

# **Present situation on influenza diagnosis and treatment in Japan**

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# Widespread use of neuraminidase inhibitors in Japan

## Standard practice

- During influenza season, all patients with influenza-like illness are tested with influenza rapid diagnostic tests.
- If positive, all of them are treated with neuraminidase inhibitors.
- Costs are covered by public health insurances.

# Widespread use of neuraminidase inhibitors in Japan

## Medical cost: example

A 40-year-old man with ILI visits a clinic.

Physician's consultation fee	2820 yen
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Rapid influenza test	2890 yen
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The result is positive, and he is treated with Tamiflu two capsules a day for 5 days.	3200 yen
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Other fees	1010 yen
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<u>Total</u>	<u>9960 yen</u>
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<u>The patient pays 30% of the total.</u>	<u>2990 yen</u>
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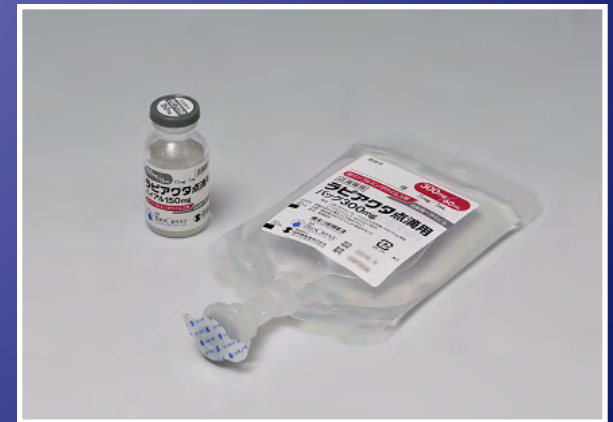
(about 25 US\$)

# Neuraminidase inhibitors approved for use in Japan

- Oseltamivir ( Tamiflu® )
- Zanamivir ( Relenza® )
- Laninamivir octanoate ( Inavir® )  
**Inhaler**
- Peramivir ( Rapiacta® )  
**Intravenous drip infusion**



Inavir



Rapiacta

# Laninamivir

- Only one inhalation, on the first day of treatment
- Compliance is better than with oseltamivir or zanamivir.
- If inhalation fails, the patient receives no treatment at all.
- Clinical effectiveness is sometimes low, probably because of inhalation failure.
- No resistant strains have been reported thus far.



# Daiichi Sankyo, Biota's laninamivir fails to meet goal of mid-stage influenza trial

Biota Pharmaceuticals announced Friday that a Phase II study of laninamivir octanoate failed to meet its primary endpoint of significantly reducing the median time to alleviation of influenza symptoms versus placebo. CEO Russell H. Plumb said "at this time we do not have any plans to independently advance the development of [laninamivir] for the treatment of influenza and intend to evaluate next steps...outside of Japan with our partner, Daiichi Sankyo."

The IGLOO trial enrolled 639 patients in the Northern and Southern Hemisphere from June 2013 to April 2014, with 39 percent, or 248 patients, having confirmed infection with the influenza A or B virus. Biota noted that approximately 75 percent and 19 percent of the influenza-confirmed patients were infected with influenza A H1N1 2009 and H3N2, respectively, with 6 percent being infected with influenza B.

## Laninamivir



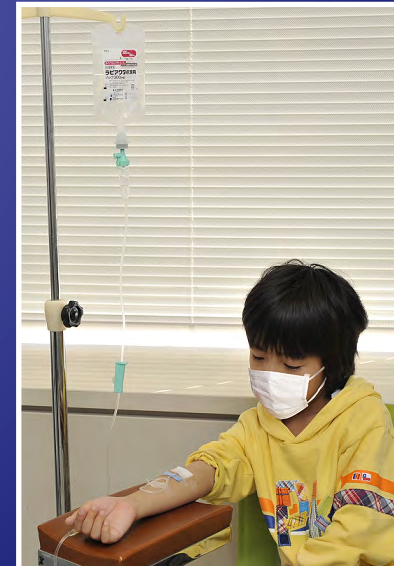
## Double-blind, randomized controlled trials of Laninamivir versus Oseltamivir in Japan

- RCTs comparing Laninamivir with Oseltamivir in children and adults were conducted concurrently during the 2008-09 season.
- The main epidemic virus was seasonal influenza A H1N1 with H274Y mutation.
- Patients were randomly assigned to:  
  
Laninamivir 40-mg group, Laninamivir 20-mg group,  
  
or Oseltamivir group.

# Intravenous Peramivir

## Certainty of drug delivery

- Only one infusion (300 mg) on the first day of treatment
- Peramivir should be infused within 48 hours after the onset of illness for adequate effectiveness.
- Peramivir is mainly used for hospitalized patients.
- Peramivir is also used for outpatients who can not have oseltamivir orally or inhale zanamivir or laninamivir.





# Abnormal behavior and NAIs

- 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.
- In Japan, it is thought that abnormal behavior is caused by influenza virus infection.
- Abnormal behavior may be an extension of delirium or hallucinations caused by the influenza itself.

# Abnormal behavior and NAIs

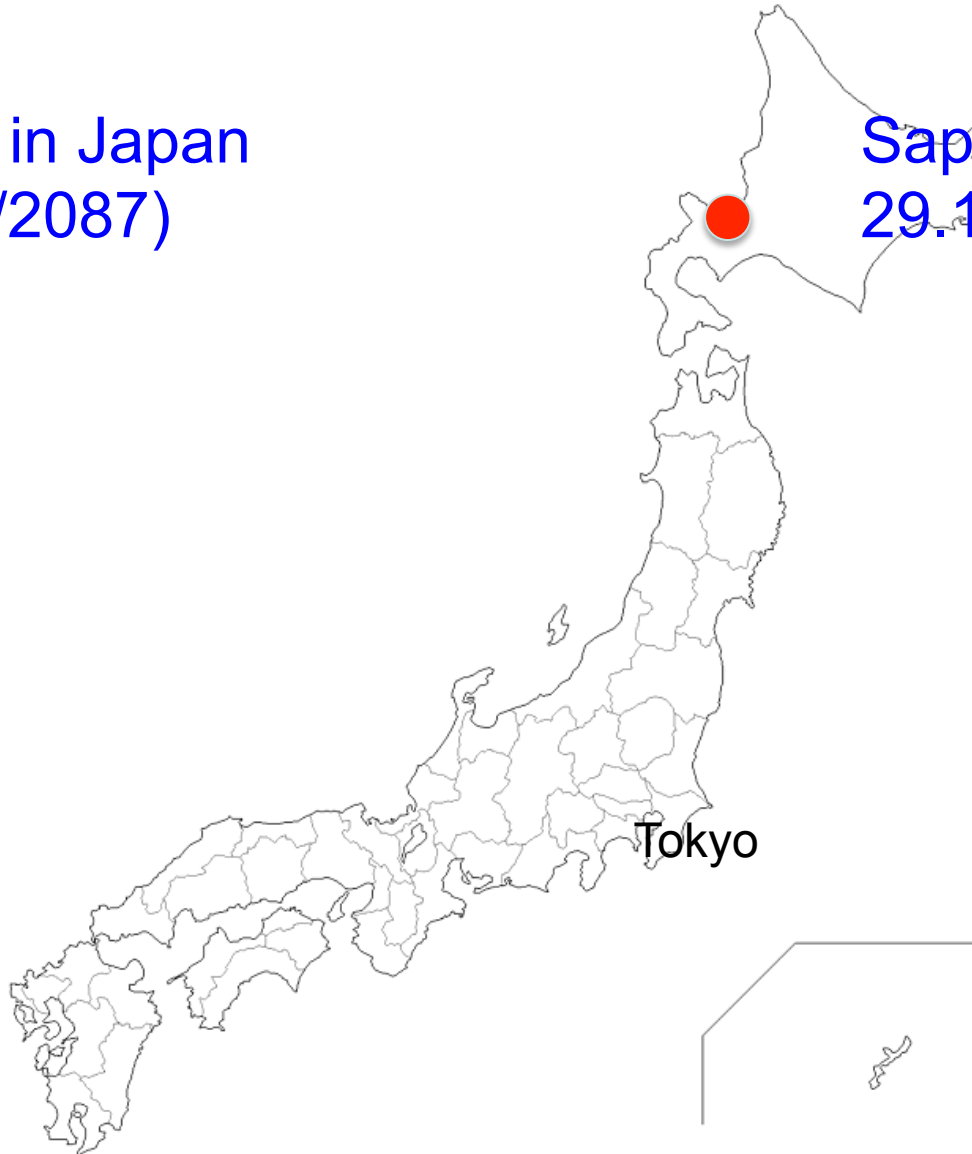
## Fatal cases (10 to 19 year-old) reported

Oseltamivir	8 cases
2004	1 case
2005	2 cases
2006	3 cases
2007	2 cases
Zanamivir	1 case (2009)
Laninamivir	1 case (2012)
Influenza patients not treated with a NAI	1 case (2007)

# Widespread community transmission of H275Y oseltamivir-resistant H1N1/09 in 2013-2014

Other areas in Japan  
2.3% (47/2087)

Sapporo  
29.1% (39/134)



# Susceptibility of influenza A(H1N1)pdm09 viruses with detected in Sapporo, Japan

Takashita E, et al. Euro Surveill 19(1) 2014

**TABLE 2**

Susceptibility of five influenza A(H1N1)pdm09 viruses with H275Y substitution to neuraminidase inhibitors, detected in Sapporo, Japan, November–December 2013

Isolate name	NA substitution	IC <sub>50</sub> (nM)			
		Oseltamivir	Peramivir	Zanamivir	Laninamivir
A/SAPPORO/107/2013	H275Y	240.60	35.28	0.50	0.81
A/SAPPORO/114/2013	H275Y	193.05	22.86	0.50	0.63
A/SAPPORO/116/2013	H275Y	257.10	23.97	0.43	0.53
A/SAPPORO/119/2013	H275Y	189.25	23.19	0.43	0.58
A/SAPPORO/120/2013	H275Y	192.44	22.35	0.45	0.54
Reference isolates <sup>a</sup>					
A/PERTH/261/2009	H275Y	257.88	34.30	0.30	0.35
A/PERTH/265/2009	275H	0.31	0.13	0.30	0.29

IC<sub>50</sub>: drug concentrations required to inhibit NA activity by 50%; NA: neuraminidase.

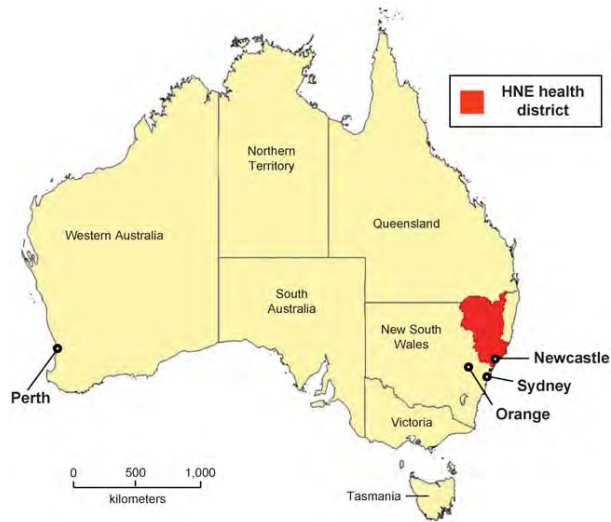
# Clinical findings in children of H275Y influenza A(H1N1)pdm09 infection

Kakuya F, et al. Pediatric International, 2015 April

- 10 children were infected with H1N1/09 with H275Y  
Mean duration of fever after treatment with NAI  
**25.3h**
- 4 patients were treated with oseltamivir or peramivir,  
**7.5-21.0 h**
- 6 patients were treated with zanamivir or laninamivir.  
**20.5-42.0 h**

# Resistance by mutation

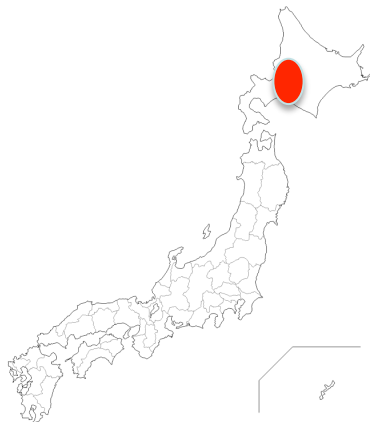
H275Y oseltamivir-resistant A H1N1/09 in Newcastle



Newcastle in 2011

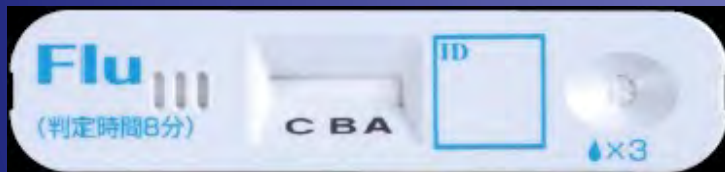
Hurt AC, et al. J Infect Dis 2012

H275Y oseltamivir-resistant A H1N1/09 in Sapporo originated in China



Sapporo in 2014

# Universal use of rapid diagnostic tests for influenza in Japan



Sensitivity for seasonal influenza infection has been reported to be over 90% in Japan.

# Lower Clinical Effectiveness of Oseltamivir against Influenza B Contrasted with Influenza A Infection in Children

Sugaya N, et al.  
Clin Infect Dis.  
2007;44:197.

**Norio Sugaya,<sup>1</sup> Keiko Mitamura,<sup>3</sup> Masahiko Yamazaki,<sup>7</sup> Daisuke Tamura,<sup>1</sup> Masataka Ichikawa,<sup>8</sup> Kazuhiro Kimura,<sup>8</sup> Chiharu Kawakami,<sup>2</sup> Maki Kiso,<sup>4,9</sup> Mutsumi Ito,<sup>4</sup> Shuji Hatakeyama,<sup>4,6</sup> and Yoshihiro Kawaoka<sup>4,5,9,10</sup>**

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The mean duration of fever after the start of oseltamivir therapy was significantly greater in the influenza B group than in the influenza A (H3N2) group (2.18 days vs. 1.31 days).



# Comparison of the Clinical Effectiveness of Oseltamivir and Zanamivir against Influenza Virus Infection in Children

Sugaya N, et al.  
Clin Infect Dis.  
2008;47;339

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Oseltamivir and zanamivir were equally effective in reducing the febrile period of children with influenza A (H1N1), influenza A (H3N2), and influenza B virus infection.

**Comparison between the effectiveness of 3 NAIs**  
**Mean duration of fever (days  $\pm$ SD)**  
 Observational study

	<b>peramivir</b>	<b>oseltamivir</b>	<b>laninamivir</b>
A/H1N1/09	0.75 $\pm$ 0.27 days (n=8)	1.27 $\pm$ 0.64 days (n=24) P<0.01*	1.5 $\pm$ 1.19 days (n=13) P<0.05*
A/H3N2	0.89 $\pm$ 0.60 days (n=9)	1.29 $\pm$ 0.80 days (n=139) P>0.05*	1.98 $\pm$ 1.52 days (n=20) P<0.01*

\*:The results of log-rank test

# Conclusions

Widespread use of NAIs in Japan is based on the routine use of rapid diagnostic tests.

Rapid diagnostic tests for influenza are essential for proper use of NAIs.

Test-negative case-control design based on the results of the rapid diagnostic test has become a standard investigation in a clinical ground.