

# Finding Tamiflu/NAI susceptibility mutations with FluSurver in GISAID

platform.gisaid.org/epi3/frontend#1ed3a3

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Count **6 isolates** | GISAID published **151,238 isolates (672,017 sequences)** | Total isolate count **286,487 isolates (1,197,990 sequences)**

### Basic filters

Predefined search:

Search in:  Released files  Worksets

Search patterns:

Type	H	N	Lineage	Host	Location
A	1	1	unknown	-all-	-all-
B	2	2	pdm09	Human	Africa
C	3	3	seasonal	Animal	Antarctica
	4	4		Avian	Asia
	5	5		Chicken	Europe

### Additional filters

Collection date (YYYY-MM-DD): From  To

Submission date (YYYY-MM-DD): From  To

Originating Laboratory:   
[Albania, Tirana] Institute of Public Health  
[Algeria, Algiers] Institut Pasteur d'Algerie  
[Argentina, Buenos Aires] CEMIC University Hospital  
[Argentina, Buenos Aires] Instituto Nacional Enfermedades Infecciosas C.G.Malbran

Submitting Laboratory:   
[Argentina, Buenos Aires] Instituto Nacional de Tecnología Agropecuaria (INTA)  
[Argentina, Mar del Plata] Instituto Nacional de Epidemiología Juan Hector Jara  
[Australia, Casuarina] Royal Darwin Hospital  
[Australia, Geelong] CSIRO Australian Animal Health Laboratory

Required Segments:  PB2  PB1  PA  HA  NP  NA  MP  NS  HE  P3  
 only complete Min Length   
 Direct submissions to GISAID  Import from public-domain (INSDC)

**Find your isolate of interest in GISAID**  
e.g. Singapore H1N1pdm from May 2009

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# Finding Tamiflu/NAI susceptibility mutations with FluSurver in GISAID

platform.gisaid.org/epi3/frontend#3e8220



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## Released files

<input checked="" type="checkbox"/>	edit	Name	Isolate ID	Subtype	Host	Collection date	Passage	PB2	PB1	PA	HA	NP	NA	MP	N
<input checked="" type="checkbox"/>		A/Singapore/GN285/2009	EPI_ISL_70517	H1N1	Human	2009-05-30	C1	2341	2341	2221	1778	1529	1458	1027	85
<input checked="" type="checkbox"/>		A/Singapore/ON129/2009	EPI_ISL_61435	H1N1	Human	2009-05-29	p1	2316	2288	2188	1743	1510	1411	970	85
<input checked="" type="checkbox"/>		A/Singapore/57/2009	EPI_ISL_33583	H1N1	Human	2009-05-30	C1/C1	---	---	---	1701	---	1410	982	---
<input checked="" type="checkbox"/>		A/Singapore/ON132/2009	EPI_ISL_31613	H1N1	Human	2009-05-30	c1	2251	---	2168	1549	---	1279	956	---
<input checked="" type="checkbox"/>		A/Singapore/ON126/2009	EPI_ISL_30514	H1N1	Human	2009-05-28	original	1019	970	---	1135	1330	---	796	---
<input checked="" type="checkbox"/>		A/Singapore/ON124/2009	EPI_ISL_30513	H1N1	Human	2009-05-28	original	---	---	---	---	---	1405	883	---

Select, “Add to analysis”, then “FluSurver”

Total: 6 isolates

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## FluSurver

Filter  Align DNA (NC)  Align Proteins (AA)  
 all  PB2  PB1  PA  HA  NP  NA  MP  NS  HE  P3

<input type="checkbox"/>	Sequence name	EPI/WSS-Nr	Isolate name	NCBI-Id	Length
<input checked="" type="checkbox"/>	#182530	EPI182530	A/Singapore/ON124/2009		1405
<input checked="" type="checkbox"/>	#184539	EPI184539	A/Singapore/ON132/2009		1279
<input checked="" type="checkbox"/>	2009021345C1C1_6	EPI189162	A/Singapore/57/2009		1410
<input checked="" type="checkbox"/>	A/Singapore/GN285/2009	EPI244409	A/Singapore/GN285/2009	CY055305	1458
<input checked="" type="checkbox"/>	A/Singapore/ON129/2009	EPI213501	A/Singapore/ON129/2009	CY049070	1411

Select "NA", then "Continue"

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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 (including the recent H7N9 and avian H5N8/H5N6, for GISAID users only) and novel reassortant swine flu H3N2v.** Please take a look at the [Frequently Asked Questions](#) and [Tutorial](#) if you are new to FluSurver. You could also look at this [NA example analysis walkthrough](#) and the [GISAID access preview poster](#).

Note for H7N9 analysis: A tutorial with example analysis and interpretation is available [here](#).

Loaded protein sequences of your selected isolates for FluSurver analysis:

```
>NA_A/Singapore/ON132/2009_31613
NIISIWISHSIQLGNQNIETCNQSVITYENNTWVNTQTYVNIISNTNFAAGQSVVSVKLAGNSSLCPVSGWAIYSKDNSIRIGSKGDVFIREFPFISCSPLECRTFFLTQGAL
LNDKHSNGTIKDRSPYRTLMSCPIGEVPSYNSRFESVAWSASACHDGINWLTIGISGPDNGAVAVLKYNGIITDTIKSWRNNILRTQSEECACVNGSCFTVMTDGPDSGQA
SYKIFRIEKGKIVKSVEMNAPNYHYEECSYDSEITCVCRDNWHGSRNPWVSNQNLLEYQIGYICSGIFGDNPRPNDKTGSCGPVSSNGANGVKGFSFKYNGVWIGRTK
SISRRNGFEMIWDPNGWGTDDNPFISIKQDIVGINESWGSYGSFVQHPGLTGLDCIRPCFWVELIRGRPKENTIWTSGSSISFCGVNSDTV
>NA_A/Singapore/ON129/2009_61435
MNPNQKIITIGSVCMTIGMANLILQIGNIISIWISHSIQLGNQNIETCNQSVITYENNTWVNTQTYVNIISNTNFAAGQSVVSVKLAGNSSLCPVSGWAIYSKDNSIRIGSKG
DVFVIREPFISCSPLECRTFFLTQGALLNDKHSNGTIKDRSPYRTLMSCPIGEVPSYNSRFESVAWSASACHDGINWLTIGISGPDNGAVAVLKYNGIITDTIKSWRNNIL
RTQSEECACVNGSCFTVMTDGPDSGQASYKIFRIEKGKIVKSVEMNAPNYHYEECSYDSEITCVCRDNWHGSRNPWVSNQNLLEYQIGYICSGIFGDNPRPNDKTGSCG
PVSSNGANGVKGFSFKYNGVWIGRTKSISRRNGFEMIWDPNGWGTDDNPFISIKQDIVGINESWGSYGSFVQHPGLTGLDCIRPCFWVELIRGRPKENTIWTSGSSISFCGV
```

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

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

Analyze with FluSurver



Select reference to compare to (Current vaccine reference for recent seasonal surveillance samples, default automatic for all others), then “Analyze with FluSurver”

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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: autorefall [Back to Reference Selection](#)

Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
NA_A/Singapore/57/2009_33583	NA A/California/07/2009(H1N1) <a href="#">find closest related sequences</a>	99.360	<a href="#">100.000</a>	3	<a href="#">V106I</a> <a href="#">N248D</a> <a href="#">H275Y</a> <a href="#">show in structure</a> NA drug sensitivity positions: <b>34_0_1</b> Reduced sensitivity or resistance!
NA_A/Singapore/GN285/2009_70517	NA A/California/07/2009(H1N1) <a href="#">find closest related sequences</a>	99.360	<a href="#">100.000</a>	3	<a href="#">V106I</a> <a href="#">N248D</a> <a href="#">H275Y</a> <a href="#">show in structure</a> NA drug sensitivity positions: <b>34_0_1</b> Reduced sensitivity or resistance!
NA_A/Singapore/ON124/2009_30513	NA A/California/07/2009(H1N1) <a href="#">find closest related sequences</a>	99.356	<a href="#">99.360</a>	3	<a href="#">I23V</a> <a href="#">V106I</a> <a href="#">N248D</a> <a href="#">show in structure</a> NA drug sensitivity positions: <b>35_0_0</b>
NA_A/Singapore/ON129/2009_61435	NA A/California/07/2009(H1N1) <a href="#">find closest related sequences</a>	99.573	<a href="#">99.787</a>	2	<a href="#">V106I</a> <a href="#">N248D</a> <a href="#">show in structure</a> NA drug sensitivity positions: <b>35_0_0</b>
NA_A/Singapore/ON132/2009_31613	NA A/California/07/2009(H1N1) <a href="#">find closest related sequences</a>	99.531	<a href="#">90.832</a>	2	<a href="#">V106I</a> <a href="#">N248D</a> <a href="#">show in structure</a> NA drug sensitivity positions: <b>35_0_0</b>

[Right-click here to save/download detailed mutation report table for archiving or import to Excel \(Tab-separated, one mutation per line\)](#)  
[Right-click here to save/download query summary report table for archiving or import to Excel \(Comma-separated, one query per line\)](#)

**Warning:** this reference selection includes sequences of strains without complete genomes, e.g. only HA and NA available/included. Therefore, hits of other segments to different reference strains do not represent reassortments. Please see also [this help section](#) regarding reassortments.

[Go back](#)

Susceptibility mutations highlighted in red, click on mutation...

# Finding Tamiflu/NAI susceptibility mutations with FluSurver in GISAID

platform.gisaid.org/epi3/frontend#2b7751

Follow up to literature reference for phenotype info

The image shows the top part of the GISAID website. It includes the GISAID logo, a world map, and navigation links for 'Registered Users', 'EpiFlu™', and 'My profile'. Below this is a menu with options like 'Browse', 'Back to results', 'Worksets', 'Upload', 'Batch Upload', 'Settings', and 'Analysis'. A user is logged in as 'Sebastian Maurer-Stroh'.

View in 3D structure

This panel shows the 'EFFECTS' page for a mutation. It lists the protein as 'NA' and the influenza type as 'Human H1N1 (2006)'. The mutation is identified as 'H274Y' with a neutral amino acid 'H' and a negative effect amino acid 'Y'. The effect is 'strong drug resistance (drug name in comments)'. A comment mentions 'Tamiflu but not Relenza resistance (Table 3)' and provides a 'Literature reference' link. The protein is also listed as 'Human H3N2 (2005)' with mutation 'H274N'.

This panel provides detailed information for the 'NA H275Y' mutation. It includes a key to alternative position numbering (FluSurver, Classical H3N2, and Classical H1N1), the chosen reference (NA\_H1N1\_Human\_2009\_California07), and position/AA in reference (275, H). It notes that the mutation has occurred 324 times (1.80% of samples) and is related to 'strong drug resistance and mild drug resistance'. It also mentions that a combination of mutations including this position is related to 'strong drug resistance' and that the mutation is predicted to be 'strongly destabilizing'.

This panel shows a 3D ribbon structure of the NA protein in yellow. The mutation site is highlighted with red and pink atoms. The interface includes 'Spin ON', 'Spin OFF', and 'Save IMAGE' buttons. A description states: 'The mutation position (red atoms) corresponds to position 273 on viral chain A (yellow backbone) and is within 5 Å from drug RA2 (pink atoms)'. A 'PubMed search for this mutation' link is also present.

# Finding Baloxavir susceptibility mutations with FluSurver in GISAID

Home / Eurosurveillance / Volume 24, Issue 12, 21/Mar/2019 / Article

## Rapid communication

### Influenza A(H3N2) virus exhibiting reduced susceptibility to baloxavir due to a polymerase acidic subunit I38T substitution detected from a hospitalised child without prior baloxavir treatment, Japan, January 2019

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Emi Takashita<sup>1</sup>, Chiharu Kawakami<sup>2</sup>, Rie Ogawa<sup>1</sup>, Hiroko Morita<sup>1</sup>, Seiichiro Fujisaki<sup>1</sup>, Masayuki Shirakura<sup>1</sup>, Hideka Miura<sup>1</sup>, Kazuya Nakamura<sup>1</sup>, Noriko Kishida<sup>1</sup>, Tomoko Kuwahara<sup>1</sup>, Akira Ota<sup>3</sup>, Hayato Togashi<sup>3</sup>, Ayako Saito<sup>4</sup>, Keiko Mitamura<sup>5</sup>, Takashi Abe<sup>6</sup>, Masataka Ichikawa<sup>7</sup>, Masahiko Yamazaki<sup>8</sup>, Shinji Watanabe<sup>1</sup>, Takato Odagiri<sup>1</sup>

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Abstract



Full-Text



Figures & Tables



References (9)



Supplementary Material



Metrics/Cited By



Related Content

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The cap-dependent endonuclease inhibitor baloxavir marboxil became available in Japan in March 2018 for the treatment of influenza virus infection in patients aged 12 years and older and children younger than 12 years weighing at least 10 kg. Between October 2018 and January 2019, baloxavir was supplied to medical institutions that together serve ca 5.5 million people. In December 2018, we detected influenza A(H3N2) viruses exhibiting reduced susceptibility to baloxavir from baloxavir-treated children aged 6 and 7 years [1]. These viruses possessed an I38T substitution in the polymerase acidic subunit (PA), which confers reduced susceptibility to baloxavir [2]. We subsequently increased nationwide monitoring of the baloxavir susceptibility of circulating influenza viruses, irrespective of antiviral treatment [3].

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News/announcements

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# Finding Baloxavir susceptibility mutations with FluSurver in GISAID

## Detection of polymerase acidic subunit I38T mutant influenza A(H3N2) viruses from hospitalised children

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In January 2019, we isolated two influenza A(H3N2) viruses, A/YOKOHAMA/87/2019 and A/YOKOHAMA/88/2019, from two hospitalised children (Table 1). Prior to hospitalisation and virus isolation, both children had received antiviral treatment against influenza. The primary-school child aged 6 years who was infected with A/YOKOHAMA/87/2019 had been treated with a single oral dose of baloxavir on the day of symptom onset and fever resolved within one day of baloxavir administration. Face oedema had developed 2 days after baloxavir administration, although this patient had no underlying diseases. The child was diagnosed with nephritis and hospitalised. The preschool child aged 5 years who was infected with A/YOKOHAMA/88/2019 had received oseltamivir 3 days after onset of illness, although its clinical benefit is greatest when administered within 48 hours of illness onset. Fever tended to resolve after oseltamivir administration. This child had no underlying diseases but was subsequently hospitalised for pneumothorax and subcutaneous emphysema. No epidemiological link was identified between these patients.

**Table 1.** Influenza A(H3N2) viruses detected from hospitalised children, Japan, January 2019 (n = 2)

Toggle display:  ▼

Open fullscreen 

GISAID isolate ID	Isolate name	Age in years	Onset of symptoms	Antiviral treatment	Day of hospitalisation	Specimen collection	PA substitution <sup>a</sup>	
							Clinical specimen	Virus isolate
EPI_ISL_341452	A/YOKOHAMA/87/2019	6	19 Jan 2019	19 Jan 2019 baloxavir	21 Jan 2019	25 Jan 2019	I38T/I mix (T: 28%)	I38T
EPI_ISL_341454	A/YOKOHAMA/88/2019	5	25 Jan 2019	28–30 Jan 2019 oseltamivir	31 Jan 2019	31 Jan 2019	I38T	I38T

GISAID: Global Initiative on Sharing All Influenza Data; ID: identity; PA: polymerase acidic subunit.

<sup>a</sup> For deep sequencing analysis, the mean sequencing depth, threshold used and limit of quantitation used were 14,200, 5% and 2, respectively.

Deep sequencing analysis of the isolates using MiSeq (Illumina, San Diego, California, United States) revealed that A/YOKOHAMA/87/2019 and A/YOKOHAMA/88/2019 possessed the PA I38T substitution. These PA I38T mutant viruses possessed different PA sequences and therefore originated from different sources of infection. PA I38 is highly conserved in influenza A and B viruses [1,2]. The I38T substitution was not detected in the Influenza Research Database ([www.fludb.org](http://www.fludb.org)) including 17,227 PA sequences from A(H3N2) viruses until December 2018 [1] or during surveillance studies of baloxavir susceptibility of influenza viruses in Japan (2017/18 influenza season) and the United States prior to the introduction of baloxavir (2016/17 and 2017/18 seasons) [3,4]. Therefore, previous studies concluded that the PA I38T substitution was a baloxavir treatment-emergent substitution [1,2]. The patient infected

ECDC Fellowship Programme EPIET and EUPHEM paths, are invited to submit their applications by 8 September 2019. [Learn more.](#)

### News/announcements

**Call for Expression of Interest:** ECDC invites candidates to express their interest in one or more of the following services: (1) rapporteurs services, (2) editing and proofreading services for the scientific journal *Eurosurveillance* and (3) editing and proofreading services for ECDC technical and scientific reports.

EPI\_ISL\_341454

A/YOKOHAMA/88/2019





# Finding Baloxavir susceptibility mutations with FluSurfer in GISAID



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Count  GISAID published  Total isolate count

### Basic filters

Predefined search

Search in  Released files  Worksets

Search patterns

Type	H	N	Lineage	Host	Location
A	1	1		-all-	-all-
B	2	2		Human	Africa
C	3	3		Animal	Antarctica
	4	4		Avian	Asia
	5	5		Chicken	Europe

### Additional filters

Collection date (YYYY-MM-DD) From  To

Submission date (YYYY-MM-DD) From  To

Originating Laboratory   
[Albania, Tirana] Institute of Public Health  
[Algeria, Algiers] Institut Pasteur d'Algerie  
[Argentina, Buenos Aires] CEMIC University Hospital  
[Argentina, Buenos Aires] Instituto Nacional Enfermedades Infecciosas C.G.Malbran

Submitting Laboratory   
[Argentina, Buenos Aires] Instituto Nacional de Tecnología Agropecuaria (INTA)  
[Argentina, Mar del Plata] Instituto Nacional de Epidemiología Juan Hector Jara  
[Australia, Casuarina] Royal Darwin Hospital  
[Australia, Geelong] CSIRO Australian Animal Health Laboratory

Required Segments  PB2  PB1  PA  HA  NP  NA  MP  NS  HE  P3  
 only complete Min Length   
 Direct submissions to GISAID  Import from public-domain (INSDC)

# Finding Baloxavir susceptibility mutations with FluSurver in GISAID

## Released files

<input type="checkbox"/>	edit	Name	Isolate ID	Subtype	Host	Collection date	Passage	PB2	PB1	PA	HA	NP	NA	MP	NS
<input checked="" type="checkbox"/>		A/YOKOHAMA/88/2019	EPI_ISL_341454	H3N2	Human	2019-01-31	MDCK 2	2280	2274	2151	1701	1497	1410	982	838

Total: 1 isolates << first < prev **1** next > last >>

Search in results

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## FluSurver

Filter  Align DNA (NC)  Align Proteins (AA)  
 all  PB2  PB1  PA  HA  NP  NA  MP  NS  HE  P3

<input type="checkbox"/>	Sequence name	EPI/WSS-Nr	Isolate name	NCBI-Id	Length
<input checked="" type="checkbox"/>	A/YOKOHAMA/88/2019_hCK2_HA	EPI1370467	A/YOKOHAMA/88/2019		1701
<input checked="" type="checkbox"/>	A/YOKOHAMA/88/2019_hCK2_MP	EPI1370462	A/YOKOHAMA/88/2019		982
<input checked="" type="checkbox"/>	A/YOKOHAMA/88/2019_hCK2_NA	EPI1370466	A/YOKOHAMA/88/2019		1410
<input checked="" type="checkbox"/>	A/YOKOHAMA/88/2019_hCK2_NP	EPI1370460	A/YOKOHAMA/88/2019		1497
<input checked="" type="checkbox"/>	A/YOKOHAMA/88/2019_hCK2_NS	EPI1370461	A/YOKOHAMA/88/2019		838
<input checked="" type="checkbox"/>	A/YOKOHAMA/88/2019_hCK2_PA	EPI1370463	A/YOKOHAMA/88/2019		2151
<input checked="" type="checkbox"/>	A/YOKOHAMA/88/2019_hCK2_PB1	EPI1370465	A/YOKOHAMA/88/2019		2274
<input checked="" type="checkbox"/>	A/YOKOHAMA/88/2019_hCK2_PB2	EPI1370464	A/YOKOHAMA/88/2019		2280

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### Important usage notes:

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Note for H7N9 analysis: A tutorial with example analysis and interpretation is available [here](#).

Loaded protein sequences of your selected isolates for FluSurfer analysis:

```
>PB2_A/YOKOHAMA/88/2019_341454
MERIKELRNLMQSRTREILTKTITVDHMAI IKKYTSGRQEKNP SLRMKWMAMKYPITADKRITEMVPERNEQGQTLWSKMSDAGSDRVMVSP LAVTWNNRNGPVTNTVHYP
KVKYKTYFDKVERLKHGTFGPVHFRNQVKIRRRVDINPGHADLSAKEAQDVIMEVFPNEVGARILTSESQLTITKEKKEELRDCKISPLMVAYMLERELVRKTRFLPVAGGT
SSIYIEVLHLTQGTCEQMYTPGGVRRNDVDQSLIIAARNIVRRAAVSADPLASLLEMCHSTQIGGTRMVDILRQNPTEEQAVIDICKAAMGLRISSSFSGGTFKRTSGS
SVKREEEVL TGNLQTLRIRVHEGYEEFTMVGKRATAILRKATRRLVQLIVSGRDEQSAEAIIVAMVFSQEDCVIKAVRGDLNFVNRANQRLNPMHQLLRHFQKDAKVL FQN
WGVEHIDSVGMVGVLPDMTPSTEMSMRGIRVSKMGVDEYSSTERVVVSDIRFLRVRDQRGNVLLSPEEVSETQGTERTLITYS SMMWEINGPESVLVNTYQWIIRNWEAV
KIQWSQNPAMLYNKMEFEPFQSLVPKATRSQYSGFVRTLFQQMRDVLGTFDTAQI IKLLPFAAAPPKQSRMQFSSLTVNVRGSGMRILVRGNSPVFNYNKTTKRLTILGKDA
GTLIEDPDESTSGVESAVLRGFLIIGKEDRRYPALSINELSNLAKGKANVLIQGQDVVLMKRKRDS SILTDSQTATKRIRMAIN
>PA_A/YOKOHAMA/88/2019_341454
MEDFVRQCFNPMIVELAEKAMKEYGEDLKIETNKAFAATCTHLEVCFMYSDFHINEQGESIVVELDDPNALLKHRFEIIEGRDRTMANTVVNSICNTTGAGKPKFLPDLDY
```

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

Automatic detection of closest reference (among current vaccine strains, full genomes)

Analyze with FluSurfer



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Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
HA_A/YOKOHAMA/88/2019_341454 <a href="#">Show in NEXTFLU tree</a>	HA A/Kansas/14_cell/2017(H3N2) <a href="#">find closest related sequences</a>	96.466	<a href="#">100.000</a>	20	<a href="#">C9Y</a> , <a href="#">E78G</a> , <a href="#">N107S</a> , <a href="#">K108R</a> , <a href="#">N137K</a> , <a href="#">A144T</a> , <a href="#">T147K</a> , <a href="#">S154A</a> , <a href="#">K160S</a> , <a href="#">S175Y</a> , <a href="#">K176T</a> , <a href="#">N187K</a> , <a href="#">S209F</a> , <a href="#">Q213R</a> , <a href="#">S235F</a> , <a href="#">R342K</a> , <a href="#">V363M</a> , <a href="#">I422V</a> , <a href="#">M494I</a> , <a href="#">V545I</a> <a href="#">show in structure</a>
M1_A/YOKOHAMA/88/2019_341454	M1 A/Kansas/14/2017(H3N2) <a href="#">find closest related sequences</a>	100.000	<a href="#">100.000</a>	0	no mutations
M2_A/YOKOHAMA/88/2019_341454	M2 A/Kansas/14/2017(H3N2) <a href="#">find closest related sequences</a>	96.907	<a href="#">100.000</a>	3	<a href="#">P25L</a> , <a href="#">I27V</a> , <a href="#">C52Y</a> <a href="#">show in structure</a> M2 drug sensitivity positions: <b>17, 0, 1</b> Reduced sensitivity or resistance!
NA_A/YOKOHAMA/88/2019_341454	NA A/Kansas/14/2017(H3N2) <a href="#">find closest related sequences</a>	98.081	<a href="#">100.000</a>	9	<a href="#">R75K</a> , <a href="#">P126L</a> , <a href="#">I140L</a> , <a href="#">A149V</a> , <a href="#">H155Y</a> , <a href="#">K220N</a> , <a href="#">V303I</a> , <a href="#">S315R</a> , <a href="#">T329S</a> <a href="#">show in structure</a> NA drug sensitivity positions: <b>38, 0, 0</b>
NEP_A/YOKOHAMA/88/2019_341454	NS2 A/Kansas/14/2017(H3N2) <a href="#">find closest related sequences</a>	100.000	<a href="#">100.000</a>	0	no mutations
NP_A/YOKOHAMA/88/2019_341454	NP A/Kansas/14/2017(H3N2) <a href="#">find closest related sequences</a>	99.398	<a href="#">100.000</a>	3	<a href="#">V197I</a> , <a href="#">V363I</a> , <a href="#">L418I</a> <a href="#">show in structure</a>
NS1_A/YOKOHAMA/88/2019_341454	NS1 A/Kansas/14/2017(H3N2) <a href="#">find closest related sequences</a>	96.833	<a href="#">96.087</a>	7	<a href="#">R41K</a> , <a href="#">A56S</a> , <a href="#">A60V</a> , <a href="#">I65V</a> , <a href="#">E71G</a> , <a href="#">K127N</a> , <a href="#">N207H</a> <a href="#">show in structure</a>
PA_A/YOKOHAMA/88/2019_341454	PA A/Kansas/14/2017(H3N2) <a href="#">find closest related sequences</a>	99.721	<a href="#">100.000</a>	2	<a href="#">I38T</a> , <a href="#">K158R</a> <a href="#">show in structure</a> Reduced sensitivity or resistance!
PB1-F2_A/YOKOHAMA/88/2019_341454	PB1-F2 A/Kansas/14/2017(H3N2) <a href="#">find closest related sequences</a>	94.253	<a href="#">96.667</a>	0	no mutations
PB1_A/YOKOHAMA/88/2019_341454	PB1 A/Kansas/14/2017(H3N2) <a href="#">find closest related sequences</a>	99.868	<a href="#">100.000</a>	1	<a href="#">E618D</a> <a href="#">show in structure</a>



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# Finding Baloxavir susceptibility mutations with FluSurver in GISAID

platform.gisaid.org/epi3/frontend#25a661

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

**Protein:** PA  
**Influenza type:** Human H1N1, H3N2, B (N/A)  
**Mutation (as in paper):** I38T  
**neutral AA:** I  
**neg. eff. AA:** T  
**Effect:** strong drug resistance (drug name in comments)

**Comment:**  
Reduced susceptibility against Baloxavir (27.2 fold change in H1N1, 56.6 in H3N2, 5.8 in flu B)  
[Literature reference](#)  
(Mutation I38T in the paper is at an equivalent position of the mutation in your query)

**Protein:** PA  
**Influenza type:** Human H1N1, H3N2, B (N/A)

Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
A/Kansas/14/2017(H3N2)	99.868	100.000	1	N137K A144T T147K S154A K160S D209F Q213R S235F R342K V363M 2V M494I V545I <a href="#">View in structure</a>
A/Kansas/14/2017(H3N2)	99.868	100.000	1	no mutations
A/Kansas/14/2017(H3N2)	99.868	100.000	1	55L I27V C52Y <a href="#">View in structure</a>
A/Kansas/14/2017(H3N2)	99.868	100.000	1	g sensitivity positions: 17 0 1 sensitivity or resistance!
A/Kansas/14/2017(H3N2)	99.868	100.000	1	V H155Y K220N V303I S315R T329S <a href="#">View in structure</a>

### PA I38T

Key to alternative position numbering:

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

Chosen reference: PA\_H3N2\_Human\_2017\_Kansas14  
Position in reference: 38  
AA in reference: I  
AA in query: T

Mutation PA I38T is not found in sequences used to derive the mutation statistics.  
[See detailed global statistics for this position](#)

A mutation at the position equivalent to PA 38 has been reported in the literature to be related to [strong drug resistance and mild drug resistance](#).

As seen in resolved structures of proteins from related strains, the PA position equivalent to your mutation is involved in:  
[- viral oligomerization interfaces](#)  
[- binding small ligand\(s\)](#)

[See all interactions for this position](#)  
[PubMed search for this mutation](#)

Characterization of influenza virus variants induced by treatment with the endonuclease inhibitor baloxavir marboxil.

SciBull. 2018 Jun 25;8(1):9633. doi: 10.1038/s41598-018-27890-4.

Omoto S<sup>1</sup>, Soranzini V<sup>2</sup>, Hashimoto T<sup>3</sup>, Noshi T<sup>3</sup>, Yamaguchi Li<sup>3</sup>, Kanai M<sup>3</sup>, Kawaguchi K<sup>3</sup>, Ushara L<sup>3</sup>, Shibahara T<sup>3</sup>, Naito A<sup>3</sup>, Casadei S<sup>4</sup>.

**Abstract**  
Baloxavir acid (BXA), derived from the prodrug baloxavir marboxil (BXM), potently and selectively inhibits the cap-dependent endonuclease within the polymerase PA subunit of influenza A and B viruses. In clinical trials, single doses of BXM profoundly decrease viral titers as well as alleviating influenza symptoms. Here, we characterize the impact on BXA susceptibility and replicative capacity of variant viruses detected in the post-treatment monitoring of the clinical studies. We find that the PA I38T substitution is a major pathway for reduced susceptibility to BXA, with 30- to 50-fold and 7-fold EC<sub>50</sub> changes in A and B viruses, respectively. The viruses harboring the I38T substitution show severely impaired replicative fitness in cells, and correspondingly reduced endonuclease activity in vitro. Crystal structures of wild-type and I38T influenza A and B endonucleases bound to BXA show that the mutation reduces van der Waals contacts with the inhibitor. A reduced affinity to the I38T mutant is supported by the lower stability of the BXA-bound endonuclease. These mechanistic insights provide markers for future surveillance of treated populations.

PMID: 29941893 | PMCID: PMC6028108 | DOI: 10.1038/s41598-018-27890-4

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