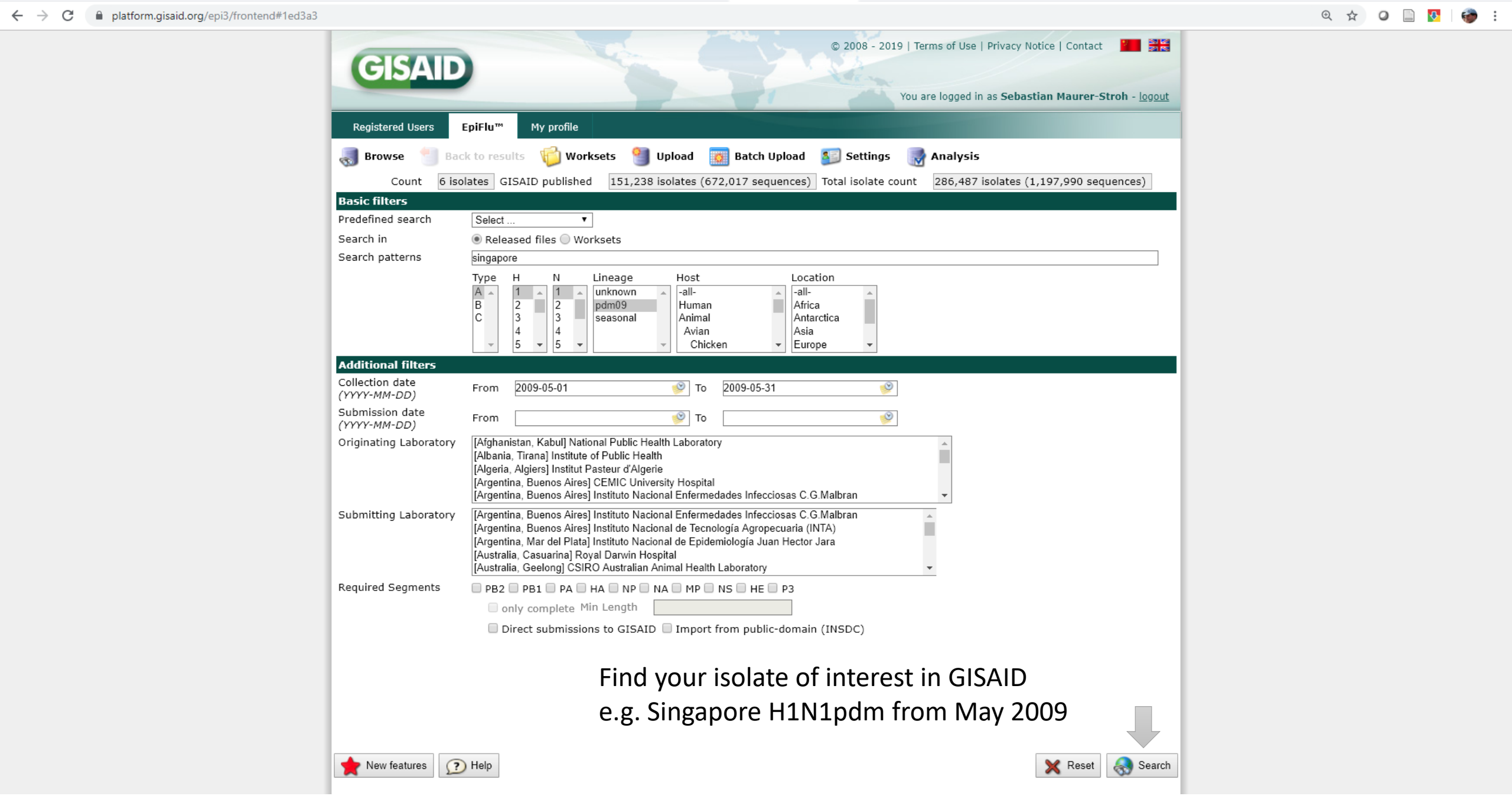
Finding Tamiflu/NAI susceptibility mutations with FluSurver in GISAID



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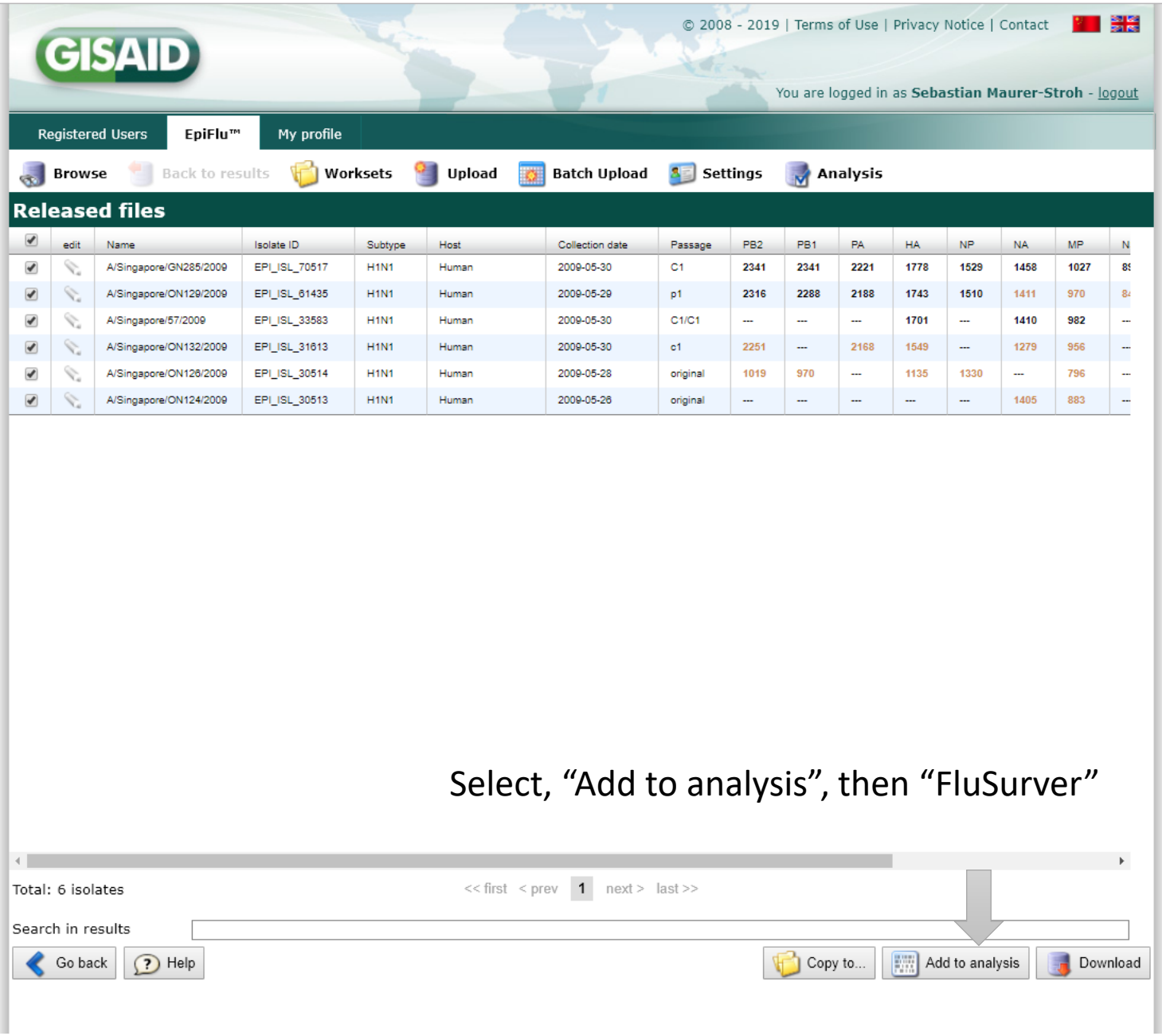
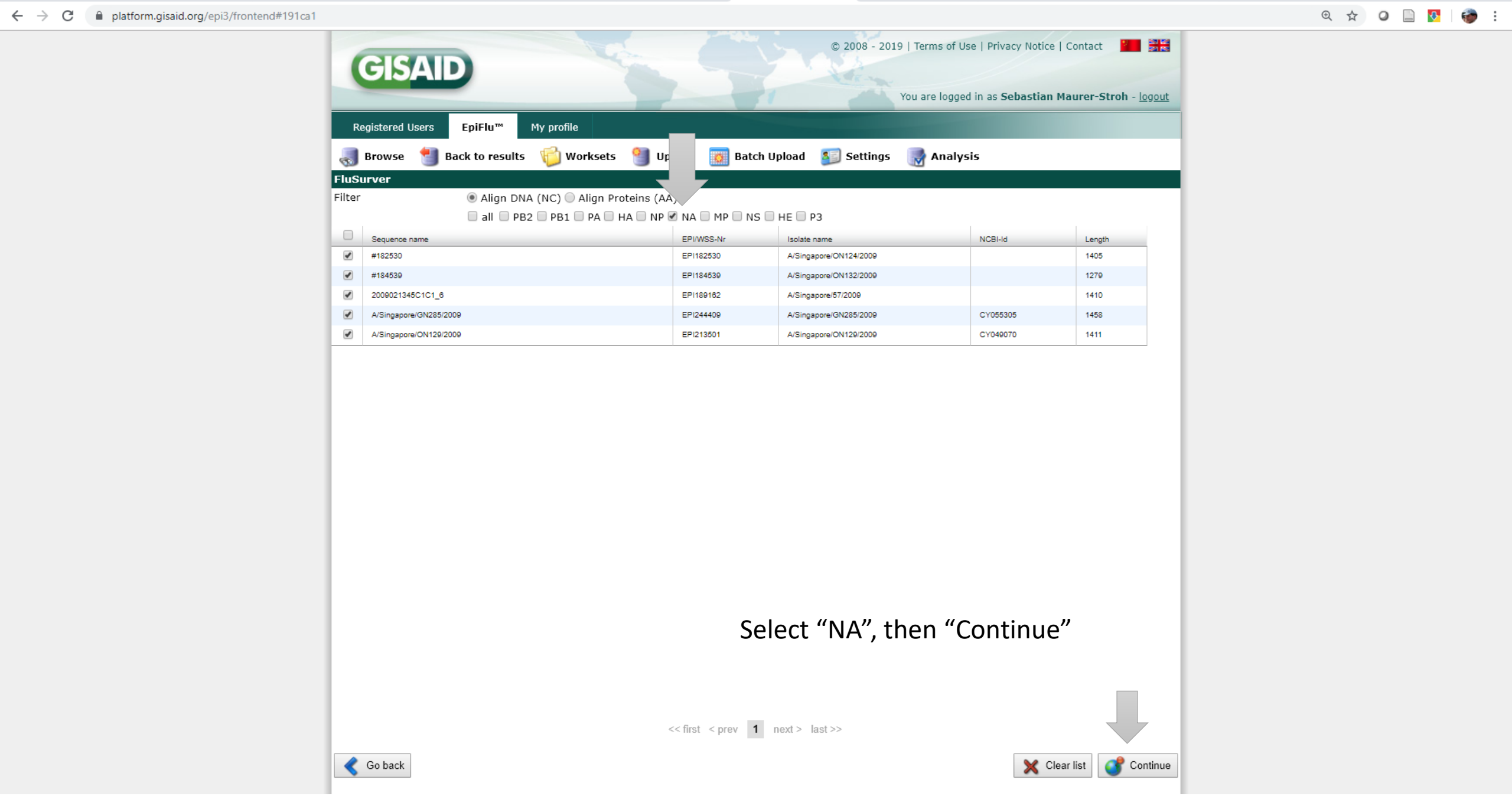
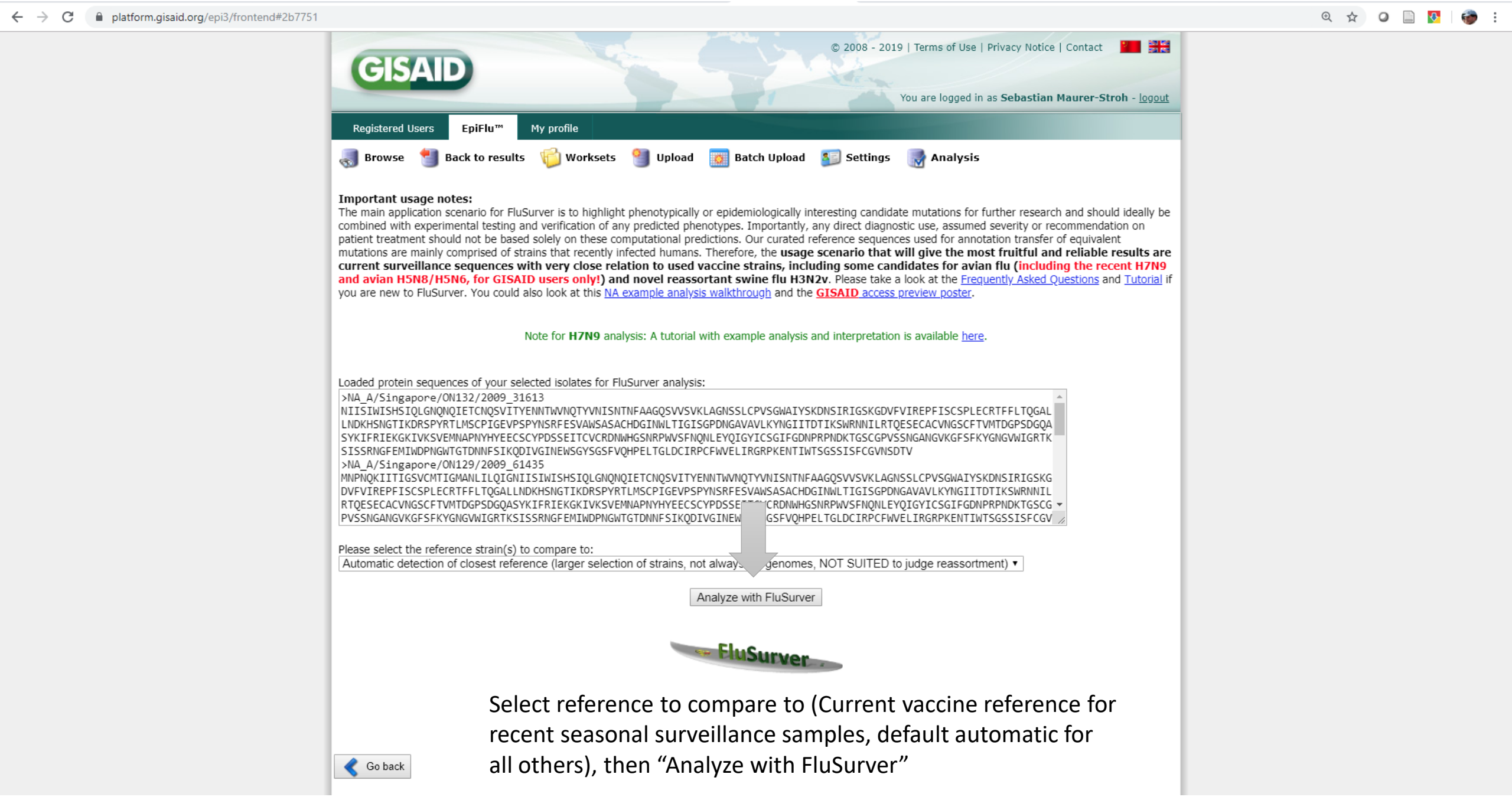


Finding Tamiflu/NAI susceptibility mutations with FluSurver in GISAID



Select “NA”, then “Continue”

Finding Tamiflu/NAI susceptibility mutations with FluSurver in GISAID



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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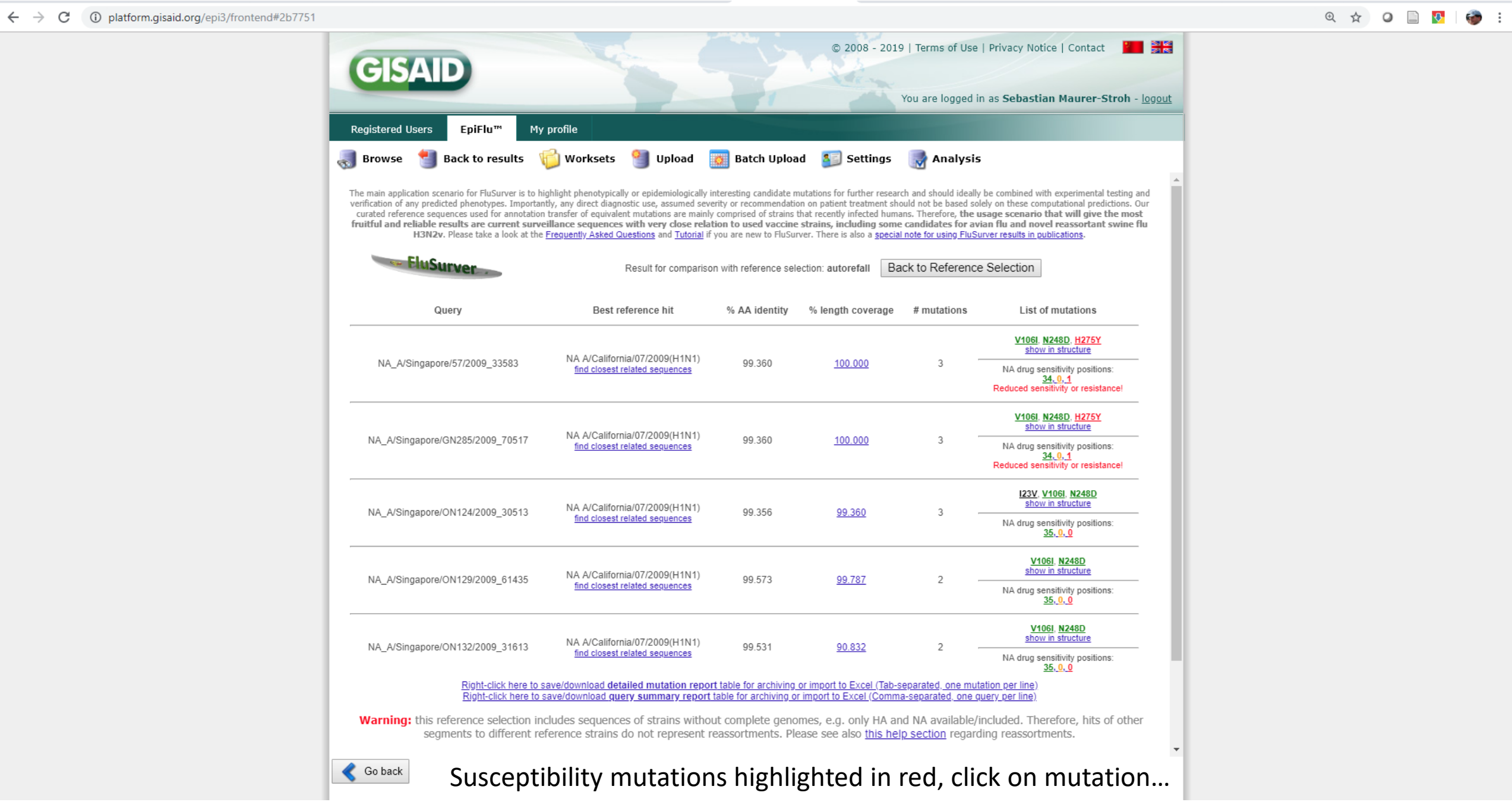
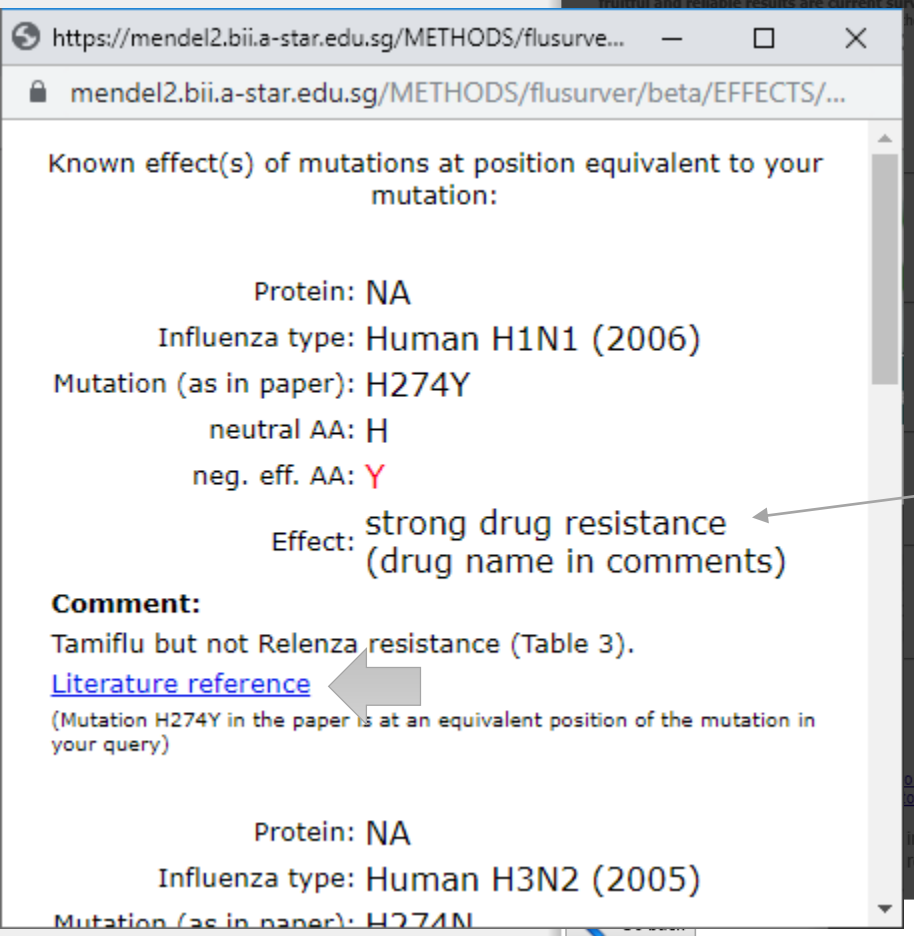


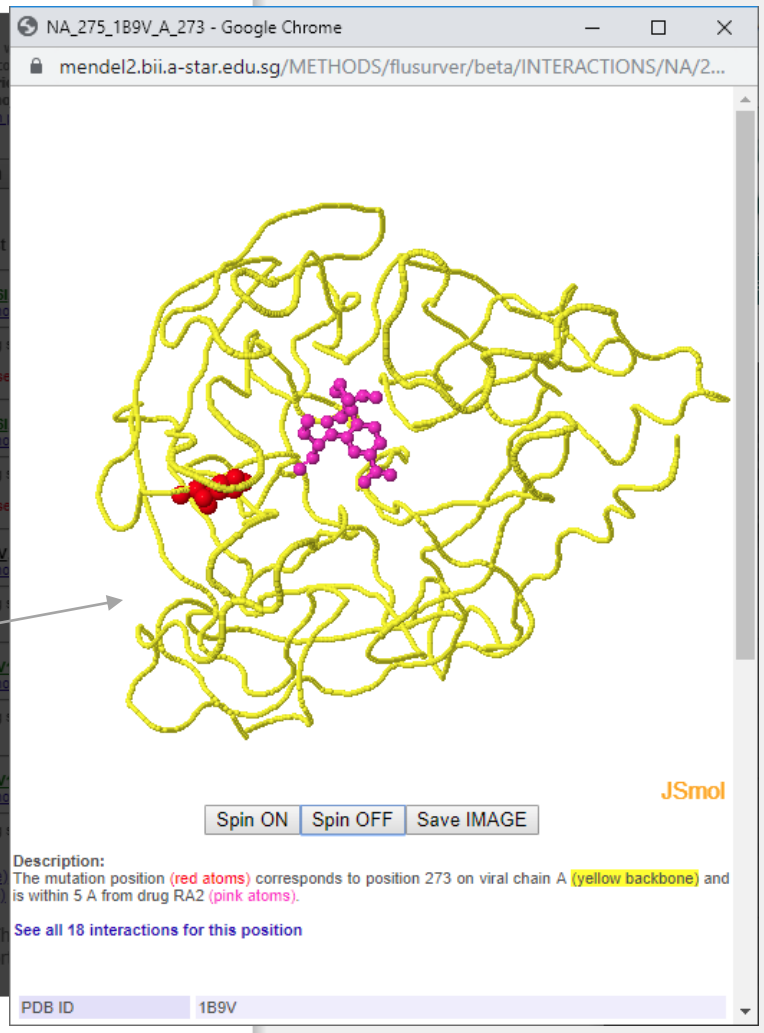
Susceptibility mutations highlighted in red, click on mutation…

Finding Tamiflu/NAI susceptibility mutations with FluSurver in GISAID

Follow up to literature reference for phenotype info

View in 3D structure





Finding Baloxavir susceptibility mutations with FluSurver in GISAID

Rapid communication

Open Access

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

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

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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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eurosurveillance.org/content/10.2807/1560-7917.ES.2019.24.12.1900170

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[a]	
							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.

[a] 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) 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

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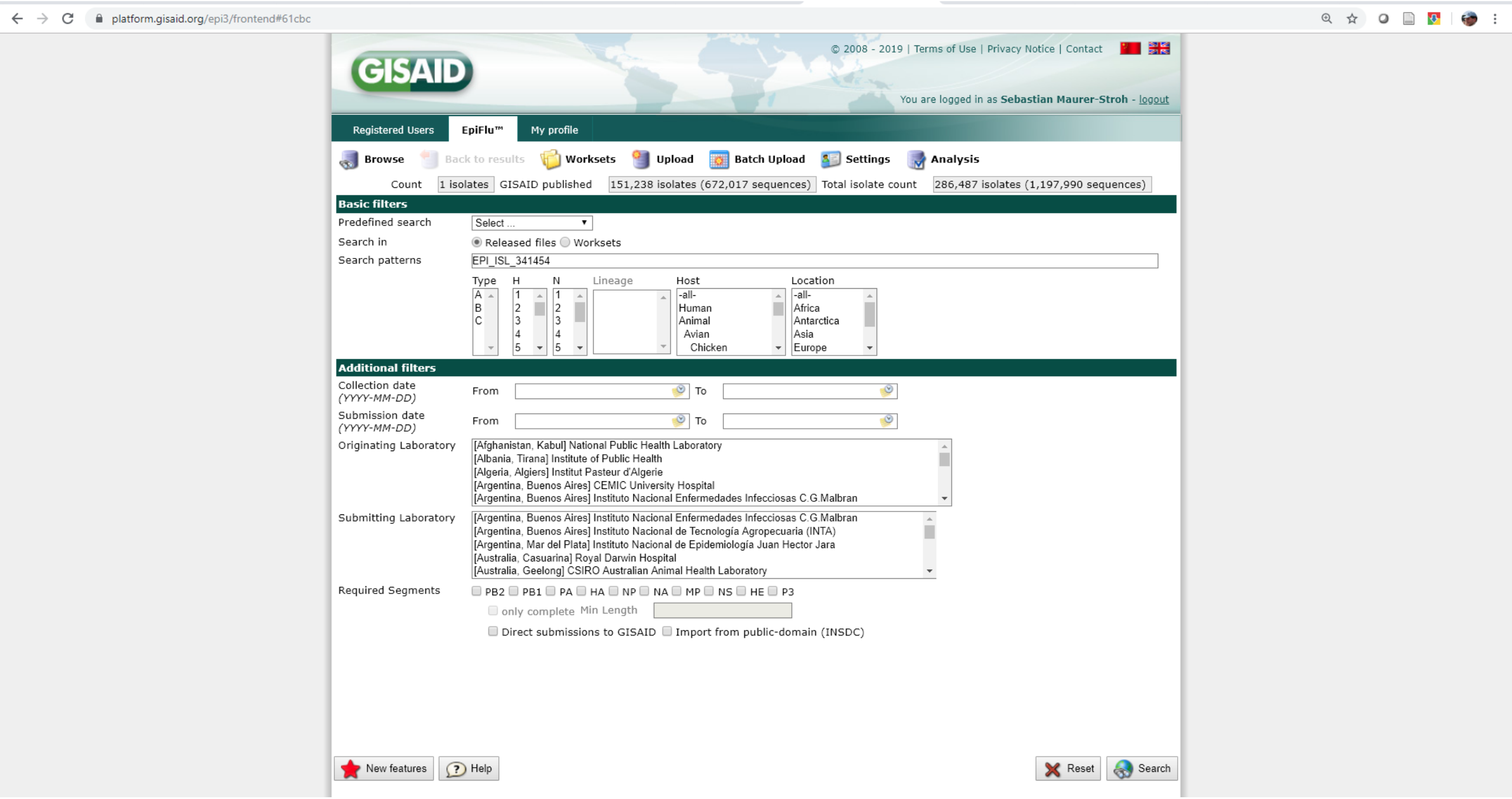
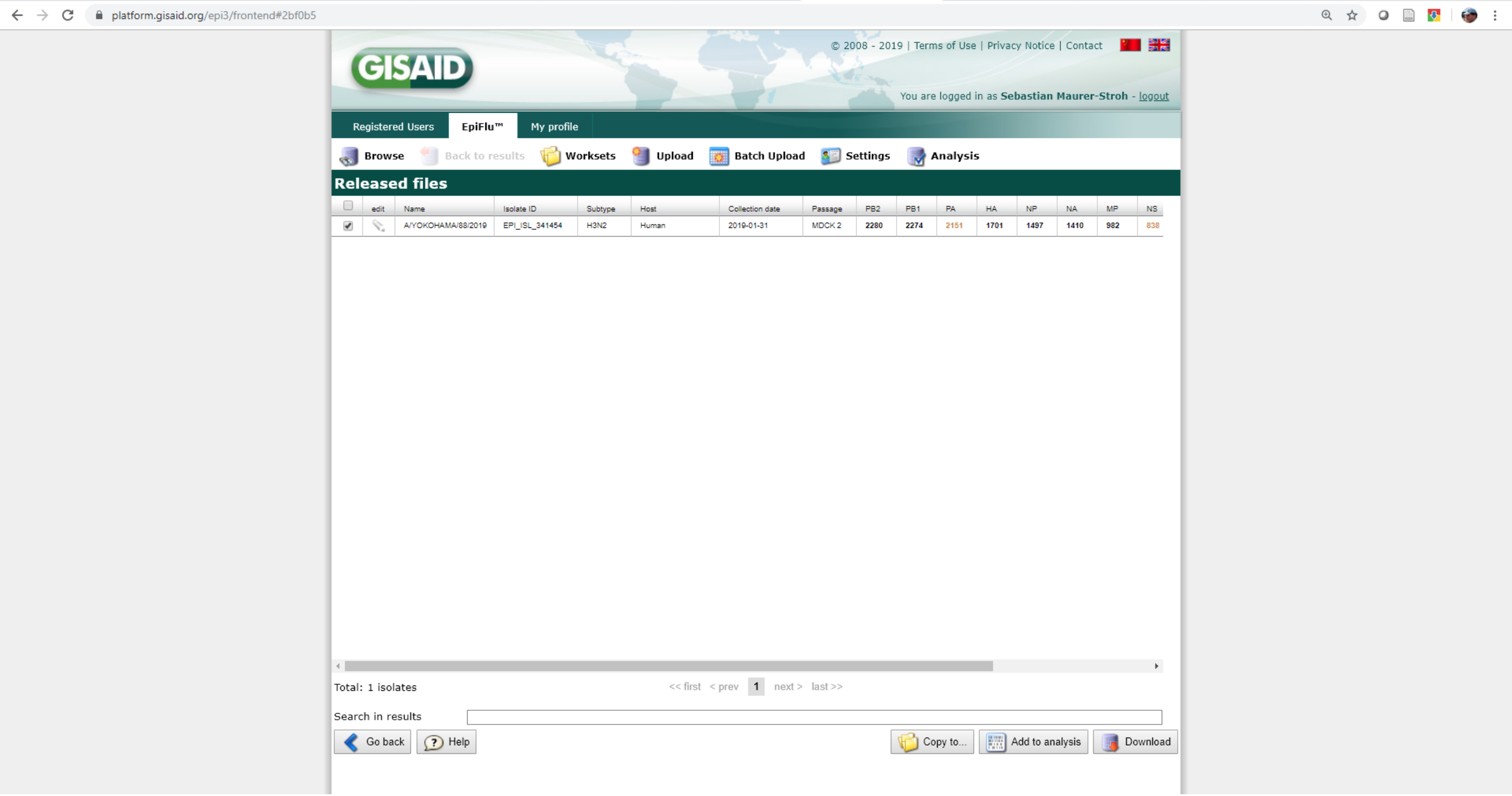
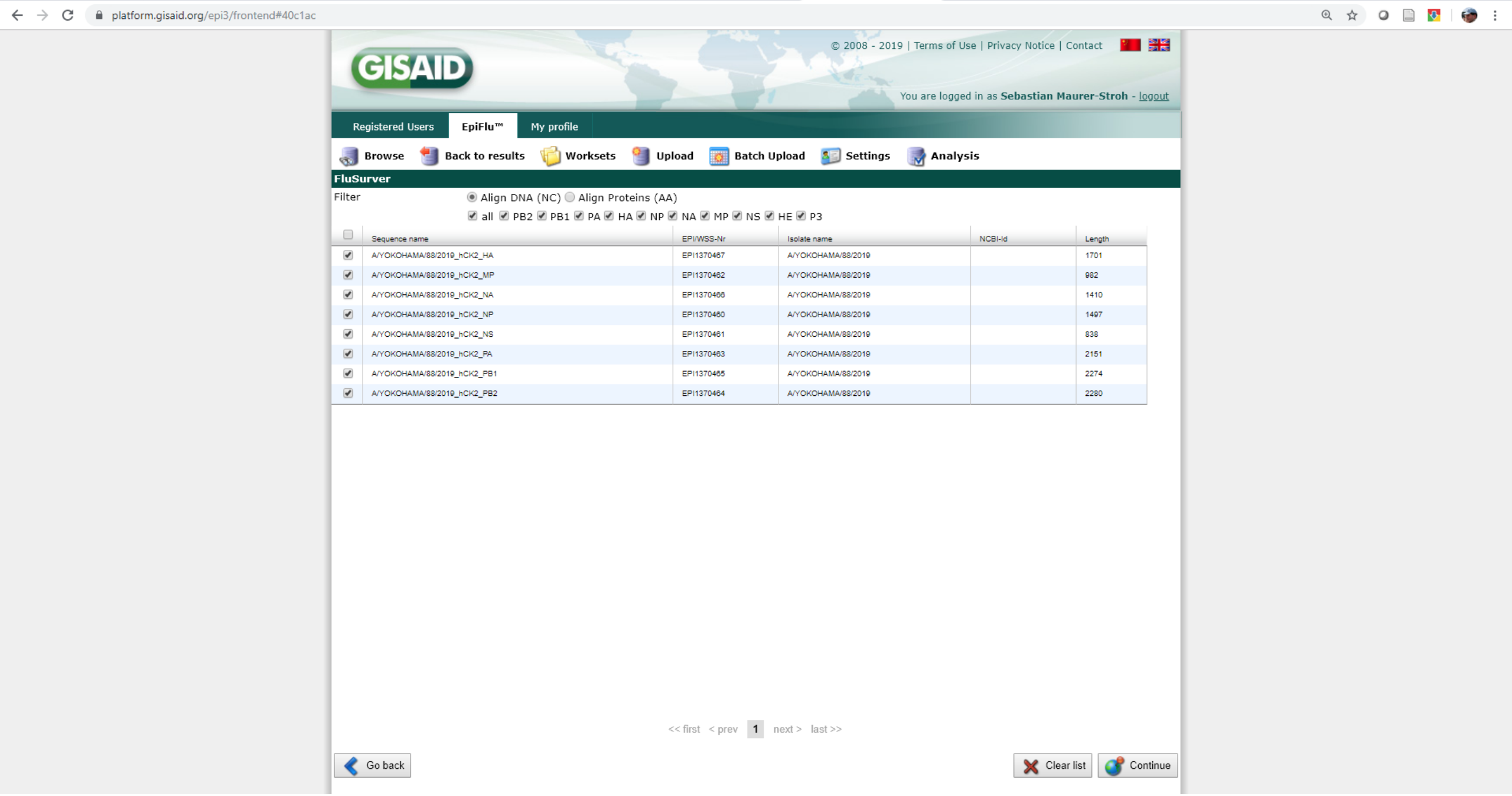


Finding Baloxavir susceptibility mutations with FluSurver in GISAID



Finding Baloxavir susceptibility mutations with FluSurver in GISAID



Finding Baloxavir susceptibility mutations with FluSurver in GISAID

platform.gisaid.org/epi3/frontend#14b769

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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:

```
>PB2_A/YOKOHAMA/88/2019_341454
MERIKELRNLMSQSRTREILTKTTVDHMAIIKKYTSGRQEKNPSLRMKWMMAMKYPITADKRITEMVPERNEQGQTLWSKMSDAGSDRVMVSPLAVTWWNRNGPVTNTVHYP
KVYKTYFDKVERLKHGTFGPVHFRNQVKIRRRVDINPGHADLSAKEAQDVIMEVVFPNEVGARILTSESQLTITKEKKEELRDCKISPLMVAYMLERELVRKTRFLPVAGGT
SSIYIEVLHLTQGTCWEQMYTPGGGVRNDDVDQSLIIAARNIVRRAAVSADPLASLLEMCHSTQIGGTRMVDILRQNPTEEQAVDICKAAMGLRISSSFSFGGFTFKRTSGS
SVKREEEVLTGNLQTLRIRVHEGYEEFTMVGKRATAILRKATRRLVQLIVSGRDEQSIAEAIIVAMVFSQEDCVIKAVRGDLNFVNRANQRLNPMHQLLRHFQKDAKVLFQN
WGVEHIDSVMGMVGVLPDMTPSTEMSMRGIRVSKMGVDEYSSTERVVVSIDRFLRVRDQRGNVLLSPEEVSETQGTERLTITYSSSMMWEINGPESVLVNTYQWIIRNWEAV
KIQWSQNPAMLYNKMEFEPFQSLVPKATRSQYSGFVRTLFQQMRDVLGTFDTAQIIKLLPFAAAPPKQSRMQFSSLTVNVRGSGMRILVRGNSPVFNYNKTTKRLTILGKDA
GTLIEDPDESTSGVESAVLRGFLIIGKEDRRYGPALSINELSNLAKGEKANVLIGQGDVVLVMKRKRDSSILTDSQTATKRIRMAIN
>PA_A/YOKOHAMA/88/2019_341454
MEDFVRQCFNPMIVELAEKAMKEYGEDLKIETNKFAATCTHLEVCFMYSDFHFINEQGESIVVELDDPNALLKHRFEIIEGRDRTMAWTVVNSICNTTGAGKPKFLPDLYDY
```

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

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

Analyze with FluSurver

FluSurver

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

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Query	Best reference hit	% AA identity	% length coverage	# mutations	List of mutations
HA_A/YOKOHAMA/88/2019_341454 Show in NEXTFLU tree	HA A/Kansas/14_cell/2017(H3N2) find closest related sequences	96.466	100.000	20	C9Y, E78G, N107S, K108R, N137K, A144T, T147K, S154A, K160S, S175Y, K176T, N187K, S209F, Q213R, S235F, R342K, V363M, I422V, M494I, V545I show in structure
M1_A/YOKOHAMA/88/2019_341454	M1 A/Kansas/14/2017(H3N2) find closest related sequences	100.000	100.000	0	no mutations
M2_A/YOKOHAMA/88/2019_341454	M2 A/Kansas/14/2017(H3N2) find closest related sequences	96.907	100.000	3	P25L, I27V, C52Y show in structure M2 drug sensitivity positions: 17, 0, 1 Reduced sensitivity or resistance!
NA_A/YOKOHAMA/88/2019_341454	NA A/Kansas/14/2017(H3N2) find closest related sequences	98.081	100.000	9	R75K, P126L, I140L, A149V, H155Y, K220N, V303I, S315R, T329S show in structure NA drug sensitivity positions: 36, 0, 0
NEP_A/YOKOHAMA/88/2019_341454	NS2 A/Kansas/14/2017(H3N2) find closest related sequences	100.000	100.000	0	no mutations
NP_A/YOKOHAMA/88/2019_341454	NP A/Kansas/14/2017(H3N2) find closest related sequences	99.398	100.000	3	V197I, V363I, L418I show in structure
NS1_A/YOKOHAMA/88/2019_341454	NS1 A/Kansas/14/2017(H3N2) find closest related sequences	96.833	96.087	7	R41K, A56S, A60V, I65V, E71G, K127N, N207H show in structure
PA_A/YOKOHAMA/88/2019_341454	PA A/Kansas/14/2017(H3N2) find closest related sequences	99.721	100.000	2	I38T, K158R show in structure Reduced sensitivity or resistance!
PB1-F2_A/YOKOHAMA/88/2019_341454	PB1-F2 A/Kansas/14/2017(H3N2) find closest related sequences	94.253	96.667	0	no mutations
PB1_A/YOKOHAMA/88/2019_341454	PB1 A/Kansas/14/2017(H3N2) find closest related sequences	99.868	100.000	1	E618D show in structure

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