

# ***Accessing the FluSurver in GISAID***

Please send questions and feedback to:  
**flusurver@gisaid.org**

The FluSurver team is located in Singapore and our working day for fast replies may be shifted depending on your local time zone.



Bioinformatics  
Institute



**First steps:** find, select and add isolates to analyze from the EpiFlu™ database

The screenshot shows the GISAID EpiFlu™ web interface. At the top, there's a header with the GISAID logo, copyright information (© 2008 - 2013 | The GISAID Foundation | Terms of Use | Contact | System Requirements), and flags for China and the UK. Below the header is a navigation bar with tabs: Welcome, News, Registered Users, EpiFlu™, FAQ, My profile, and About GISAID. Underneath is another set of icons for Browse, Back to results, Worksets, Upload, Batch Upload, Settings, and Analysis. The main section is titled 'Released files' and contains a table with columns: Name, Isolate ID, Subtype, Host, Collection date, Passage, PB2, PB1, PA, HA, NP, NA, MP, and I. The table lists three isolates, all of which are selected with checkboxes. Below the table, there's a pagination bar showing 'Total: 3 isolates' and navigation links like '<< first', '< prev', '1', 'next >', and 'last >>'. There's also a search bar labeled 'Search in results'. At the bottom, there are buttons for 'Go back', 'Help', 'Copy to...', 'Add to analysis', and 'Download'. A blue arrow points to the 'Add to analysis' button.

Released files

<input checked="" type="checkbox"/>	edit	Name	Isolate ID	Subtype	Host	Collection date	Passage	PB2	PB1	PA	HA	NP	NA	MP	I
<input checked="" type="checkbox"/>		A/Anhui/1/2013	EPI_ISL_138739	H7N9	Human	2013	E1	2280	2274	2151	1683	1497	1398	982	1
<input checked="" type="checkbox"/>		A/Shanghai/2/2013	EPI_ISL_138738	H7N9	Human	2013	E1	2280	2274	2151	1683	1497	1398	982	1
<input checked="" type="checkbox"/>		A/Shanghai/1/2013	EPI_ISL_138737	H7N9	Human	2013	E1	2280	2274	2151	1683	1497	1398	982	1

...

Total: 3 isolates

<< first < prev 1 next > last >>

Search in results

Go back Help Copy to... Add to analysis Download

After selecting strains on the left, click add to analysis

This screenshot shows the 'Choose analysis' dialog box that appears after clicking 'Add to analysis'. The dialog has a title bar 'Choose analysis' and a list of analysis options. The first option is 'Alignment' with the subtext 'Align DNA or Proteins'. Below this is a section titled 'List of third party servers' which contains the 'FluSurver' option. A blue arrow points to the 'FluSurver' option. The background shows the same 'Released files' table as the previous screenshot, but it's partially obscured by the dialog box.

Choose analysis

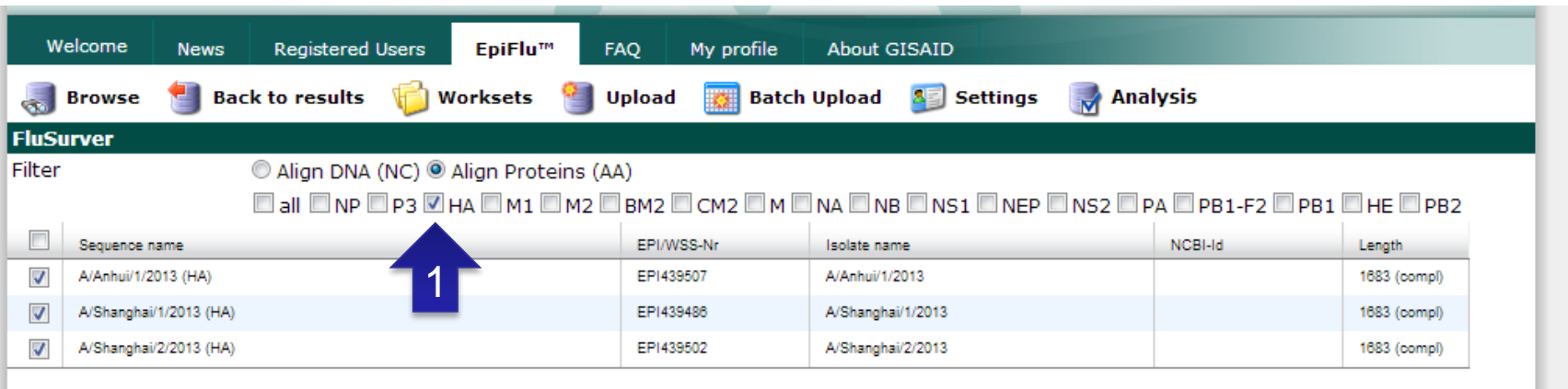
Alignment  
Align DNA or Proteins

List of third party servers

FluSurver  
FluSurver

2 Select "FluSurver"

**Next steps:** Select proteins to analyze[1] , e.g. HA, then click on continue [2], wait for submission form to load and then click “Analyze with FluSurver” [3].



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Browse Back to results Worksets Upload Batch Upload Settings Analysis

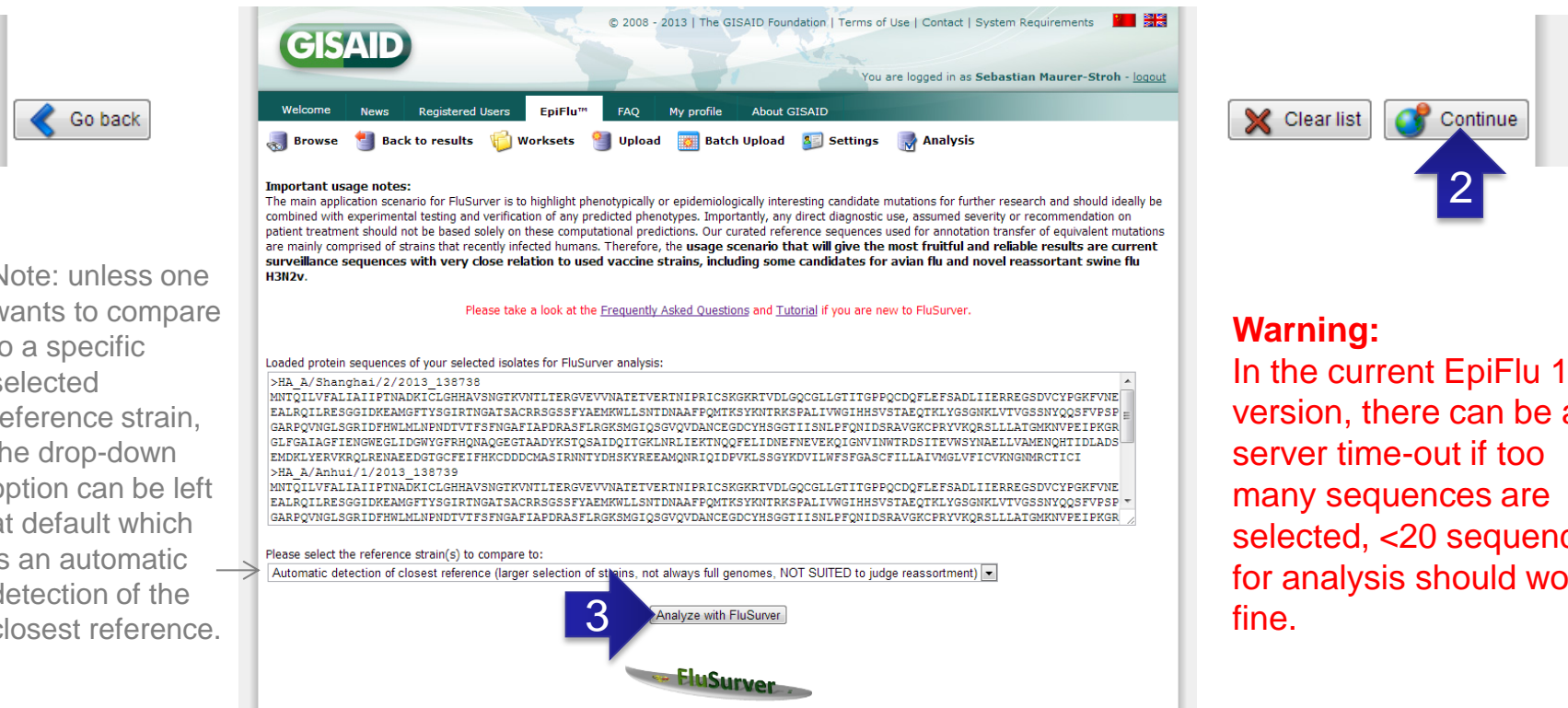
**FluSurver**

Filter

☐ Align DNA (NC) ☒ Align Proteins (AA)

☐ all ☐ NP ☒ P3 ☒ HA ☐ M1 ☐ M2 ☐ BM2 ☐ CM2 ☐ M ☐ NA ☐ NB ☐ NS1 ☐ NEP ☐ NS2 ☐ PA ☐ PB1-F2 ☐ PB1 ☐ HE ☐ PB2

<input type="checkbox"/>	Sequence name	EPI/WSS-Nr	Isolate name	NCBI-Id	Length
<input checked="" type="checkbox"/>	A/Anhui/1/2013 (HA)	EPI439507	A/Anhui/1/2013		1883 (compl)
<input checked="" type="checkbox"/>	A/Shanghai/1/2013 (HA)	EPI439488	A/Shanghai/1/2013		1883 (compl)
<input checked="" type="checkbox"/>	A/Shanghai/2/2013 (HA)	EPI439502	A/Shanghai/2/2013		1883 (compl)



Go back

**GISAID**

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**Important usage notes:**  
The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the **usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v.**

Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver.

Loaded protein sequences of your selected isolates for FluSurver analysis:

```
>HA_A/Shanghai/2/2013_198738
MNTQILVFALIAIIPINADKICLGHAVSNGTKVNTLTERGVEVVNATETVERTNIPRICSGKGRITVDLGCGLLGTITGFPQCQDFLEFSADLIERREGSDVCYFGKRVNE
EALRQILRESGGIDKEAMGFTYSGIRTINGATSACRRSGSSFYAEMKWLSTNDNAAFPQMTKSYKNTKRSFALIVNGIHHSVSTAEQTKLYGSGNKLTVGSSNYQQSFVPSF
GARFQVNLGSGRIDFHWMLNPNNDTVTFSGNFIAPDRASFLRGKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNDISRAVGKCPRYVKRSLLLATGMKNVFEIPKGR
GLFGAIGAGFIENGWGLIDGWYGRHQAQEGTAADYKSTQSAIDQITGKLNRLIEKTNQQFELIDNEFNEVEKQIGNVINWTRDSITEVNSYNAELLVAMENQHTIDLADS
EMDKLYERVKRQLRENAEEDGTGCFEIFHKCDDDCMASIRNNTYDHSKYREEMQNRQIDPFVKLSGGYKDVILWFSFGASCIFLLAIVMGLVFCVKNGNMRCITCI
>HA_A/Anhui/1/2013_138739
MNTQILVFALIAIIPINADKICLGHAVSNGTKVNTLTERGVEVVNATETVERTNIPRICSGKGRITVDLGCGLLGTITGFPQCQDFLEFSADLIERREGSDVCYFGKRVNE
EALRQILRESGGIDKEAMGFTYSGIRTINGATSACRRSGSSFYAEMKWLSTNDNAAFPQMTKSYKNTKRSFALIVNGIHHSVSTAEQTKLYGSGNKLTVGSSNYQQSFVPSF
GARFQVNLGSGRIDFHWMLNPNNDTVTFSGNFIAPDRASFLRGKSMGIQSGVQVDANCEGDCYHSGGTIIISNLPFQNDISRAVGKCPRYVKRSLLLATGMKNVFEIPKGR
```

Please select the reference strain(s) to compare to:

Automatic detection of closest reference (larger selection of strains, not always full genomes, NOT SUITED to judge reassortment) ▼

Analyze with FluSurver

**FluSurver**

Clear list Continue

Note: unless one wants to compare to a specific selected reference strain, the drop-down option can be left at default which is an automatic detection of the closest reference.

**Warning:**  
In the current EpiFlu 1.0 version, there can be a server time-out if too many sequences are selected, <20 sequences for analysis should work fine.

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## FluSurver

The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, the usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v. Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Result for comparison with reference selection: H7N7\_Human\_2003\_Netherlands219 [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
HA_A/Anhui/1/2013_138739	HA A/Netherlands/219/2003(H7N7) <a href="#">find closest related sequences</a>	96.071	<a href="#">98.418</a>	22	<a href="#">V18I</a> , <a href="#">S20I</a> , <a href="#">V63I</a> , <a href="#">T137A</a> , <a href="#">T150A</a> , <a href="#">D190S</a> , <a href="#">I195V</a> , <a href="#">G202V</a> , <a href="#">T205A</a> , <a href="#">I218V</a> , <a href="#">Q242L</a> , <a href="#">I252M</a> , <a href="#">E286G</a> , <a href="#">N314D</a> , <a href="#">E328R</a> , <a href="#">R347G</a> , <a href="#">T419N</a> , <a href="#">R423K</a> , <a href="#">M436I</a> , <a href="#">N464D</a> , <a href="#">I515M</a> , <a href="#">A550V</a> <a href="#">show in structure</a>
HA_A/Shanghai/1/2013_138737	HA A/Netherlands/219/2003(H7N7) <a href="#">find closest related sequences</a>	96.071	<a href="#">98.418</a>	22	<a href="#">V18I</a> , <a href="#">S20I</a> , <a href="#">V63I</a> , <a href="#">T137A</a> , <a href="#">T150A</a> , <a href="#">A153S</a> , <a href="#">D190N</a> , <a href="#">I195V</a> , <a href="#">T205A</a> , <a href="#">I218V</a> , <a href="#">P237T</a> , <a href="#">I252M</a> , <a href="#">E286G</a> , <a href="#">N292D</a> , <a href="#">H299Y</a> , <a href="#">N314D</a> , <a href="#">E328R</a> , <a href="#">R347G</a> , <a href="#">R423K</a> , <a href="#">M436I</a> , <a href="#">N464D</a> , <a href="#">I515M</a> <a href="#">show in structure</a>
HA_A/Shanghai/2/2013_138738	HA A/Netherlands/219/2003(H7N7) <a href="#">find closest related sequences</a>	96.071	<a href="#">98.418</a>	22	<a href="#">V18I</a> , <a href="#">S20I</a> , <a href="#">V63I</a> , <a href="#">T137A</a> , <a href="#">T150A</a> , <a href="#">D190S</a> , <a href="#">I195V</a> , <a href="#">G202V</a> , <a href="#">T205A</a> , <a href="#">I218V</a> , <a href="#">Q242L</a> , <a href="#">I252M</a> , <a href="#">E286G</a> , <a href="#">N314D</a> , <a href="#">E328R</a> , <a href="#">R347G</a> , <a href="#">T419N</a> , <a href="#">R423K</a> , <a href="#">M436I</a> , <a href="#">N464D</a> , <a href="#">I515M</a> , <a href="#">A550V</a> <a href="#">show in structure</a>

[Right-click here to save/download mutation report table for archiving or import to Excel](#)

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For each of the query sequences, there are six columns of information generated in the result summary page. From here, users may proceed to look at the query sequence's alignment to the reference strain, get more information on each mutation, generate a structural view of all the mutations in the query sequence ("show in structure") or view a summary of the mutations in a table to download (at end of results).

More details on browsing the results further can be found online at:  
<http://flusurver.bii.a-star.edu.sg/help/tutorialpage.html#part2>



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Result for comparison with reference selection: **H7N7\_Human\_2003\_Netherlands219** [Back to Reference Selection](#)

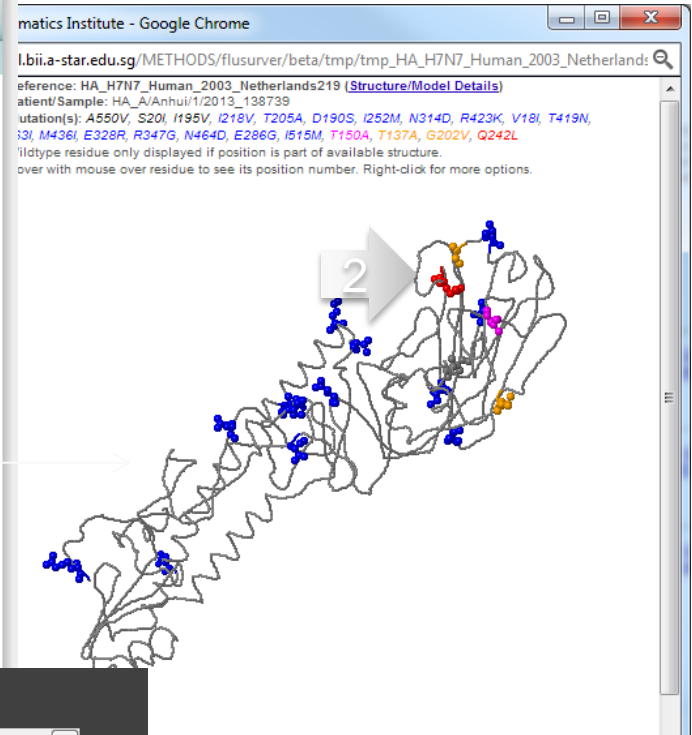
Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
HA_A/Anhui/1/2013_138739	HA A/Netherlands/219/2003(H7N7) <a href="#">find closest related sequences</a>	96.071	98.418	22	<a href="#">V18I</a> <a href="#">S20I</a> <a href="#">V63I</a> <a href="#">T137A</a> <a href="#">T150A</a> <a href="#">D190S</a> <a href="#">I195V</a> <a href="#">G202V</a> <a href="#">T205A</a> <a href="#">I218V</a> <a href="#">Q242L</a> <a href="#">I262M</a> <a href="#">E286G</a> <a href="#">N314D</a> <a href="#">E328R</a> <a href="#">R347G</a> <a href="#">T419N</a> <a href="#">R423K</a> <a href="#">M436I</a> <a href="#">show in structure</a>
HA_A/Shanghai/1/2013_138737	A/Netherlands/219/2003(H7N7) <a href="#">find closest related sequences</a>	96.071	98.418	22	<a href="#">V18I</a> <a href="#">S20I</a> <a href="#">V63I</a> <a href="#">T137A</a> <a href="#">T150A</a> <a href="#">A153S</a> <a href="#">D190N</a> <a href="#">I195V</a> <a href="#">T205A</a> <a href="#">I218V</a> <a href="#">P217T</a> <a href="#">I262M</a> <a href="#">E286G</a> <a href="#">N292D</a> <a href="#">H295Y</a> <a href="#">N314D</a> <a href="#">E328R</a> <a href="#">R347G</a> <a href="#">R423K</a> <a href="#">M436I</a> <a href="#">show in structure</a>
HA_A/Shanghai/2/2013_138738	HA A/Netherlands/219/2003(H7N7) <a href="#">find closest related sequences</a>	96.071	98.418	22	<a href="#">V18I</a> <a href="#">S20I</a> <a href="#">V63I</a> <a href="#">T137A</a> <a href="#">T150A</a> <a href="#">D190S</a> <a href="#">I195V</a> <a href="#">G202V</a> <a href="#">T205A</a> <a href="#">I218V</a> <a href="#">Q242L</a> <a href="#">I262M</a> <a href="#">E286G</a> <a href="#">N314D</a> <a href="#">E328R</a> <a href="#">R347G</a> <a href="#">T419N</a> <a href="#">R423K</a> <a href="#">M436I</a> <a href="#">show in structure</a>

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# Mutation Effect Analysis Example



mendel.bii.a-star.edu.sg/METHODS/flusurver/beta/EFFECTS/HA

Protein: HA  
Influenza type: Human H3N2 (N/A)  
Mutation (as in paper): Q226L  
neutral AA: Q  
neg. eff. AA: L  
Effect: host specificity shift

**Comment:**  
Increasing affinity of receptor-binding to SA<sub>2</sub>,6Gal and decreasing affinity to SA<sub>2</sub>,3Gal (Table1.).  
[Literature reference](#)  
(Mutation Q226L in the paper is at an equivalent position of the mutation in your query)

**HA Q242L**

Key to alternative position numbering:

FluSurver numbering	(absolute as in 2009 H1N1 pandemic)
240	
HA1 226	Classical H3N2 strain numbering
HA1 223	Classical H1N1 strain numbering
Chosen reference:	HA_H7N7_Human_2003_Netherlands219
Position in reference:	242
AA in reference:	Q
AA in query:	L

A mutation at the position equivalent to HA 242 has been reported in the literature to be related to [antigenic drift / escape mutant and host specificity shift and other](#).

A combination of mutations including the position equivalent to HA 242 has been reported in the literature to be related to [host specificity shift](#).

As seen in resolved structures of proteins from related strains, the HA position equivalent to your mutation is involved in:

- [host cell receptor binding](#)
- [antibody recognition sites](#)

[See all interactions for this position](#)

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1. H7N9 HA example: closest annotated reference strain in FluSurver was an H7 from an outbreak in the Netherlands in 2003. With 96% identity, or 22 mutations, this is close enough for first interpretation.
2. The structure view shows that the highlighted red and orange mutations are located in the host receptor binding pocket.
3. The "red" Q242L mutation is equivalent to Q226L (in H3 numbering) which has been reported to increase 2,6 host receptor affinity, which is one important factor why this avian strain can infect humans.

# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier



The main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing and verification of any predicted phenotypes. Importantly, any direct diagnostic use, assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. Our curated reference sequences used for annotation transfer of equivalent mutations are mainly comprised of strains that recently infected humans. Therefore, **the usage scenario that will give the most fruitful and reliable results are current surveillance sequences with very close relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu H3N2v.** Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Result for comparison with reference selection: auto

[Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
A/Singapore/GN285/2009(H1N1)	NA A/California/07/2009(H1N1) <a href="#">find closest related sequences</a>	99.360	<a href="#">100.000</a>	3	<p>V106I, N248D, H275Y <a href="#">show in structure</a></p> <p>NA drug sensitivity positions: 26, 0, 1 Reduced sensitivity or resistance!</p>

[Right-click here to save/download mutation report table for archiving or import to Excel](#)

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Tachyon 11364 hits

Time: 15.89s

Length: 469 Views: [Plain](#) | [Jalview](#) | [Raw](#) Downloads: [FASTA](#) | [MAFFT](#) | [Raw](#) Params: internal, NCBI NR-24070523 sequer

Rank	Score	FASTA	BLAST	ANNIE	UniProt	Hit Seq	Filter	Databases	Limit
1	1.0	GFBAT				gi 251748198 gb ACT10319.1  neuraminidase [Influenza A virus (A/Hong Kong/2369/2009(H1N1))]		All PDB RefSeq SwissProt/UniProtKB	250 1000 None
2	0.9914	GFBAT				gi 300117086 gb ABJ67981.1  neuraminidase, partial [Influenza A virus (A/Perth/262/2009(H1N1))]			
3	0.98718	GFBAT				gi 326320245 gb ADZ53143.1  neuraminidase [Influenza A virus (A/Hong Kong/FPD/2009(H1N1))]			
4	0.98294	GFBAT				gi 291219999 gb ADD84685.1  neuraminidase [Influenza A virus (A/Mexico/InDRE797/2010(H1N1))]			
5	0.97872	GFBAT				gi 251833646 gb ACT22016.1  neuraminidase [Influenza A virus (A/Osaka/180/2009(H1N1))]			
6	0.97872	GFBAT				gi 294544923 gb ADF10109.1  neuraminidase [Influenza A virus (A/Ontario/25913/2009(H1N1))]			
7	0.97872	GFBAT				gi 294544441 gb ADF10049.1  neuraminidase [Influenza A virus (A/Ontario/10016/2009(H1N1))]			
8	0.97872	GFBAT				gi 299781814 gb ADJ40477.1  neuraminidase [Influenza A virus (A/Netherlands/2445b/2009(H1N1))]			
9	0.97872	GFBAT				gi 325451706 gb ADZ13521.1  neuraminidase [Influenza A virus (A/Lyon/48.49/2009(H1N1))]			
10	0.97872	GFBAT				gi 294611208 gb ADF27356.1  neuraminidase [Influenza A virus (A/Taiwan/6663/2009(H1N1))]			
11	0.97872	GFBAT				gi 326320207 gb ADZ53124.1  neuraminidase [Influenza A virus (A/Hong Kong/23669/2009(H1N1))]			
12	0.97872	GFBAT				gi 425786025 gb AFX96841.1  neuraminidase [Influenza A virus (A/Viet Nam/12032005/2009(H1N1))]			
13	0.97872	GFBAT				gi 316986112 gb ADU76312.1  neuraminidase [Influenza A virus (A/England/00380009/2009(H1N1))]			
14	0.97872	GFBAT				gi 295147036 gb ADF80503.1  neuraminidase [Influenza A virus (A/Seoul/1870/2009(H1N1))]			
15	0.97872	GFBAT				gi 307071034 gb ADN24718.1  neuraminidase, partial [Influenza A virus (A/Canada-AB/RV2828/2009(H1N1))]			
16	0.97872	GFBAT				gi 296840062 gb ADN24491.1  neuraminidase [Influenza A virus (A/Guangzhou/236/2009(H1N1))]			

Find closest reference strain and database hits!



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Result for comparison with reference selection: auto

[Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
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```
>NA_H1N1_Human_2009_California07
gi|229396469|gb|ACQ63272|neuraminidase[Influenza A virus
(A/California/07/2009(H1N1))] USA20090409
Length = 469
```

```
Score = 989 bits (2558), Expect = 0.0
Identities = 466/469 (99%), Positives = 469/469 (100%)
Frame = +3
```

```
Query: 21  MNPNQKIITIGSVCHTIGHANLILQIGNIISIVISHSIQLGNQNIETCNQSVITYENNT 200
          MNPNQKIITIGSVCHTIGHANLILQIGNIISIVISHSIQLGNQNIETCNQSVITYENNT
Sbjct: 1   MNPNQKIITIGSVCHTIGHANLILQIGNIISIVISHSIQLGNQNIETCNQSVITYENNT 60
```

```
Query: 201 VVNQTYVNISNTNFAAGQSVVSVKLAGNSLCPVSGHAIYSKDNSIRIGSGDVFVIREP 380
          VVNQTYVNISNTNFAAGQSVVSVKLAGNSLCPVSGHAIYSKDNSIRIGSGDVFVIREP
Sbjct: 61  VVNQTYVNISNTNFAAGQSVVSVKLAGNSLCPVSGHAIYSKDNSVRIGSGDVFVIREP 120
```

```
Query: 381 FISCSPLECRFTFFLTQALLNDKHSNGTIKDRSPYRTLMSCPIGEVPSPYNSRFESVAWS 560
          FISCSPLECRFTFFLTQALLNDKHSNGTIKDRSPYRTLMSCPIGEVPSPYNSRFESVAWS
Sbjct: 121 FISCSPLECRFTFFLTQALLNDKHSNGTIKDRSPYRTLMSCPIGEVPSPYNSRFESVAWS 180
```

```
Query: 561 ASACHDGINWLITIGISGPDNGAVAVLYKNGIITDTIKSWMMNILLRTQESACVNGSCFT 740
          ASACHDGINWLITIGISGPDNGAVAVLYKNGIITDTIKSWMMNILLRTQESACVNGSCFT
Sbjct: 181 ASACHDGINWLITIGISGPDNGAVAVLYKNGIITDTIKSWMMNILLRTQESACVNGSCFT 240
```

```
Query: 741 VMTDGPSDGQASTYKIFRIEKGKIVKSEVMNAPNTTYECCSCYPDSSEITCVRDNNVHGSN 920
          VMTDGPSDGQASTYKIFRIEKGKIVKSEVMNAPNTTYECCSCYPDSSEITCVRDNNVHGSN
Sbjct: 241 VMTDGPSDGQASTYKIFRIEKGKIVKSEVMNAPNTTYECCSCYPDSSEITCVRDNNVHGSN 300
```

```
Query: 921 RPUVSFNQMLEYQIGYICSGIFGDNPPNDKTSQCPVSSNGANGVKGFSFKYGNQGVIG 1100
          RPUVSFNQMLEYQIGYICSGIFGDNPPNDKTSQCPVSSNGANGVKGFSFKYGNQGVIG
Sbjct: 301 RPUVSFNQMLEYQIGYICSGIFGDNPPNDKTSQCPVSSNGANGVKGFSFKYGNQGVIG 360
```

```
Query: 1101 RTKSISSRNQFEMIWDNGWTGTDNNFSIKQDIVGNEWSGYSGFVQPELTGLDCIRP 1280
          RTKSISSRNQFEMIWDNGWTGTDNNFSIKQDIVGNEWSGYSGFVQPELTGLDCIRP
```

[download mutation report table for archiving or import to Excel](#)

[Back to Reference Selection](#)

atics Institute ([BI](#)), Singapore  
Medicina Genomica ([INMEGEN](#)), Mexico

Check alignment to reference hit!

# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

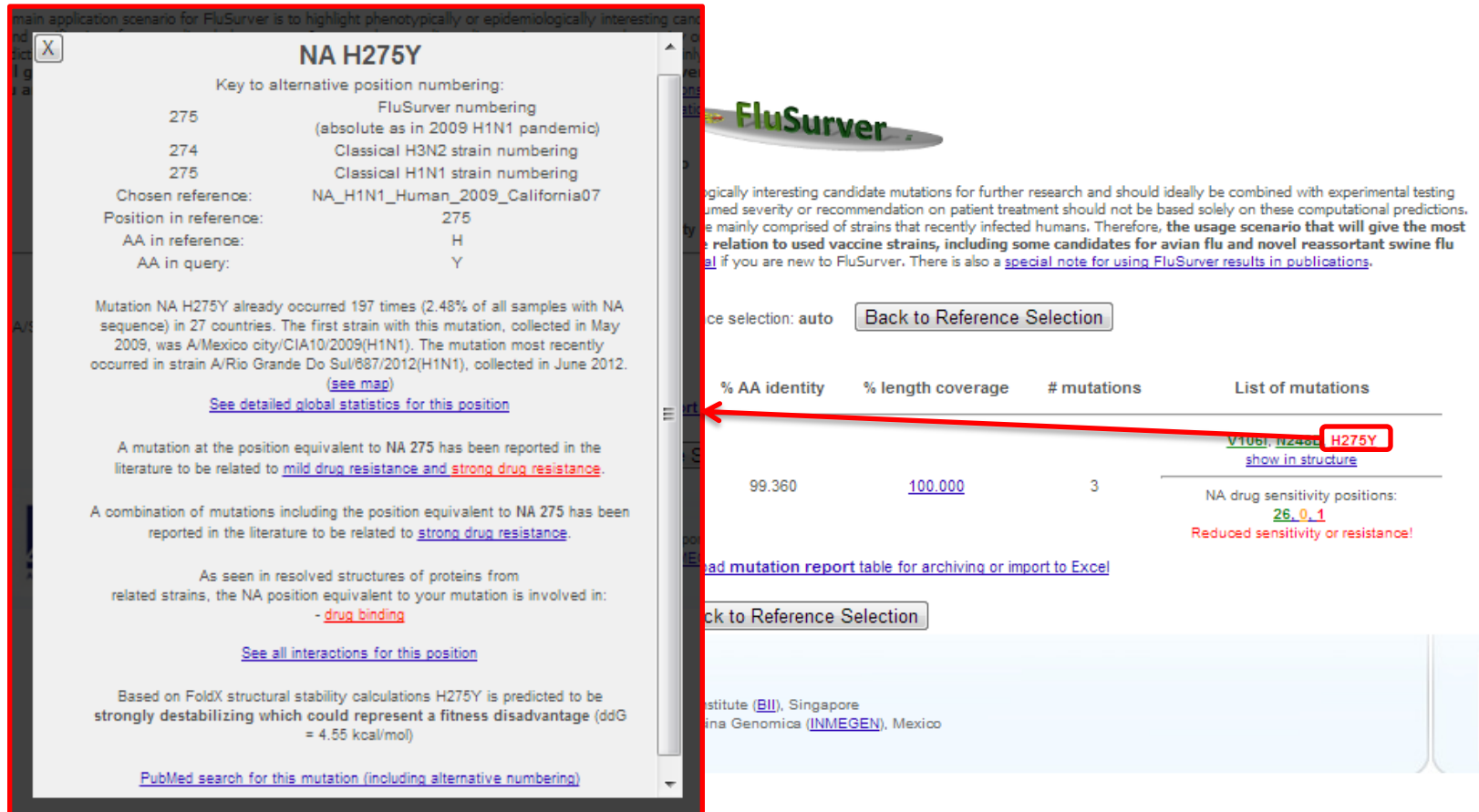
Color	Interest level	Remarks
<b>Black</b>	0 (least significant)	No known effects
<b>Green</b>	0	Common
<b>Blue</b>	1	At site of interaction
<b>Orange</b>	2	At site known to involved in drug-binding, alter host-specificity.
<b>Red</b>	3 (most significant)	At site known to alter virulence, cause drug resistance, reverses premature STOP codon in PB1-F2.

The screenshot shows the FluSurver web interface. At the top, there is a header with the text 'FluSurver'. Below the header, there is a paragraph of text: 'Testing candidate mutations for further research and should ideally be combined with experimental testing...'. Below this, there is a button labeled 'Back to Reference Selection'. Below the button, there is a table with columns: 'Entity', '% length coverage', and '# mutations'. The table has one row with the following data: '100.000', '3', and a box labeled 'List of mutations'. The box contains the text 'V106I, N248D, H275Y' and a link 'show in structure'. Below the box, there is text: 'NA drug sensitivity positions: 26, 0, 1' and 'Reduced sensitivity or resistance!'. Below this, there is a link 'on report table for archiving or import to Excel'. Below the link, there is a button labeled 'Reference Selection'. Below the button, there is text: 'Singapore' and 'ca (INMEGEN), Mexico'.

Check list of mutations!



# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier



main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing. The usage scenario that will give the most relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Back to Reference Selection

% AA identity	% length coverage	# mutations	List of mutations
99.360	100.000	3	<a href="#">V106I, H244S, H275Y</a> <a href="#">show in structure</a> NA drug sensitivity positions: 26, 0, 1 Reduced sensitivity or resistance!

[Load mutation report table for archiving or import to Excel](#)

Back to Reference Selection

Institute (BII), Singapore  
 Influenza Genomics (INMEGEN), Mexico

Key to alternative position numbering:

FluSurver numbering	Classical H3N2 strain numbering	Classical H1N1 strain numbering
275	(absolute as in 2009 H1N1 pandemic)	275

Chosen reference: NA\_H1N1\_Human\_2009\_California07  
 Position in reference: 275  
 AA in reference: H  
 AA in query: Y

Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance and strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:

- [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

Click on mutation of interest for details!

# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidates

**NA H275Y**

Key to alternative position numbering:

FluSurver numbering	Classical H3N2 strain numbering	Classical H1N1 strain numbering
275	(absolute as in 2009 H1N1 pandemic)	274
274	Classical H3N2 strain numbering	275

Chosen reference: NA\_H1N1\_Human\_2009\_California07

Position in reference: 275

AA in reference: H

AA in query: Y

Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012. ([see map](#))

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[PubMed search for this mutation \(including alternative numbering\)](#)

**FluSurver**

Map of cities with the NA H275Y mutation

The city with **red** label indicates first appearance of the mutation. City with **yellow** label indicate later appearance of the mutation. The city with the most recent appearance of the mutation has the **green** label. Number in the label indicates frequency of occurrence of the mutation in that city. A dot in the label indicates that there are 10 or more occurrences in that city.

As there are too many cities with viral isolates carrying this mutation, cities with number of occurrences below 2 are not labeled in the map above.

Map of countries with the NA H275Y mutation

Number of occurrences

Countries without data: 1 44

Region	# Occ.	Date of collection(YYYYMMDD)
Sheffield	1	20110105
Catalonia	1	20091126
North Carolina	2	20091016
Kurume	35	20100118
Thailand	4	20100104
Sydney	8	20100916
Denmark	2	20090809
Seoul	4	20091100
Kyoto	4	20091204

Check for geographic occurrence pattern!

# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

**NA H275Y**

Key to alternative position numbering:

275	FluSurver numbering (absolute as in 2009 H1N1 pandemic)
274	Classical H3N2 strain numbering
275	Classical H1N1 strain numbering

Chosen reference: NA\_H1N1\_Human\_2009\_California07  
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AA in reference: H  
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Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012.

[See detailed global statistics for this position](#)

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As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:

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[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

**FluSurver**

Biologically interesting candidate mutations for further research and should ideally be combined with experimental testing. Assumed severity or recommendation on patient treatment should not be based solely on these computational predictions. The results are mainly comprised of strains that recently infected humans. Therefore, **the usage scenario that will give the most relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu** if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Force selection: auto [Back to Reference Selection](#)

% AA identity	% length coverage	# mutations	List of mutations
99.360	100.000	3	<a href="#">V106I, H249G, H275Y</a> <a href="#">show in structure</a>

NA drug sensitivity positions:  
**26, 0, 1**  
Reduced sensitivity or resistance!

[Download mutation report table for archiving or import to Excel](#)

[Back to Reference Selection](#)

**Mutation statistics for NA at position 275**

AA	# Occ.	%	Geo Distribution	Co-occurrences
X	8	0.10		
Y	197	2.48	(geo)	(co-occur)
-	13	0.16		
H	7740	97.26	reference aa	reference aa
ALL	7958	100.00		

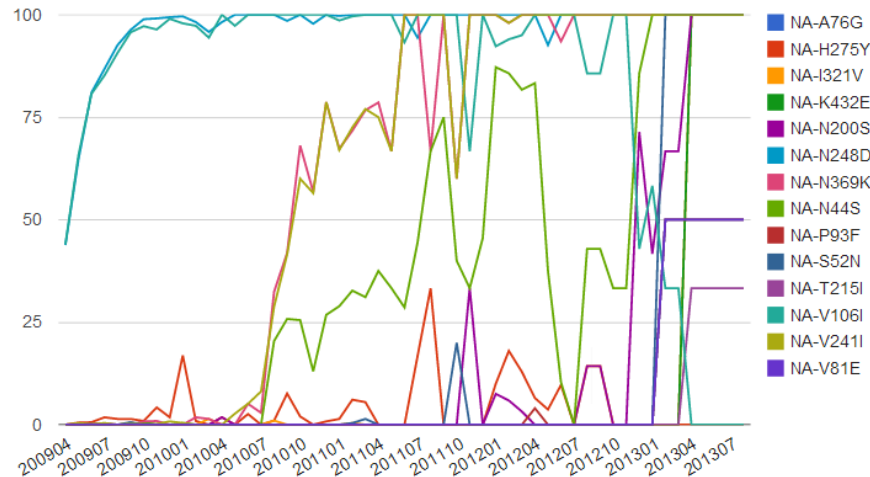
Sequences were compared to reference strain A/California/07/2009(H1N1) [AGM53851](#).  
Last updated on Sep 02nd 2013 by Raphael Tze Chuen Lee

Above are the occurrences of all amino acid residues at position 275 in NA. For statistics of all position in NA in this subtype click here: [H1N1 NA mutations table](#)

Check if there are other mutations at same position!

# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

Frequency of mutation over time



The line chart above shows the frequency of mutations in NA over time. Only mutations that were present in more than 30 percent of circulating strains in any of the months were represented in the line chart. Please note that the frequency of mutation in the most recent months tends to fluctuate as the database are still being populated.

Accession	Protein	Strain	WildtypeAA	Position	MutatedAA	Frequency	Date of collection(YYYYMMDD)	Remarks
ACY03001	NA	(A/Italy/137/2009(H1N1))	M	1	L	1	20090700	(co-occur)
ACU68826	NA	(A/Poland/303/2009(H1N1))	N	2	I	4 (geo)	20090710	(co-occur)
AFB77614	NA	(A/Kenya/071/2010(H1N1))	N	2	H	2 (geo)	20101129	(co-occur)
ACR08462	NA	(A/New York/3099/2009(H1N1))	N	2	S	1	20090429	(co-occur)
ACZ96222	NA	(A/Texas/44313703/2009(H1N1))	P	3	S	2 (geo)	20090831	(co-occur)
AGQ02440	NA	(A/Pernambuco/120924/2012(H1N1))	P	3	Q	1	20121002	(co-occur)
ACX66671	NA	(A/Lorestan/1599/2009(H1N1))	N	4	K	5 (geo)	20090727	(co-occur)
ADR32078	NA	(A/Jiangsu/S62/2009(H1N1))	N	4	T	5 (geo)	20091110	(co-occur)
AEG94621	NA	(A/Hualong/SWL1313/2009(H1N1))	N	4	I	2 (geo)	20091118	(co-occur)
AGI54909	NA	(A/South Carolina/29/2009(H1N1))	Q	5	R	3 (geo)	20090723	(co-occur)
ADK90313	NA	(A/Lisboa/60/2009(H1N1))	Q	5	H	2 (geo)	20090914	(co-occur)
ACY30121	NA	(A/Italy/161/2009(H1N1))	Q	5	K	2 (geo)	20090700	(co-occur)
ADY46355	NA	(A/Singapore/ON975/2009(H1N1))	Q	5	P	3 (geo)	20090706	(co-occur)
ADD84500	NA	(A/Xian/001/2009(H1N1))	K	6	N	7 (geo)	20090903	(co-occur)
ADG42646	NA	(A/California/VRDL89/2009(H1N1))	K	6	R	4 (geo)	20091017	(co-occur)
ADV17285	NA	(A/Thailand/CU-B2357/2010(H1N1))	K	6	E	3 (geo)	20100420	(co-occur)
ADX96969	NA	(A/Lima/WRAIR8689F/2009(H1N1))	K	6	M	1	20090627	(co-occur)
ADK87312	NA	(A/Qingdao/1215/2009(H1N1))	K	6	T	1	20090912	(co-occur)
AFB77614	NA	(A/Kenya/071/2010(H1N1))	I	7	V	1	20101129	(co-occur)

Check for temporal occurrence patterns!

ch and should ideally be combined with experimental testing should not be based solely on these computational predictions. ns. Therefore, the usage scenario that will give the most candidates for avian flu and novel reassortant swine flu ate for using FluSurver results in publications.

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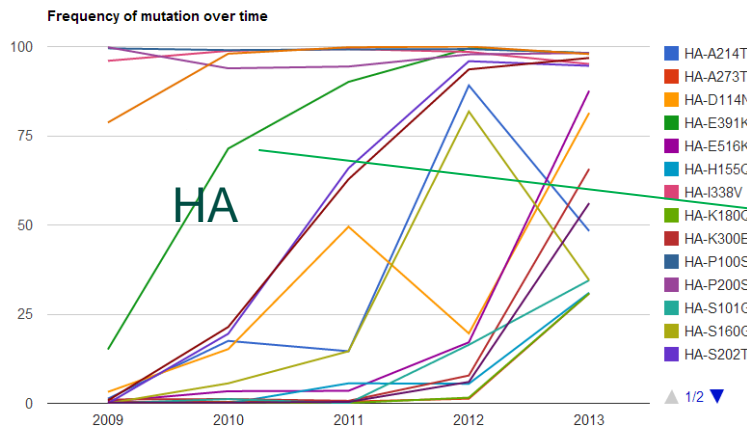
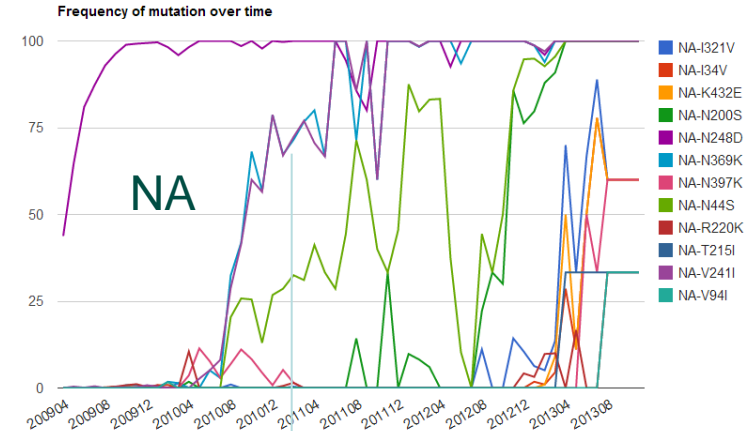
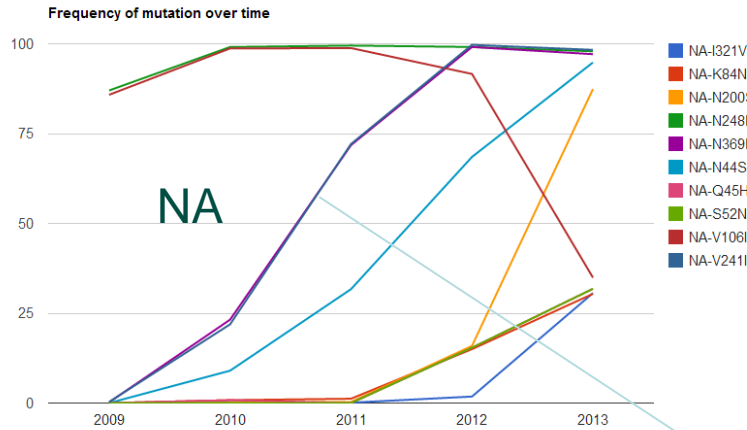
Mutation statistics for NA at position 275

AA	# Occ.	%	Geo Distribution	Co-occurrences
X	8	0.10		
Y	197	2.48	(geo)	(co-occur)
-	13	0.16		
H	7740	97.26	reference aa	reference aa
ALL	7958	100.00		

Sequences were compared to reference strain A/California/07/2009(H1N1) [AGM53851](#).  
Last updated on Sep 02nd 2013 by Raphael Tze Chuen Lee

Above are the occurrences of all amino acid residues at position 275 in NA. For statistics of all position in NA in this subtype click here: [H1N1\\_NA\\_mutations\\_table](#)

# Mutation frequency pattern highlights relevant changes



## New H275Y permissive mutations

Hurt *et al.* J Infect Dis. 2012 Jul 15;206(2):148-57.

Butler *et al.* PLoS Pathog. 2014 Apr 3;10(4):e1004065.

## Change in pH-dependency of fusion

Maurer-Stroh *et al.* PLoS Curr. 2010 Jun 1;2:RRN1162.

Cotter *et al.* PLoS Pathog. 2014 Jan;10(1):e1003831.

Example H1N1pdm in FluSurver

# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

Country	Strain	PB2	PB1	PB1-F2	PA	HA	NP	NA	M1	M2	NS1	NS2	Date of collection(YYYYMMDD)
Taiwan	(A/Taiwan/7336/2009(H1N1))	-	-	-	-	A26T P100S P200S S220T I338V E391K	-	V106I N248D H275Y	-	-	-	-	20091105
Japan	(A/Kurume/R8/2010(H1N1))	-	-	-	-	-	-	V53A V80M S82P V106I N248D H275Y Y282H	-	-	-	-	20100118
South Korea	(A/Daejeon/1871/2009(H1N1))	-	-	-	-	K39R N73S P100S S145P G172E P200S S220T I338V	-	A88T V106I I117M N248D H275Y	-	-	-	-	20091215
United Kingdom	(A/England/94840152/2009(H1N1))	-	-	-	-	P100S P200S S220T I338V	-	V106I N248D H275Y E482K	-	-	-	-	20091119
Japan	(A/Kurume/N8/2010(H1N1))	-	-	-	-	-	-	V80M S82P V106I N248D H275Y	-	-	-	-	20100118
United Kingdom	(A/England/00380015/2009(H1N1))	-	-	-	-	P100S P200S S220T I338V	-	V106I N248D H275Y E482K	-	-	-	-	20091117
USA	(A/California/21/2012(H1N1))	-	-	-	-	S86T P100S K136N S160G P200S S220T A214T S220T D239G N277D I338V F347L E391K S468N V537A	-	A20V G41R N44S V106I V241I N248D H275Y N369K	V80I	S13N	-	-	20120220
Viet Nam	(A/Viet Nam/835/2009(H1N1))	-	-	-	P224S	P100S P200S S220T I338V	V100I	V106I N248D H275Y	-	-	L115F I123V	-	20090727
Mexico	(A/Mexico/INDRE3354/2012(H1N1))	-	-	-	-	S86T P100S S160G P200S S220T A214T S220T N277D I338V E391K S468N V537A	-	G41R N44S S95I V106I V241I N248D H275Y N369K	-	-	-	-	20120208
Japan	(A/Kurume/N1/2010(H1N1))	-	-	-	-	-	-	V80M S82P V106I N248D H275Y	-	-	-	-	20100118
USA	(A/Bethesda/NIH108-D14/2009(H1N1))	R591Q	K736G	-	V14I P224S K718Q	A15T P100S P200S S220T I338V E391K F432L	V100I V270I V444I	V106I N248D H275Y	-	-	I123V	-	20091105
Japan	(A/Kurume/L19/2010(H1N1))	-	-	-	-	-	-	V80M S82P V106I N248D H275Y	-	-	-	-	20100118
China	(A/Haishu/SWL110/2010(H1N1))	-	-	-	-	P100S S179N P200S S220T I338V	-	V106I N248D H275Y	-	-	-	-	20100104
Germany	(A/Munich/INS541/2011(H1N1))	R299K V344M I354L N456S	V645I	-	P224S N321K I330V M549I	P100S D114N P200S S220T I338V E391K S468N	V100I	V106I V241I N248D K280R H275Y I321V N369K	V80I	-	I123V	-	20110218
Canada	(A/Canada-AB/RV2828/2009(H1N1))	-	M82V N158S	-	P224S	P100S P200S S220T T258I I338V	-	V106I N248D H275Y V394I	-	-	-	-	20090804
USA	(A/Texas/33/2012(H1N1))	-	-	-	-	S86T P100S S160G P200S S220T A214T S220T N277D I338V E391K S468N V537A	-	G41R N44S V106I L127W V241I N248D H275Y N369K	V80I	S13N	-	-	20120312
USA	(A/Texas/48/2012(H1N1))	-	-	-	-	S86T P100S S160G P200S S220T A214T S220T N277D I338V E391K S468N V537A	-	G41R N44S S95N V106I V241I N248D H275Y N369K	V80I	S13N	-	-	20120316
United Kingdom	(A/England/00380020/2009(H1N1))	-	-	-	-	P100S P200S S220T I338V	-	V106I N248D H275Y E482K	-	-	-	-	20091120
USA	(A/North Carolina/59/2009(H1N1))	-	-	-	-	P100S V169I P200S S220T P288Q I312V I338V	-	V106I V234I N248D H275Y	-	P25T	-	-	20091107
Spain	(A/Catalonia/NS7362/2009(H1N1))	-	-	-	-	P100S S179N P200S S220T T249A I338V G411D	-	V106I N248D H275Y	-	-	-	-	20091128

reported in the literature to be related to **strong drug resistance**.

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:

- **drug binding**

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage ( $\Delta\Delta G = 4.55$  kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

[Read mutation report table for archiving or import to Excel](#)

[Click to Reference Selection](#)

Reduced sensitivity or resistance!

Mutation statistics for NA at position 275

AA	# Occ.	%	Geo Distribution	Co-occurrences
X	8	0.10		
Y	197	2.48	(geo)	(co-occur)
-	13	0.16		
H	7740	97.26	reference aa	reference aa
ALL	7958	100.00		

Sequences were compared to reference strain A/California/07/2009(H1N1) [AGM53851](#).  
Last updated on Sep 02nd 2013 by Raphael Tze Chuen Lee

Above are the occurrences of all amino acid residues at position 275 in NA. For statistics of all position in NA in this subtype click here: [H1N1 NA mutations table](#)

Check for co-occurring mutations!



# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidates

**NA H275Y**

Key to alternative position numbering:

FluSurver numbering	(absolute as in 2009 H1N1 pandemic)	Classical H3N2 strain numbering	Classical H1N1 strain numbering
275			
274			
275			

Chosen reference: NA\_H1N1\_Human\_2009\_California07

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[PubMed search for this mutation \(including alternative numbering\)](#)

Known effect(s) of mutations at position equivalent to your mutation:

Protein: NA

Influenza type: Human H1N1 (2006)

Mutation (as in paper): H274Y

neutral AA: H

neg. eff. AA: Y

Effect: strong drug resistance  
(drug name in comments)

#### Comment:

Tamiflu but not Relenza resistance (Table 3)

[Literature reference](#)

(Mutation H274Y in the paper is at an equivalent position of the mutation in your query)

NCBI Resources How To

PubMed US National Library of Medicine National Institutes of Health

Advanced

Display Settings: Abstract

Antimicrob Agents Chemother. 2008 Sep;52(9):3284-92. doi: 10.1128/AAC.00555-08. Epub 2008 Jul 14.

**Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008.**

Sheu TG, Devde VM, Okomo-Adhiambo M, Garten RJ, Xu X, Bright RA, Butler EN, Wallis TR, Klimov AI, Gubareva LV.

Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333, USA.

PubMed influenza AND (neuraminidase OR NA) AND (H275Y OR H274Y)

RSS Save search Advanced

Show additional filters

Display Settings: Summary, 20 per page, Sorted by Pub Date

Send to:

Results: 1 to 20 of 239

Article types  
Clinical Trial  
Review  
More ...

Text availability  
Abstract available  
Free full text available  
Full text available

Publication dates  
5 years  
10 years  
Custom range...

1. [Neuraminidase inhibitor susceptibility surveillance of influenza viruses circulating worldwide during the 2011 Southern Hemisphere season.](#)  
Okomo-Adhiambo M, Sleeman K, Lysén C, Nguyen HT, Xu X, Li Y, Klimov AI, Gubareva LV. *Influenza Other Respi Viruses*. 2013 Sep;7(5):645-58. doi: 10.1111/irv.12113. Epub 2013 Apr 10. PMID: 23575174 [PubMed - in process] [Related citations](#)

2. [Functional and structural analysis of influenza virus neuraminidase n3 offers further insight into the mechanisms of oseltamivir resistance.](#)  
Li Q, Qi J, Wu Y, Kiyota H, Tanaka K, Suhara Y, Ohnishi H, Suzuki Y, Vavricka CJ, Gao GF. *J Virol*. 2013 Sep;87(18):10016-24. doi: 10.1128/JVI.01129-13. Epub 2013 Jul 3. PMID: 23824808 [PubMed - in process] [Related citations](#)

Check for associated literature!



# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

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**NA H275Y**

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[See detailed global statistics for this position](#)

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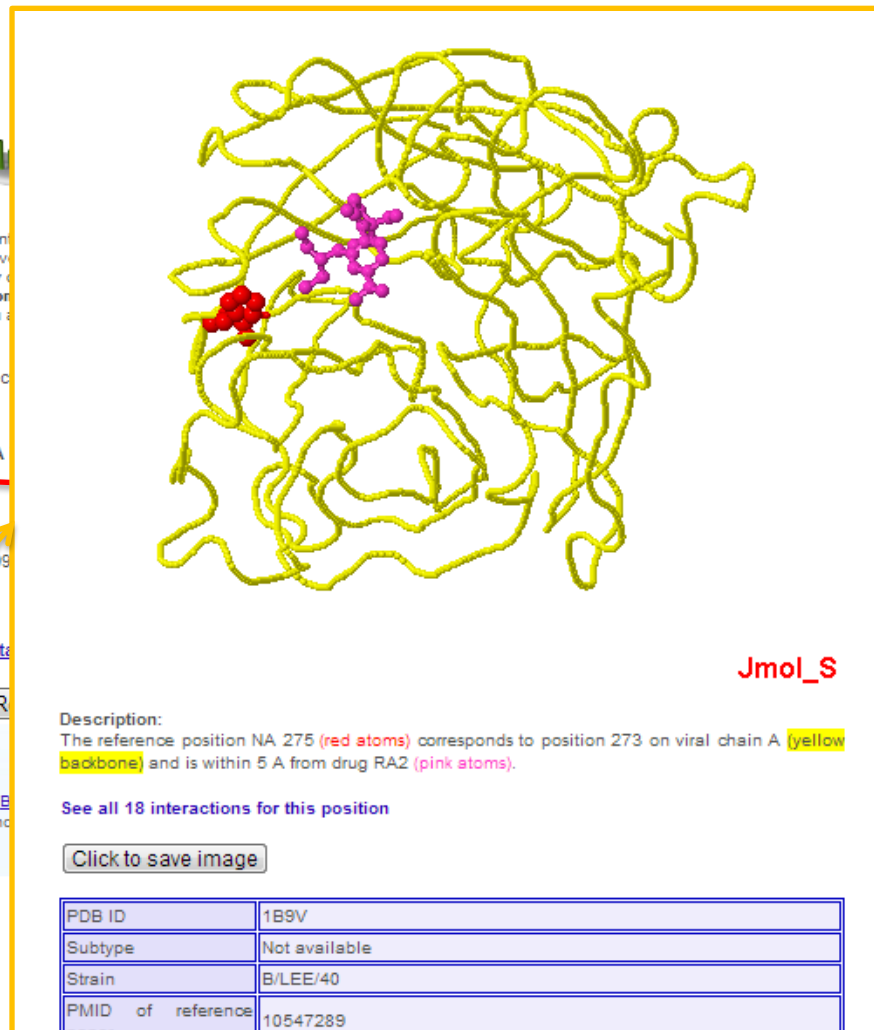
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[See all interactions for this position](#)

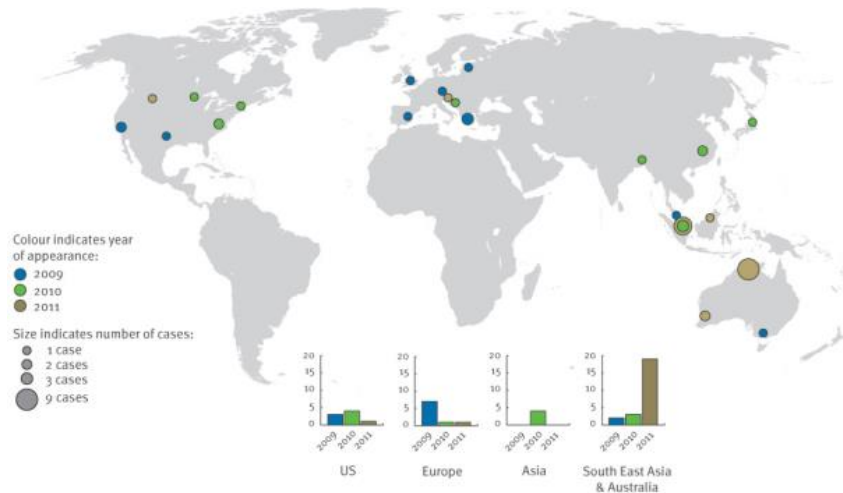
Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

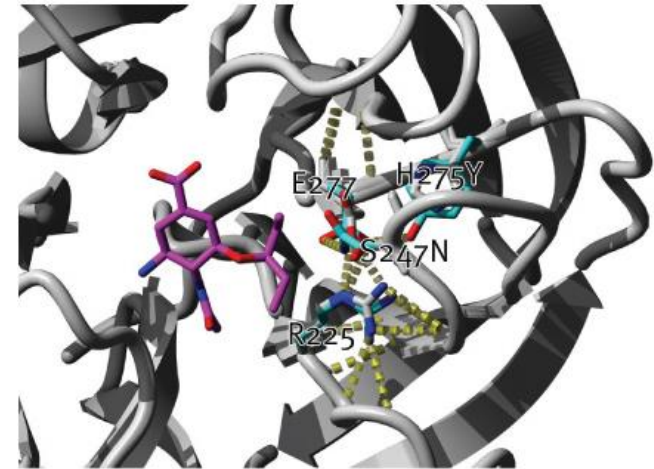


Check for structural interactions!

# New drug sensitivity altering mutation NA S247N



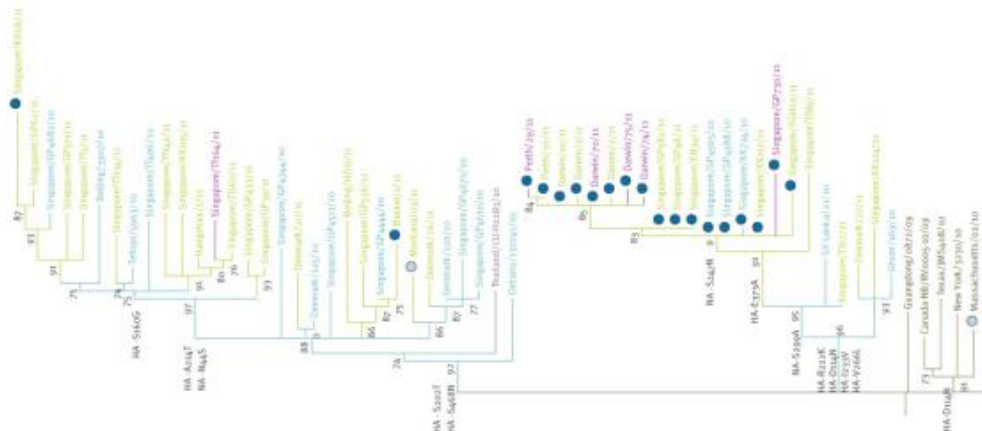
Global occurrence of new variant



Structural context of mutation

Found circulating in 10% of samples in Singapore and 30% of samples in Northern Australia in early 2011.

Experimentally measured increase of IC<sub>50</sub> for Tamiflu by 6-fold and Relenza by 3-fold but **normally administered dose of drugs still sufficient.**



Phylogenetic context of new variant

*Collaboration between Bioinformatics Institute, A\*STAR with NPHL/Ministry of Health Singapore and WHO Collaborating Centre for Reference and Research on Influenza.*

**Euro Surveill. 2011;16(23):pii=19884.**

# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

main application scenario for FluSurver is to highlight phenotypically or epidemiologically interesting candidate mutations for further research and should ideally be combined with experimental testing. The usage scenario that will give the most relation to used vaccine strains, including some candidates for avian flu and novel reassortant swine flu if you are new to FluSurver. There is also a [special note for using FluSurver results in publications](#).

Key to alternative position numbering:

FluSurver numbering	Classical H3N2 strain numbering	Classical H1N1 strain numbering
275	(absolute as in 2009 H1N1 pandemic)	275

Chosen reference: NA\_H1N1\_Human\_2009\_California07  
 Position in reference: 275  
 AA in reference: H  
 AA in query: Y

Mutation NA H275Y already occurred 197 times (2.48% of all samples with NA sequence) in 27 countries. The first strain with this mutation, collected in May 2009, was A/Mexico city/CIA10/2009(H1N1). The mutation most recently occurred in strain A/Rio Grande Do Sul/887/2012(H1N1), collected in June 2012. ([see map](#))

[See detailed global statistics for this position](#)

A mutation at the position equivalent to NA 275 has been reported in the literature to be related to [mild drug resistance](#) and [strong drug resistance](#).

A combination of mutations including the position equivalent to NA 275 has been reported in the literature to be related to [strong drug resistance](#).

As seen in resolved structures of proteins from related strains, the NA position equivalent to your mutation is involved in:

- [drug binding](#)

[See all interactions for this position](#)

Based on FoldX structural stability calculations H275Y is predicted to be strongly destabilizing which could represent a fitness disadvantage (ddG = 4.55 kcal/mol)

[PubMed search for this mutation \(including alternative numbering\)](#)

Back to Reference Selection

% AA identity	% length coverage	# mutations	List of mutations
99.360	<a href="#">100.000</a>	3	<a href="#">V106I, N245S, H275Y</a> <a href="#">show in structure</a> NA drug sensitivity positions: <a href="#">26, 0, 1</a> Reduced sensitivity or resistance!

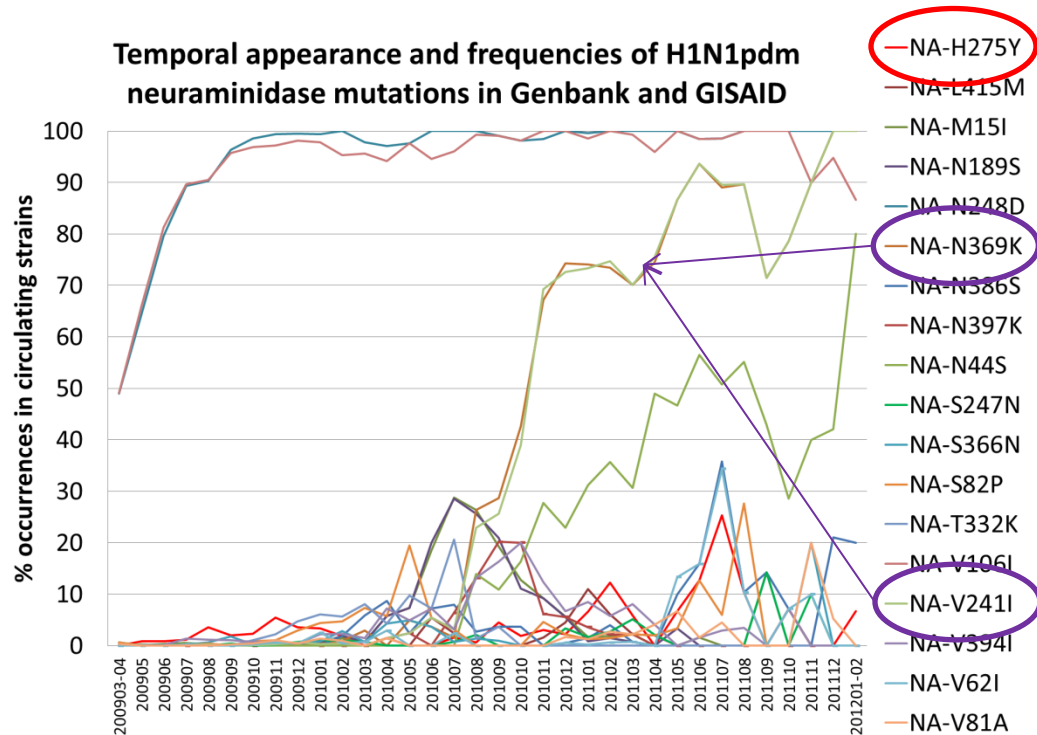
[Load mutation report table for archiving or import to Excel](#)

Back to Reference Selection

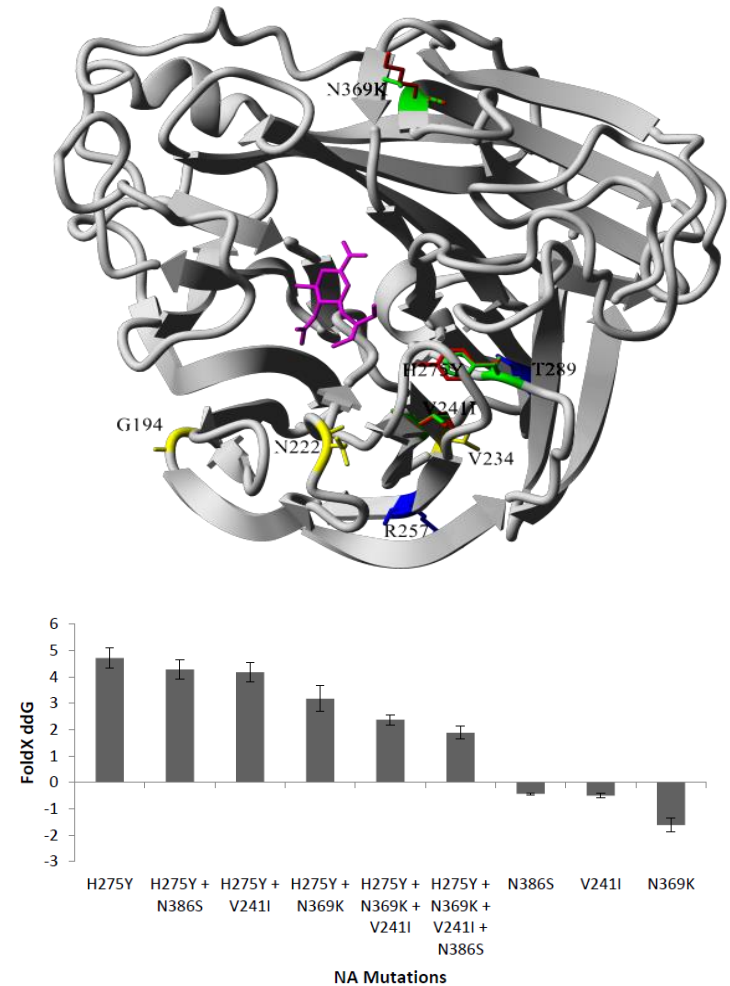
Institute ([BII](#)), Singapore  
 Institute Genomica ([INMEGEN](#)), Mexico

Check for stability  
or passage effect  
(if available)!

# Frequency rise points to role of permissive mutations



FoldX predicts increase in structural stability for mutations that were increasing in frequency and were fixed in Newcastle strains.



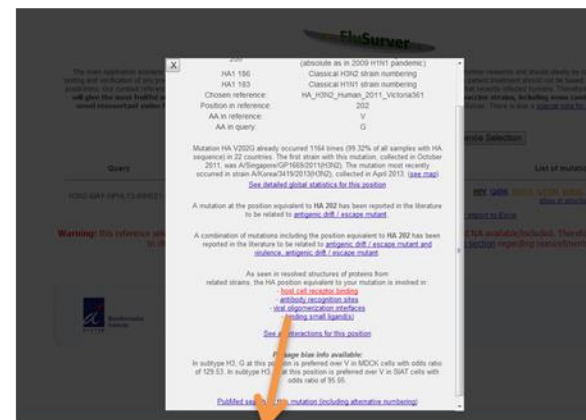
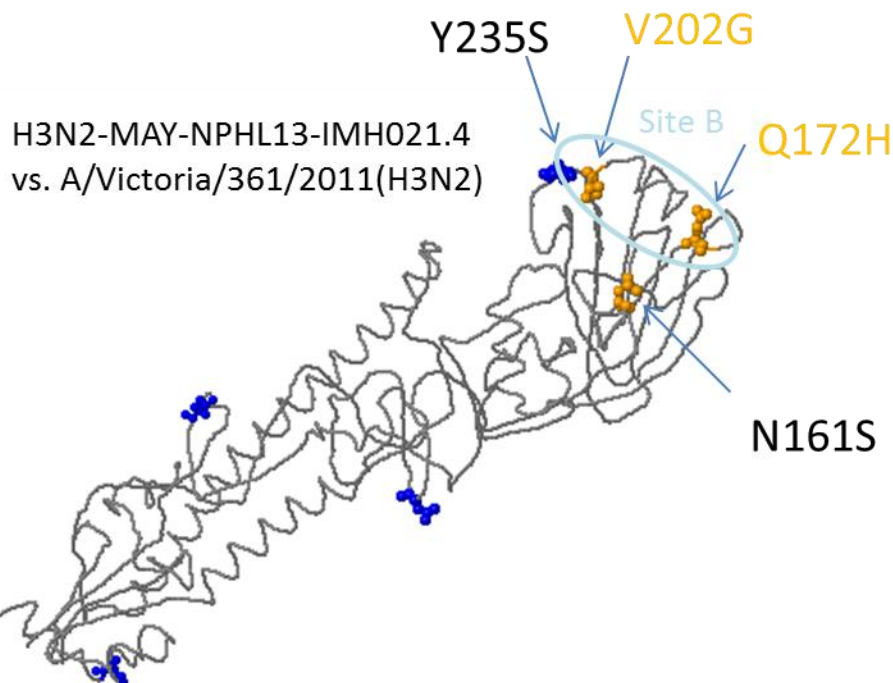
Hurt AC, Hardie K, Wilson NJ, Deng YM, Osbourn M, Leang SK, Lee RT, Iannello P, Gehrig N, Shaw R, Wark P, Caldwell N, Givney RC, Xue L, Maurer-Stroh S, Dwyer DE, Wang B, Smith DW, Levy A, Booy R, Dixit R, Merritt T, Kelso A, Dalton C, Durrheim D, Barr IG.

*Characteristics of a widespread community cluster of H275Y oseltamivir-resistant A(H1N1)pdm09 influenza in Australia.*

J Infect Dis. 2012 Jul 15;206(2):148-57.



# Current H3N2 strains have HA passage bias mutations in antigenic sites



As seen in resolved structures of proteins from related strains, the HA position equivalent to your mutation is involved in:

- [host cell receptor binding](#)
- [antibody recognition sites](#)
- [viral oligomerization interfaces](#)
- [binding small ligand\(s\)](#)

**V202G**

[See all interactions for this position](#)

**Passage bias info available:**

In subtype H3, G at this position is preferred over V in MDCK cells with odds ratio of 129.53. In subtype H3, G at this position is preferred over V in SIAT cells with odds ratio of 95.05.

**Q172H**

As seen in resolved structures of proteins from related strains, the HA position equivalent to your mutation is involved in:

- [host cell receptor binding](#)
- [antibody recognition sites](#)
- [binding small ligand\(s\)](#)
- is involved in [binding host protein\(s\)](#)
- [viral oligomerization interfaces](#)

[See all interactions for this position](#)

**Passage bias info available:**

In subtype H3, H at this position is preferred over Q in SIAT cells with odds ratio of 67.59.

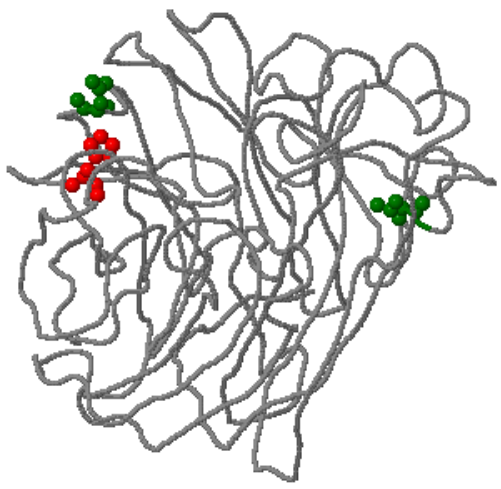
**Same isolate but different passage**  
(A/SINGAPORE/22/2012 NPHL: GP1187-2012)

GISAID ID	Submitter	Passage	Mutations relative to Victoria/361
EPI_ISL_128750	WHO CC Melbourne via NPHL	MDCK0, MDCK1	H9Y, Q49R, N161S, Q172H, V202G, Y235S, N294K
EPI_ISL_135838	US CDC via WHO CC Melbourne	E4/E1	H9Y, Q49R, N161S, N294K

# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

The main application is for the analysis and verification of any protein structure. Our curated reference sequences are fruitful and reliable.

Reference: NA\_H1N1\_Human\_2009\_California07 ([Structure/Model Details](#))  
 Patient/Sample: A/Singapore/GN285/2009(H1N1)  
 Mutation(s): **N248D**, **V106I**, **H275Y**  
 Wildtype residue only displayed if position is part of available structure.  
 Hover with mouse over residue to see its position number. Right-click for more options.



A/Singapore/GN2

See interactions of position NA 248 in related structures.  
 See interactions of position NA 106 in related structures.  
 See interactions of position NA 275 in related structures.  
[Click to save image](#)

er research and should ideally be combined with experimental testing. Treatment should not be based solely on these computational predictions. For humans, Therefore, **the usage scenario that will give the most** some candidates for avian flu and novel reassortant swine flu. [Special note for using FluSurver results in publications.](#)

Selection

# mutations	List of mutations
3	<b>V106I, N248D, H275Y</b> <a href="#">show in structure</a>

NA drug sensitivity positions:  
**26, 0, 1**  
 Reduced sensitivity or resistance!

[Import to Excel](#)

**Jmol\_S**

View all mutations together in structure or homology model of reference strain!

# FluSurver – an online tool to make sequence analysis and mutation detection/interpretation easier

Reference: NA\_H1N1\_Human\_2009\_California07  
 Patient/Sample: A/Singapore/GN285/2009(H1N1)  
 Mutation(s): **N248D**, **V106I**, **H275Y**  
 Wildtype residue only displayed if position is part of available structure.  
 Hover with mouse over residue to see its position number. Right-click for more options.

The main application is for the verification of any prediction. Our curated reference sequences are fruitful and reliable. H3N2v. P

Que

A/Singapore/GN2

Bioinforma  
Institute

**(Structure/Model Details)**

Further research and should ideally be combined with experimental testing. Prediction should not be based solely on these computational predictions.

### Information of the template of 3NSS used to model NA\_H1N1\_Human\_2009\_California07

PDB ID	3NSS
Subtype	H1N1
Strain	A/CALIFORNIA/04/2009
Structure Title	THE 2009 PANDEMIC H1N1 NEURAMINIDASE N1 LACKS THE 150-CAVITY IN ITS ACTIVE SITES
PMID of Reference	Not Available
Viral Protein	NEURAMINIDASE
Corresponding Chain	A

### Information of the alignment of NA\_H1N1\_Human\_2009\_California07 with 3NSS

Identity	Alignment Length	E-Value	Bit Score
100.00	388	0.0	797

### Alignment of NA\_H1N1\_Human\_2009\_California07 with 3NSS used for structural modeling

	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150
3NSS	SVELAGNSSLCPVSGWAIYSKDNVIRIGSGKGVFVIREPFISCSFLECRITFFLTQALLNDKHSNGTIDKRSFYRTLMSCPIGEVFPYNSRFESVANSASACHDGINWLTIGISGPDNGAVAVLYNGIITDTIKSRWNILRTQSEEC														
NA_H1N1_2009_California07	SVELAGNSSLCPVSGWAIYSKDNVIRIGSGKGVFVIREPFISCSFLECRITFFLTQALLNDKHSNGTIDKRSFYRTLMSCPIGEVFPYNSRFESVANSASACHDGINWLTIGISGPDNGAVAVLYNGIITDTIKSRWNILRTQSEEC														
_consrvd	.....														

	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
3NSS	ACVNGSCFTTMTDGPSSGQASVKIFRIEGRKIVKSVEMNAPHYHVEECSCVPDSSEITCVCRDNNHGSNRPFWISFMQWLEYQIGVICSQIFGDNFRPDKTIGSCGFVSNANGANGVGFSTFYNGGVWIGRIKSISSRNGFEMINDPFWGT														
NA_H1N1_2009_California07	ACVNGSCFTTMTDGPSSGQASVKIFRIEGRKIVKSVEMNAPHYHVEECSCVPDSSEITCVCRDNNHGSNRPFWISFMQWLEYQIGVICSQIFGDNFRPDKTIGSCGFVSNANGANGVGFSTFYNGGVWIGRIKSISSRNGFEMINDPFWGT														
_consrvd	.....														

	310	320	330	340	350	360	370	380	390
3NSS	GTDNNTFSIKQDIVGINESGYSGSFVQHPFELTGLDCIRPCFWELIRGRPEENTINTSGSSISFCGVNSDTVGNWFDGAEPLPTIID								
NA_H1N1_2009_California07	GTDNNTFSIKQDIVGINESGYSGSFVQHPFELTGLDCIRPCFWELIRGRPEENTINTSGSSISFCGVNSDTVGNWFDGAEPLPTIID								
_consrvd	.....								

**Jmol\_S**

[See interactions of position NA 248 in related structures.](#)  
[See interactions of position NA 106 in related structures.](#)  
[See interactions of position NA 275 in related structures.](#)

[Click to save image](#)

Check source and template similarity of structure/homology model!



# FluSurver – an online tool to make sequence analysis and mutation effect prediction easier

Check drug summary table!

The main application scenario for FluSurver is to help in the selection and verification of any predicted phenotypes. Importantly, our curated reference sequences used for annotation are of high quality and **fruitful and reliable results are current surveillance data**. Please take a look at the [FluSurver H3N2v](#). Please take a look at the [FluSurver H3N2v](#).

Known effect(s) of mutations at position equivalent to your mutation:

Protein: NA  
Influenza type: Human H1N1 (2006)  
Mutation (as in paper): H274Y  
neutral AA: H  
neg. eff. AA: Y  
Effect: strong drug resistance (drug name in comments)

**Comment:**  
Tamiflu but not Relenza resistance (Table 3)  
**Literature reference**  
(Mutation H274Y in the paper is at an equivalent position of the mutation in your query)

NCBI Resources How To

PubMed.gov: PubMed Advanced

Display Settings: Abstract

Antimicrob Agents Chemother. 2008 Sep;52(9):3284-92. doi: 10.1128/AAC.00555-08. Epub 2008 Jul 14.

**Surveillance for neuraminidase inhibitor resistance among human influenza A and worldwide from 2004 to 2008.**

Sheu TG, Deyde VM, Okomo-Adhiambo M, Garten RJ, Xu X, Bright RA, Butler EN, Wallis TR, Klimov AI, Gubareva LV. Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia.

Residue	Type	Ref.num.	Effect annotation	Close to drug in 3D structure (<5Å)
V116	wt	116 (N2)	sensitive	-
R118	wt	118 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
E119	wt	119 (N2)	sensitive	<a href="#">3D</a>
L134	wt	134 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
Q136	wt	136 (N2)	sensitive	-
D151	wt	151 (N2)	sensitive	<a href="#">3D</a>
Y155	wt	155 (N2)	sensitive	-
R156	wt	156 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
S180	wt	179 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
I223	wt	222 (N2)	sensitive	<a href="#">3D</a>
L224	wt	223 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
R225	wt	224 (N2)	sensitive	<a href="#">3D</a>
T226	wt	225 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
Q227	wt	226 (N2)	sensitive	-
E228	wt	227 (N2)	sensitive	<a href="#">3D</a>
G245	wt	244 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
P246	wt	245 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
S247	wt	246 (N2)	sensitive	<a href="#">3D</a>
N248D	mt	247 (N2)	no known effect (mt)	<a href="#">3D</a>
H275Y	mt	274 (N2)	effect	<a href="#">3D</a>
E277	wt	276 (N2)	sensitive	<a href="#">3D</a>
R293	wt	292 (N2)	sensitive	<a href="#">3D</a>
N344	wt	347 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
G345	wt	348 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
G348	wt	351 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>
R368	wt	371 (N2)	sensitive	<a href="#">3D</a>
G401	wt	405 (N2)	no known effect (common wildtype AA)	<a href="#">3D</a>

DISCLAIMER: This table is not suitable to unambiguously determine drug resistance but should rather serve to help selecting candidate positions/mutations that may have an effect for further experimental testing. Vicinity of a mutation to the drug in 3D structures does not automatically imply an effect on the drug and requires further careful modelling and/or experimental testing. Most of the available effect annotations refer to specific subtypes and may hence not apply exactly to your query. Please read the annotation carefully and follow up the provided links to the original literature to judge whether a similar effect on drug sensitivity for your query may be plausible.

Further research and should ideally be combined with experimental testing. Treatment should not be based solely on these computational predictions. Affected humans. Therefore, the usage scenario that will give the most interesting some candidates for avian flu and novel reassortant swine flu is a special note for using FluSurver results in publications.

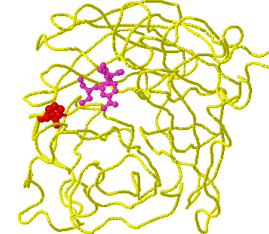
Force Selection

Force # mutations List of mutations

V106I, N248D, H275Y  
[show in structure](#)

NA drug sensitivity positions:  
26, 0, 1  
Reduced sensitivity or resistance!

or import to Excel



Jmol\_S

Description:  
The reference position NA 275 (red sphere) corresponds to position 273 on viral chain A (yellow) and is within 5 Å from drug RAZ (pink sphere).

See all 18 interactions for this position

[Click to save image](#)

PDB ID	1B9V
Subtype	Not available
Strain	BL/EE/40
PMID of reference	10547289

# Also useful for analysis of other segments!

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
RVM4541200051 H3 clade 3B N2	M2 A/Wisconsin/67/2005(H3N2) <a href="#">find closest related sequences</a>	98.780	<a href="#">84.536</a>	1	<a href="#">V271</a> <a href="#">show in structure</a> <div> M2 drug sensitivity positions:  <a href="#">16</a>, <a href="#">0</a>, <a href="#">2</a>  Reduced sensitivity or resistance! </div>

Known effect(s) of mutations at position equivalent to your mutation:

Protein: M2  
Influenza type: Duck (live poultry market) H3N2  
Mutation (as in paper): V271  
neutral AA: V  
neg. eff. AA: I  
Effect: mild drug resistance (drug name in comments)

#### Comment:

conferred Amantadine resistance (Table 1).

[Literature reference](#)

(Mutation V271 in the paper is at an equivalent position of the mutation in your query)

If WT residues in reference strains are associated with resistance it will be shown in drug summary table!

#### Summary of critical drug sensitivity positions

Residue	Type	Ref.num.	Effect annotation	Close to drug in 3D structure (<5Å)
L26	wt	26	sensitive	<a href="#">3D</a>
V271	mt	27	effect	<a href="#">3D</a>
A30	wt	30	sensitive	<a href="#">3D</a>
N31	wt	31	effect	<a href="#">3D</a>
I33	wt	33	no known effect (common wildtype AA)	<a href="#">3D</a>
G34	wt	34	sensitive	<a href="#">3D</a>
I35	wt	35	no known effect (common wildtype AA)	<a href="#">3D</a>
H37	wt	37	no known effect (common wildtype AA)	<a href="#">3D</a>
L38	wt	38	no known effect (common wildtype AA)	<a href="#">3D</a>
L40	wt	40	no known effect (common wildtype AA)	<a href="#">3D</a>
W41	wt	41	no known effect (common wildtype AA)	<a href="#">3D</a>
I42	wt	42	no known effect (common wildtype AA)	<a href="#">3D</a>
L43	wt	43	no known effect (common wildtype AA)	<a href="#">3D</a>
D44	wt	44	no known effect (common wildtype AA)	<a href="#">3D</a>
R45	wt	45	no known effect (common wildtype AA)	<a href="#">3D</a>

Known effect(s) of mutations at position equivalent to your mutation:

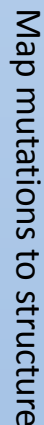
Protein: M2  
Influenza type: Human H1N1 (2007)  
Mutation (as in paper): S31N  
neutral AA: S  
neg. eff. AA: N  
Effect: strong drug resistance (drug name in comments)

#### Comment:

Amantadine resistance (Table)

[Literature reference](#)

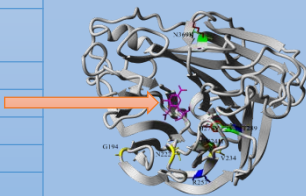
(Mutation S31N in the paper is at an equivalent position of the mutation in your query)



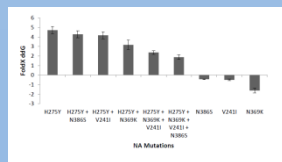
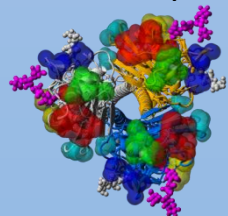
300+  
reference  
homology  
models

1568	self/oligomerization
975	other small ligand
268	antibody
188	host protein
182	antigen-presenting MHC molecule
132	other viral protein
46	drug
45	nucleic acids
13	host cell receptor
<b>3417</b>	<b>total interactions for 2062 positions</b>

## Interactions



## Glycosylation site changes

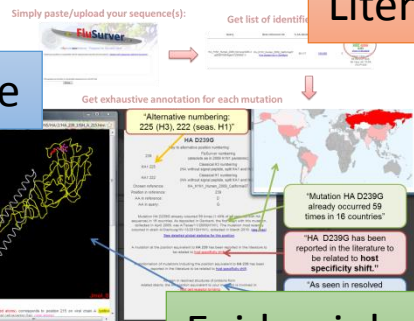


## FoldX stability calculations (for high frequency mutations in N1pdm)

Passage bias  
(egg/cell adaptation)  
for ~1300 mutations



## Literature



# Epidemiology

## Closest DB hits

[illegible]

## Temporal pattern

[illegible]

## Genomic co-occurrence

## Updated

**Literature-curated  
mutation effect database**  
~400 entries

mild drug resistance	30
strong drug resistance	40
virulence	106
antigenic drift / escape mutant	84
host specificity shift	136
other	23

## Regional & global occurrence



# Analysis – FluSurver for Mutation Interpretation



The screenshot displays the FluSurver web application interface. The top navigation bar includes 'GISAID', 'FluSurver', and 'Mendel Institute'. The main content area is divided into several panels:

- Personal Worksheet:** Contains a table of results for comparison with reference sequence HK229\_Human\_2002\_Netherlands219. The table includes columns for Query, Best reference hit, % AA identity, % length coverage, and # mutations. A green arrow points to the first row of the table.
- Map of sites with the HA Q242L mutation:** A world map showing the geographic distribution of the mutation, with a red dot in China.
- Key to alternative position numbering:** A table showing the mapping between different numbering systems (e.g., HA1 228, HA1 223, HA1 221) and the chosen reference (HA\_1797\_Human\_2002\_Netherlands219).
- Protein structure:** A 3D ribbon diagram of the protein structure, with a green arrow pointing to a specific residue.
- Comment:** A text box providing additional information about the mutation, including its effect on host specificity and its relationship to other mutations.

*Important disclaimer:*

FluSurver makes it very easy to link mutations with prior literature and potential phenotypic effects.

While we have placed great emphasis on avoiding false positive alerts and provide tutorials, one still needs to read the associated papers and interpret the provided evidence carefully to judge any effect realistically.

# Flusurver Acknowledgements

Many current and former colleagues from the A\*STAR Bioinformatics Institute (BII) contribute(d) critically to the FluSurver development and research, including:

**Sebastian Maurer-Stroh, Raphael Tze Chuen Lee, Vithiagarun Gunalan, Vachiranee Limviphuvadh, Fernanda L Sirota, Biruhalem Taye, Alvin Han, Han Hao, Dimitar Kenanov, Jianmin Ma, Swe Swe Thet Paing, Narumol Dounpan, Joy Xiang and Frank Eisenhaber.**

The FluSurver would be nothing without the valuable feedback and interaction with the influenza research and surveillance community, including especially and in chronological order:

- Genome Institute of Singapore (GIS), Singapore
- INMEGEN Mexico City, Mexico
- Experimental Therapeutics Centre (ETC), Singapore
- Tan Tock Seng Hospital (TTSH), Singapore
- National Public Health Laboratory (NPHL) of the Ministry of Health, Singapore
- IAL Sao Paulo, Brazil
- WHO Collaborating Centre for Reference and Research on Influenza, Australia
- Duke-NUS Emerging Infectious Disease Programme, Singapore
- University of Melbourne, Australia
- Global Initiative for Sharing All Influenza Data
- Centers for Disease Control (CDC) Atlanta, USA
- Research and Policy for Infectious Disease Dynamics (RAPIDD)
- Health Protection Agency of Canada
- Friedrich Loeffler Institute, Germany



Fishing for Flu Mutations since 2009!

... and thank all of you!