

# Influenza antivirals usage in pandemic situation

Antiviral Treatment in Japan and Experience  
during the Pandemic H1N1 in 2009

Norio Sugaya, M.D.  
Keiyu Hospital, Yokohama, Japan

# Neuraminidase inhibitors approved for use in Japan

2001

- Oseltamivir ( Tamiflu<sup>®</sup> )
- Zanamivir ( Relenza<sup>®</sup> )

2010

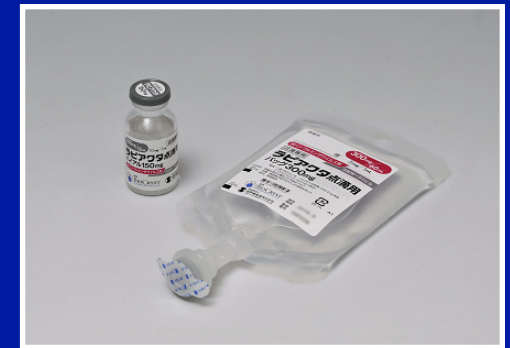
- Laninamivir ( Inavir<sup>®</sup> )  
Inhaler
- Peramivir ( Rapiacta<sup>®</sup> )  
Intravenous drip infusion

2018

RNA protease inhibitor, Baloxavir (Zofluza<sup>®</sup>)



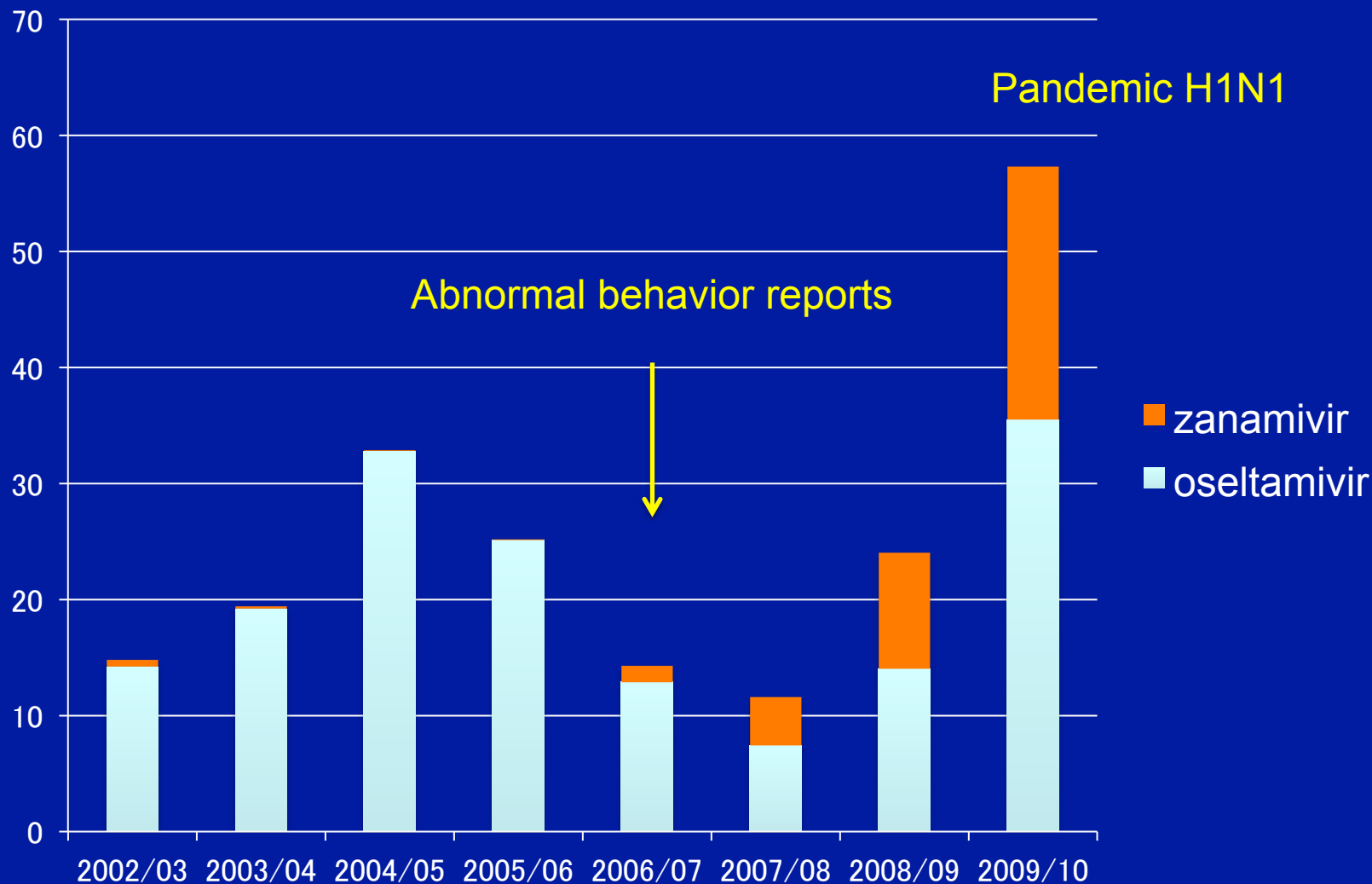
Inavir



Rapiacta

# Sales of NAIs in Japan from 2002 to 2009

Sales (in billions of  
Japanese yen)



## Falls from Buildings after Taking Oseltamivir, an Adverse Reaction?

A 14-year-old boy fell from a condominium and died Tuesday, after taking Tamiflu the day before. He was diagnosed with flu Monday morning at a hospital. He had taken one Tamiflu pill at 9:30 a.m. after seeing a doctor and another one just past 6 p.m. Sleeping in the same room as his mother, the boy woke up and left the condominium. He apparently climbed over a 1.26-meter wall along the outside corridor and fell to a parking lot. No suicide note was found. (from an article of Japan Times)

The Ministry of Health, Labour and Welfare has issued an emergency instruction to suspend the use of oseltamivir to treat patients between the ages of 10 and 19 years in 2007.

## Abnormal Behavior and NAIs Fatal Cases (10 to 19 year-old) Reported

Oseltamivir 8 cases (2004-2007)

Influenza patients  
not treated with a NAI 1 case (2007)

Zanamivir 1 case (2009)

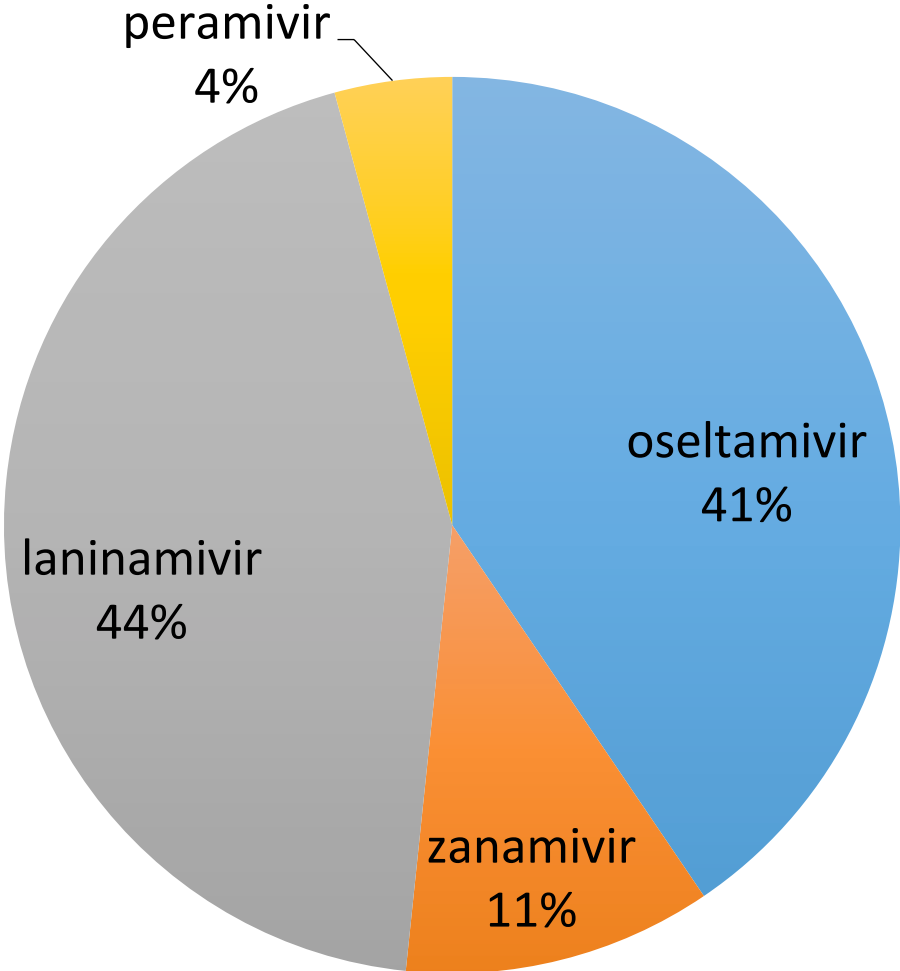
Laninamivir 1 case (2012)

In addition, there have been many cases of severe injuries, such as fractured legs as a result of falls from buildings.

# Abnormal behavior is not caused by oseltamivir MHLW in 2018

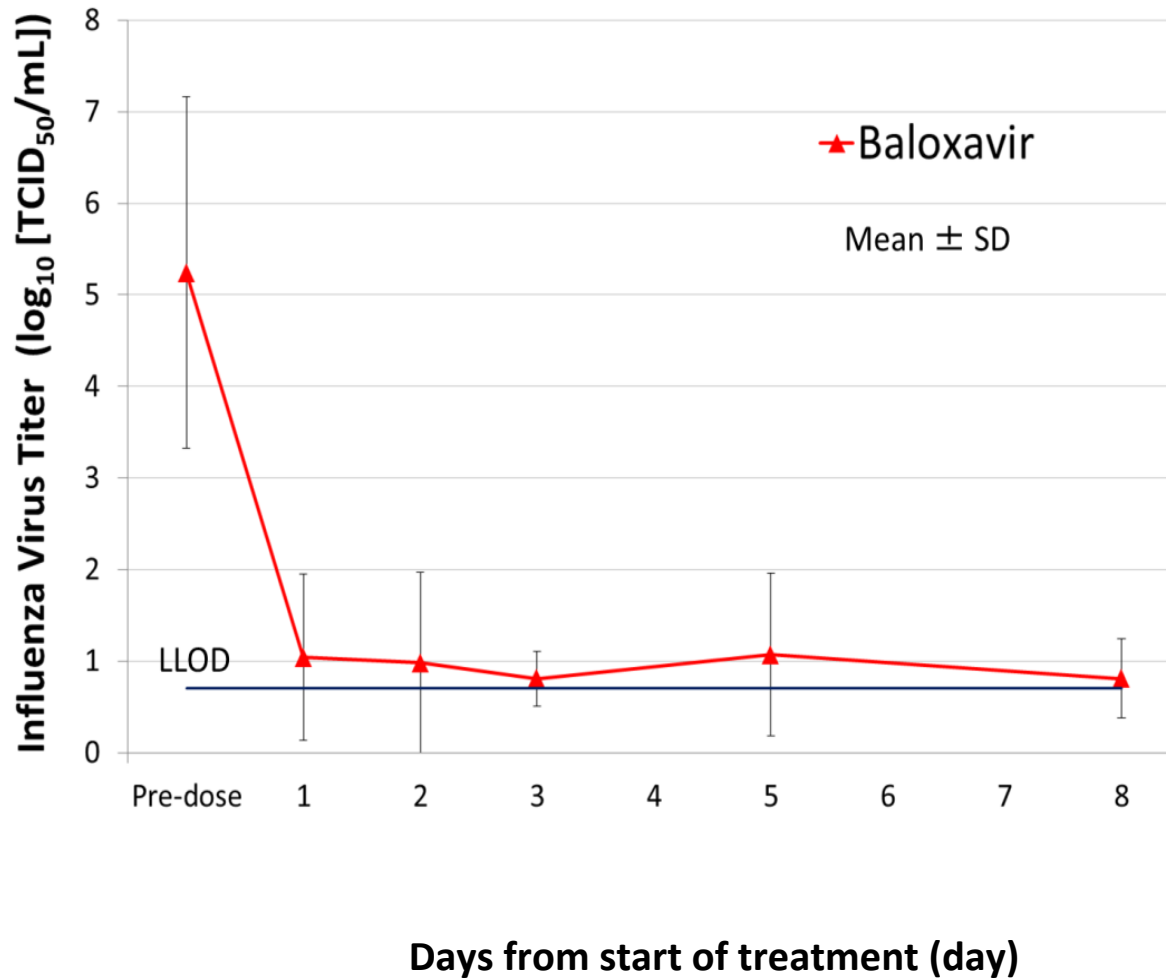
- MHLW issued an instruction to rescind the suspension for the use of oseltamivir to treat patients between the ages of 10 and 19 years in May, 2018.
- Abnormal behavior is caused by influenza virus infection and not by NAIs.
- Children with influenza virus infection should be observed by their guardians until 48 hours after the onset of influenza.

# Percentage of patients who received prescriptions for neuraminidase inhibitors 2017-2018



# Change of Virus Titer by Day Pediatric Study in 2016/17

Pediatric (<12yrs)





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## Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

Frederick G. Hayden, M.D., Norio Sugaya, M.D., Nobuo Hirotsu, M.D., Ph.D., Nelson Lee, M.D., Menno D. de Jong, M.D., Ph.D., Aeron C. Hurt, Ph.D., Tadashi Ishida, M.D., Ph.D., Hisakuni Sekino, M.D., Ph.D., Kota Yamada, M.D., Simon Portsmouth, M.D., Keiko Kawaguchi, M.Sc., Takao Shishido, Ph.D., Masatsugu Arai, M.Sc., Kenji Tsuchiya, M.Sc., Takeki Uehara, Ph.D., and Akira Watanabe, M.D., Ph.D.,  
for the Baloxavir Marboxil Investigators Group\*

### ABSTRACT

#### BACKGROUND

Baloxavir marboxil is a selective inhibitor of influenza cap-dependent endonuclease. It has shown therapeutic activity in preclinical models of influenza A and B virus infections, including strains resistant to current antiviral agents.

#### METHODS

We conducted two randomized, double-blind, controlled trials involving otherwise healthy outpatients with acute uncomplicated influenza. After a dose-ranging (10 to 40 mg) placebo-controlled trial, we undertook a placebo- and oseltamivir-controlled trial of single, weight-based doses of baloxavir (40 or 80 mg) in patients 12 to 64 years of age during the 2016–2017 season. The dose of oseltamivir was 75 mg twice daily for 5 days. The primary efficacy end point was the time to alleviation of influenza symptoms in the intention-to-treat infected population.

#### RESULTS

From the Department of Medicine, University of Virginia School of Medicine, Charlottesville (F.G.H.); the Department of Pediatrics, Keiyu Hospital, Yokohama (N.S.), Hirotsu Clinic, Kawasaki (N.H.), the Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki (T.I.), Sekino Hospital, Tokyo (H.S.), Tsuchiura Beryl Clinic, Tsuchiura (K.Y.), Shionogi, Osaka (K.K., T.S., M.A., K.T., T.U.), and the Research Division for Development of Anti-Infective Agents, Institute of Development, Aging, and Cancer, Tohoku University, Sendai (A.W.) — all in Japan; the Division of Infectious Diseases, Department of Medicine, University

## Japan had the lowest case fatality rate 2009 Pandemic H1N1

Even though 20.7 million cases of pandemic H1N1 infection occurred in Japan, only 198 deaths were reported nationwide.

	Deaths / 100,000 population	Fatal cases	Population
Japan	0. 15	198	128 million
Australia	0. 92	193	21 million
Canada	1. 26	429	34 million
United States	1. 03 (3.32)	3433 (12,000 estimated)	332 million

# Review of the pandemic (H1N1) 2009 among pregnant Japanese women

J Obstet Gynaecol Res, 2012

In Japan, 30,000-40,000 pregnant women had H1N1pdm09.

181 pregnant women were hospitalized because of H1N1pdm09 during the pandemic. 90% of them were treated with NAIs within 48 hours after the onset of illness.

No maternal deaths due to H1N1pdm09 occurred.

Only one woman with H1N1pdm09 was treated by artificial ventilation in the ICU.

# Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women

BMJ 2010

In Australia and New Zealand between 1 June and 31 August 2009, 64 pregnant or postpartum women with H1N1pdm09 were admitted to intensive care units.

44 of 64 women (69%) were mechanically ventilated.

Seven of 64 women (11%) died.

Median interval from symptom onset to oseltamivir treatment was 6 days.

	Artificial ventilation	Fatal cases	Timing of NAI treatment
Australia, New Zealand	44	7	6 days after onset of illness
Japan	1	0	Within 48 hours

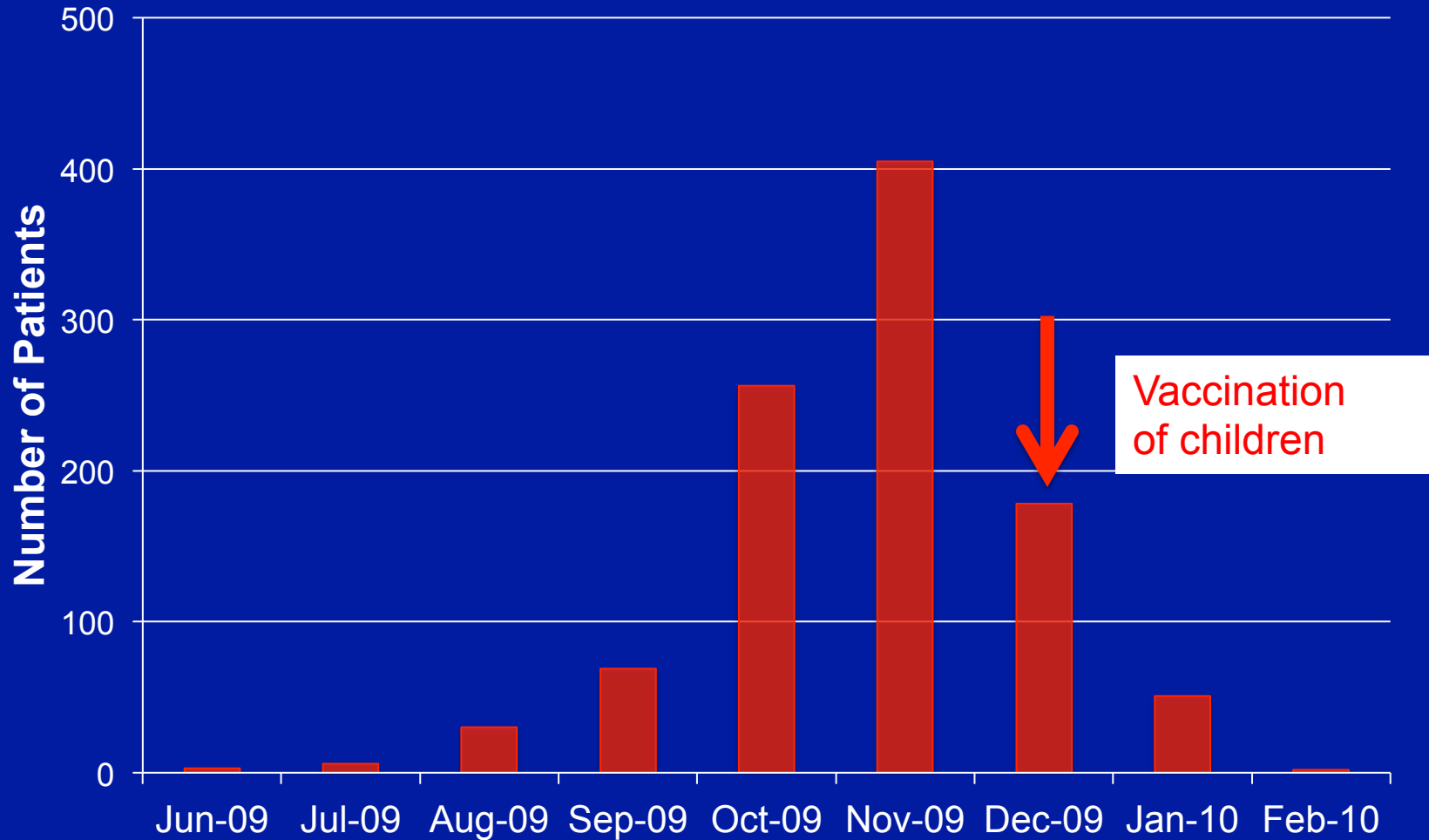
## Japan had the lowest case fatality rate 2009 Pandemic H1N1

- Even though 20.7 million cases of pandemic H1N1 infection occurred in Japan, only 197 deaths were reported nationwide.
- No reports of deaths of pregnant women
- Twelve million children <15 years of age had pandemic H1N1.
- Only 38 deaths among the group <15 years of age
- Pediatric influenza deaths did not increase during the H1N1 pandemic in Japan.

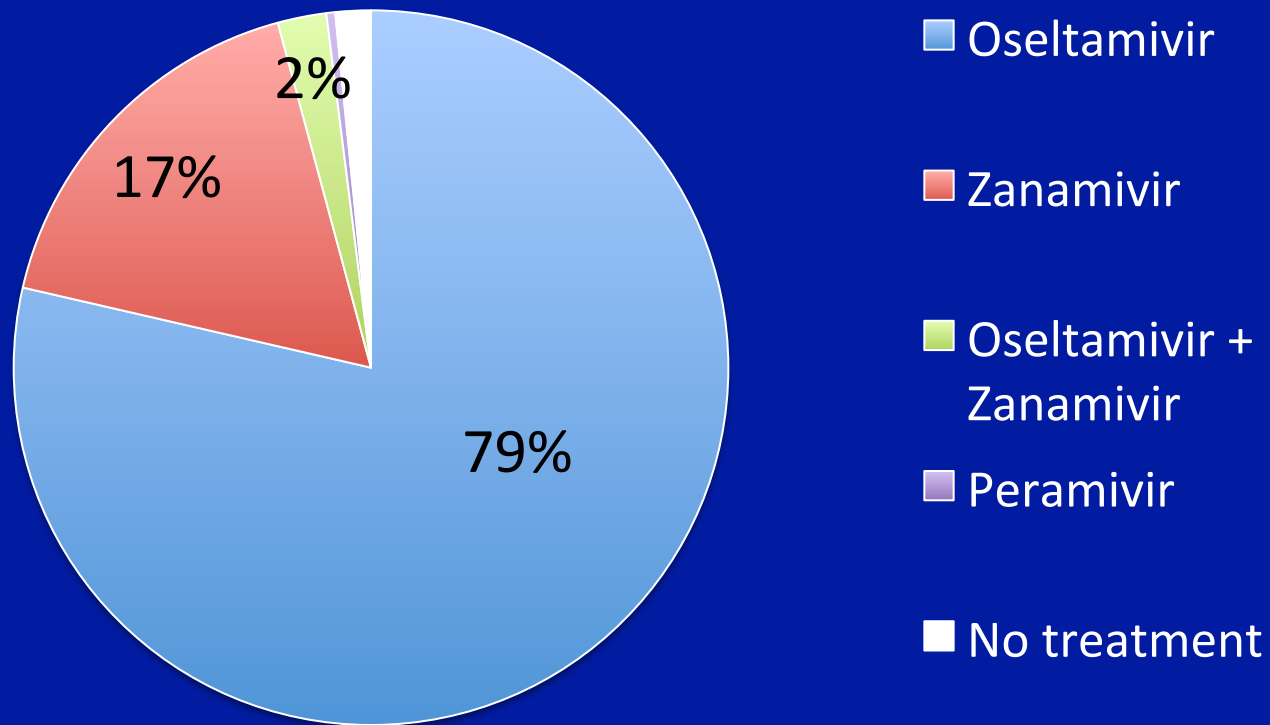
# Numbers of Pediatric Hospital Admissions for Pandemic H1N1

June 2009 to February 2010

N=1000

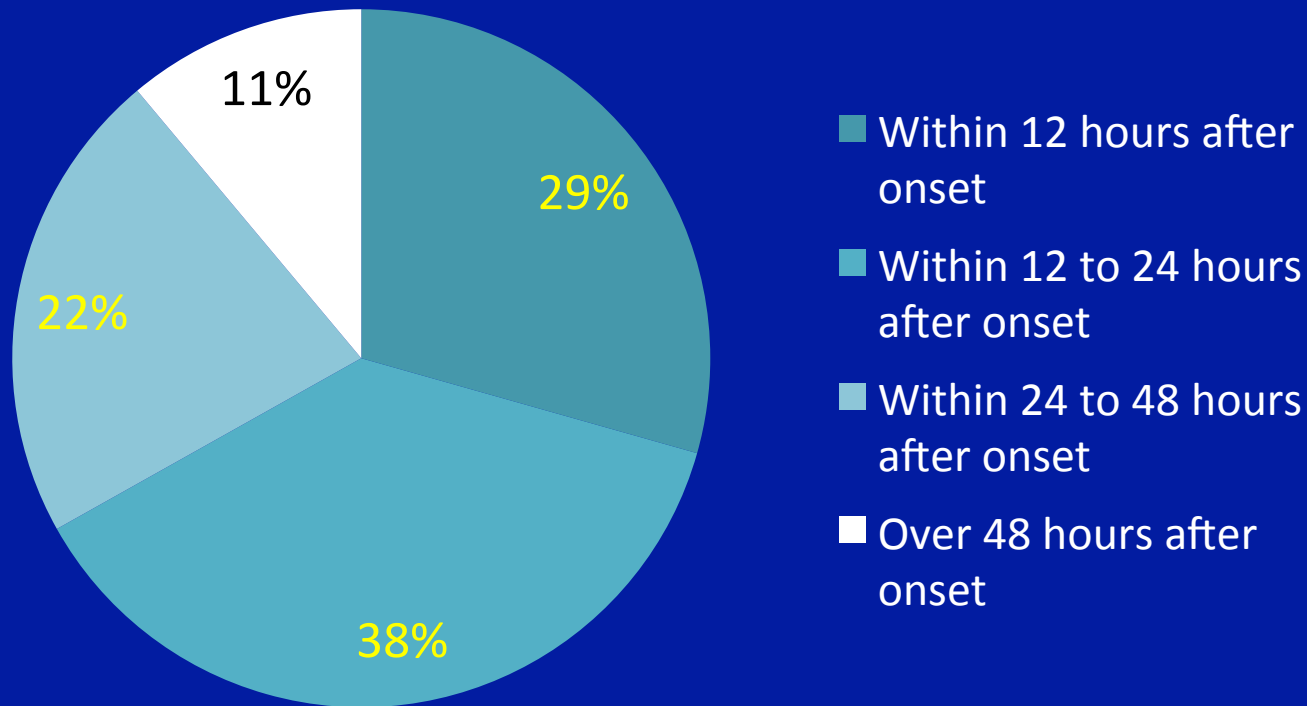


Neuraminidase inhibitors had been used to treat 984 (98.4%) of the 1000 patients.



## Timing of Neuraminidase Inhibitor Treatment

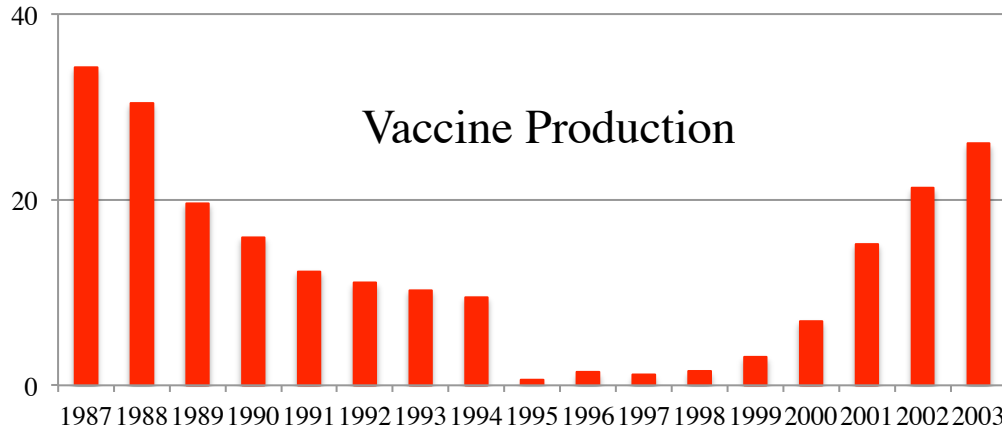
In 89% of the patients, treatment was initiated within 48 hours after the onset of illness.



Among the 1000 patients in our study, 12 patients (1.2%) were placed on mechanical ventilation, and only 1 death (0.1%) was reported.



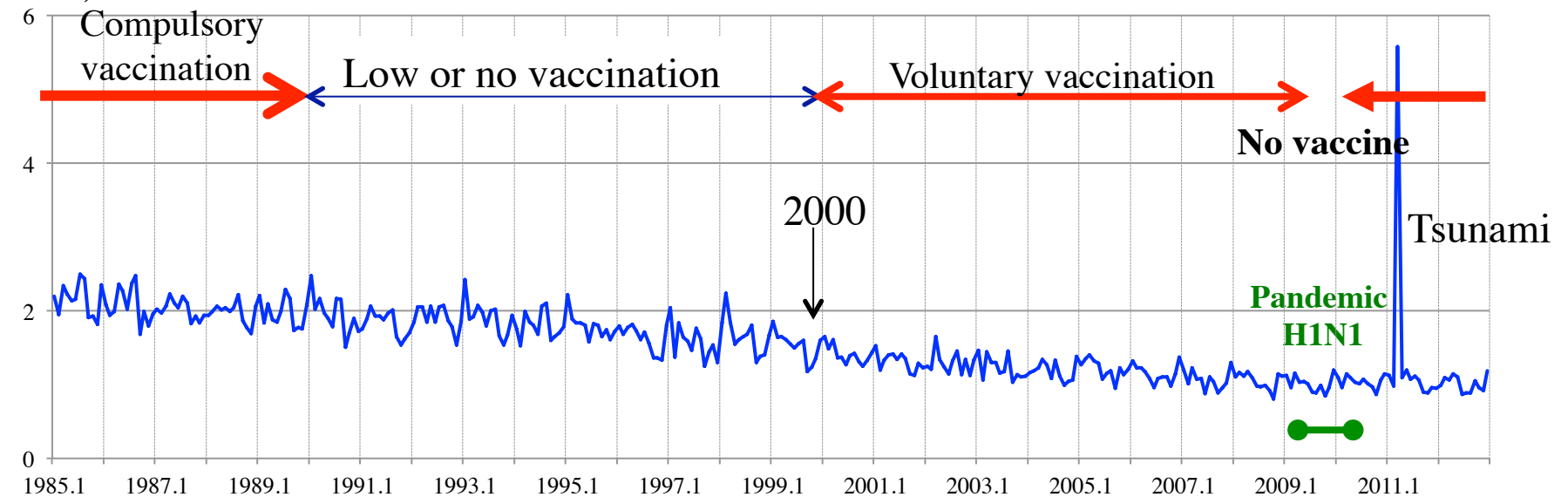
# Monthly All-Cause Mortality among Children (1-14 Years) from 1985 to 2013



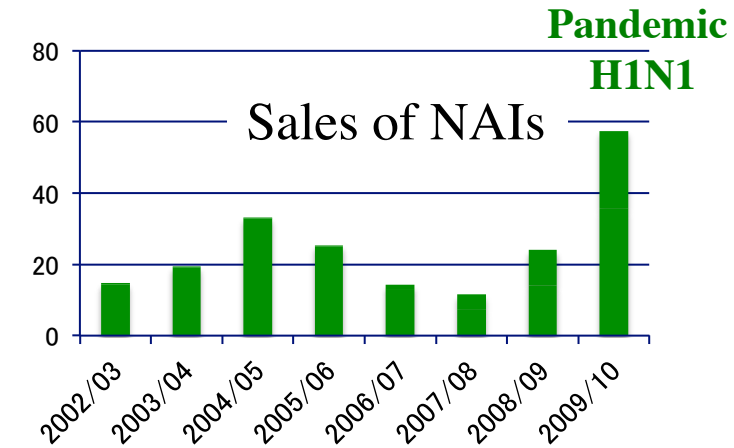
NAIs



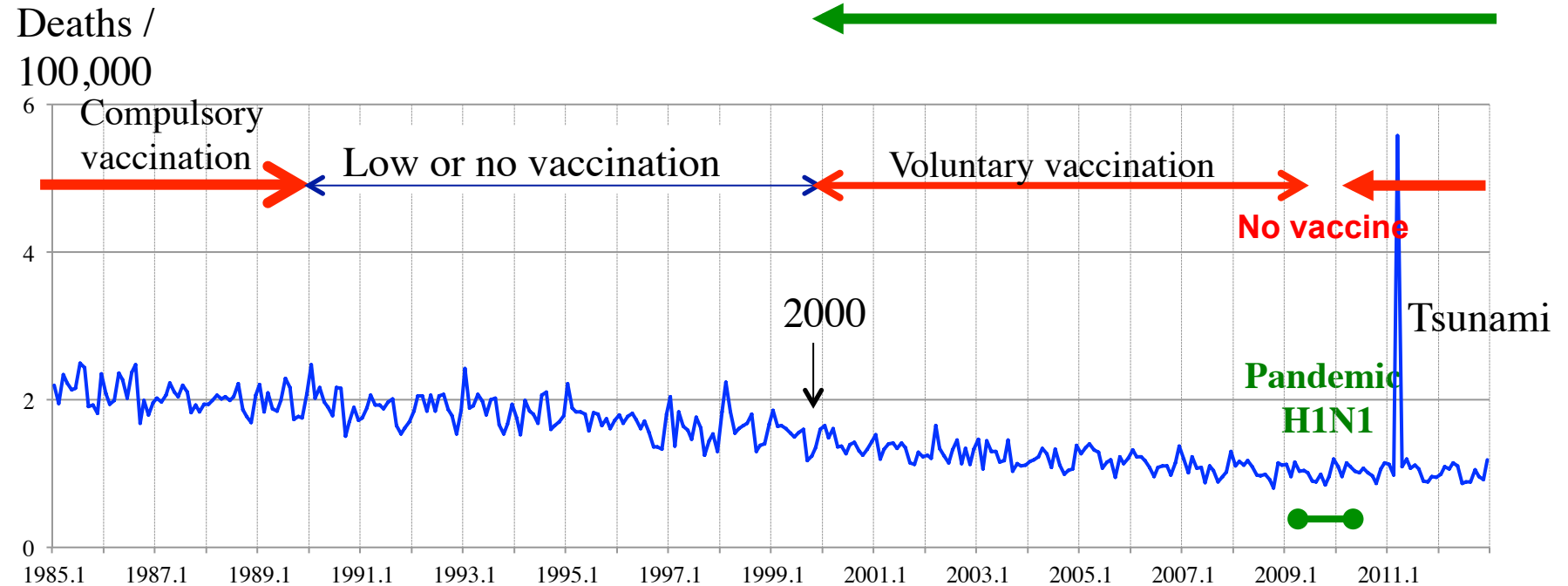
Deaths /  
100,000



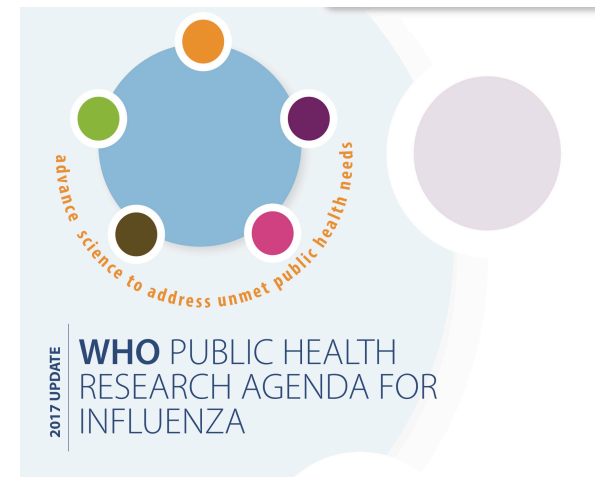
# Monthly All-Cause Mortality among Children (1-14 Years) from 1985 to 2013



← NAI's →



# WHO Influenza Agenda 2017



## Unmet public health needs and research gaps 4.2.3

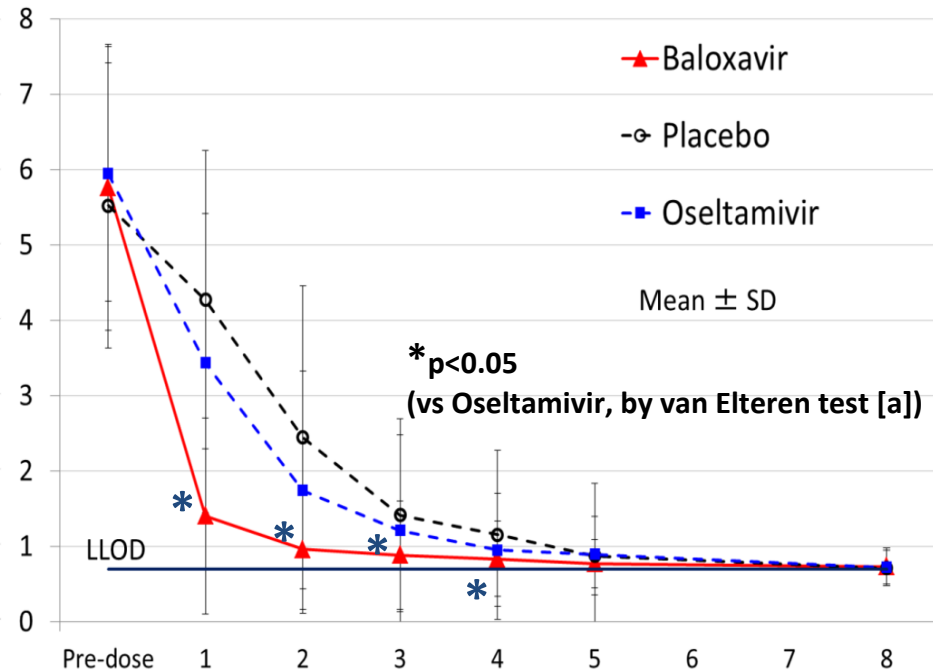
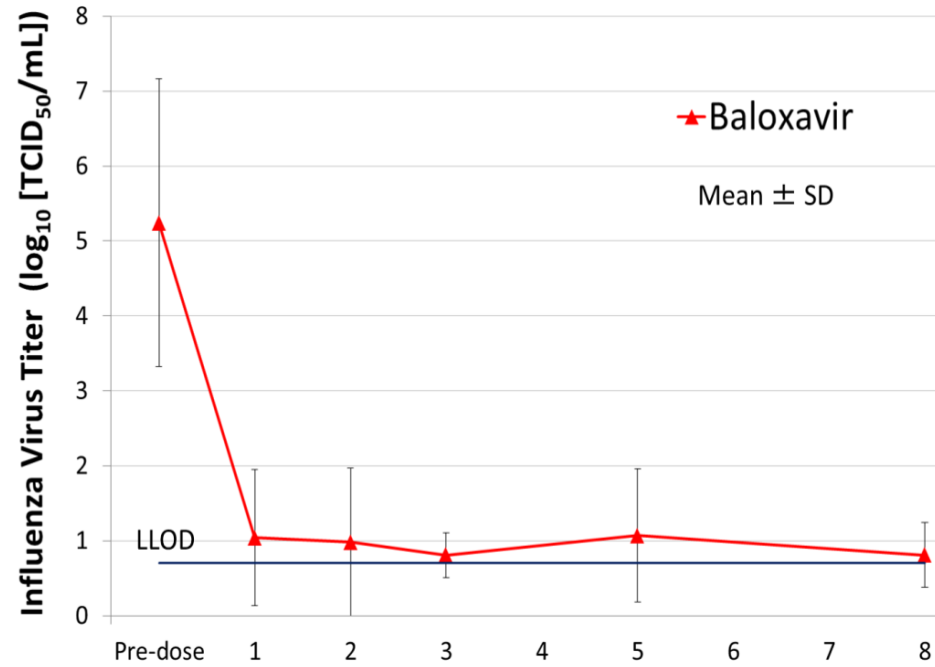
A continuing public health issue is **underuse** of current antiviral drugs and lack of timely administration in influenza patients who might benefit.

# Change of Virus Titer by Day

## Pediatric and Adults Study in 2016/17

Pediatric (<12yrs)

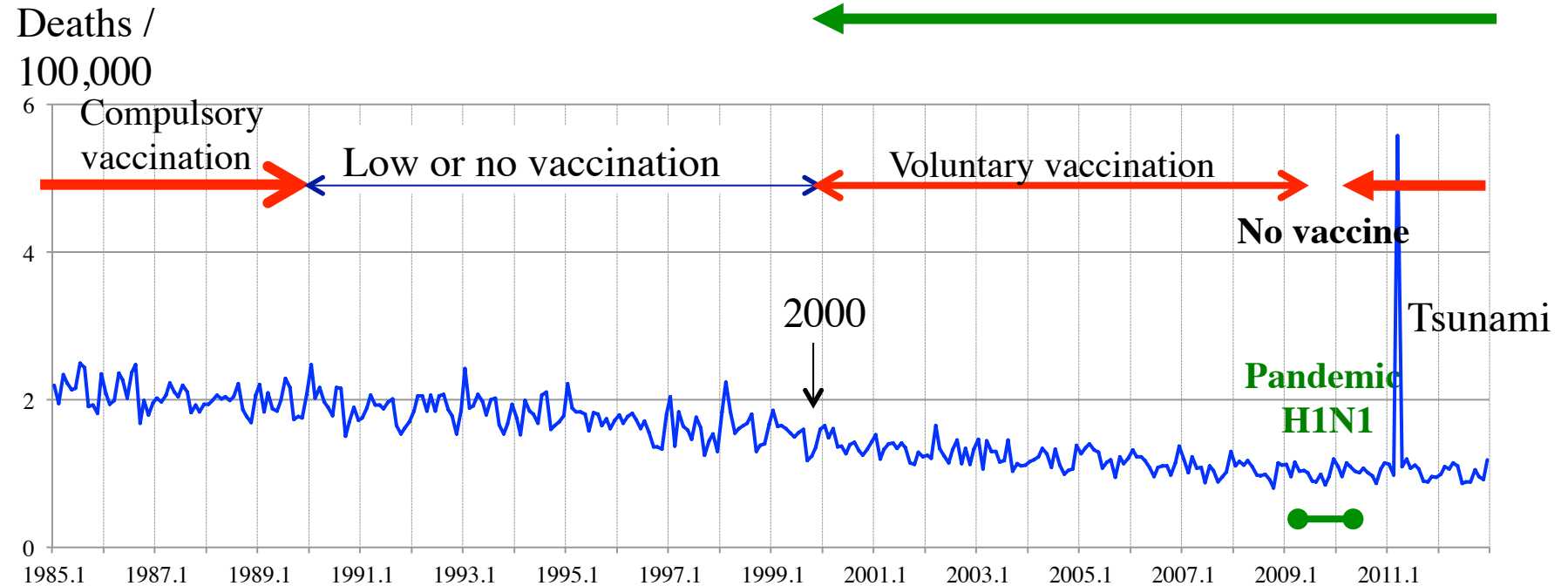
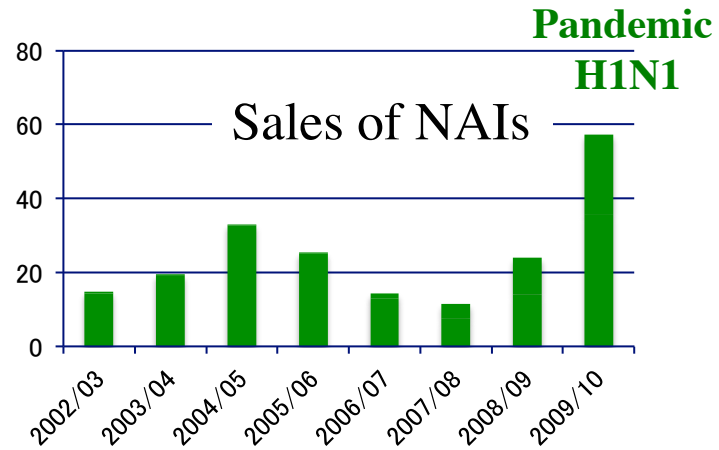
Adult ( $\geq$ 20yrs)



[a] Covariates: region and composite symptom scores at baseline  
LLOD: Lower limit of detection

Days from start of treatment (day)

# Monthly All-Cause Mortality among Children (1-14 Years) from 1985 to 2013



# Outcome

- Only 12 patients (1.2%) were placed on mechanical ventilation in our study.

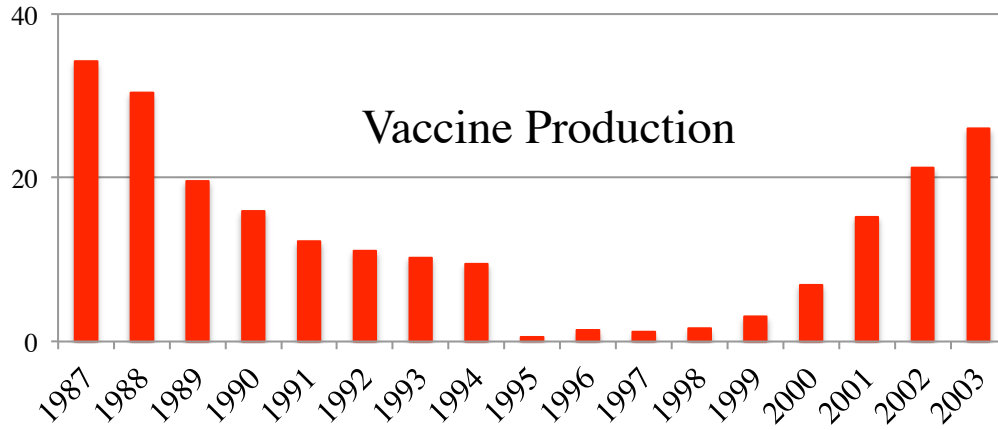
15.4% of US inpatients and 17% of Argentine pediatric inpatients

- Only 1 death (0.1%) among the 1000 patients in our study.

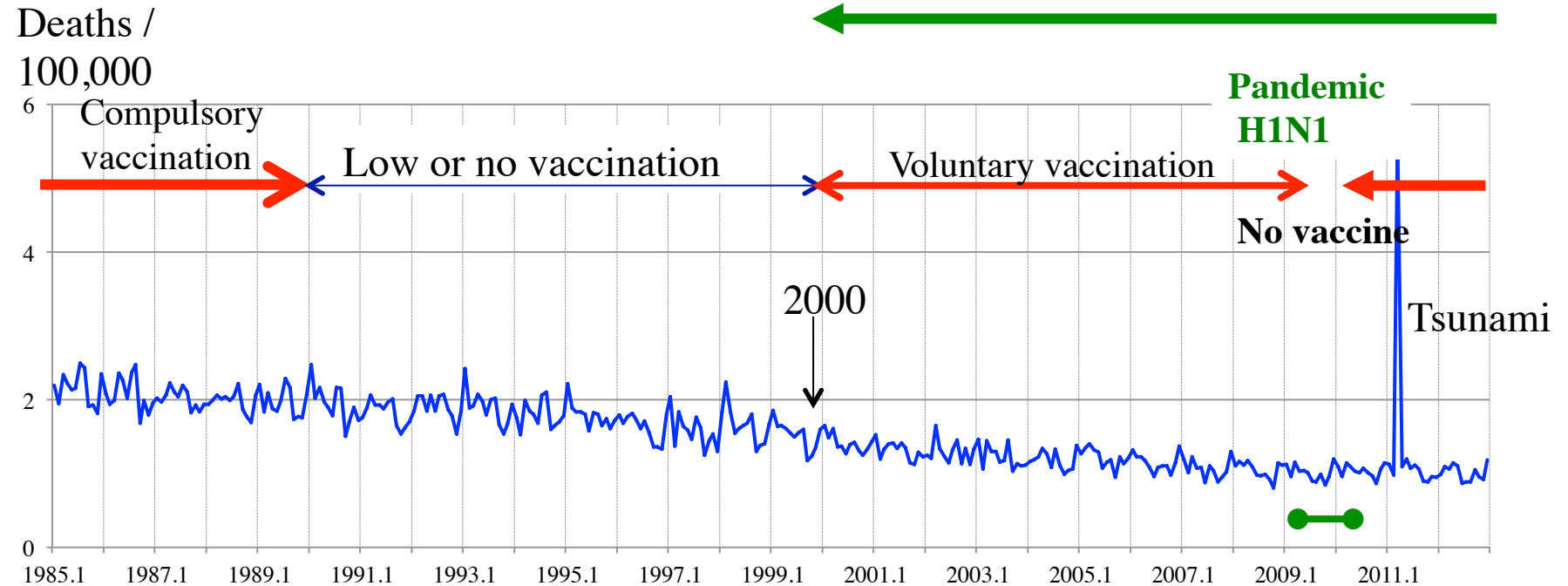
7% had died in the US study.

5% had died in the Argentine study.

# Monthly All-Cause Mortality among Children (1-14 Years) from 1985 to 2013



NAIs



# Hypoxemia

- SpO<sub>2</sub> was monitored in 962 of 1000 patients.  
In 424 (44%) of them, SpO<sub>2</sub> was 93% or less  
In 243 (25%) of them, SpO<sub>2</sub> was 90% or less
- The time between the onset of illness and hospital admission was short, with the median time being 1 day in our study (3 to 4 days in other countries).



# Hypoxemia

- SpO<sub>2</sub> was monitored in 962 of 1000 patients.
- In 424 (44%) of them, SpO<sub>2</sub> was 93% or less
- In 243 (25%) of them, SpO<sub>2</sub> was 90% or less
- The time between the onset of illness and hospital admission was short, with the median time being 1 day in our study (3 to 4 days in other countries).
- Early treatment with neuraminidase inhibitors in Japan markedly reduced the number of patients who developed serious illness 3 to 5 days after the onset, and resulted in the low mortality rate.

# oseltamivir治療はH1N1pdm09入院患者の死亡を減らした

STELLA G MUTHURI\*, Lancet Resp. Med. 2014

- 約3万人のインフルエンザ入院患者を解析
- ノイラミニダーゼ阻害薬治療により、死亡リスクが減少した
- 早期治療 (within 2 days) は、後期治療に比べて、死亡リスクが52%減少した.
- 妊婦では、早期治療は、無治療に比べて、死亡リスクが84%減少した

世界の専門家は、パンデミック(H1N1/09)の経験を通して、発症後48時間以内の「重症インフルエンザ」での死亡防止効果を確認した

# Conclusions

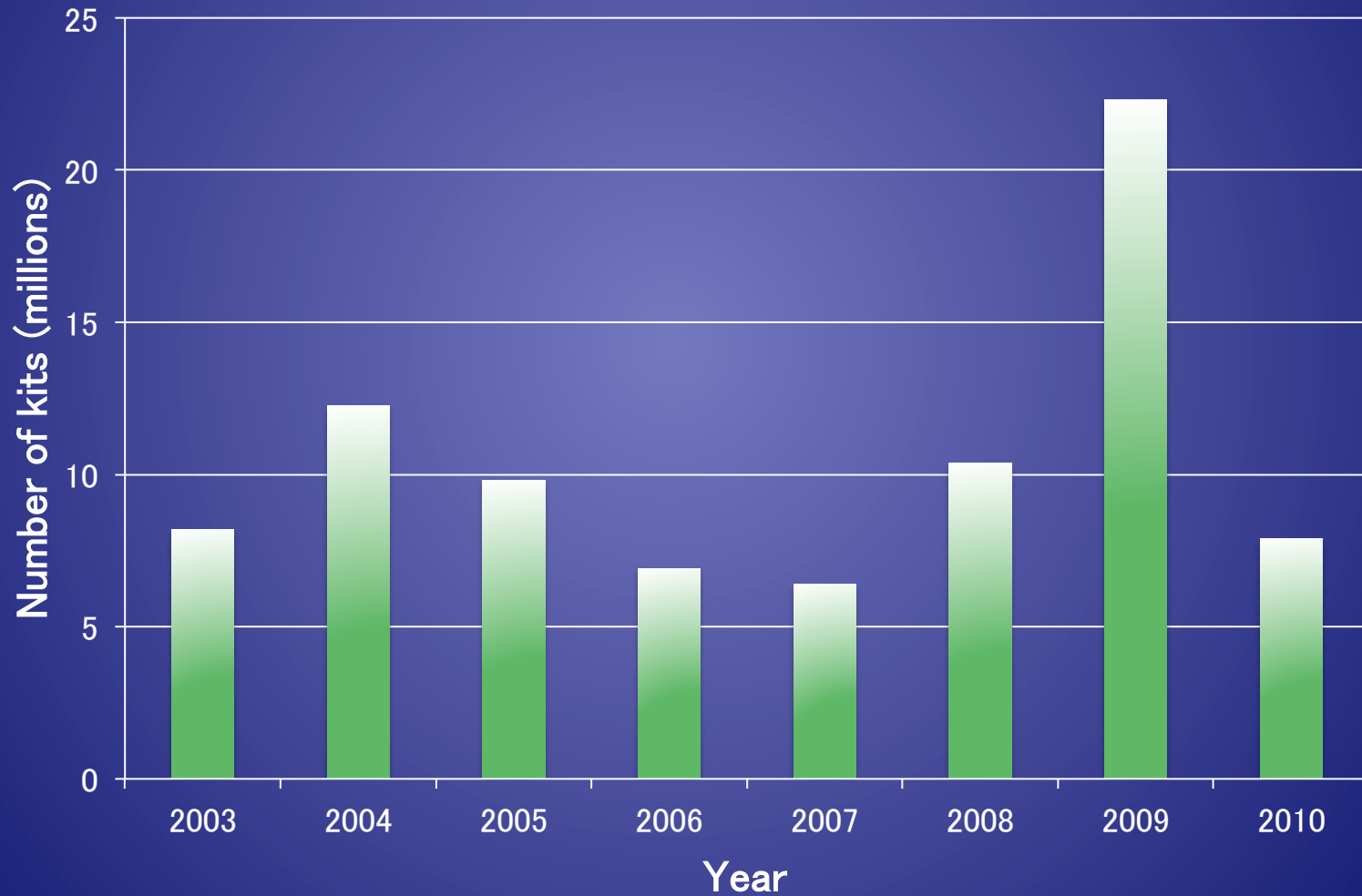
- The record low mortality rate in Japan during 2009 H1N1 pandemic was probably attributable to the almost universal implementation of the policy of early treatment with neuraminidase inhibitors for patients with influenza in Japan since the year 2000.
- In order to prevent severe illness and deaths during pandemic, all countries worldwide should first improve underuse of NAIs for seasonal influenza, promoting early treatment with NAIs for seasonal influenza.

# Pandemic H1N1/09

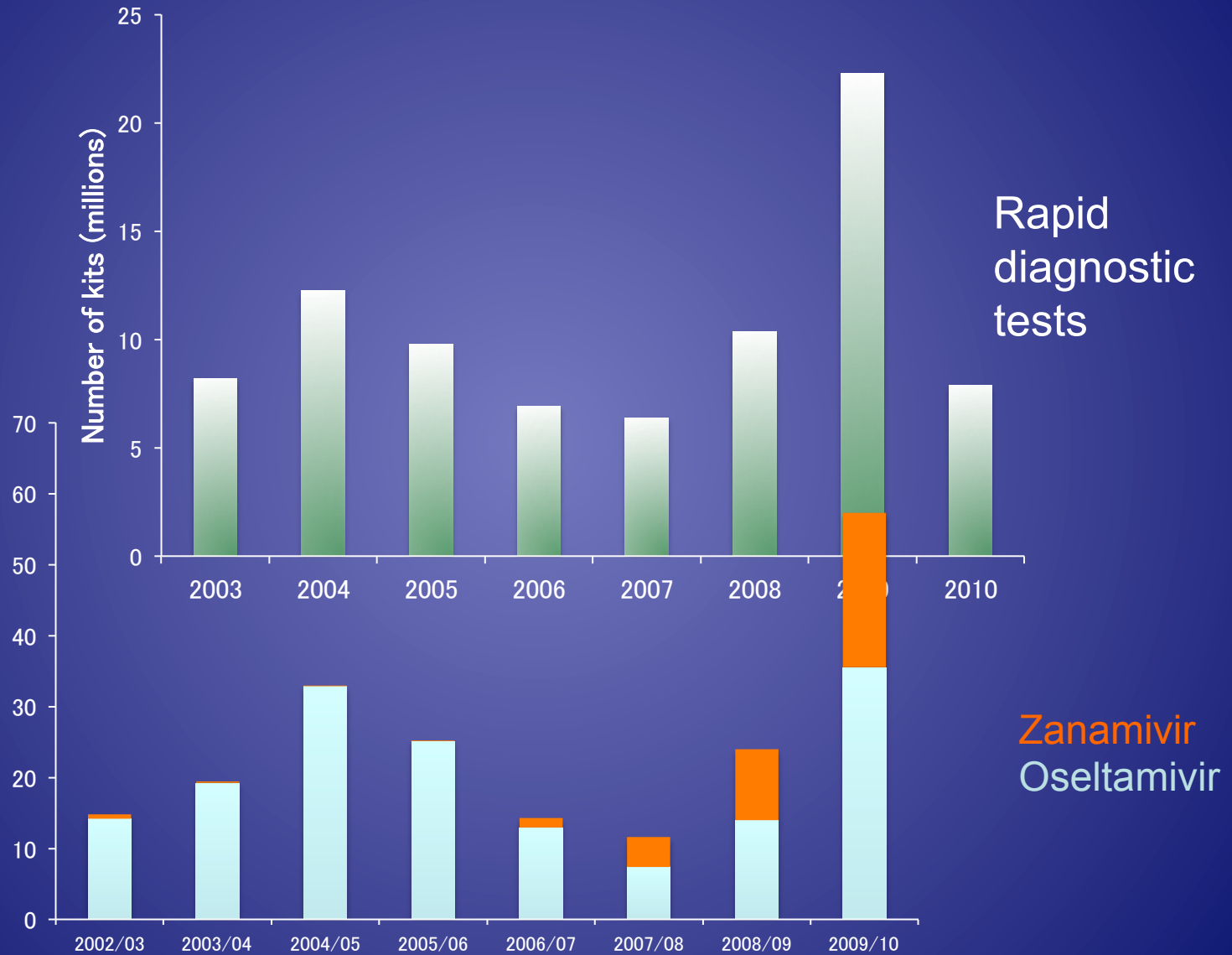
## Number of fatal cases

	Deaths / 100,000 population	Fatal cases	Population
Japan	0. 15	198	128 million
United Kingdom	0. 77	474	61 million
Australia	0. 92	193	21 million
Canada	1. 26	429	34 million
United States	1. 03 (3.32)	3433 (12,000 estimated)	332 million

# Number of rapid diagnostic test kits shipped from 2003 to 2010



# Widespread use of NAIs is based on the universal use of rapid diagnostic tests for influenza in Japan



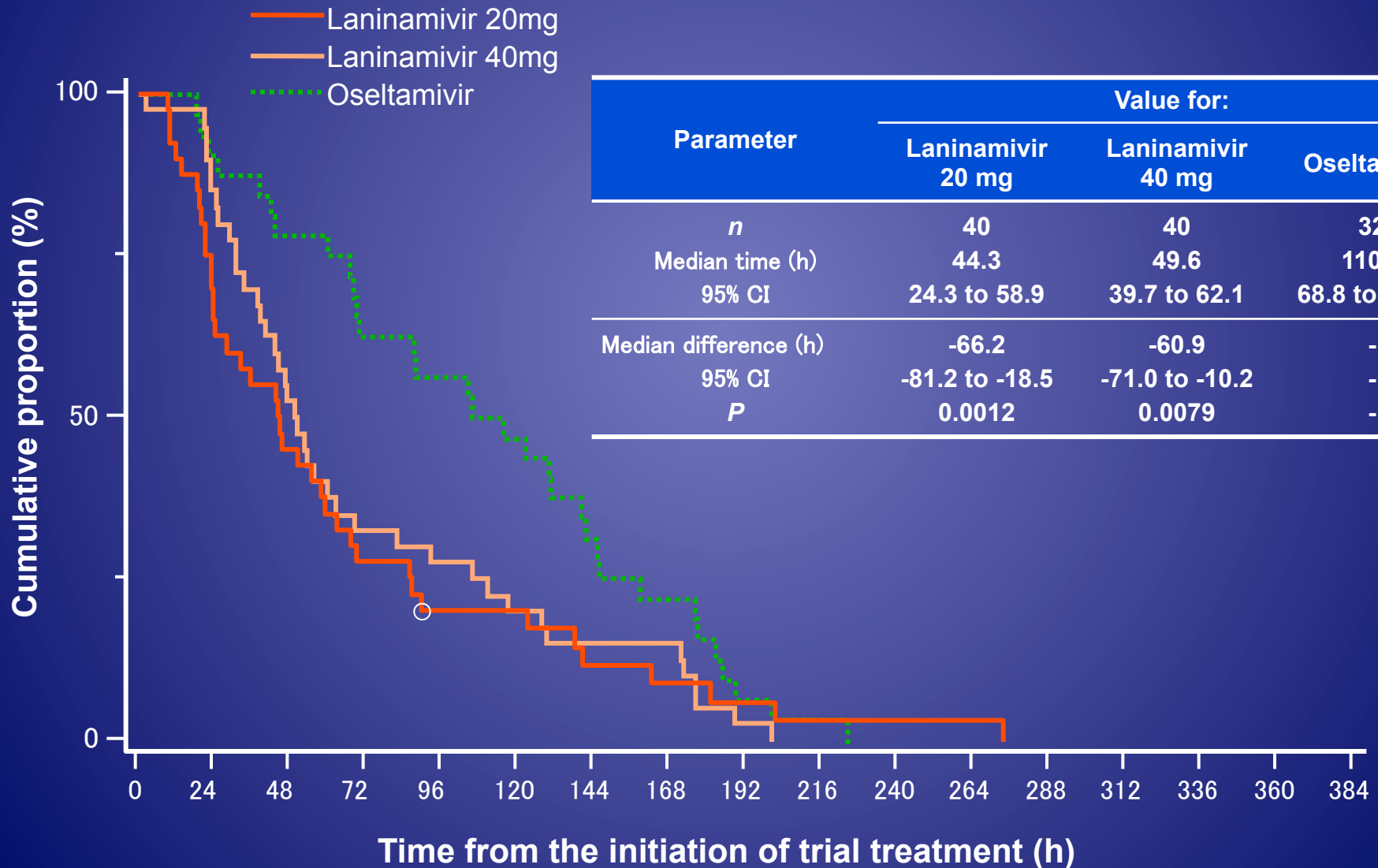
# Clinical Trials of Laninamivir

The main epidemic virus was influenza A (H1N1)  
97% of H1N1 viruses were oseltamivir-resistant strains with a H274Y mutation.

## IC<sub>50</sub> of Laninamivir and Oseltamivir

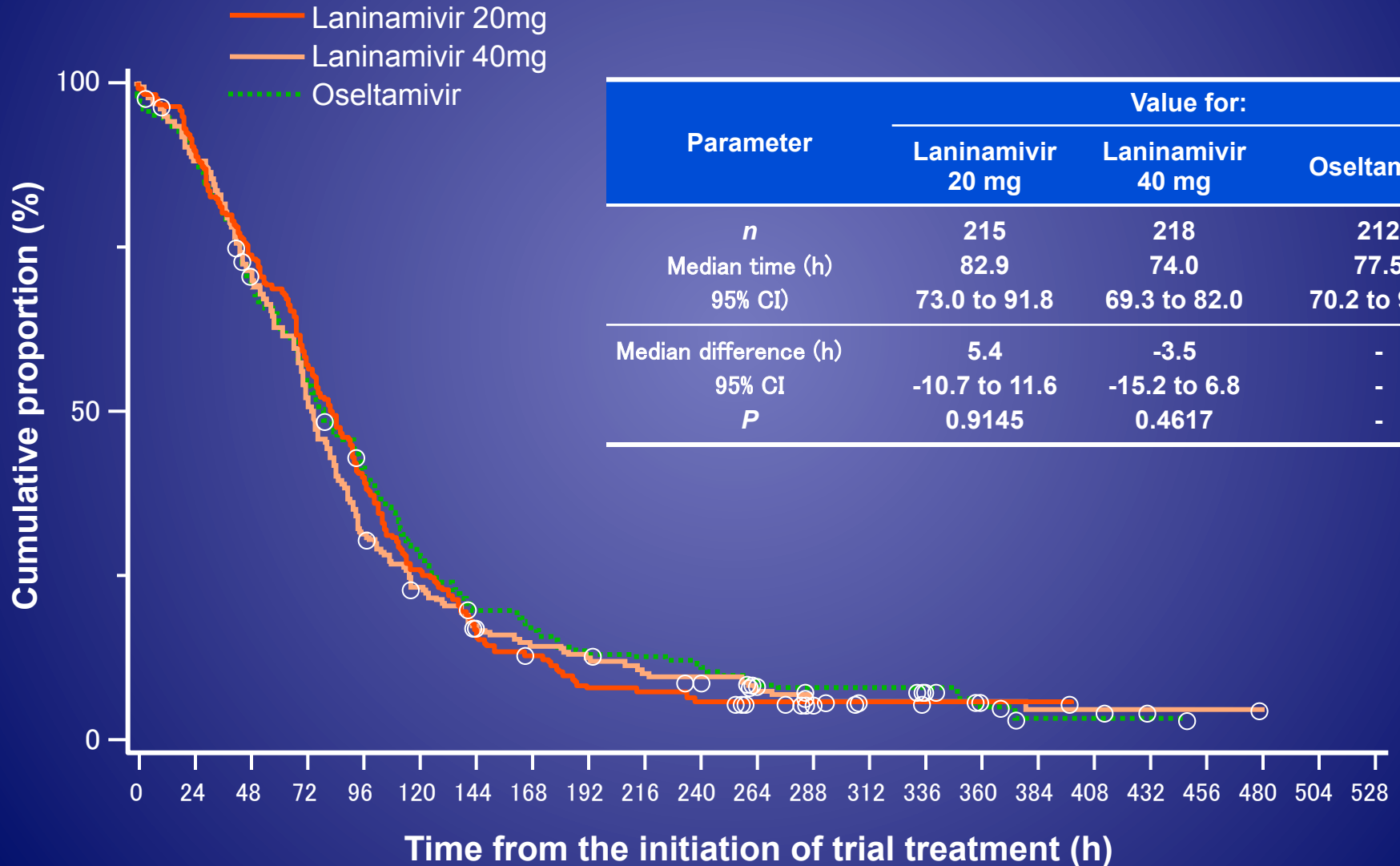
Virus type	N	The mean IC <sub>50</sub> (nM)		
		Laninamivir	Oseltamivir	
A	H1N1	95	1.8 (0.8-3.6)	641 (210-1200)
	H3N2	37	2.13 (1.20-3.00)	0.65 (0.29-0.92)
B		29	19.7 (11.0-26.0)	21.1 (12.0-53.0)

# Time to Alleviation of Illness (Children) Oseltamivir-resistant H1N1 Infection



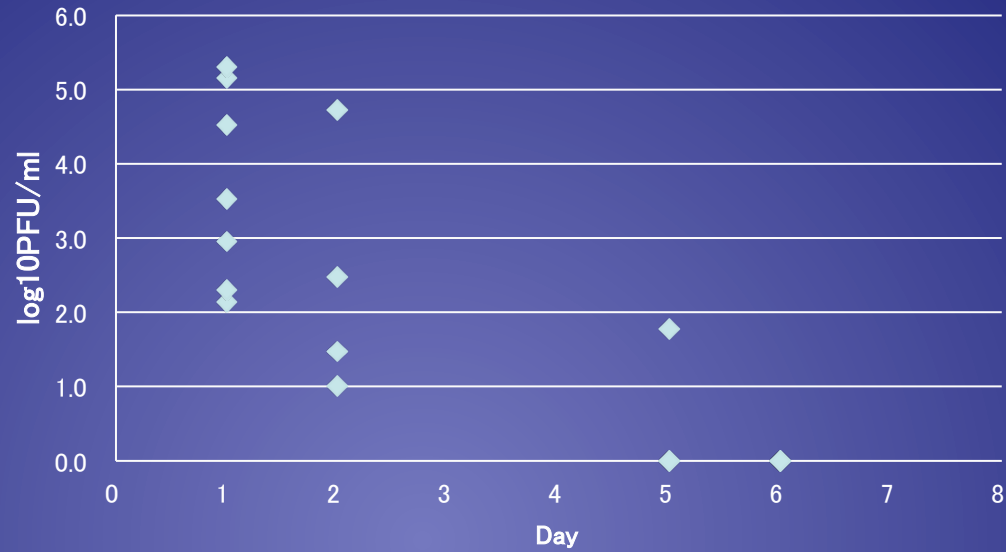


# Time to Alleviation of Illness (Adults) Oseltamivir-resistant H1N1 Infection

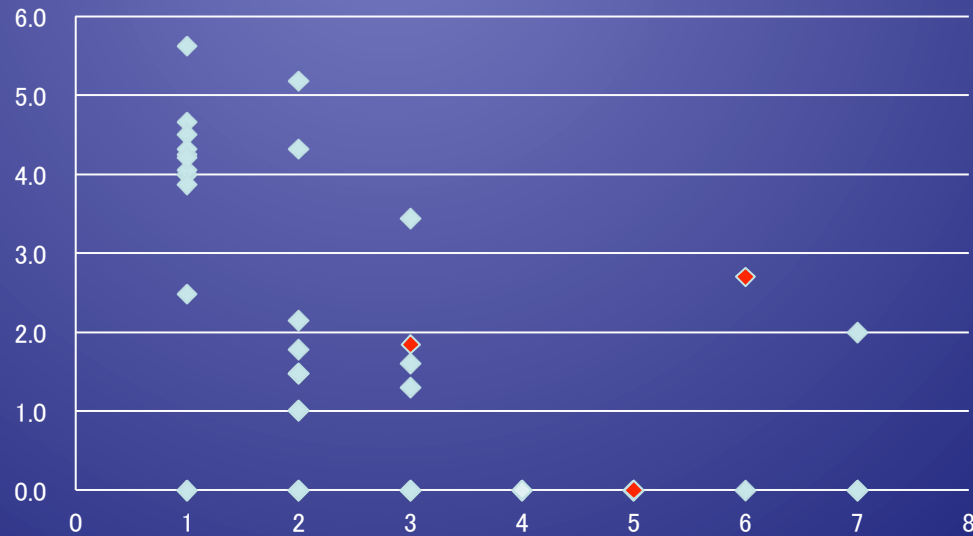


# Viral shedding and resistance strains

H1N1/09  
Laninamivir



H1N1/09  
Peramivir



# Clinical effectiveness of NAIs against A (H3N2)

	Peramivir	Oseltamivir	Zanamivir	Laninamivir
Number of patients	25	191	46	19
Age, mean years	3.5	5.1	10.6	8.5
Duration of fever, days±SD	0.9±0.6	1.3±0.8	1.6±0.9	2.0±1.6

Duration of fever after the start of therapy was significantly shorter in the peramivir group than in the other groups.

# Clinical effectiveness of NAIs against influenza B

	Peramivir	Oseltamivir	Zanamivir	Laninamivir
Number of patients	20	149	65	42
Age, mean years	5.0	5.5	9.5	8.7
Duration of fever, days±SD	1.8±1.3	2.5±1.2	2.0±1.2	2.3±1.5

Duration of fever after the start of therapy was significantly shorter in the peramivir group and the zanamivir group than in the oseltamivir group.

# Comparison of the effectiveness of NAIs Influenza A H1N1/09

Neuraminidase inhibitors	Peramivir	Laninamivir	Oseltamivir
No. of patients	13	14	50
Age, mean years	4.9	9.1	4
Total febrile period, mean no. of days $\pm$ SD	2.1 $\pm$ 0.6	2.4 $\pm$ 1.2	2.2 $\pm$ 0.8
Duration of fever after the start of therapy, mean no. of days $\pm$ SD	0.8 $\pm$ 0.3★	1.5 $\pm$ 1.2	1.2 $\pm$ 0.7

★Duration of fever after the start of therapy was significantly shorter in the peramivir group than in the laninamivir group and the oseltamivir group (P<.05)

# Lower effectiveness of NAIs against influenza B

## Influenza B

	Peramivir	Oseltamivir	Zanamivir	Laninamivir
Age, years	5.0	5.5	9.5	8.7
Duration of fever, days	1.8±1.3	2.5±1.2	2.0±1.2	2.3±1.5

## Influenza A (H3N2)

	Peramivir	Oseltamivir	Zanamivir	Laninamivir
Age, years	3.5	5.1	10.6	8.5
Duration of fever, days	0.9±0.6	1.3±0.8	1.6±0.9	2.0±1.6