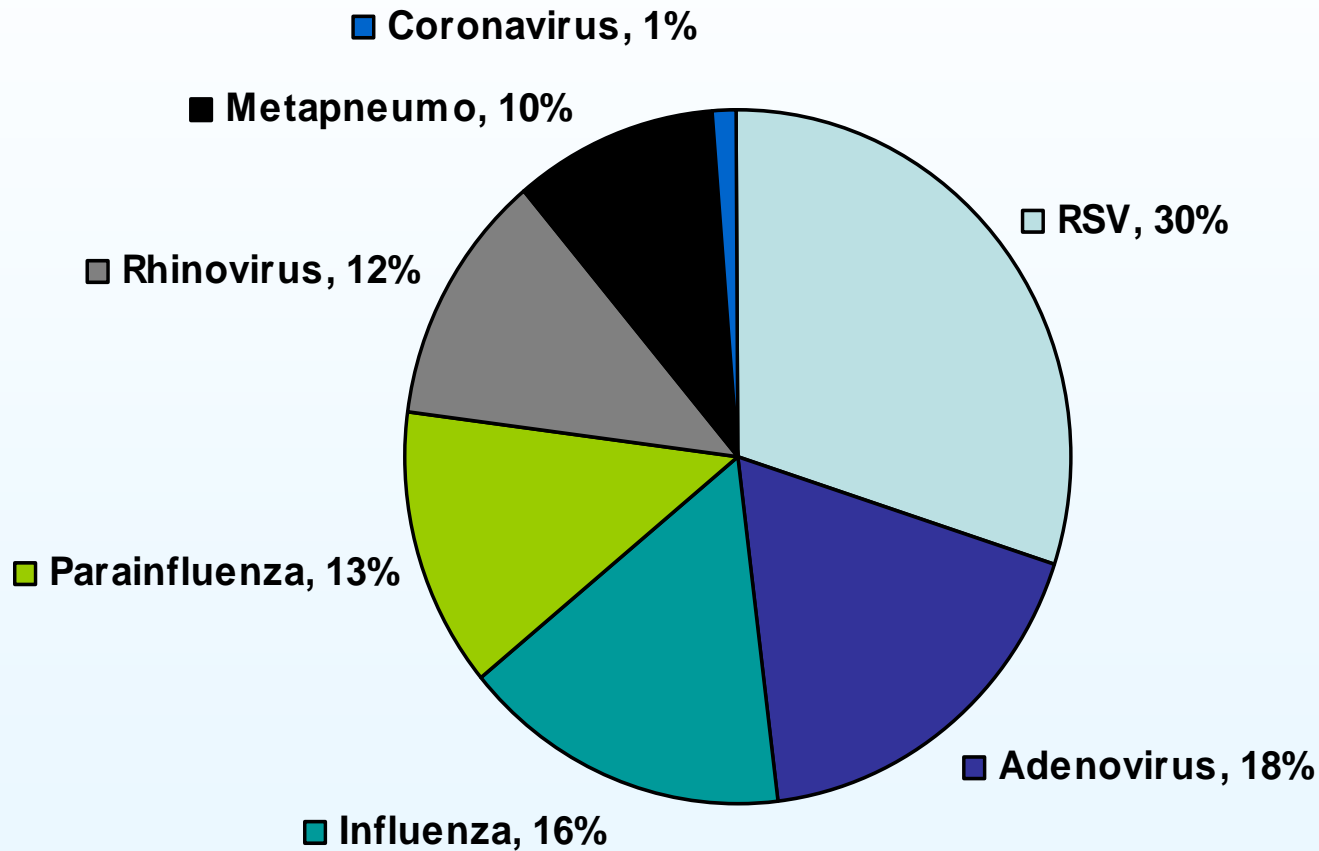
# Discharge Diagnosis in Patients Hospitalized With Influenza

*Only 17% of outpatient confirmed influenza got diagnosis of influenza*



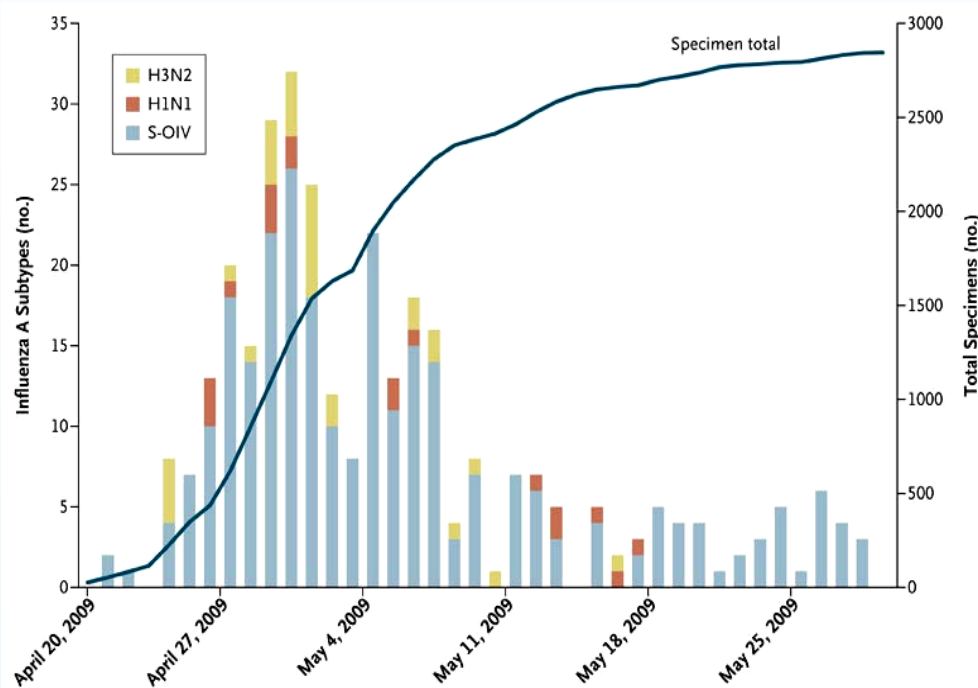
# Viral Etiologies of Pneumonia in Children: SEA Network in Thailand (N=136)

*Use Seeplex*



# Rapid-Test Sensitivity

Naval Health Research Center,  
April 20 - May 30, 2009, (N = 3066, pH1N1=767)



Rapid test (confirmed by RT-PCR)

	Sens	Spec
	95%CI	
H1N1(S-OIV)	51% (35-67)	99%
H1N1 (season)	63% (39-82)	99%
H3N2	31% (14-57)	99%

Naval Health Research Center. NEJM 2009;Jul 28.

<http://content.nejm.org/cgi/content/full/NEJMc0904264v1>

# Comparison of Rapid Antigen Detection Test, DFA, Viral Isolation for Influenza Using RT-PCR as the Gold Standard

Test	Sensitivity	Specificity	PPV	NPV
Rapid test (N=172) (QuickVue, Quidel)	18%	100%	100%	78%
DFA staining (N=172)	39%	100%	100%	82%
Viral isolation (N=526)	46%	100%	95%	95%

*Ganzenmueller T, et al. J Med Microbiol 2010;59:713-7.*

# Comparison of Specimens for Detection of Respiratory Viruses by Multiplex PCR (N=244)

<b>Samples</b>	<b># of viruses identified</b>	<b>Sensitivity (95%CI)</b>
<b>Oropharyngeal swab</b>	<b>136</b>	<b>54% (48-60)</b>
<b>Nasopharyngeal swab</b>	<b>184</b>	<b>73% (67-78)</b>
<b>Nasopharyngeal wash</b>	<b>213</b>	<b>85% (80-89)</b>
<b>OPS and/or NPS</b>	<b>212</b>	<b>85%</b>
<b>OPS and/or NPW</b>	<b>236</b>	<b>94%</b>
<b>NPS and/or NPW</b>	<b>239</b>	<b>95%</b>

# Diagnostic Testing vs Empirical Therapy for Patients Hospitalized with Suspected Influenza

## Diagnostic testing

- Reduces antibiotic use

- Reduces hospital admissions

- Misses 30%–65% of cases if PCR is not used

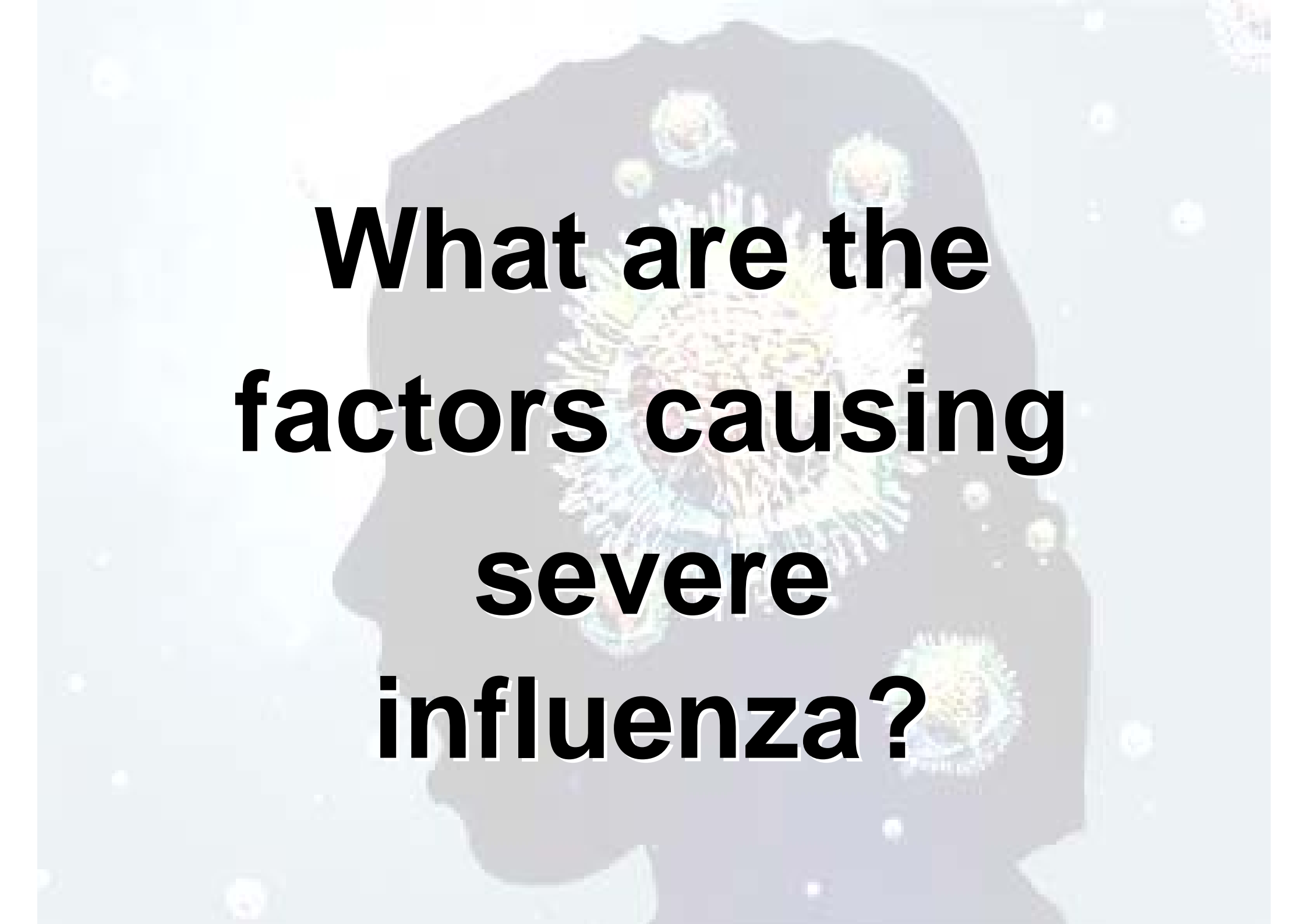
- Results in later treatment, which may not be as effective

## Empirical therapy

- Ensures timely treatment for patients with influenza

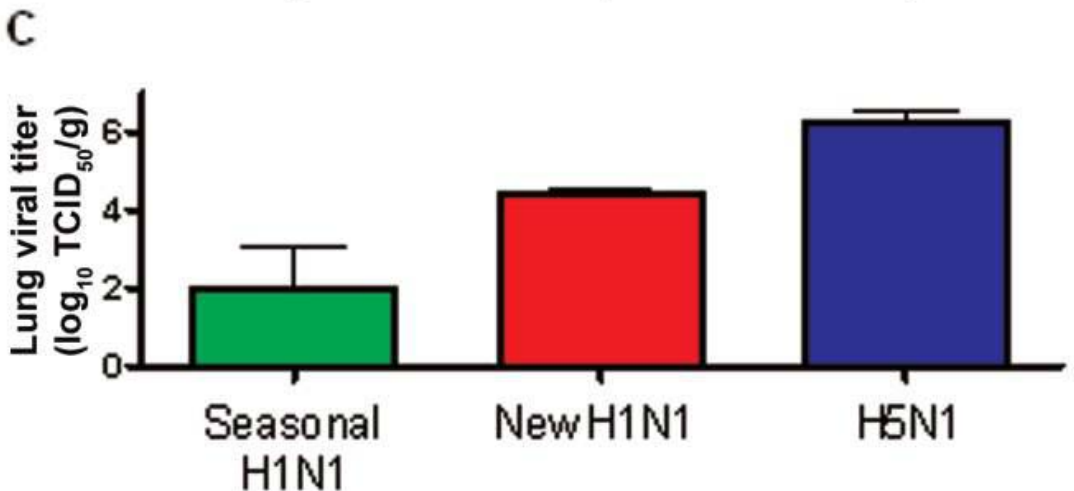
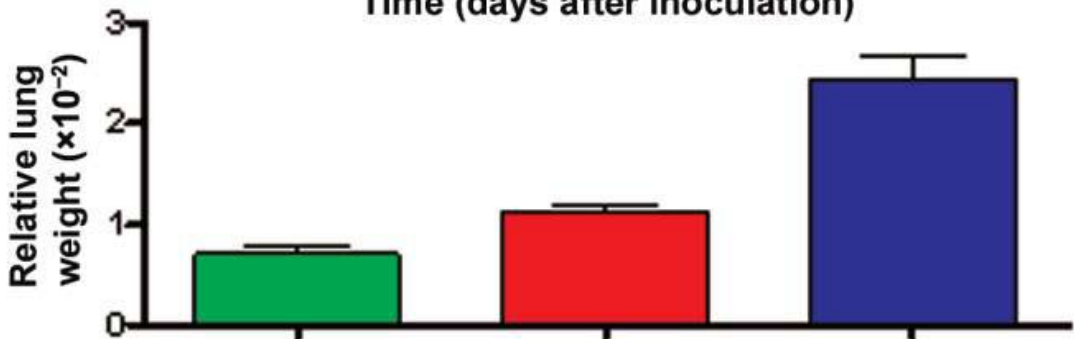
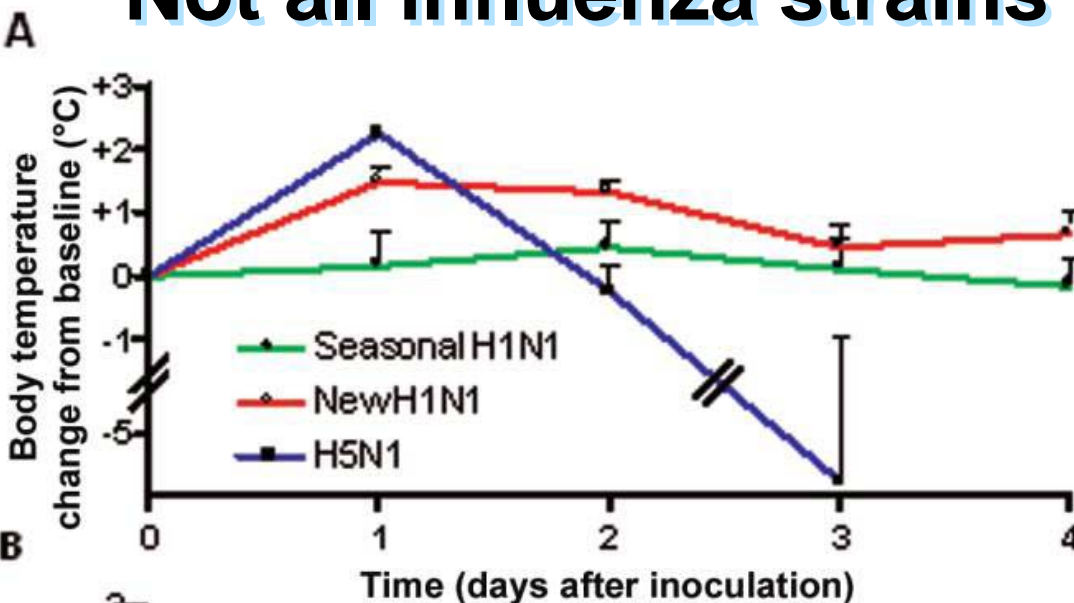
- Cost approximately the same as the cost of culture or RT-PCR

- Results in treatment for 5–15 patients without influenza for each patient with influenza



**What are the  
factors causing  
severe  
influenza?**

# Not all influenza strains were created equal!



## Severity of Pneumonia Due to New H1N1 Influenza Virus in Ferrets Is Intermediate between That Due to Seasonal H1N1 Virus and Highly Pathogenic Avian Influenza H5N1 Virus

The ferrets were intratracheally inoculated with seasonal H1N1 ( $np3$ ), new H1N1 ( $np6$ ) or highly pathogenic avian influenza (HPAI) H5N1 ( $np6$ ) influenza viruses at a dose of  $10^6$  median tissue culture infective dose (TCID<sub>50</sub>).

The increase in body temperature (A), the relative lung weight (B), and the lung viral titer (C) of the new H1N1 virus group were intermediate between those of the seasonal H1N1 virus group and that of the HPAI H5N1 virus group.

# Underlying Conditions in Hospitalized Patients with 2009 H1N1 Influenza, US, April-June 2009.

Medical Condition	All Patients (N=272)	Patients <18 yr (N=122)	Patients ≥18 yr (N=150)
		<i>number (percent)</i>	
Any one condition	198 (73)	73 (60)	125 (83)
Asthma	76 (28)	35 (29)	41 (27)
Chronic obstructive pulmonary disease	22 (8)	0	22 (15)
Diabetes	40 (15)	3 (2)	37 (25)
Immunosuppression	40 (15)	11 (9)	29 (19)
Chronic cardiovascular disease	35 (13)	5 (4)	30 (20)
Chronic renal disease	25 (9)	7 (6)	18 (12)
Neurocognitive disorder	20 (7)	14 (11)	6 (4)
Neuromuscular disorder	19 (7)	13 (11)	6 (4)
Pregnancy	18 (7)	1 (1)	17 (11)
Seizure disorder	18 (7)	13 (11)	5 (3)

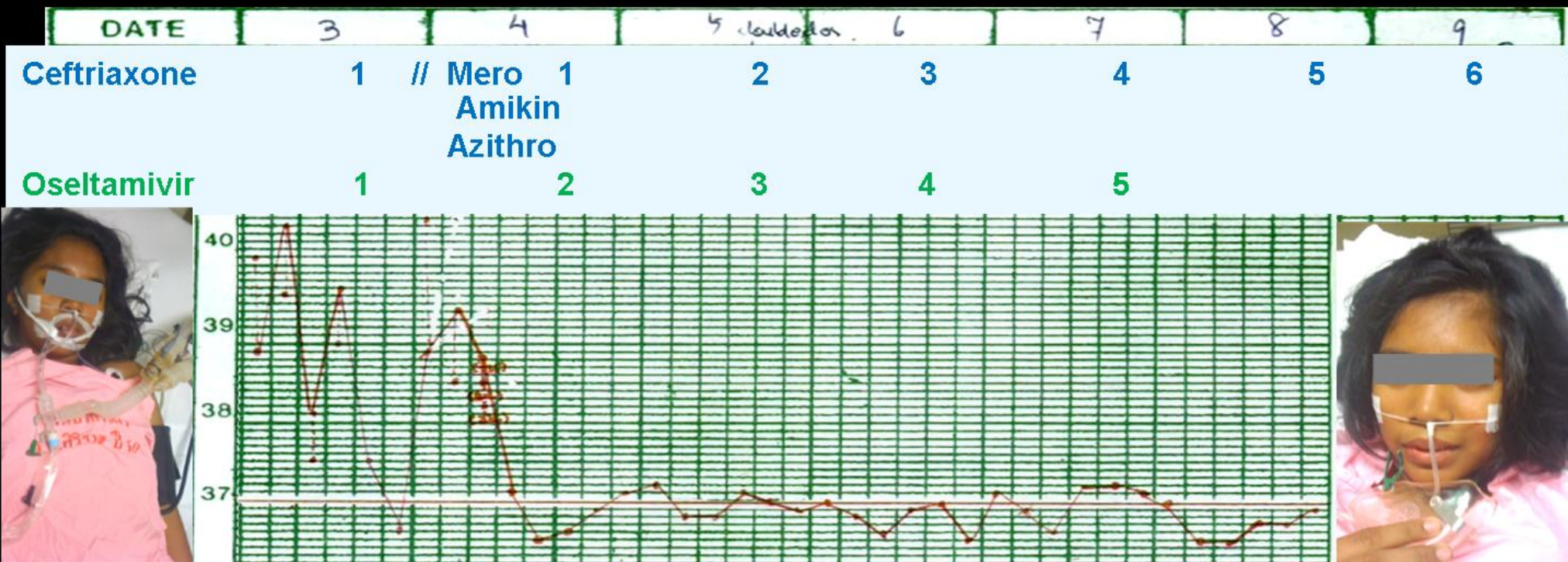
**20-40% of hospitalized pH1N1 had no underlying conditions**

# A 12 year-old girl no underlying disease

- High grade fever, rhinorrhea and cough x 5 days
- **After admission she developed respiratory failure and shock.**
- BT 40.2°C, P 130/min, RR 50/min, BP 100/60 mmHg (after NSS loading), SpO<sub>2</sub> 88-90% (mask with bag 10 LPM)
  - GA : tachypnea, dyspnea, on ET-tube
  - RS : fine crepitation both lungs
  - CVS : normal S<sub>1</sub>, S<sub>2</sub>, no murmur
  - No hepatosplenomegaly
  - Skin : no rash or petichiae



**NP wash: Positive  
PCR for pH1N1 –**



- **Treatment** : Ceftriaxone 75 mg/kg/day then Meropenam, Amikacin and Azithromycin  
: Oseltamivir - double dose (75) 2 Cap q 12 hr, 10 days.
- **Outcome** : Full conscious at discharge and normal CXR.

# Oseltamivir Can Make A Difference If Start Early

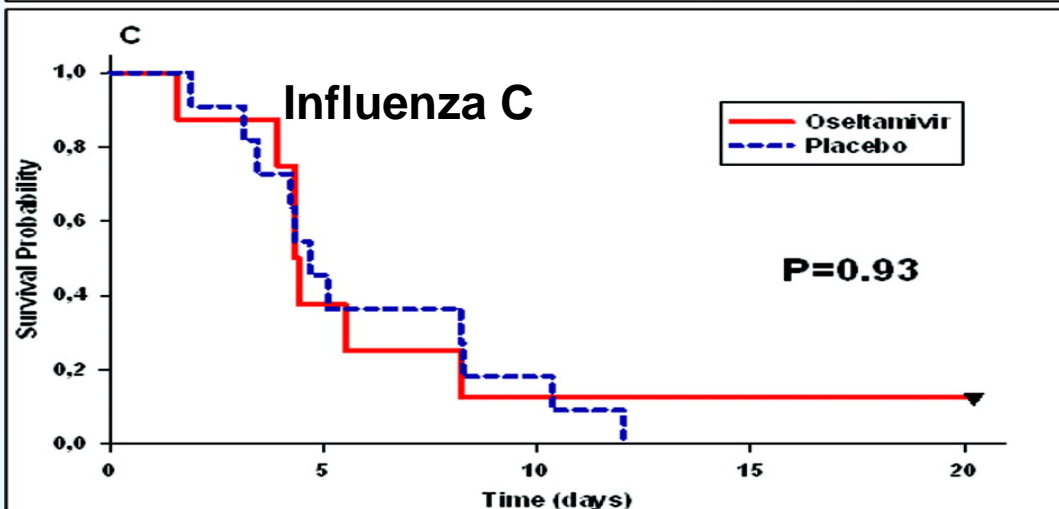
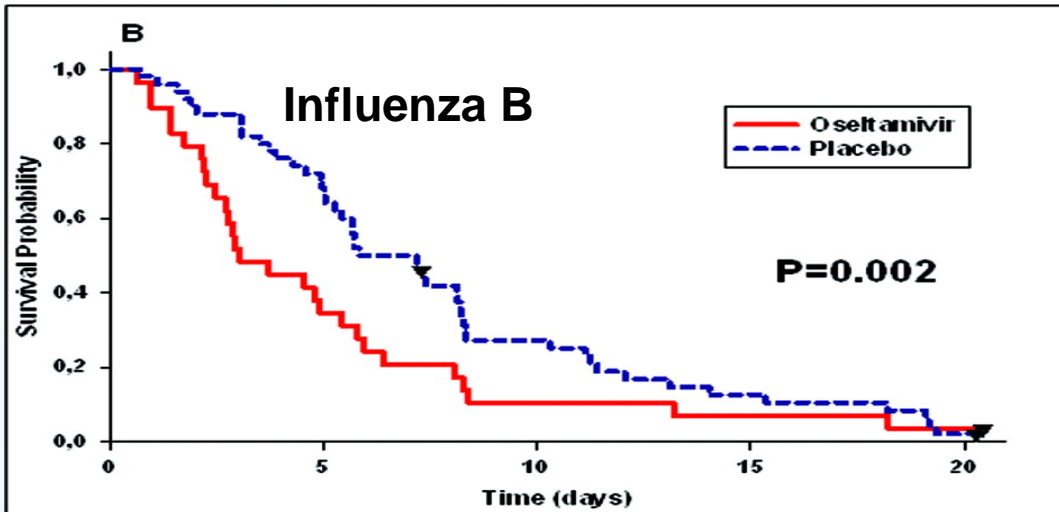
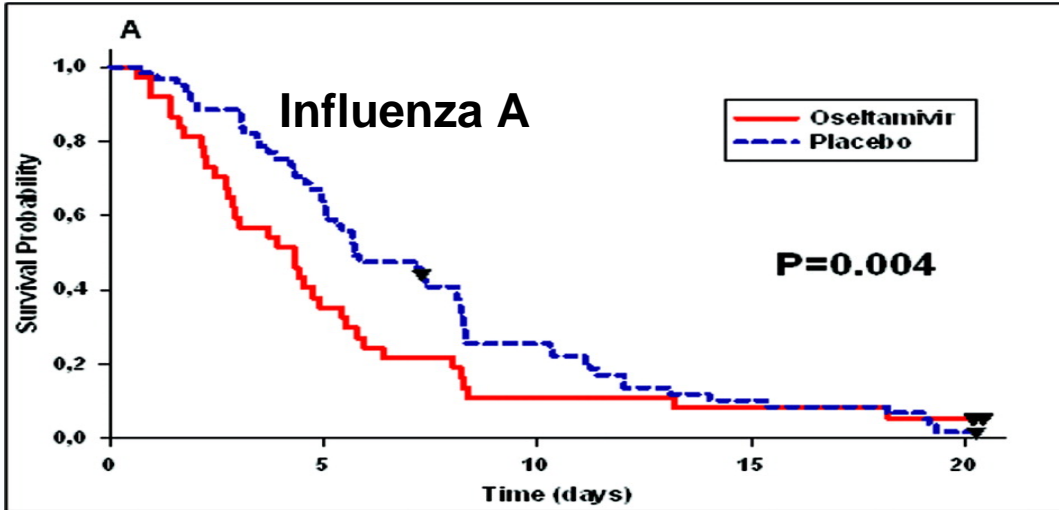


# Oseltamivir (within 48 hr of onset) Reduced Influenza Associated LRT Complications

**10 Phase 3, DB placebo controlled trials (N=3564)**

	Placebo (%)	Oseltamivir (%)	<i>P</i>
<b>All</b>	<b>109 (10.3)</b>	<b>62 (4.6)</b>	<b>&lt;0.001</b>
<b>Bronchitis</b>	<b>87 (8.2)</b>	<b>53 (3.9)</b>	
<b>Pneumonia</b>	<b>19 (1.8)</b>	<b>9 (0.7)</b>	
<b>Hospitalization</b>	<b>18 (1.7)</b>	<b>9 (0.7)</b>	<b>0.02</b>
<b>Took ATB</b>	<b>19.1%</b>	<b>14%</b>	<b>&lt;0.001</b>

# Early Oseltamivir Treatment of Influenza (within 24 hours of illness) in Children 1–3 Years of Age: A Randomized Controlled Trial (N=408)



- When start in 12 hr. reduce AOM by 85%
- When start in 24 hr. shorten illness 3.5 d of influenza A

# Impact of Oseltamivir on Mortality in Lab-Confirmed Influenza: Toronto Invasive Bacterial Diseases Network 2005-6

Variables	OR (95% CI)
• Oseltamivir therapy	0.21 (0.06-0.80)
– Initiation after 48 hr, including only death from influenza	0.24 (0.06-0.85)
• ICU admission	10.5 (3.9-27)
• Charlson score	1.3(1.0-1.6) /unit
• Time from onset to ER	0.51 (0.31-0.87)/day

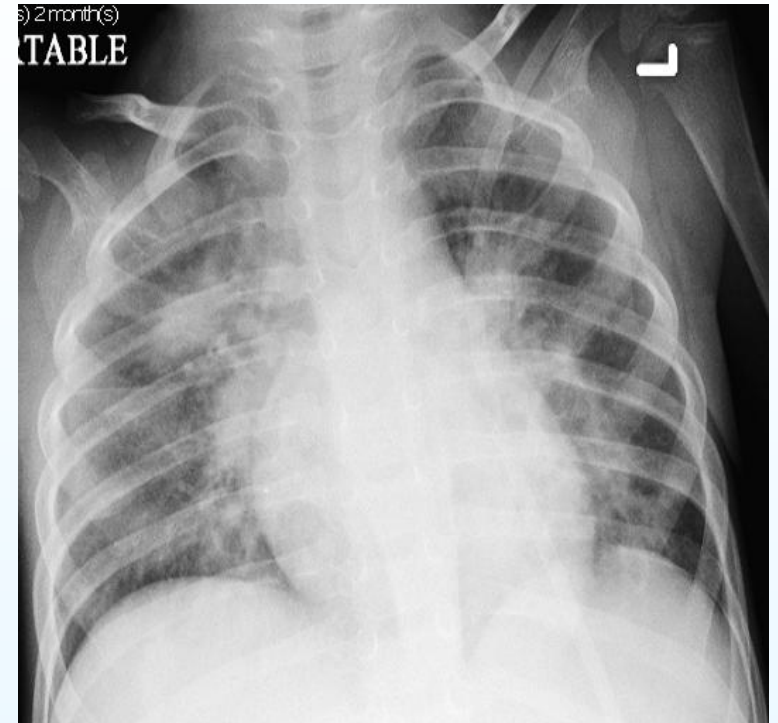


**If the patients do  
not response  
to oseltamivir...**

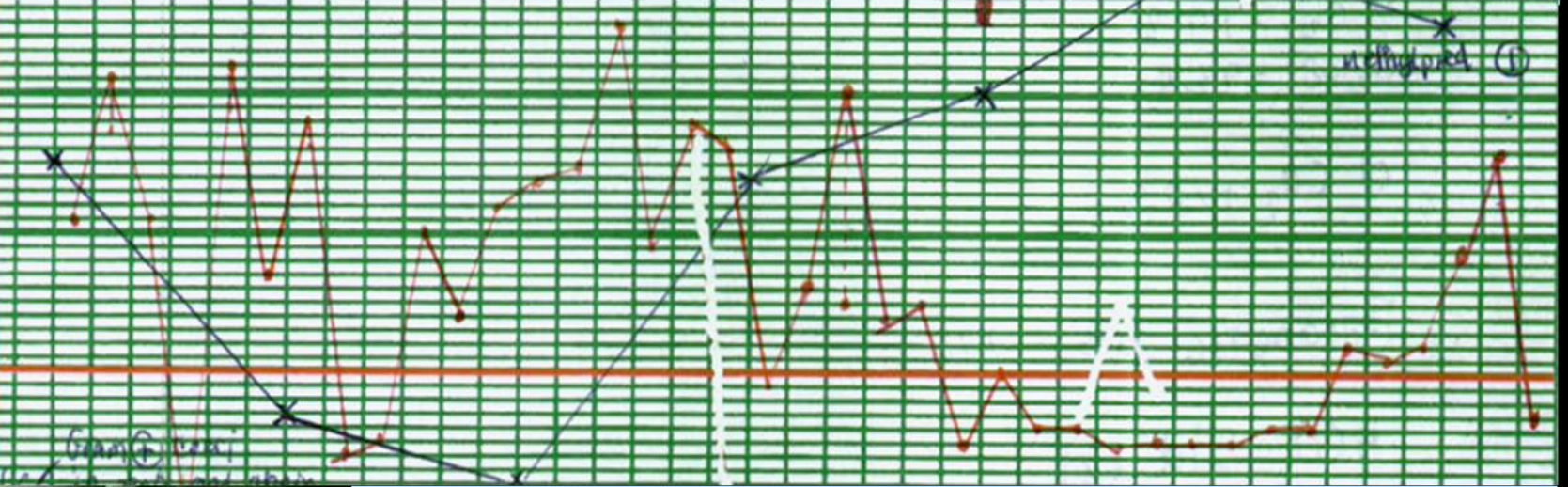
**What's next?**

# 1 year-old girl

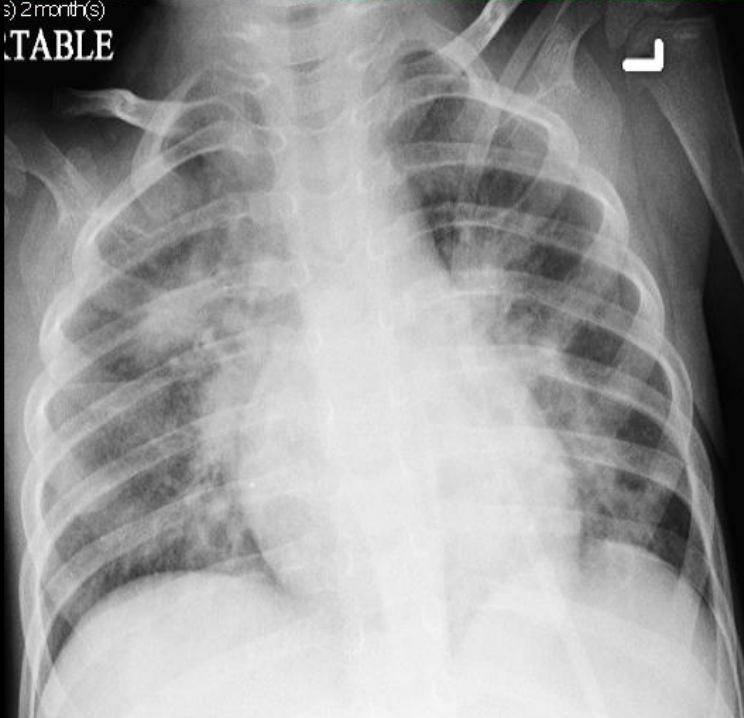
- **Underlying : First diagnosis AML (M5)**
- **2 days, high grade fever, rhinorrhea, cough and dyspnea**
- **T 39°C, P 110/min, RR 50/min, BP 100/60 mmHg, SpO<sub>2</sub> 97 %**
  - **GA : tachypnea, dyspnea**
  - **RS : wheezing and crepitation both lungs**
  - **CVS : normal S1,S2, no murmur**
  - **hepatosplenomegaly**



DATE	29	30	31	1	2	3	4
Cefatidime	1	2	3 // Mero	1	2	3	4
Gentamicin	1	2	3 // Amikin	1	2	3	4
			Osetamivir	1	2	3	4



2 month(s)  
TABLE

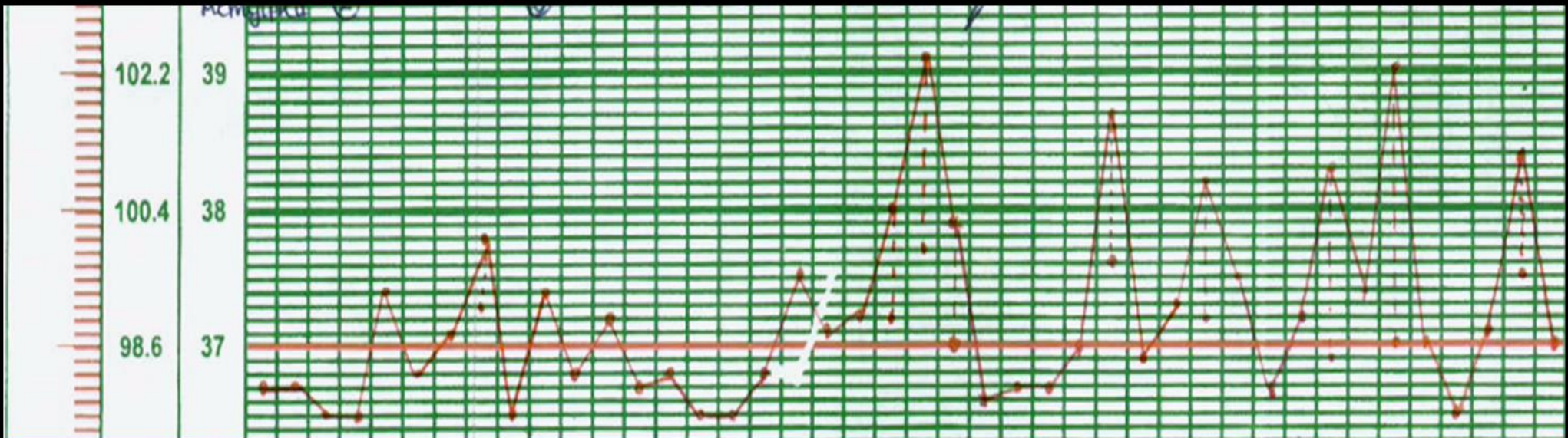


### CBC : 29/7/53

Hb 9.5 g/dL, Hct 24.1 %, WBC 33,200/mm<sup>3</sup>  
 <blast 74%, band 3%, myelocyte 6%,  
 metamyelo 3%> Plt 200,000 cell/mm<sup>3</sup>

- 1/8/53 : NP wash - PCR for pH1N1 - positive
- H/C – No growth, Sputum C/S –No growth
- Treatment : On ET-tube with ventilator

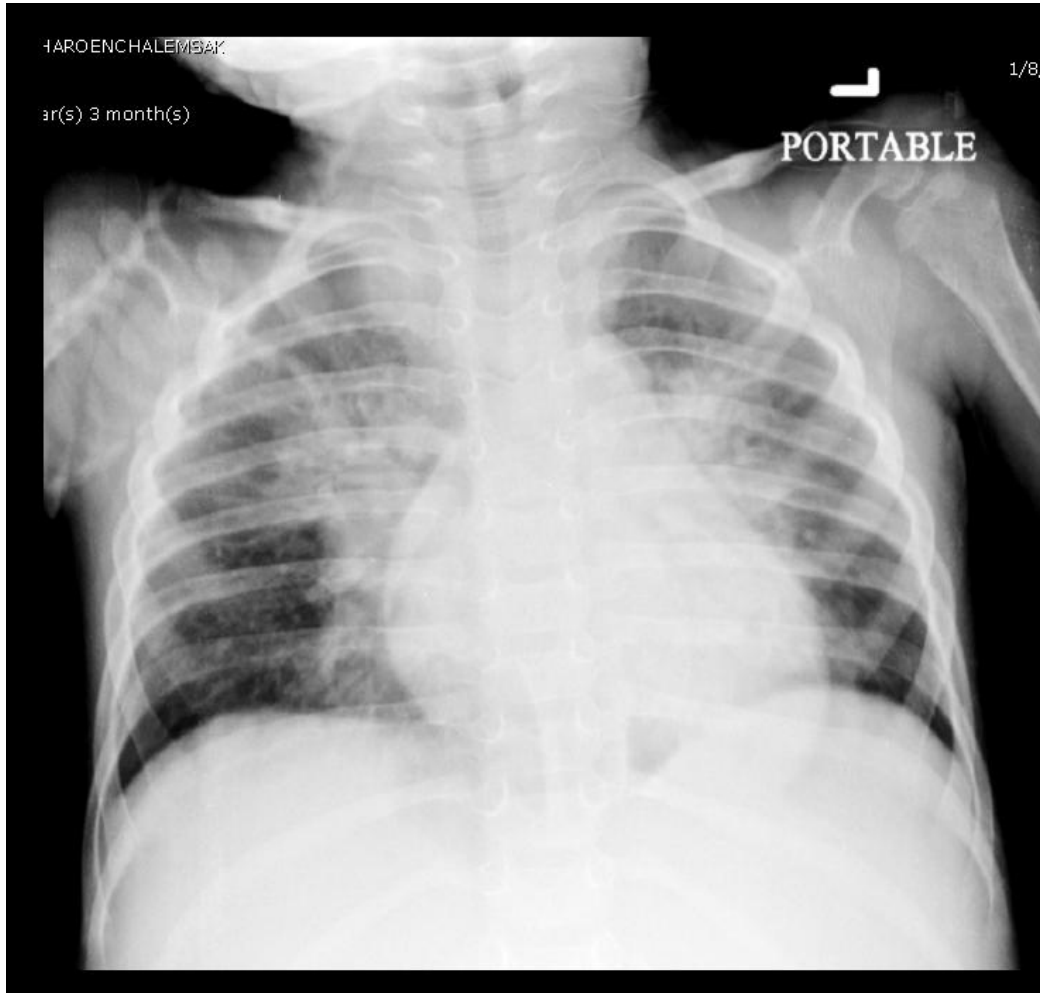
DATE	5 am	6 am	7 am	8 am	9 am	10 am	11 am
Meropenam	5	6	7	8	9	10	11
Amikacin	5	6	7 //				
Oseltamivir	5	6 //					
Chemo AraC			1	2	3	4	5
MTX			1				



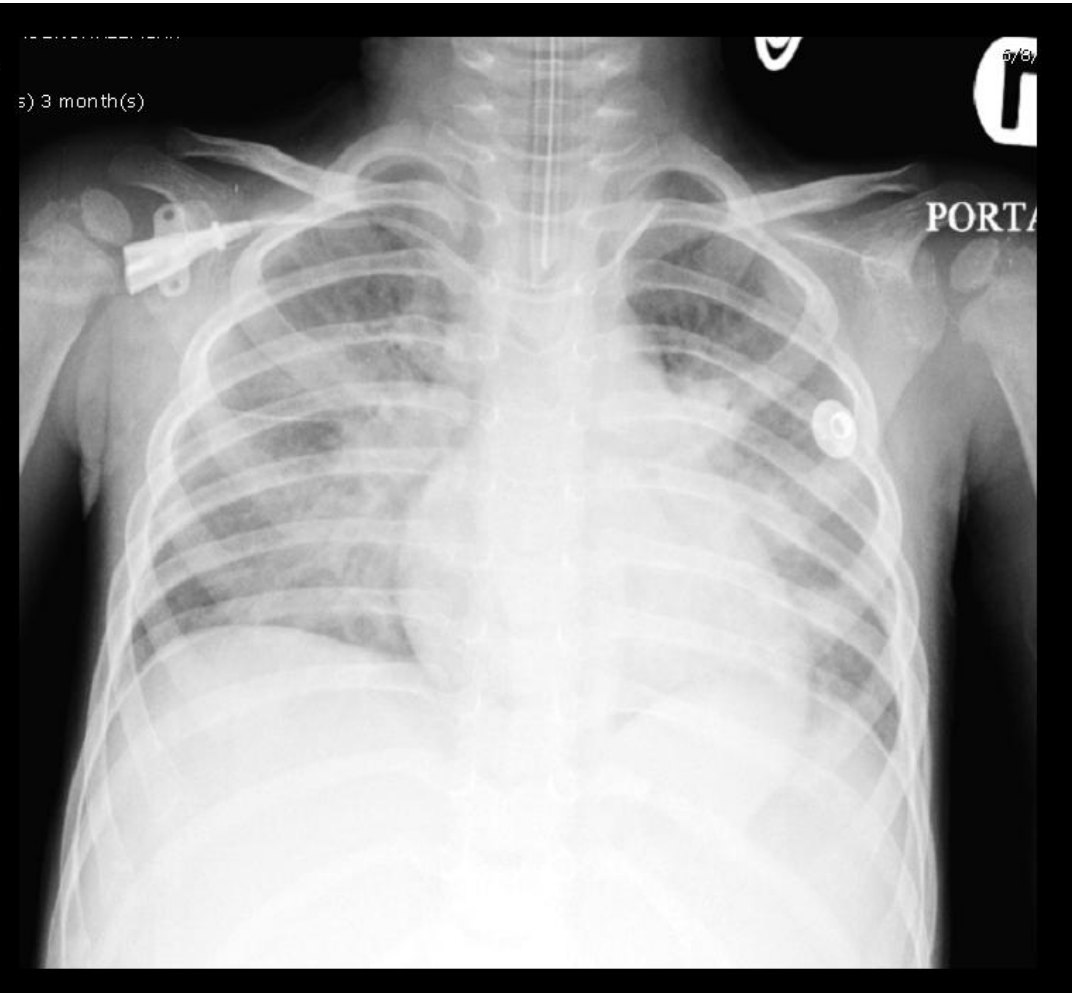
- After oseltamivir 6 days, clinical not improve and NP wash for pH1N1 persistent positive

- **5/8/53 : NP wash - PCR for pH1N1 – positive**

- **CBC : Hb 8.3, Hct 25.6, WBC 118,850 (blast 62%, N 2%, lymph 34), Plt 95,500/mm<sup>3</sup>**



**At day 1 of  
Oseltamivir**

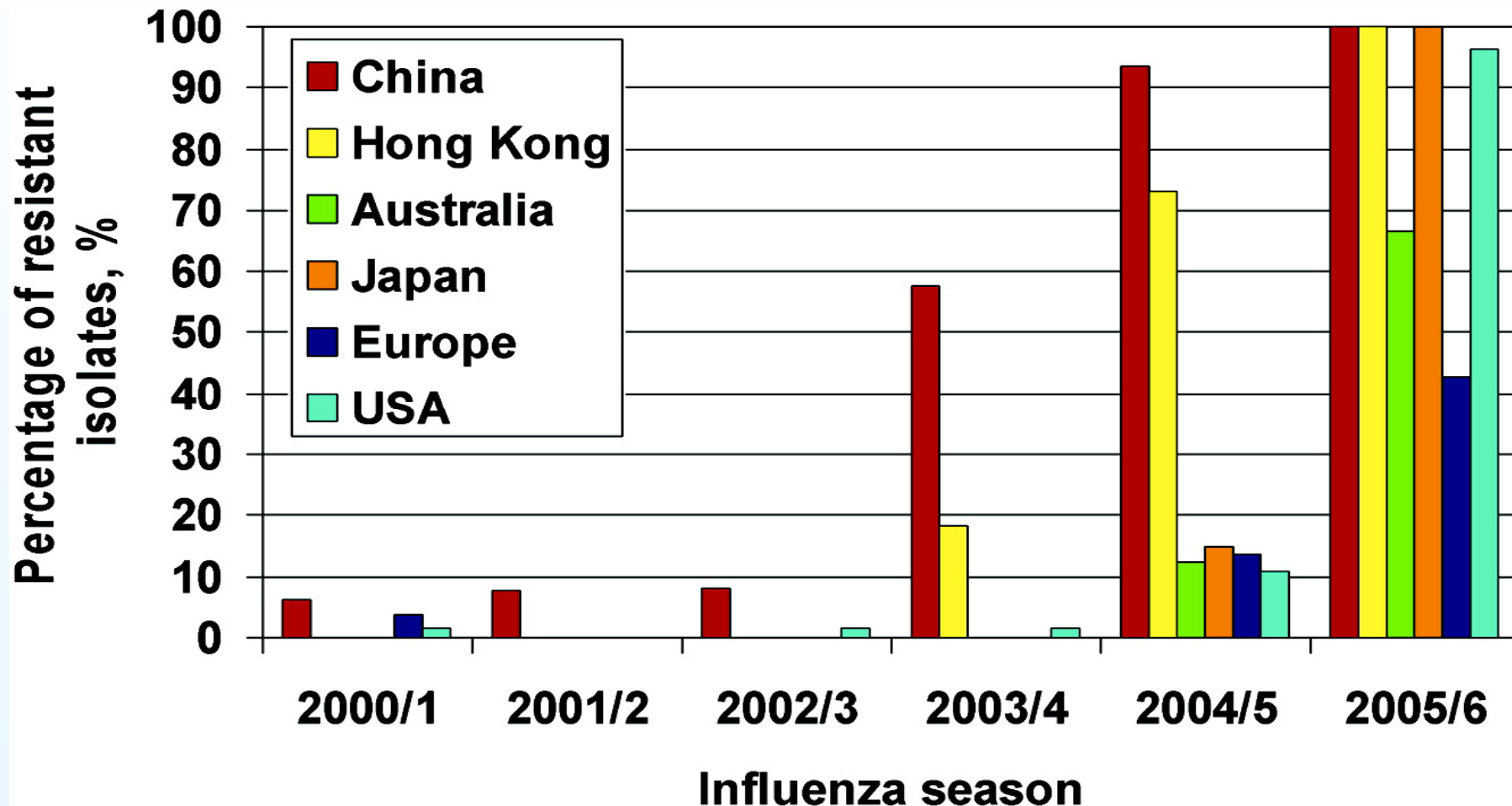


**At day 6 of Oseltamivir**

# **When the patients do not response promptly to oseltamivir, what could be the reasons:**

- **It's not just influenza**
- **Disease was just too severe or delayed treatment**
- **Less susceptible virus/ drug resistance**
- **Problems of oseltamivir administration: poor absorption, poor tissue levels**
- **Need for additional/adjunctive treatment**

# Antiviral resistance to M2 inhibitors in community isolates of influenza A(H3N2) virus, 2000–2006



# Seasonal Influenza A (H1N1)

## Resistant to Oseltamivir:

WHO Mar 2009

Some Regions	No of isolates	%resistant
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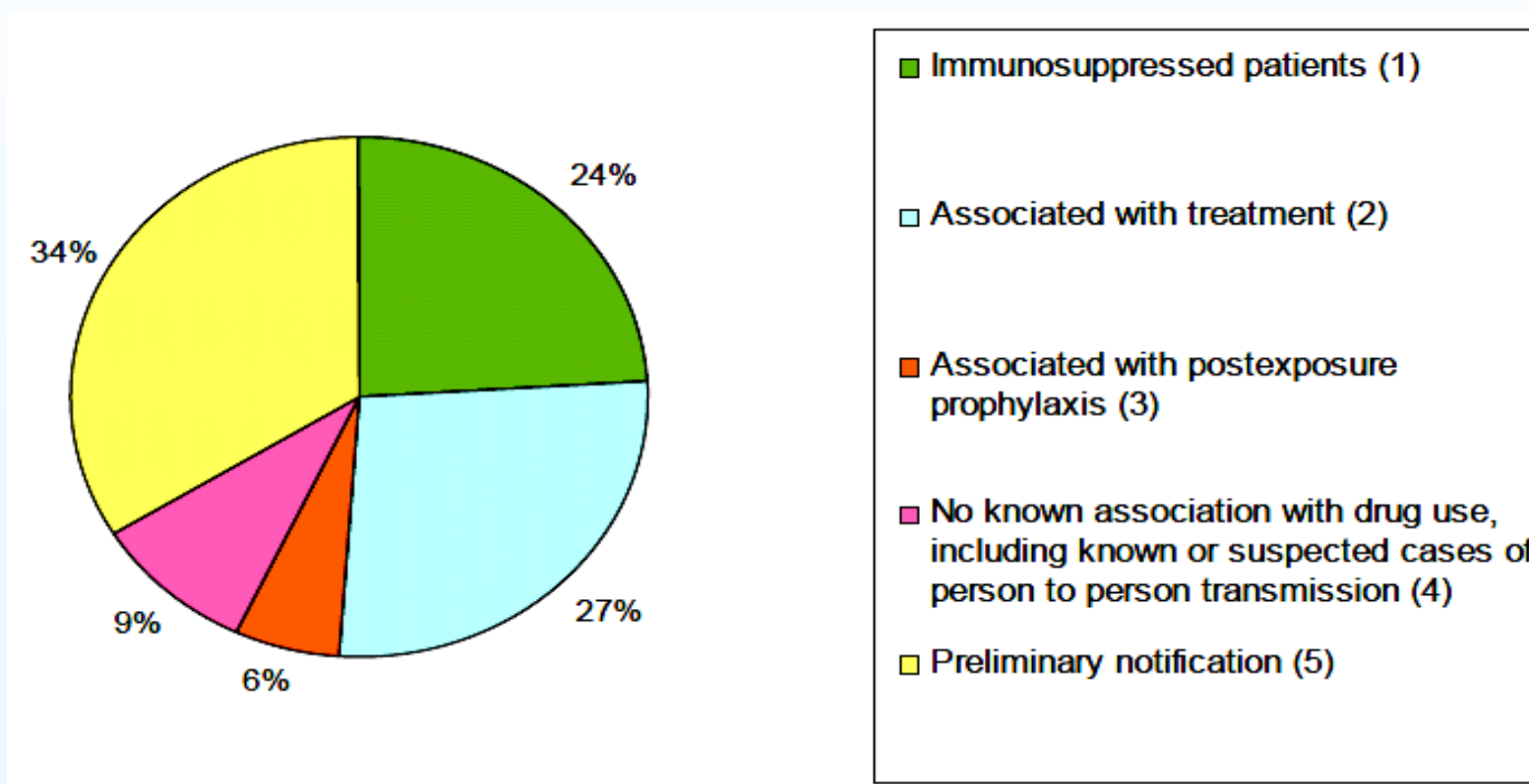
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• AMRO	301	98%
• EURO	209	98%
• SEARO	12	92%
• WPRO	822	94%
• Total	1362	95%

# Oseltamivir resistance in pandemic influenza A (H1N1) 2009 virus has been reported

Geographical distribution of oseltamivir resistance by the WHO regions (as of 9 June 2010)

	WHO Region					
	AFRO	EMRO	EURO	PAHO	SEARO	WPRO
Number of oseltamivir resistant isolates	0	1	99	82	0	16



# Neuraminidase Inhibitor Resistance after Oseltamivir Treatment of Acute Influenza A and B in Children

Virus subtype, patient number	Age	Weight, kg	IC <sub>50</sub> to oseltamivir (and zanamivir), nmol/L, by time of obtainment of a sample			NA mutation	Symptoms, by time of obtainment of a sample	
			Before treatment	Days 5–6	Day 9		Days 5–6	Day 9
A/H1N1								
34	3 years, 1 month	13.7	1.32 (0.98)	738 (2.57)	...	H274Y	Improved, afebrile	Fully recovered
37	5 years, 2 months	17	1.39 (0.27)	...	583 (1.89)	H274Y	Fully recovered	Fully recovered
42	2 years, 1 month	12.3	0.97 (1.06)	563 (1.63)	...	H274Y	Fully recovered	Fully recovered
A/H3N2: 106	1 year, 3 months	8.9	0.69 (0.51)	500 (13.49)	...	R292K	Improved, afebrile	Fully recovered

**NOTE.** IC<sub>50</sub>, 50% inhibitory concentration.

**The patients recovered well. Resistant strains were fit**

# Clinical Effectiveness of Oseltamivir and Zanamivir for Treatment of Influenza A Virus Subtype H1N1 with and without the H274Y Mutation: A Japanese, Multicenter Study of the 2007–2008 and 2008–2009 Influenza Seasons

**Table 2. Duration of Fever for Patients with Influenza Virus A Subtypes H1N1 and H3N2 Treated with Oseltamivir or Zanamivir Therapy**

Variable	H1N1 virus			H3N2 virus	
	2007–2008	2008–2009	<i>P</i> <sup>a</sup>	2008–2009	<i>P</i> <sup>b</sup>
Duration of fever after administration of the first dose, mean h ± SD					
Oseltamivir	32.0 ± 18.9 ( <i>n</i> = 41)	49.1 ± 30.2 ( <i>n</i> = 77)	<.001	33.7 ± 20.1 ( <i>n</i> = 31)	<.01
Zanamivir	31.5 ± 14.9 ( <i>n</i> = 27)	27.5 ± 18.5 ( <i>n</i> = 87)	NS	30.1 ± 18.0 ( <i>n</i> = 28)	NS
<i>P</i> value between oseltamivir and zanamivir	NS	<.001		NS	

**All H1N1 in 2007-2008 tested were susceptible to oseltamivir and all of the H1N1 in 2008-2009 tested were resistant to oseltamivir**



**Zanamivir is effective  
in oseltamivir  
resistant virus**

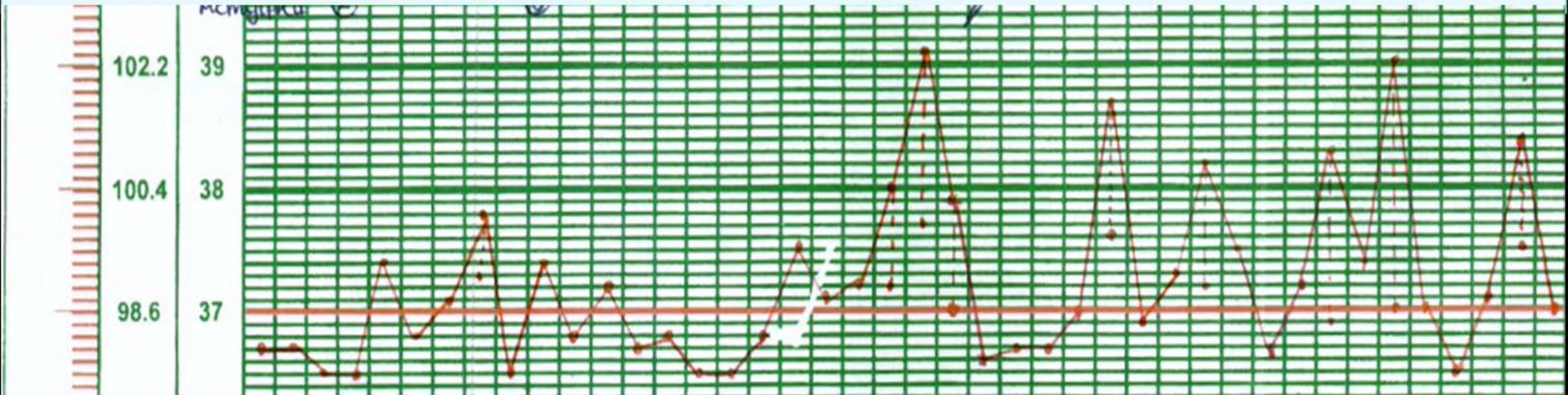
**Can Zanamivir be  
used in severe cases  
who cannot use  
Diskhaler?**

**Zanamivir is FDA approved for influenza treatment (patients aged  $\geq 7$  years) and prophylaxis (patients aged 5 years) in patients without underlying airway diseases and is to be administered using a Diskhaler device.**

**The US Food and Drug Administration (FDA) and GlaxoSmithKline are reporting the death of a person with influenza after receiving zanamivir inhalation powder (*Relenza*) that had been dissolved and administered with a nebulizer (October 10, 2009)**

- **"There is a risk that the lactose sugar in this formulation can obstruct proper functioning of mechanical ventilator equipment"**
- **The patient was a pregnant woman on mechanical ventilation who received the nebulized solution for 3 days. Death was attributed to obstruction of the ventilator.**

DATE	5 am	6 am	7 am	8 am	9 am	10 am	11 am
Meropenam	5	6	7	8	9	10	11
Amikacin	5	6	7 //				
Oseltamivir	5	6 //					
<b>Zanamivir</b>		<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>
Chemo AraC			1	2	3	4	5
MTX			1				



- After oseltamivir 6 days, clinical not improve and NP wash for pH1N1 persistent positive

- 5/8/53 : NP wash - PCR for **pH1N1 – positive**
- **Zanamivir 10 mg/k/dose nebulizer with ambu bag q 12 hrs started after D6 of oseltamivir.**

- **CBC : Hb 8.3, Hct 25.6, WBC 118,850 (blast 62%, N 2%, lymp 34), Plt 95,500/mm<sup>3</sup>**
- **Start chemotherapy 7/8/53**
- **Protocol TPOG-AML-03-08**

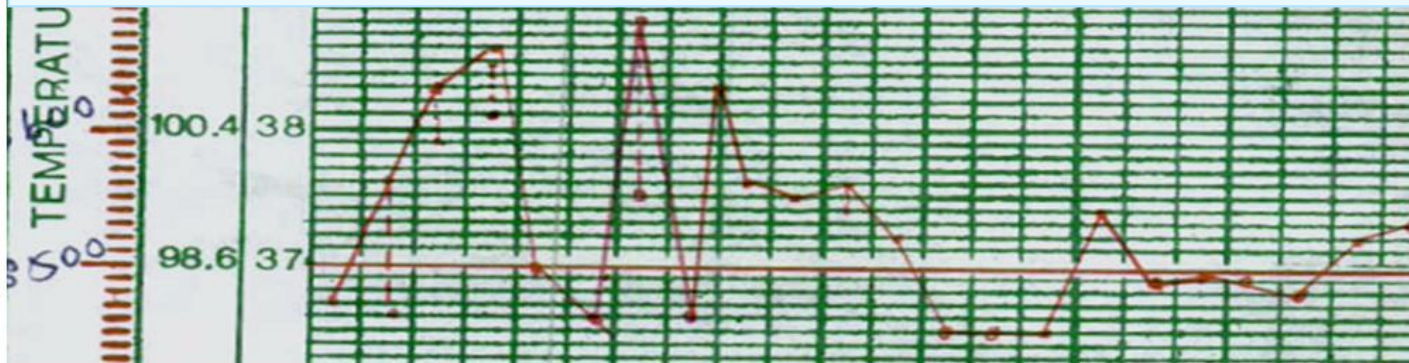
**Off-Label use:**  
**Zanamivir with ambu bag**  
**10 mg q 12 hr .**



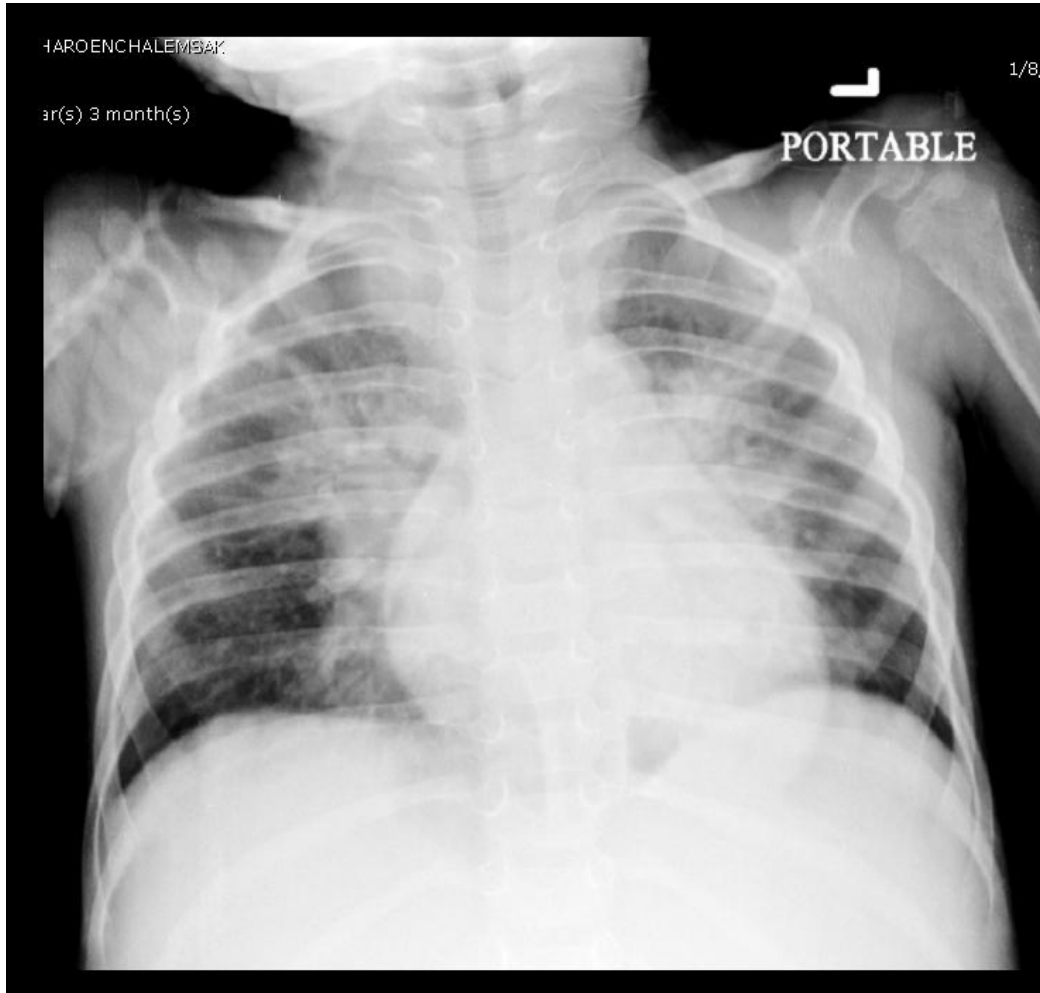
**Not Recommend** : Zanamivir dry  
 Powder nebulized with ventilator  
 because obstruction caused by lactose  
 content.



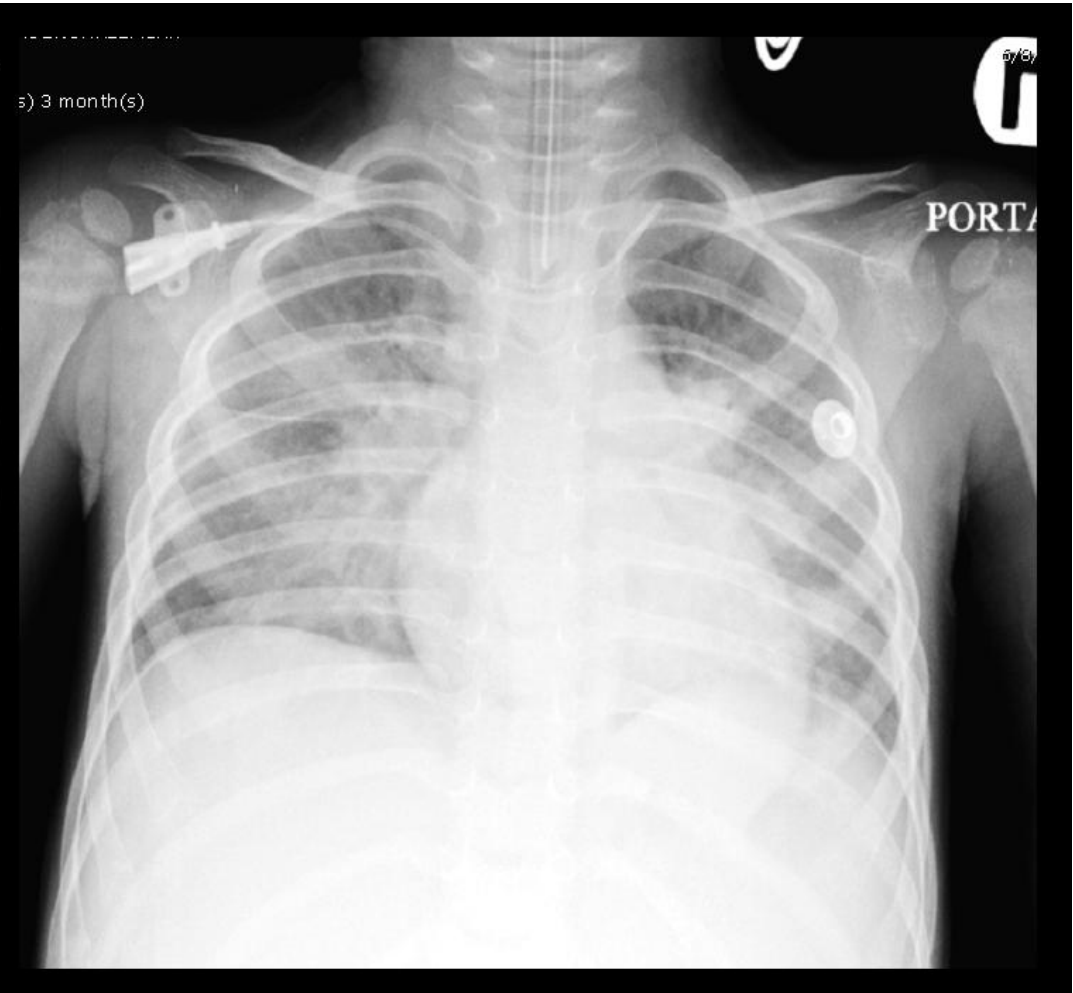
DATE	12 ธ.ค. 53	13	14	15
Meropenam	12	13	14	15
Zanamivir	7	8	9	10//
Chemo: Ara C : ETO				



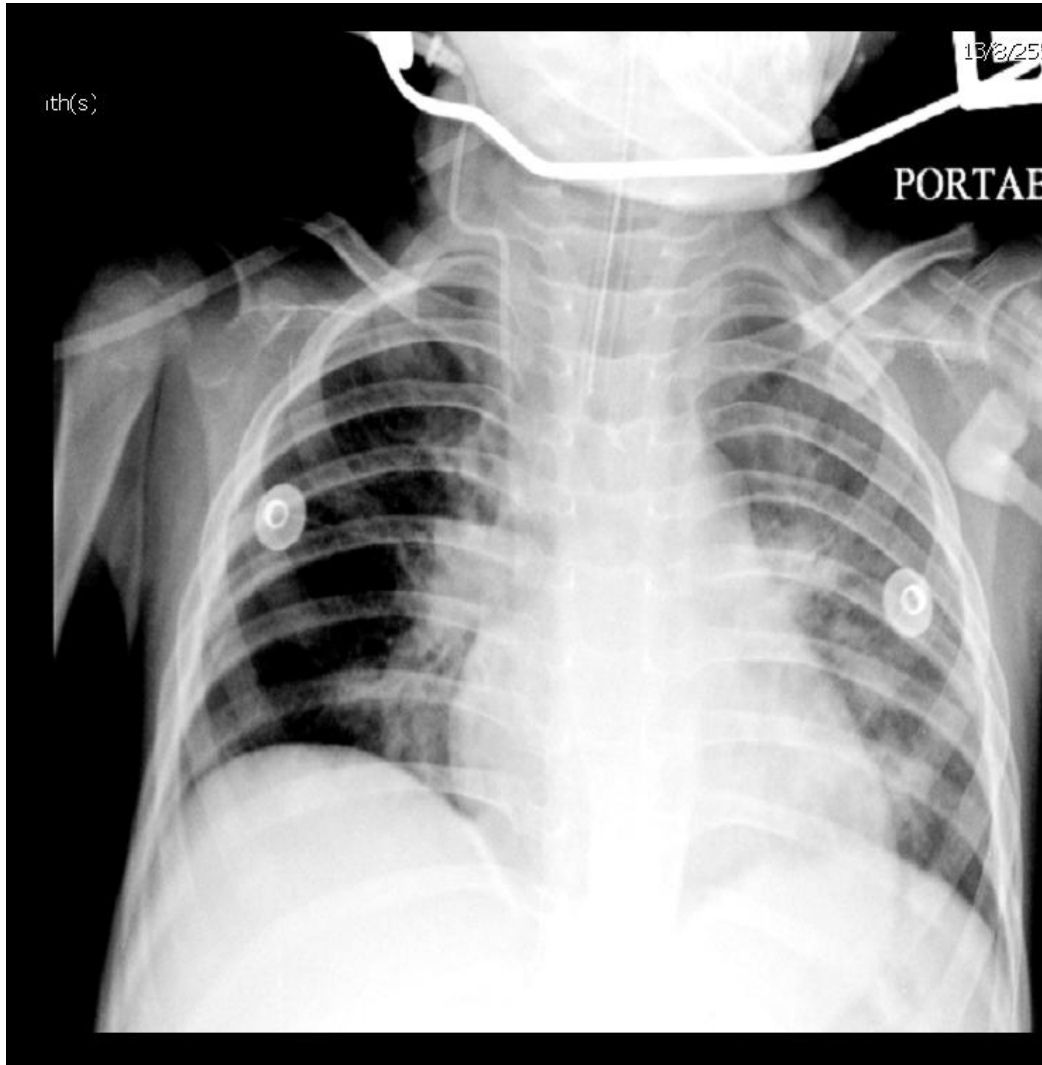
**Patient full  
 recovery**



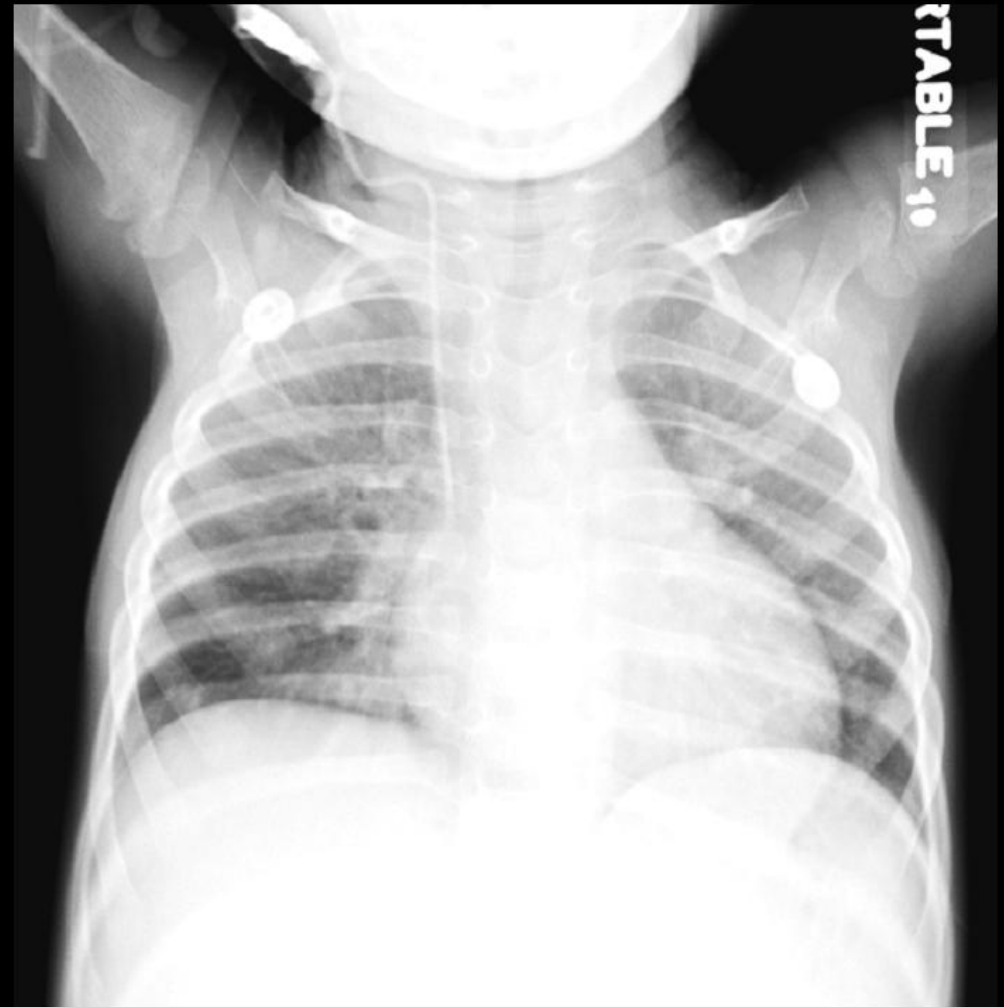
**At day 1 of  
Oseltamivir**



**At day 6 of Oseltamivir  
(end of oseltamivir),  
first day of Zanamivir  
treatment**



**At day 8 of Zanamivir  
On ET-tube**



**At day 10 of  
Zanamivir  
Off Et-tube**

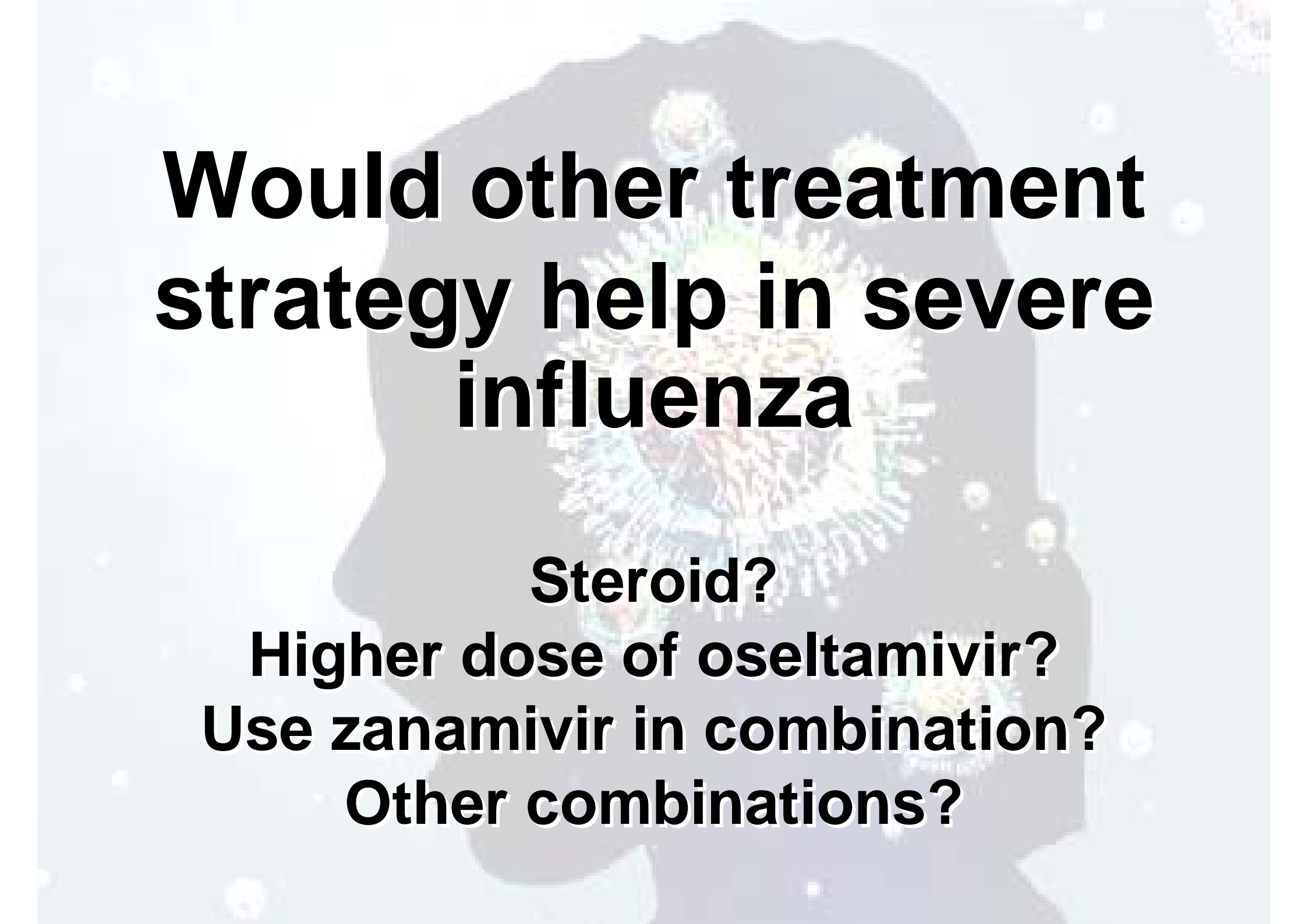
# In Vitro Neuraminidase Inhibition of Seasonal Influenza

Influenza virus strain	No. of isolates	IC <sub>50</sub> , median nmol/L (range)		
		Peramivir	Oseltamivir carboxylate	Zanamivir
A(H1N1)	5	0.34 (0.26–0.43)	0.45 (0.45–0.60)	0.95 (0.73–1.05)
A(H3N2)	6	0.60 (0.47–0.87)	0.37 (0.27–0.45)	2.34 (1.85–3.13)
B	8	1.36 (1.08–1.95)	8.50 (5.33–18.33)	2.70 (2.00–3.10)

*Hayden F. CID 2009;48 (Sup1):S3-13.*

# The Emergency Use Authorization of Peramivir for Treatment of 2009 H1N1 Influenza

- It was “reasonable to believe” that Peramivir may be effective
  - Improved symptoms 1 day sooner in uncomplicated seasonal influenza
  - No data in comparison with oseltamivir
  - No efficacy information for novel H1N1
  - **No data in children**
- It should be considered in patients with hospitalized severe influenza that may benefit from this i.v. drug
- Dose: 600 mg OD 5-10 days
- Common AE: vomiting, diarrhea, nausea, neutropenia



# **Would other treatment strategy help in severe influenza**

**Steroid?**

**Higher dose of oseltamivir?**

**Use zanamivir in combination?**

**Other combinations?**

# **Cytokine Profiles Induced by the Novel Swine-Origin Influenza A/H1N1 Virus: Implications for Treatment Strategies**

**Methods.** We assayed cytokines and their messenger RNA (mRNA) levels in culture supernatants of human macrophages infected with H5N1, S-OIV California/04/2009 (S-OIV-CA), S-OIV Hong Kong/415742 (S-OIV-HK), or seasonal H1N1 with or without celecoxib and mesalazine.

**Conclusions.** No major cytokine storm, as seen in H5N1 infection, is associated with S-OIV infection of cell lines. **The mainstay of treatment for uncomplicated S-OIV infections should be antiviral agents without immunomodulators.** For individual S-OIV–infected patients with severe primary viral pneumonia, severe sepsis, and multiorgan failure, immunomodulators may be considered as an adjunctive therapy in clinical trials.

# Is Steroid Helpful in Influenza?

## No clear evidence of benefit

- 143 hematopoietic cell transplant recipients with documented seasonal influenza infection
- In multivariable analyses, no difference between patients received no, low doses ( $< 1$  mg/kg/d) or high doses ( $\geq 1$  mg/kg/d) of corticosteroids with regards to the development of LRD, hypoxemia, need for mechanical ventilation or death.
- High dose steroids was associated with prolonged viral shedding (OR, 3.3;  $p = 0.01$ ).
- Antiviral therapy initiated to treat upper respiratory tract infection was associated with fewer cases of LRD (OR, 0.04;  $p < 0.01$ ) and fewer hypoxemia episodes (OR, 0.3;  $p = 0.03$ ).

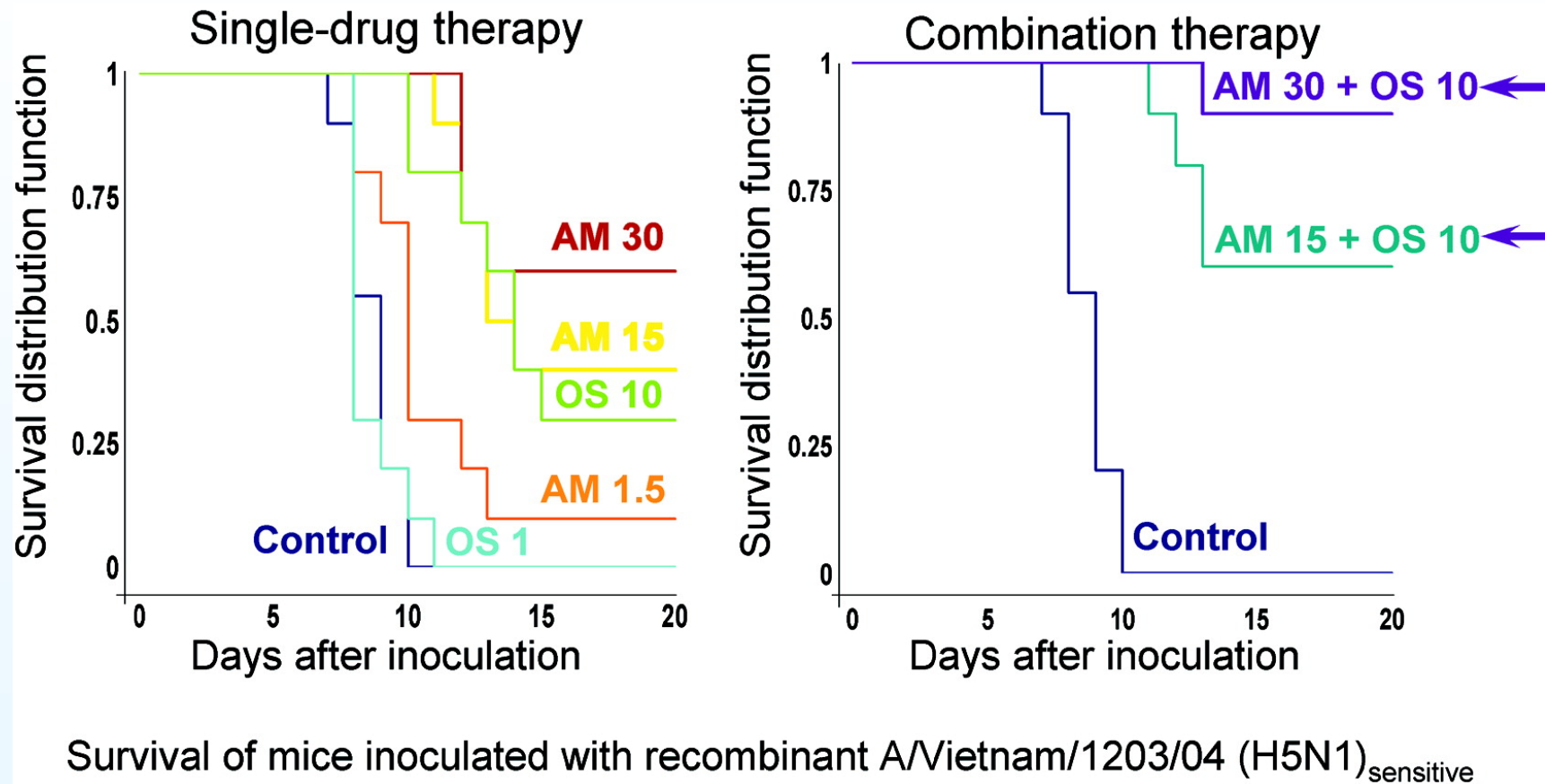
**But steroid was not harm, and can be used if indicated**

# **Would Double Dose Oseltamivir Helpful in Severe Cases?**

**Preliminary report:**

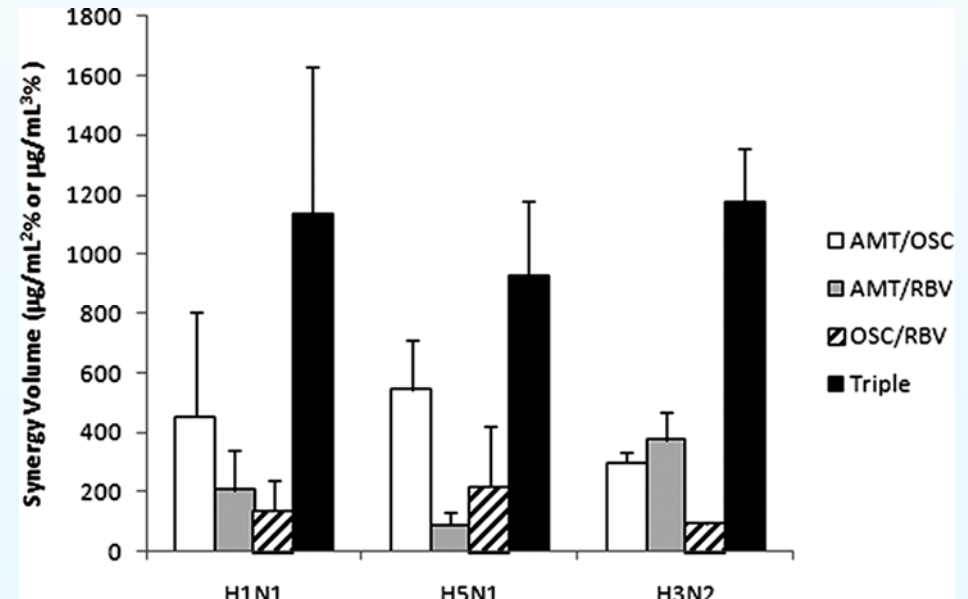
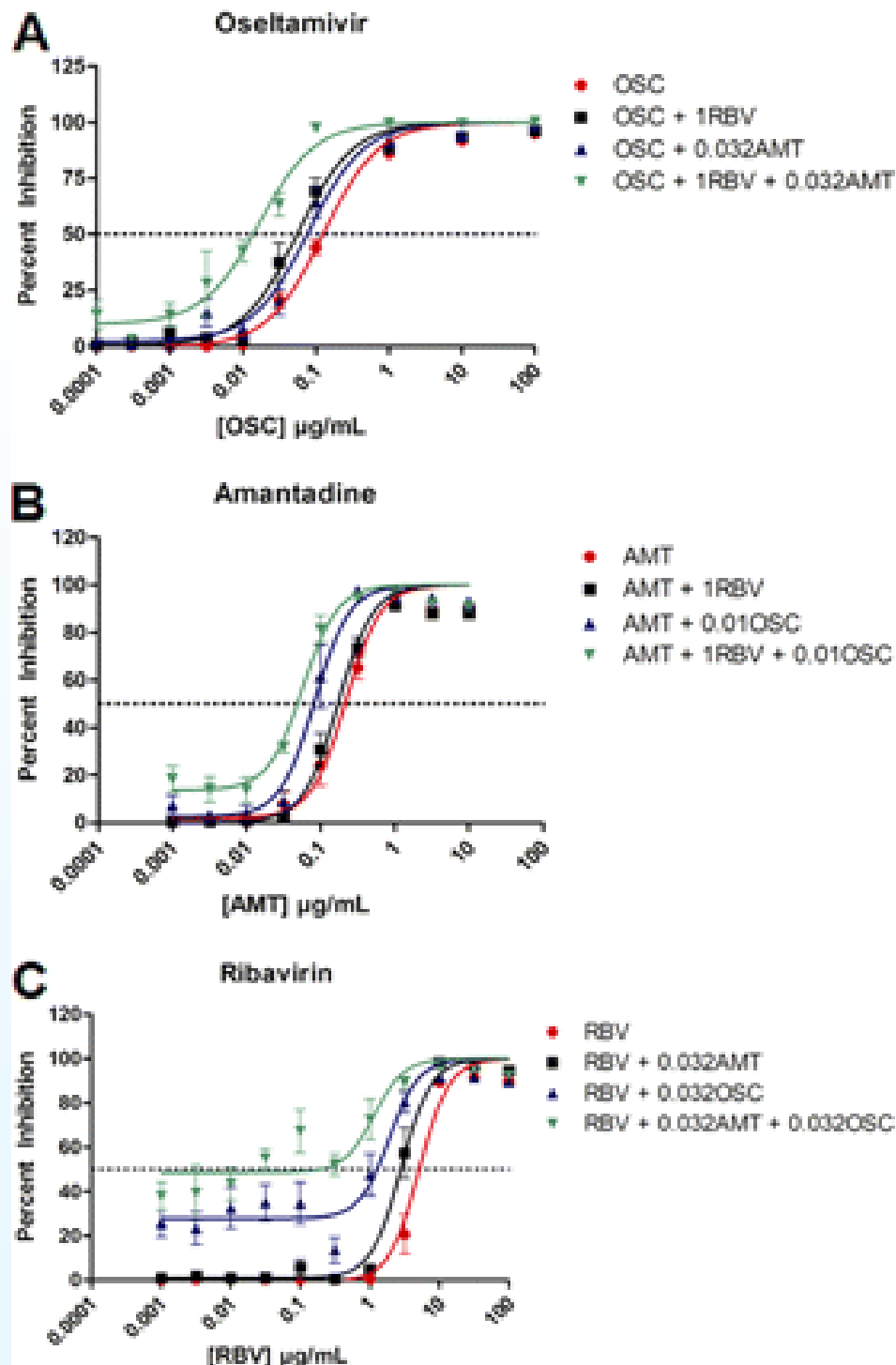
- **SEA 001: Double dose vs Standard Dose of Oseltamivir in Severe Influenza**
  - **Double dose is not better than standard dose, but not associated with more adverse events**

# Effect of amantadine (AM)–oseltamivir (OS) combination therapy on survival of mice inoculated with influenza A(H5N1) virus



Mice received treatment, on the same schedule, with AM or OS at the doses indicated (in mg/kg/day), a combination of AM and OS, or saline placebo starting 24 h before virus inoculation.

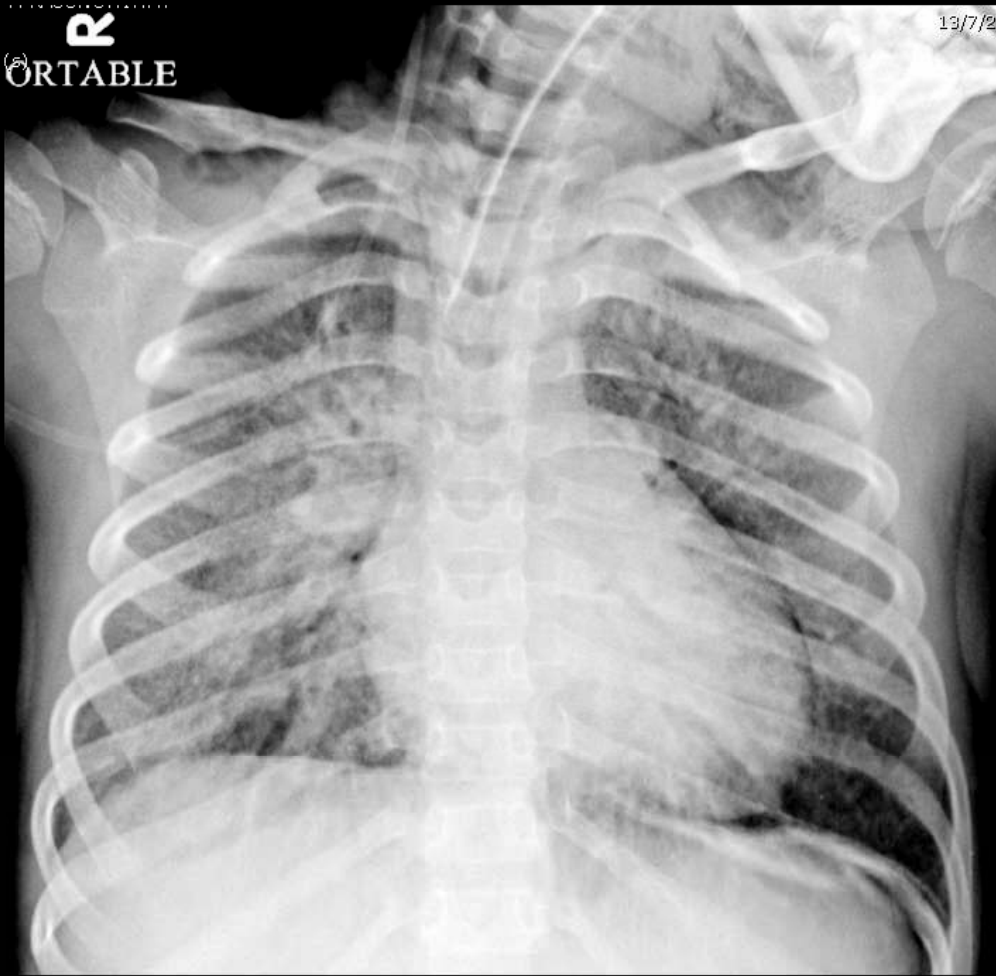
# Triple Combination of Oseltamivir, Amantadine, and Ribavirin Displays Synergistic Activity against Multiple Influenza Virus Strains In Vitro



# **Other Complications In Severe Influenza**

- **Secondary bacterial infection**
  - **Drug resistance nosocomial infections**
- **Ventilator associated**
  - **Pneumonia**
  - **Pneumothorax**
- **Other unexpected events...**

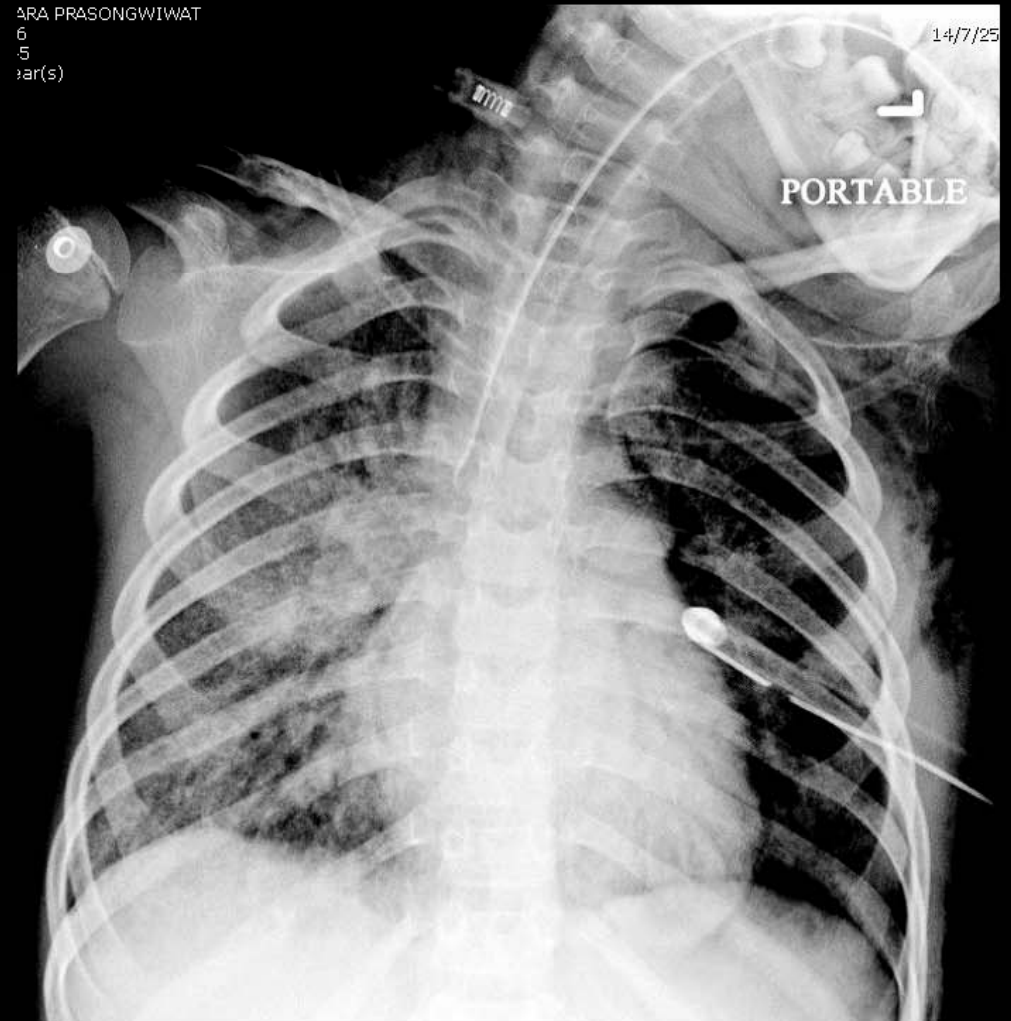
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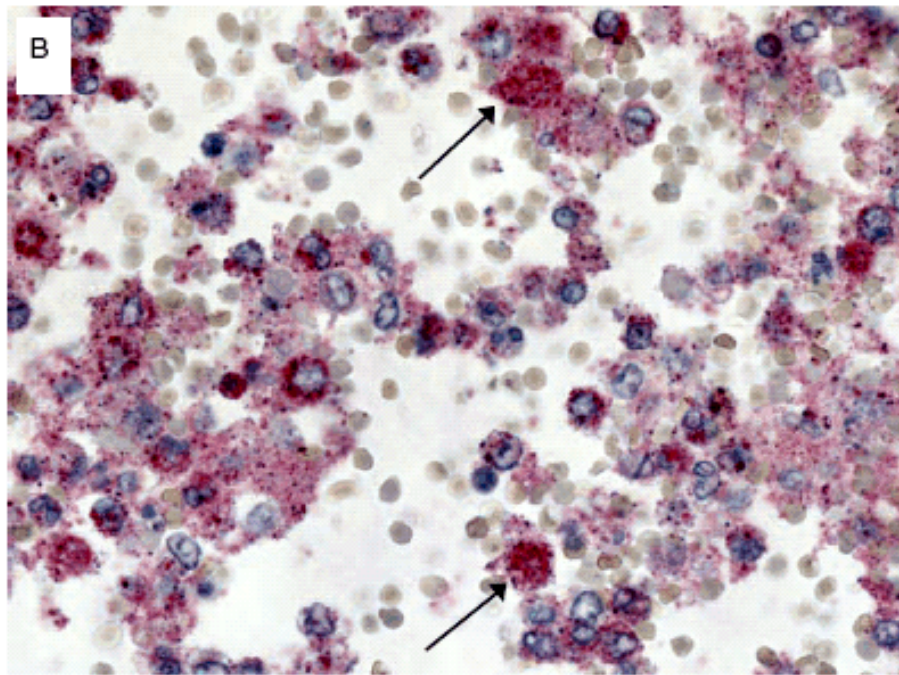
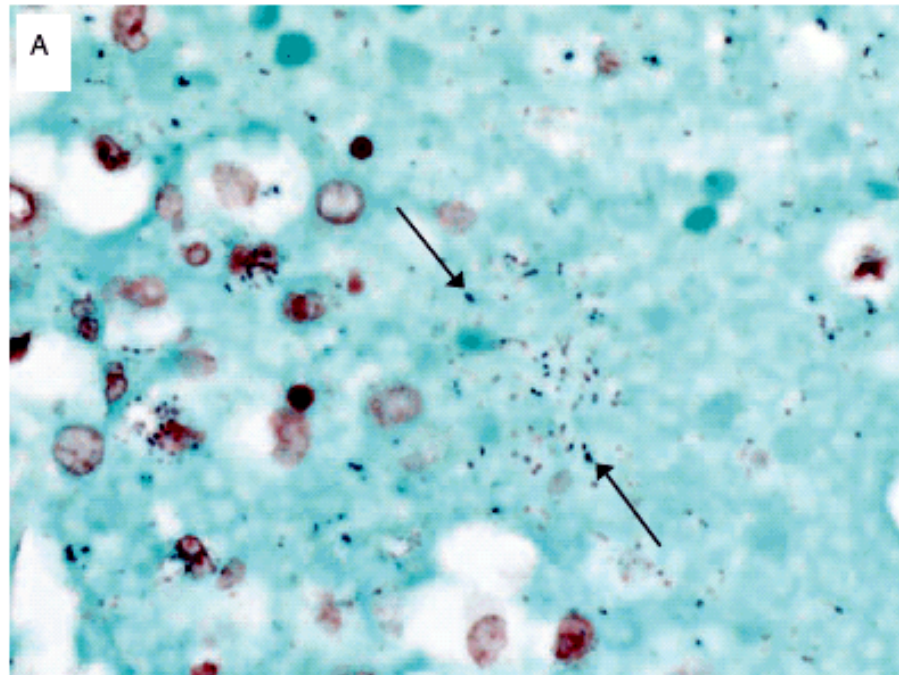
## 6 year-old boy with severe influenza, in ICU

- Day 10: Ventilator associated pneumonia by *A.baumannii* resistant to carbapenem

ARA PRASONGWIWAT  
6  
5  
mar(s)



**13/7/2552 : Day 14  
Pneumothorax**



## **Bacterial Coinfections in Lung Tissue Specimens from Fatal Cases of 2009 Pandemic Influenza A (H1N1) --- United States, May--August 2009**

**Concurrent bacterial infection was found in specimens from 22 (29%) of the 77 patients**


**(A) Detection of Gram-positive cocci (arrows) with use of Lillie- Twort Gram stain of lung tissue (original magnification ×63). (B) Immunohistochemical staining of multiple *S. pneumoniae* (arrows) with use of immunoalkaline phosphatase with naphthol-fast red and hematoxylin counterstain**

*CDC. MMER September 29, 2009 / 58(Early Release);1-4*

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm58e0929a1.htm>

# **Suggested Ventilator Settings to Avoid Complications**

- Use pressure-controlled CMV**
- Watch out for air leak, pneumothorax**
- In case that need airway pressure  $> 30$  cmH<sub>2</sub>O, consider to increase inspiratory time instead of increasing peak airway pressure.**
- Use PEEP when needed, starting from 8-10 cmH<sub>2</sub>O**
- May need high frequency ventilator**



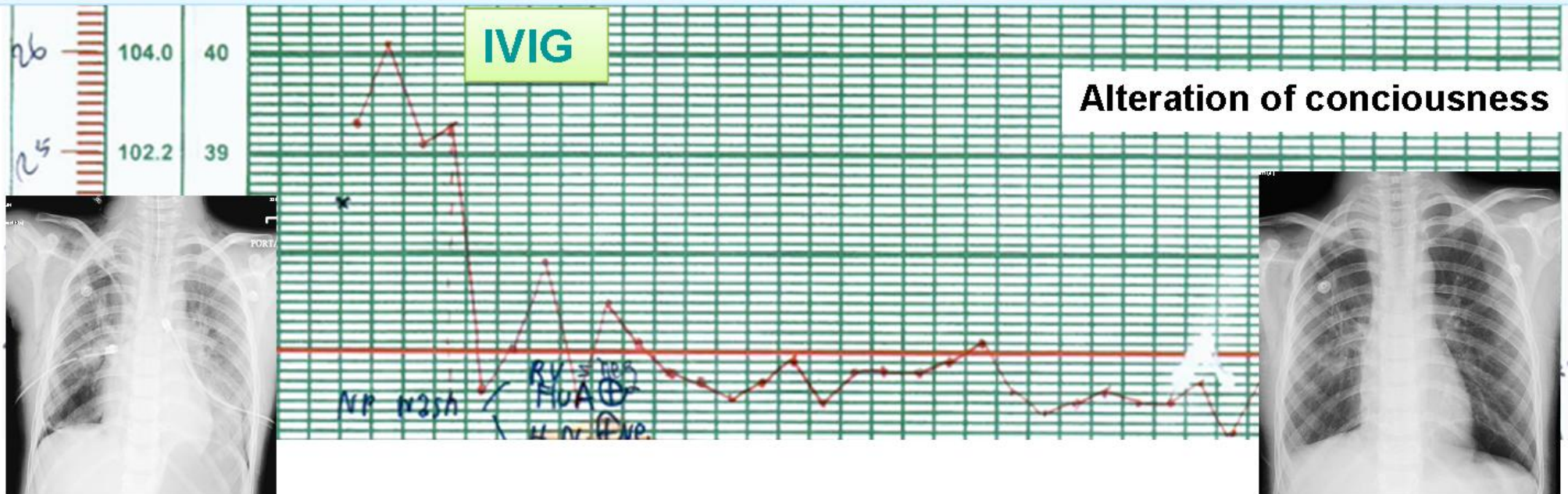
**Oseltamivir  
is not without  
adverse  
drug effects**

## 8 year-old boy

- **Underlying : Hyper IgE syndrome, IgG subclass 3 deficiency (IVIg q 4 weeks) and chronic bronchiectasis S/P RLL lobectomy.**
- **2 days, high grade fever, rhinorrhea, cough and dyspnea physical exam – T 38 °c, P 100/min, RR 24/min, BP 100/60 mmHg, SpO2 94 % (room air), wheezing and crepitation both lungs, after admission 7 hrs he developed respiratory failure require ET-tube, CXR show pneumothorax**
- **T 40°c, P 110/min, RR 40/min, BP 100/60 mmHg, SpO2 97 % (On ET-tube)**
  - **GA : tachypnea, dyspnea**
  - **RS : wheezing and crepitation both lungs**



DATE	12	25	26	27	28	29	30
Cefotaxime //	Tazocin 1	2	3	4	5	6// Cefditoren 1	
	Azithro 1	2	3	4	5//		
	Osetamivir 1	2	3	4	5//		



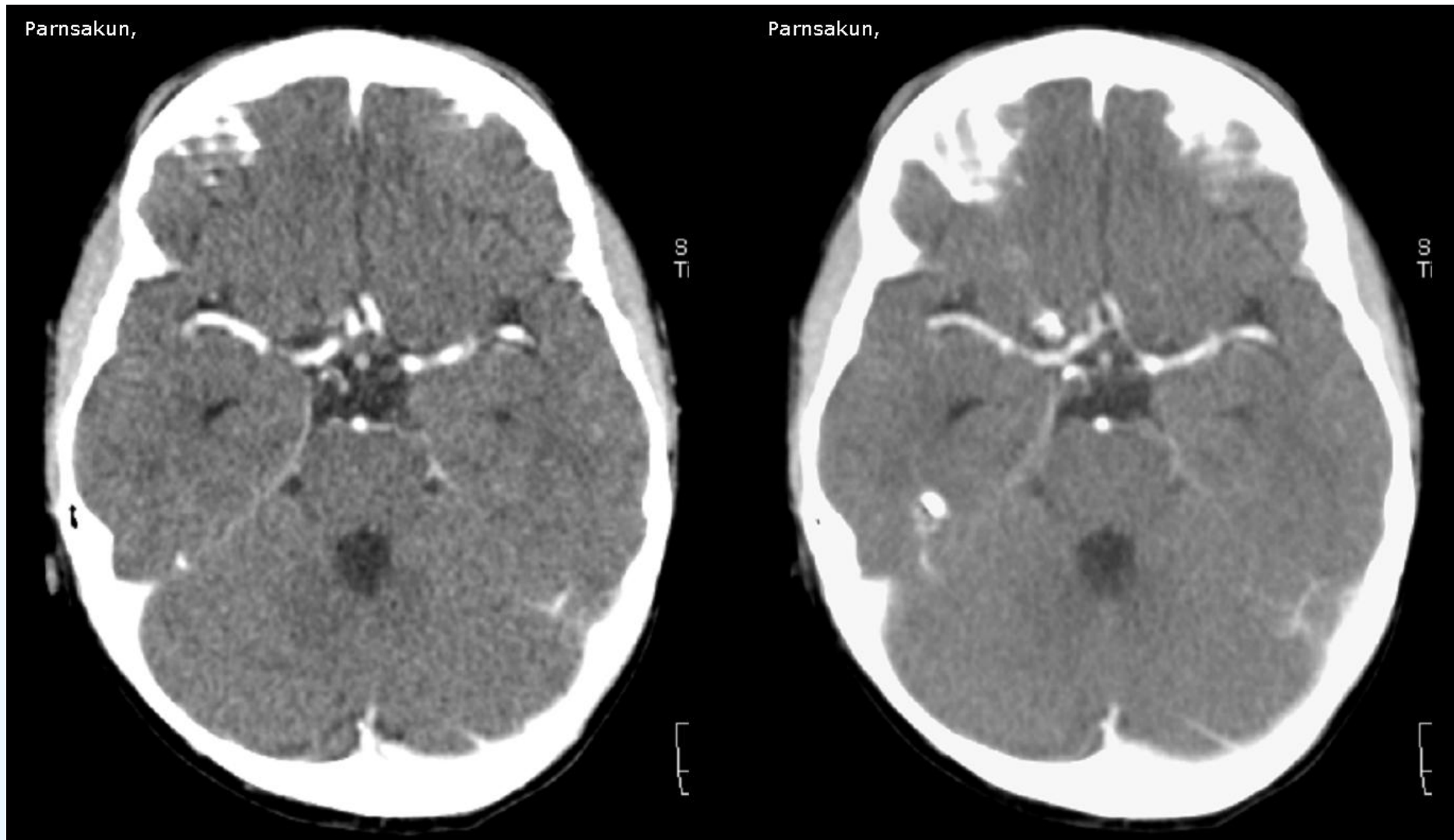
- NP wash for RV – negative
- PCR for **pH1N1** - positive
- H/C – No growth, Stool C/S –No growth

**After admission on day 6  
(post oseltamivir complete  
5 days), he developed  
alteration of consciousness**

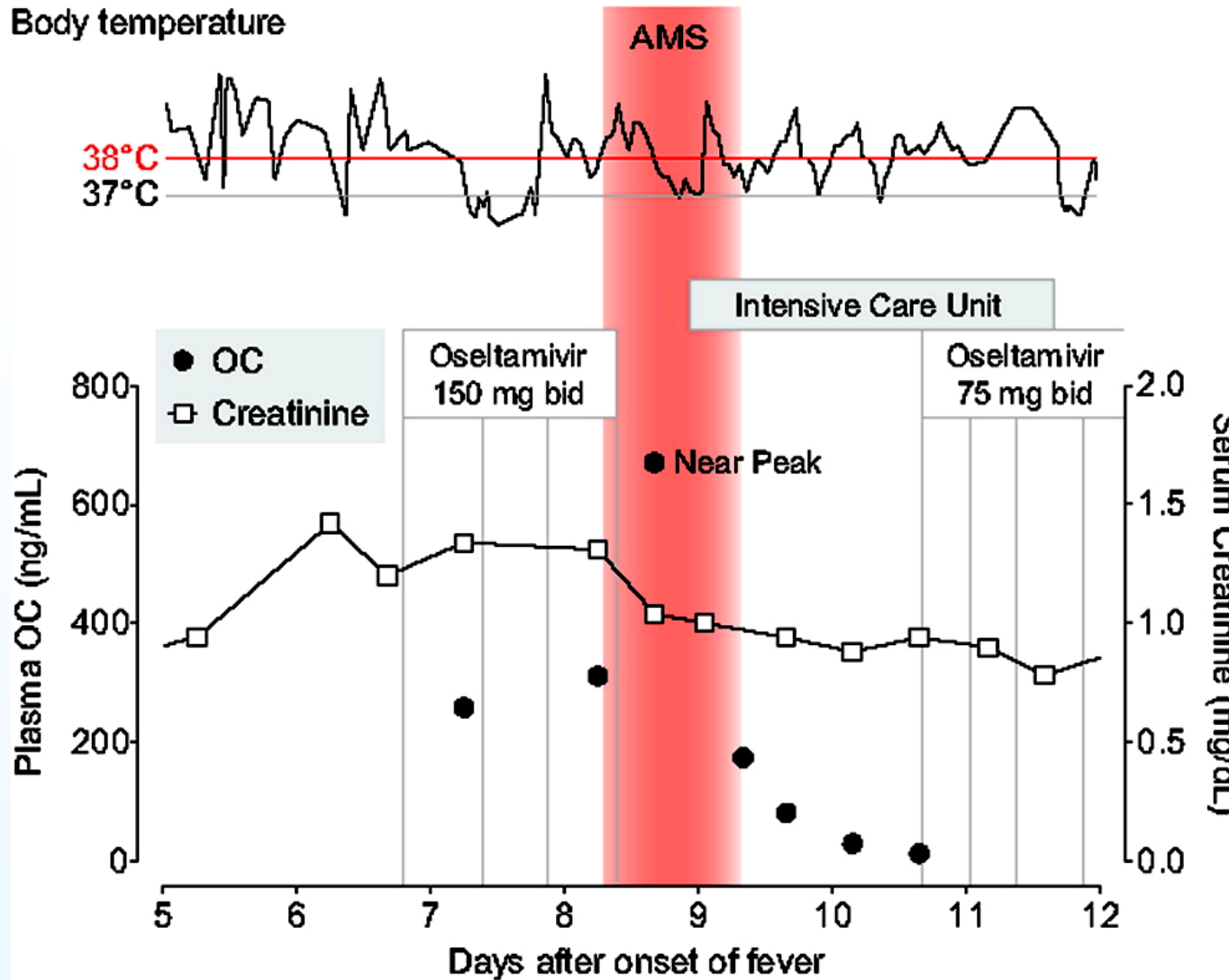
**What would this be?**

- Influenza encephalitis**
- Oseltamivir side effect**

# CT brain and CSF – normal



- Oseltamivir was stopped. He became normal.
- At discharge – full consciousness



## Possible Neuropsychiatric Reaction to High-Dose Oseltamivir during Acute 2009 H1N1 Influenza A Infection

Treatment course and oseltamivir carboxylate (OC) plasma levels. A 43-year-old man with novel 2009 H1N1 influenza infection experienced severe altered mental status (AMS) with high-dose oseltamivir (150 mg twice daily [bid]). The vertical grey lines denote times of oseltamivir administration.

# Conclusions

- **Diganosis of influenza cannot be based only on clinical ground**
  - **If influenza is in the differential diagnosis in the cases with:**
    - **high risk factors**
    - **severe symptoms**
    - **LRI**
    - **other organ involvement**
- >>Start empirical oseltamivir without delayed**
- **Do Zanamivir is the only alternative available in practice. Nebulized zanamivir is not generally recommended, use with caution**
  - **Other antiviral agents are needed for resistance virus**



**Thank you  
for your attention**