

A/pdm(H1N1) 09 Antiviral Resistance Surveillance in Japan (n=159)

All screen clippings from NIID
Accessed 20-Nov-13 & 1-Dec-13

Thank you to all at National Institute of Infectious Disease
(NIID) for updated information on the NIID website!

Antiviral resistance surveillance in Japan (n=159)

2009-10: 79/8145 (1.0%)

2010-11: 78/3844 (2.0%)

2011-12: 0/11 (0.0%)

2012-13: 2/113 (1.8%)

Interim 2013-14: 0/9

Updated Total : 159/ 12,127 (1.3%)

Antiviral resistance surveillance in Japan (as of November 18, 2013)

<http://www.nih.go.jp/niid/en/influenza-e/2132-flu/flu-dr-e/4112-flu-dr-e20131118.html>

2009/2010 influenza season (Sep. 2009-Aug. 2010)

Detection of A(H1N1)pdm09 viruses with H275Y mutation in Japan

Table 2 . Report by prefecture during the 2009/2010 influenza season

as of June 17, 2011

Prefecture	Number of viruses tested	Number of H275Y mutant viruses
HOKKAIDO	773	4
AOMORI	170	0
IWATE	183	1
MIYAGI	201	2
AKITA	2	0
YAMAGATA	235	2
FUKUSHIMA	50	1
NIIGATA	129	6
IBARAKI	934	1
TOCHIGI	106	4
GUNMA	61	0
SAITAMA	338	5
CHIBA	400	2
TOKYO	546	1
KANAGAWA	920	4
YAMANASHI	83	1
NAGANO	51	0
SHIZUOKA	464	6
ISHIKAWA	27	0
FUKUI	136	1
Gifu	7	0
AICHI	248	5
MIE	180	2
SHIGA	11	3
KYOTO	20	0
OSAKA	266	5
HYOGO	97	2
NARA	60	3
WAKAYAMA	159	4
TOTTORI	36	1
SHIMANE	117	2
OKAYAMA	77	1
HIROSHIMA	291	1
YAMAGUCHI	24	2
TOKUSHIMA	9	1
EHIME	61	0
KOUCHI	7	0
FUKUOKA	274	2
NAGASAKI	19	1
KUMAMOTO	19	1
OOTA	235	1
MIYAZAKI	66	1
KAGOSHIMA	11	0
OKINAWA	42	0
Total number of viruses tested	8,145	
Total number of H275Y mutant viruses	79 (1.0%)	

Table 1. Detection of antiviral drug-resistant viruses in Japan during the 2009/2010 influenza season

as of February 6, 2013

	A(H1N1)pdm09				A(H3N2)				B		
	Oseltamivir	Peramivir	Zanamivir	Amantadine	Oseltamivir	Peramivir	Zanamivir	Amantadine	Oseltamivir	Peramivir	Zanamivir
Resistant (%)	79 ^a (1.0%)	79 ^a (1.0%)	0	7 ^b (100%)	0	0	0	9 ^b (100%)	0	0	0
Number of viruses tested	8,145	8,145	694	7	49	49	49	9	113	113	113
Number of viruses reported	13,261				81				136		

Viruses were examined by chemiluminescent-based NA-Star assay, fluorescence-based NA-Fluor assay, TaqMan RT-PCR and/or NA sequencing.

^a All viruses possessed H275Y mutation in NA protein.

^b All viruses possessed S31N mutation in M2 protein.

^c The virus possessed R292K mutation in NA protein.

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2010/2011 influenza season (Sep. 2010-Aug. 2011)

Detection of A(H1N1)pdm09 viruses with H275Y mutation in Japan

Table 3. Report by week during the 2010/2011 influenza season

as of November 2, 2011

Sampling week	Number of viruses tested	Number of H275Y mutant viruses	Number of 275H/Y mixed populations
2010, Week 35	3	0	0
Week 36	18	0	0
Week 37	6	0	0
Week 38	8	0	0
Week 39	6	0	0
Week 40	11	0	0
Week 41	6	0	0
Week 42	8	0	0

Detection of A(H1N1)pdm09 viruses with H275Y mutation in Japan

Table 2. Report by prefecture during the 2010/2011 influenza season

as of November 2, 2011

Prefecture	Number of viruses tested	Number of H275Y mutant viruses	Number of 275H/Y mixed populations
HOKKAIDO	151	2	1
AOMORI	35	0	0
IWATE	35	1	0
MIYAGI	59	0	0
AKITA	71	1	1
YAMAGATA	207	0	0
FUKUSHIMA	104	1	0
NIIGATA	158	5	0
IBARAKI	147	6	0
TOCHIGI	51	2	0
GUNMA	21	0	0
SAITAMA	246	7	0

Table 1. Detection of antiviral drug-resistant viruses in Japan during the 2010/2011 influenza season

as of February 6, 2013

	A(H1N1)pdm09					A(H3N2)					B			
	Oseltamivir	Peramivir	Zanamivir	Laninamivir	Amantadine	Oseltamivir	Peramivir	Zanamivir	Laninamivir	Amantadine	Oseltamivir	Peramivir	Zanamivir	Laninamivir
Resistant (%)	78 ^a (2.0%)	78 ^a (2.0%)	0	0	99 ^b (100%)	1 ^c (0.7%)	1 ^c (0.7%)	0	0	61 ^b (100%)	0	0	0	0
Number of viruses tested	3,844	3,844	256	256	99	135	135	135	135	61	147	147	147	147
Number of viruses reported	4,538					2,985					1,620			

Viruses were examined by chemiluminescent-based NA-Star assay, fluorescence-based NA-Fluor assay, TaqMan RT-PCR and/or NA sequencing.

^a All viruses possessed H275Y mutation in NA protein.

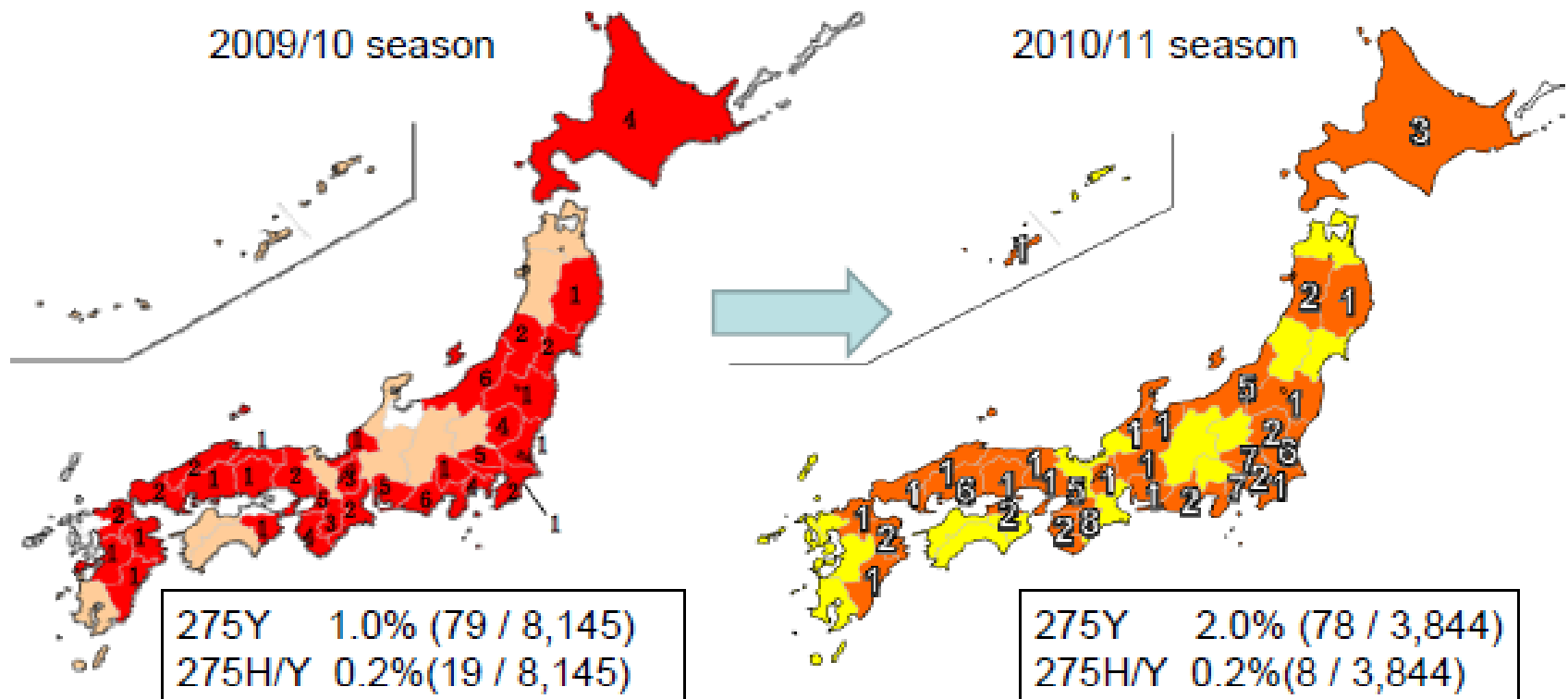
^b All viruses possessed S31N mutation in M2 protein.

^c The virus possessed R292K mutation in NA protein.

Week 12	5	0	0
Week 13	2	0	0
Week 14	2	0	0
Week 15	1	0	0
Week 16	1	0	0
2011, unknown	2	0	0
Total	3,844	69	9

SAGA	40	0	0
NAGASAKI	2	0	0
KUMAMOTO	33	0	0
OOTA	80	2	0
MIYAZAKI	10	1	0
KAGOSHIMA	4	0	0
OKINAWA	86	1	0
Total number of viruses tested	3,844		
Total number of H275Y mutant viruses	78 (2.0%)		

Detection of A(H1N1)pdm09 viruses with H275Y mutation in Japan



All resistant viruses were sensitive to zanamivir and laninamivir

Emi Takashita slide WHO-CC NIID

The clinical background of A(H1N1)pdm09 viruses with H275Y mutation

Clinical background	2009-2010 season		2010-2011 season	
	No. of viruses tested	No. of viruses with H275Y	No. of viruses tested	No. of viruses with H275Y
Treated with oseltamivir	511	52	50	19
Prophylaxed with oseltamivir	14	12	16	14
Treated with peramivir	0	0	13	6
Treated with zanamivir	117	0	22	1
Prophylaxed with zanamivir	1	0	0	0
Treated with laninamivir	0	0	4	0
Treated with oseltamivir and peramivir	0	0	6	2
Treated with oseltamivir and zanamivir	9	2	0	0
Treated with peramivir and zanamivir	0	0	1	0
No known exposure to drug	2,236	13	225	33
Insufficient information	5,257	0	3,349	2
Total	8,145	79	3,686	77

Lets dig dipper:

If you leave out insufficient information (5,257 viruses tested)

Of known results 66/652 viruses tested which is 10.1%

If you include No known exposure to drug 79/2,888 (2.7%)

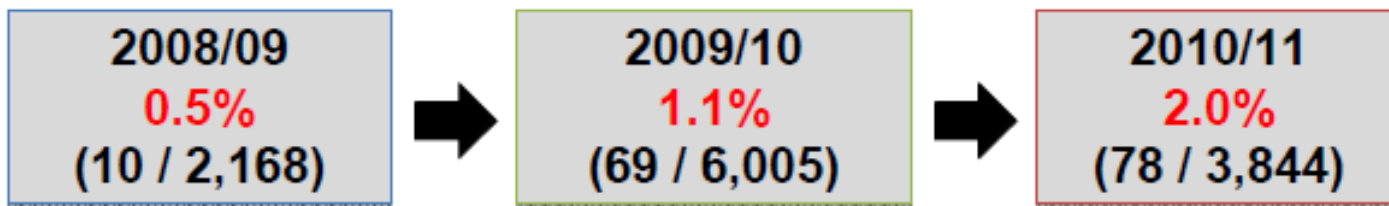
No known exposure increased from 2009 13/2,236 (0.6%) to 33/225 (14.7%) in 2010-2011 influenza seasons.

79/8,145 (0.9%)

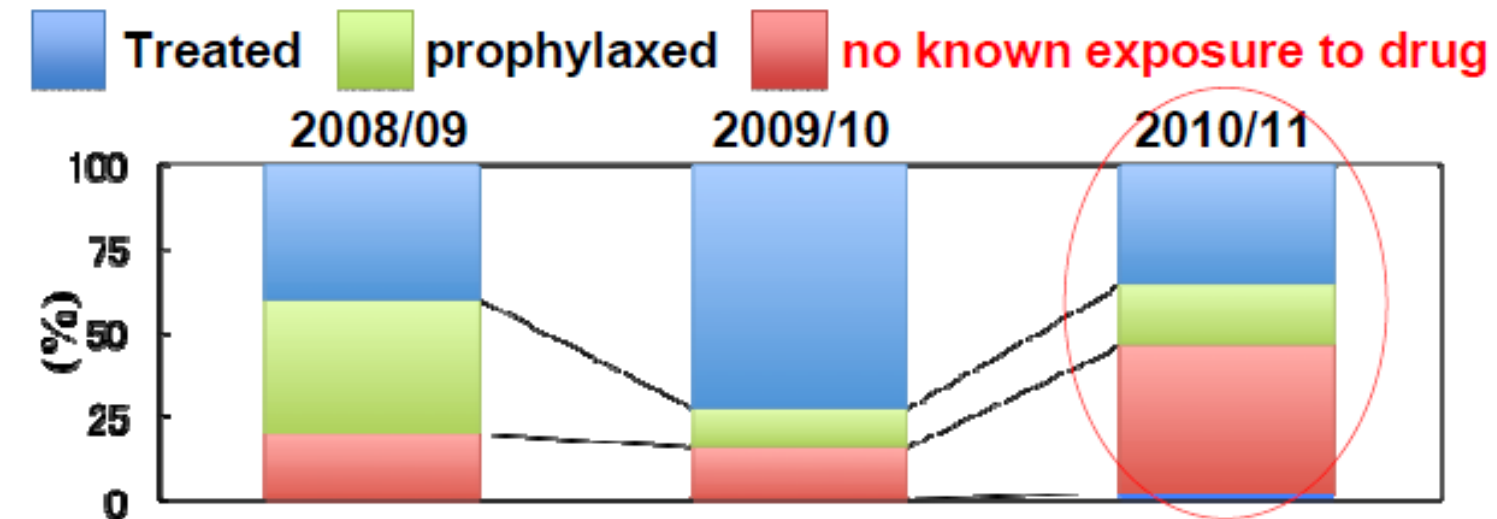
Emi Takashita slide WHO-CC NIID

http://www.flu.mn/mgl/images/stories/Sudalgaa_shinjiilgee/2011/Takashita.NIID.IVRC_antiviral.resistance_2011.11.22.pdf

Proportion of A(H1N1) pdm09 viruses with H275Y mutation is increasing in Japan



Clinical background of A(H1N1)pdm09 viruses with H275Y mutation in Japan



6th Meeting of NICs in the WPR and SEAR 29-31 May, 2012 Hanoi VN

http://www.wpro.who.int/emerging_diseases/meetings/docs/AntiviralResistantBVirusesinJapan.pdf

Masaki Imai slide WHO-CC NIID

2011/2012 influenza season (Sep. 2011-Aug. 2012)

Detection of A(H1N1)pdm09 viruses with H275Y mutation in Japan

Table 3 . Report by week during the 2011/2012 influenza season

as of Apr 9, 2013

Sampling week	Number of viruses tested	Number of H275Y mutant viruses	Number of 275H/Y mixed populations
2011, Week 36	0	0	0
Week 37	0	0	0
Week 38	0	0	0
Week 39	0	0	0
Week 40	0	0	0
Week 41	0	0	0
Week 42	1	0	0
Week 43	0	0	0
Week 44	0	0	0
Week 45	0	0	0
Week 46	0	0	0
Week 47	0	0	0
Week 48	0	0	0
Week 49	0	0	0
Week 50	0	0	0
Week 51	1	0	0

Detection of A(H1N1)pdm09 viruses with H275Y mutation in Japan

Table 2 . Report by prefecture during the 2011/2012 influenza season

as of Apr 9, 2013

Prefecture	Number of viruses tested	Number of H275Y mutant viruses	Number of 275H/Y mixed populations
HOKKAIDO	2	0	0
AOMORI	0	0	0
IWATE	0	0	0
MIYAGI	0	0	0
AKITA	0	0	0
YAMAGATA	0	0	0
FUKUSHIMA	0	0	0
NIIGATA	0	0	0
IBARAKI	2	0	0
TOCHIGI	0	0	0
GUNMA	0	0	0
SAITAMA	2	0	0
CHIBA	0	0	0
TOKYO	0	0	0
KANAGAWA	0	0	0
YAMANASHI	0	0	0

Table 1. Detection of antiviral drug-resistant viruses in Japan during the 2011/2012 influenza season

as of Apr 9, 2013

	A(H1N1)pdm09					A(H3N2)					B			
	Oseltamivir	Peramivir	Zanamivir	Laninamivir	Amantadine	Oseltamivir	Peramivir	Zanamivir	Laninamivir	Amantadine	Oseltamivir	Peramivir	Zanamivir	Laninamivir
Resistant (%)	0	0	0	0	9 ^a (100%)	1 ^b (0.3%)	1 ^b (0.3%)	0	0	137 ^a (100%)	0	0	0	0
Number of viruses tested	11	11	9	9	9	300	300	300	300	137	265	265	265	265
Number of viruses reported	15					4,230					1,773			

Viruses were examined by fluorescence-based NA-Fluor assay, real time RT-PCR allelic discrimination and/or NA sequencing.

^a All viruses possessed S31N mutation in M2 protein.

^b The virus possessed R292K mutation in NA protein.

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Week 29	0	0	0
Week 30	0	0	0
Week 31	1	0	0
Total	11	0	0

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OKINAWA	0	0	0
Total number of viruses tested	11		
Total number of H275Y mutant viruses	0 (0%)		

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2012/2013 influenza season (Sep. 2012-Aug. 2013)

Detection of A(H1N1)pdm09 viruses with H275Y mutation in Japan

Table 3 . Report by week during the 2012/2013 influenza season

as of Oct 10, 2013

Sampling week	Number of viruses tested	Number of H275Y mutant viruses	Number of 275H/Y mixed populations
2012, Week 36	0	0	0
Week 37	1	0	0
Week 38	0	0	0
Week 39	0	0	0
Week 40	0	0	0
Week 41	0	0	0
Week 42	0	0	0
Week 43	0	0	0
Week 44	1	0	0
Week 45	2	0	0
Week 46	1	0	0
Week 47	1	0	0
Week 48	1	0	0
Week 49	0	0	0
Week 50	3	0	0
Week 51	3	0	0
Week 52	4	0	0
2013, Week 1	2	0	0
Week 2	8	0	0
Week 3	14	0	0
Week 4	11	0	0
Week 5	5	1	0
Week 6	6	1	0

Detection of A(H1N1)pdm09 viruses with H275Y mutation in Japan

Table 2 . Report by prefecture during the 2012/2013 influenza season

as of Oct 10, 2013

Prefecture	Number of viruses tested	Number of H275Y mutant viruses	Number of 275H/Y mixed populations
HOKKAIDO	2	0	0
AOMORI			
IWATE			
MIYAGI	1	0	0
AKITA	2	0	0
YAMAGATA	9	0	0
FUKUSHIMA	4	0	0
NIIGATA	6	0	0
IBARAKI	3	0	0
TOCHIGI			
GUNMA	1	0	0
SAITAMA	8	0	0
CHIBA	2	0	0
TOKYO	5	0	0
KANAGAWA	12	2	0
YAMANASHI	2	0	0
NAGANO	3	0	0
SHIZUOKA	3	0	0
TOYAMA	1	0	0
ISHIKAWA			
FUKUI	1	0	0
GIFU	1	0	0
AICHI	6	0	0

Table 1. Detection of antiviral drug-resistant viruses in Japan during the 2012/2013 influenza season

as of Nov 18, 2013

	A(H1N1)pdm09					A(H3N2)					B			
	Oseltamivir	Peramivir	Zanamivir	Laninamivir	Amantadine	Oseltamivir	Peramivir	Zanamivir	Laninamivir	Amantadine	Oseltamivir	Peramivir	Zanamivir	Laninamivir
Resistant (%)	2 ^a (1.8%)	2 ^a (1.8%)	0	0	43 ^b (100%)	0	0	0	0	108 ^b (100%)	0	0	0	0
Number of viruses tested	111	111	105	105	43	295	295	295	295	108	333	333	333	333
Number of viruses reported	175					5,044					1,452			

Viruses were examined by fluorescence-based NA-Fluor assay, NA-XTD assay, real time RT-PCR allelic discrimination and/or NA sequencing.

^aAll viruses possessed H275Y mutation in NA protein.

^b All viruses possessed S31N mutation in M2 protein.

Week 31	1	0	0
Total	111	2	0

viruses tested	
Total number of H275Y mutant viruses	2 (1.8%)

2012/2013 influenza season (Sep. 2012-Aug. 2013)

IASR

Vol. 34 No. 11 November 2013
Infectious Agents Surveillance Report
<http://www.nih.go.jp/niid/en/iasr-e.html>

National Institute of Infectious Diseases and
Tuberculosis and Infectious Diseases
Control Division,
Ministry of Health, Labour and Welfare

Antigenic characteristics of 2012/13 isolates and their drug resistance (see p. 328 of this issue): Ninety percent of the 94 AH1pdm09 isolates from Japan and abroad tested in National Institute of Infectious Diseases, were similar to A/California/2009 (2009/10-2012/13 vaccine strain) in the antigenicity. The remaining 10% were variants with reduced reactivity (≥ 8 -fold lower in HI titer) to the A/California/7/2009 antiserum. Ninety-nine percent of 236 AH3 isolates (most isolated in Japan and very few in abroad) similar to A/Victoria/361/2011 (2012/13 vaccine strain). Among type B isolates, 96% of 120 Yamagata lineage isolates similar to B/Wisconsin/1/2010 (2012/13 vaccine strain) in antigenicity, while 99% of 95 Victoria lineage isolates have antigenically similar to that of B/Brisbane/60/2008 (2009/10-2011/12 season vaccine strain).

The oseltamivir resistance-related mutation, H275Y, was observed in 2 out of 103 AH1pdm09 Japanese isolates (1.9%), which was not found in the 2011/12 season. Twenty subtype AH3 isolates tested were all sensitive to oseltamivir, zanamivir, peramivir and laninamivir.

<http://www0.nih.go.jp/niid/idsc/iasr/34/405e.pdf>

2013/2014 influenza season (Sep. 2013-Aug. 2014)

- Antiviral resistance surveillance in Japan (as of November 18, 2013)
- <http://www.nih.go.jp/niid/en/influenza-e/2132-flu/flu-dr-e/4112-flu-dr-e20131118.html>

Detection of A(H1N1)pdm09 viruses with H275Y mutation in Japan

Table 3 . Report by week during the 2013/2014 influenza season

as of Nov 18, 2013

Sampling week	Number of viruses tested	Number of H275Y mutant viruses	Number of 275H/Y mixed populations
2013, Week 36	0	0	0
Week 37	1	0	0
Week 38	5	0	0
Week 39	3	0	0
Week 40	0	0	0
Week 41	0	0	0
Week 42	0	0	0
Week 43	0	0	0
Week 44	0	0	0
Week 45	0	0	0
Week 46	0	0	0
Week 47	0	0	0
Week 48	0	0	0
Week 49	0	0	0
Week 50	0	0	0
Total	9	0	0

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Infectious Agents Surveillance Report

week 45/2013

A/pdm(H1N1) 09 Antiviral Resistance Surveillance in Japan (n=159)

- **Clip:**
- The susceptibility of viruses was expressed as the drug concentrations required to inhibit NA activity by 50% (IC50). Results:
- During pandemic (2008-2009 to 2009-2010) and post-pandemic (2010-2011 to 2012-2013) periods, we found that 159 (1.3%) of 12,099 A(H1N1)pdm09 viruses possessed the H275Y substitution and 2 (0.2%) of 902 A(H3N2) viruses possessed an R292K substitution in the NA protein.
- The mutant viruses were resistant to oseltamivir and peramivir, but not to zanamivir and laninamivir. The highest detection rate of the resistant A(H1N1)pdm09 viruses was found in patients who were 0-9 years old.
- The detection rate of the resistant viruses increased from 1.0% during the pandemic period to 2.0% during the postpandemic period.
- Furthermore, among the cases with resistant A(H1N1)pdm09 viruses, the percentage of no known exposure to antivirals significantly increased from 16% during the pandemic period to 44% during the post-pandemic period.
-
- **Conclusions:** A(H1N1)pdm09 viruses resistant to oseltamivir and peramivir were sporadically detected in Japan, and they did not spread throughout the community. However, suspected human-to-human transmission of the resistant viruses gradually increased in the post pandemic period. Consequently, sustained monitoring of resistant viruses is important to explore the possibility of human-to-human transmission of the resistant viruses. This study was conducted by collaboration with the influenza virus surveillance group of Japan
- P1-271 (pg 215)
- Detection of antiviral-resistant influenza viruses in Japan during pandemic and post-pandemic periods *E Takashita*, S Fujisaki, N Kishida, H Xu, M Imai, M Tashiro, T Odagiri* Influenza Virus Research Center, National Institute of Infectious Diseases, Musashimurayama, Tokyo
- Accessed and clipping taken: 17-Dec-13
- http://optionsviii.controlinfluenza.com/optionsviii/assets/File/Options_VIII_Abstracts_2013.pdf

Please see updated NIID website at hyperlink:

<http://www.nih.go.jp/niid/en/influenza-e/2132-flu/flu-dr-e/4112-flu-dr-e20131118.html>

2010/2011 influenza season (Sep. 2010-Aug. 2011)

- 6th Meeting of NICs in the WPR and SEAR 29-31 May, 2012 Hanoi VN, Antiviral-resistant B viruses with a novel mutation detected by antiviral resistance surveillance in Japan, Masaki Imai WHO-CC
- http://www.wpro.who.int/emerging_diseases/meetings/docs/AntiviralResistantBVirusesinJapan.pdf
- Interesting PDF: Antiviral-resistant B viruses with a novel mutation

Old slides from PPT in 2011

Mutation Relevance in Japan 2009-10

- Figure 5- Two model structures of NA created from the crystal structure of N1 neuraminidase (PDB entry: 2HU4). The left panel shows the NA protein with the N248D substitution, representing locations of the amino acid substitution as well as H275 and E277. Substitution of N248 to D248 appears to have little effect on the side chain of E277. The right panel shows the NA protein with the H275Y substitution, revealing that the side chain of E277 is shifted by 1.62 Å in the oseltamivir-resistant variant found in samples “II.”

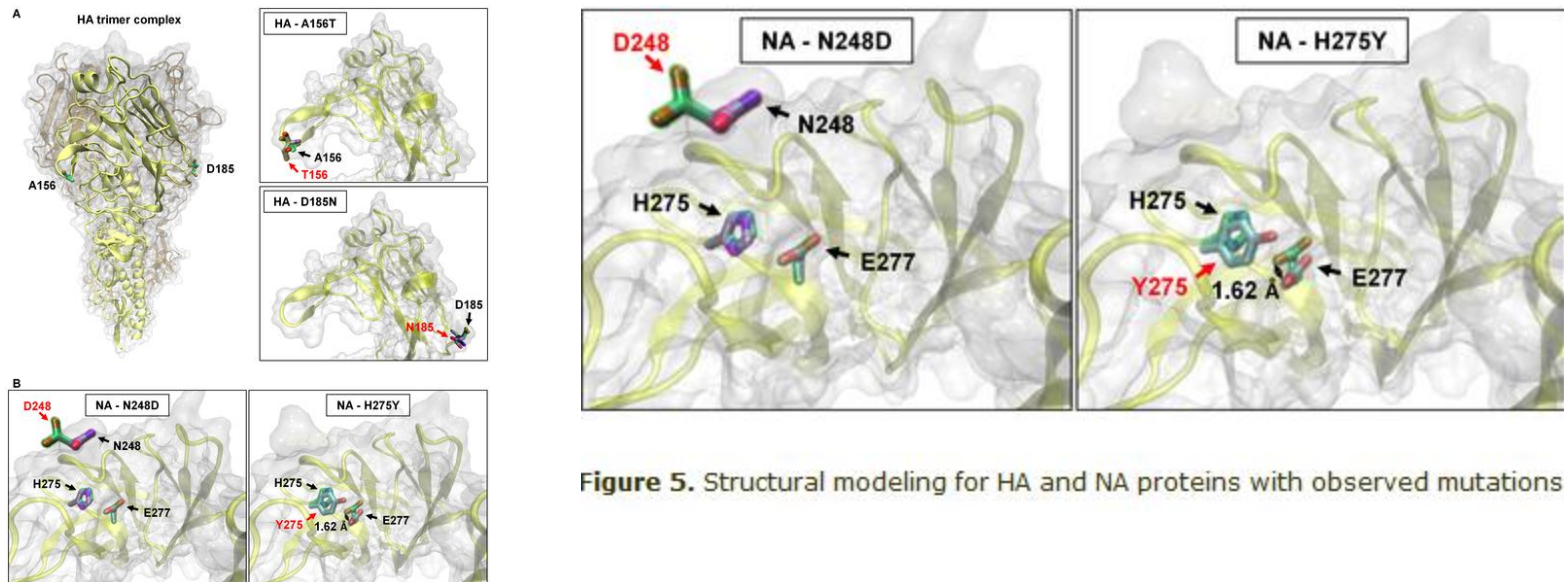


Figure 5. Structural modeling for HA and NA proteins with observed mutations.

Morlinghem, J. E. et al. 2011. Mutation Analysis of 2009 Pandemic Influenza A(H1N1) Viruses Collected in Japan during the Peak Phase of the Pandemic. PLoS ONE 6(4): e18956. doi:10.1371/journal.pone.0018956. Available from: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0018956>

Pandemic (H1N1) 2009 Virus

Mutation Relevance in Japan 2009-10

Two cases studies:

- “Almost all OR pandemic (H1N1) 2009 cases emerged sporadically and were not epidemiologically linked. However, 2 cases of human-to-human transmission were suspected.
- **(More likely)** One was observed in Niigata Prefecture where 2 children hospitalized in the same room were infected with OR pandemic (H1N1) 2009 virus within a few days. Symptoms developed first in a 4-year-old girl on October 10, 2009, and she received oseltamivir. OR pandemic (H1N1) 2009 virus was isolated from this patient on October 14. A 6-year-old boy in the same room received prophylaxis (by treatment dosage) with oseltamivir beginning October 10. However, he experienced symptoms on October 13, and OR pandemic (H1N1) 2009 virus was isolated on October 14. The patients were in a double room, and patients with pandemic (H1N1) 2009 were not around them. Genetic analyses of the 2 viruses (i.e., A/Niigata/1233/2009 and A/Niigata/1234/2009) showed only 1 aa difference (D to G), at position 256 in PB2, and they also shared unique changes in NS1 and in PB1 (Table 2).
- Transmission possibilities were as follows: 1) OR pandemic (H1N1) 2009 was directly transmitted from the female patient or 2) an OS pandemic (H1N1) 2009 was transmitted from the female patient and an OR pandemic (H1N1) 2009 virus emerged in the male patient.
- **(less likely)** The other suspected instance of human-to-human transmission occurred in Tottori Prefecture. In a 9-year-old boy, symptoms developed on December 18, 2009, and OR pandemic (H1N1) 2009 virus was isolated from a sample collected on the same day, before oseltamivir use.
- However, the patient’s 2 brothers were both infected with pandemic (H1N1) 2009 virus and had received oseltamivir since December 15. Although samples from these persons were not available, OR pandemic (H1N1) 2009 likely emerged in 1 patient and was transmitted to the other.”

Ujike et al. 2011

- 2011 -Japan NIID reported a case of influenza A(H1N1)2009 virus carrying the H275Y substitution isolated from a patient undergoing peramivir treatment, showing resistance to oseltamivir and peramivir. The clinical implications of this finding and the association with drug use are not yet clear as no sample was tested for resistance before the onset of the treatment. (WHO 2011)

Pandemic (H1N1) 2009 Virus Mutation Relevance in Japan 2009-10

- A report for 1997–2007 showed that Japan accounted for ≈70% of the world's oseltamivir consumption (10). From August 2009 to March 2010, 9.76 million doses of oseltamivir were supplied in Japan, ≈2.3× that of the 2008–09 seasons (data from Chugai Co. Ltd, Tokyo, Japan).
- Prior to this report in Japan: Haruo Watanabe National Institute of Infectious Disease, Japan 67 Resistant / 5422 tested (1.2%) All were sensitive to zanamivir On July 2, 2009, a person infected with an oseltamivir-resistant novel influenza A (H1N1) virus was reported from Japan from an illness on May 15, 2009. This patient also became ill while receiving oseltamivir for chemoprophylaxis.
- Results- Overall prevalence in Japan was 1.4% (61/4,307). (Ujike et al. 2011)
- Geographic Distribution of OR Pandemic (H1N1) 2009
- The 4,307 clinical specimens isolated during May 2009–February 2010 were collected from 41 of 47 prefectures in Japan, and the H275Y mutation was detected by NA sequencing.
- In total, 61 (1.4%) OR pandemic (H1N1) 2009 viruses possessed the H275Y (n = 48) or 275H/Y mixed (n = 13) mutations
- Patient Treatment History and Epidemiologic Background
- Of 4,307 case-patients, 516 had oseltamivir treatment, 103 had zanamivir treatment, 1,088 were NAI-untreated, and the treatment history of 2,600 was unknown.
- Of the 61 cases of OR pandemic (H1N1) 2009, 45 were associated with oseltamivir treatment, 10 with postexposure prophylaxis, and 6 occurred in NAI-untreated patients (2/6 in household community acquired!); thus, oseltamivir treatment and prophylaxis likely accelerated emergence of OR pandemic (H1N1) 2009.
- The relationship between time of sampling (days after oseltamivir treatment) and OR pandemic (H1N1) 2009 detection showed that OR pandemic (H1N1) 2009 was generally detected at least 4 days after oseltamivir treatment (This timing is consistent with that for OR seasonal influenza A
- (H1N1, H3N2) and pandemic (H1N1) 2009 viruses, which typically emerge 3–6 days after oseltamivir treatment (36–38).
- Of the 61 case-patients, 36 (59%) were male; 19 (31%) were 0–4 years, 25 (41%) were 5–18 years, 12 (20%) were 19–50 years, and 5 (8%) were >50 years. Underlying medical conditions were known for 41; 24 had chronic underlying medical conditions (**pulmonary** [13], neurologic [4], blood [3], diabetes [1], kidney disease [1], **immunocompromised** [5], other conditions [2]).
- Two Possible Cases of Human-to-Human Virus Transmission see narration!
- Almost all OR pandemic (H1N1) 2009 cases emerged sporadically and were not epidemiologically linked. However, 2 cases of human-to-human transmission were suspected



Table 1. Relationship between detection of oseltamivir-resistant pandemic (H1N1) 2009 and interval from oseltamivir treatment to sample collection, Japan, 2009–2010*

	Days after oseltamivir treatment, N = 516†											
No. samples	Unknown	0‡	1	2	3	4	5	6	7	8	9	>10
Total no.	169	54	116	54	37	31	36	7	6	1	3	2
No. oseltamivir-resistant pandemic (H1N1) 2009	3	0	4	2	4 (1)	13 (1)	19 (1)	3 (2)	2	1 (1)	2 (2)	2 (2)

*Of total 4,307 specimens tested, neuraminidase inhibitor treatment history was available for 1,707; of these specimens, 516 were from patients who had received oseltamivir treatment.

†Parentheses indicate prophylactic use, e.g., 4 (1) = 1 of 4 total uses was for prophylaxis.

‡Day 0 represents the samples collected within 24 h after oseltamivir use.

Emergence of Oseltamivir-resistant in Prolonged Antiviral Treatment

Emergence of Oseltamivir-resistant in Tamiflu Treatment and Prophylaxis in Pandemic (H1N1) 2009

Study	Vietnam (9) Moscana et al.	Seattle, Washington (1) CDC-MMWR	North Carolina (2) CDC-MMWR		Scotland (4) Harala et al.	Taiwan (7)	US Memoli et al.	Canada (13)	Australia (7) Wang et al	Australia (14) Tramontana et al.	Israel (9) Mandelboim et al 2010	Japan (14) Inoue et al.2010	USA ¹⁵ Couturier et al. 2010	Japan ¹⁸ Ujike et al. 2011	
Number of pts confirmed		1 2	1	2	9/1802 Highlight 2 cases	3	2			4	2/7	1	3 of 4	61	
Medical Condition		Both HSCT	healt hy	healt hy	2 Haematological malignancies (immunosupressed)	Mental retardation	blood stem cell transplant		Renal transplant	Malignancy and HSCT	Immunosuppres sed	immunosuppres sed	HCST/AML ¹⁸	Not mentioned	
Tamiflu Treatment or prophylaxis		Extended use			yes	Yes	One pt 24 days of treatment 10 days of the changed to peramivir iv 10 days. With no resolution Zanamivir given x 10 days- resolved			1/4	a. Yes (60mgx 5 days) b. Yes x 5 days	Given on day 4 Dose N/A	Pt-1 150mg BID Pt-2 – 150mg BID Pt-3-70mg BID Pt-4 - none	See case study Increase use and double dosing HX of 70% of worl'sa's consumption	
Initial Isolate date		11-23 days			8-12 days showed replication of mutation	4 days	9 and 14 days Following treatment	8-12 days following treatment		4 days showed resistance	- Not identified in EID letter however suggests emergence occurred during treatment	48 hrs- 48 hours after initiation of therapy showed 20k and 12k resistant sequences A sample 25 sample 16 in other receiving influenza virus 100% G B Virus 10, 18 sample shows 100% G and 100% A C Virus 10 sample 16 in house 48% G D Virus 10 sample 16 in house 48% G E Virus 10 sample 16 in house 48% G F Virus 10 sample 16 in house 48% G G Virus 10 sample 16 in house 48% G H Virus 10 sample 16 in house 48% G I Virus 10 sample 16 in house 48% G J Virus 10 sample 16 in house 48% G K Virus 10 sample 16 in house 48% G L Virus 10 sample 16 in house 48% G M Virus 10 sample 16 in house 48% G N Virus 10 sample 16 in house 48% G O Virus 10 sample 16 in house 48% G P Virus 10 sample 16 in house 48% G Q Virus 10 sample 16 in house 48% G R Virus 10 sample 16 in house 48% G S Virus 10 sample 16 in house 48% G T Virus 10 sample 16 in house 48% G U Virus 10 sample 16 in house 48% G V Virus 10 sample 16 in house 48% G W Virus 10 sample 16 in house 48% G X Virus 10 sample 16 in house 48% G Y Virus 10 sample 16 in house 48% G Z Virus 10 sample 16 in house 48% G	Pt-1-day 9/10- died	36 of 55 cases occurred at 3-6 days with 3 cases during PEP	
Positive /negative													-		Pt-2 22 days after completion of 10 day course, Died
Second isolate													-		Pt-3 day8/10 days prophylaxis- recovered
Positive/negativ e													-		Pt-4- none - recovered
Onward transmission	Yes- among train passengers only	Yes, possible transmission	No		No	No	No	No	No	No	Possible 1 to 2 nd pt or transmitted by a third	No	No	2 cases of suspected transmission	
Prolonged shedding					Up to 61 days		Prolonged shedding (24days)		Yes	Yes	N/A	N/A	79 days in pt 2	>10 days(2/55)	
Mutation	H275Y	H275Y										H275Y	H275Y	H275Y	

The overview of recent articles Oseltamivir-resistant pandemic (H1N1) 4-9 days with initial doses of Tamiflu and up to 9-41 days in immunocompromised. There an emerging trend of evolutionary change in the H275Y mutation that can occur as early as 48 hrs-4 days but in prolonged treatment with Tamiflu increase prevalence at -12 days. Initial isolates are usually negative and the second positive hence a evolutionary relationship with prolonged treatment of Tamiflu past 9 days increases likelihood of H275Y mutation at D225G amino acid position.. Emergence of a pandemic influenza virus in a patients treated with neuraminidase inhibitors, with a novel resistance pattern that conferred resistance to Oseltamivir, and Zanamivir, and Peramivir can be caused by the Dual H275Y/I223R (isoleucine-to-arginine amino acid substitution at residue 223) which shows greater resistance, seasonal H1N1 OS usually occur 3-6 days (18)

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3. A Community Cluster of Oseltamivir-Resistant Cases of 2009 H1N1 Influenza -Mai et al December 9, 2009, at NEJM.org
4. The Emergence Of Oseltamivir-resistant Pandemic Influenza A(H1N1) 2009 Virus Amongst Hospitalised Immunocompromised Patients In Scotland, November-December, 2009- Harvala et al April 2010 EID
5. Rapid Emergence of Oseltamivir Resistance- Sy et al April 2010 EID
6. Possible Transmission of Pandemic (H1N1) 2009 Virus with Oseltamivir Resistance- Mandelboim et al April 2010 EID
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Recombinomics Commentary 11:2 August 17, 2009
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19. Ujike M, Ejima M, Anraku A, Shimabukuro K, Obuchi M, Noriko Kishida N, et al. Monitoring and characterization of oseltamivir-resistant pandemic (H1N1) 2009 virus, Japan, 2009–2010 Emerg Infect Dis. 2011 Mar; [Epub ahead of print]

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Thanks “Biological”
Michael Fraser RN (CNO)