The GISAID Initiative

Real Time Global Communication In Disease Prevention

GISAID

Bioinformatics Workshop
26-27 August 2019
Singapore

WHO Global Influenza Programme (GIP)
National Centre for Infectious Diseases (NCID) Singapore
Bioinformatics Institute (BII)
Global Initiative on Sharing All Influenza Data (GISAID)

Naomi Komadina

www.influenzacentre.org

WHO Collaborating Centre
for Reference and
Research on Influenza
VIDRL

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Challenges in 2006-2007

- Access to the latest genetic data for highly pathogenic H5N1 influenza zoonotic infections was often restricted, in part due to the hesitancy by MS to share their information.

- Scientists' reticence to share data pre-publication (fear of being scooped[1]) delayed sharing.

- Public-domain archives (anonymous access - use of data) offered: no protection of owners' interests (IP rights); limited incentive to share data; no transparency on the use of data; no effective mechanisms to ensure acknowledgement of labs providing viruses or contributing data.

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[1] Pearson H. - Competition in biology: It's a scoop! *Nature* 2003; DOI: 10.1038/news031124-9

GISAID data access and sharing principles

- Data Submitters grant Data Users an irrevocable licence for the use of their data, providing legal certainty for use in research and publications and for the development, testing and dissemination of interventions such vaccines, diagnostics and therapeutics

- Access to the GISAID EpiFLu Database is free of charge and open to every one provided that they identify themselves in order to foster collaboration and permit an effective oversight to uphold the enshrined sharing principles

- The guiding principle for those who use the Data in particular in publications is the need to acknowledge the contribution of both the suppliers and the submitters of the data

- Whilst all Data are publicly accessible, Submitters do not forfeit their rights (IPR) to the data they deposit in GISAID

See: GISAID EpiFlu™ Database Access Agreement

EpiFlu™ Database

- The most complete set of influenza sequences (>283K isolates & >1.1 million sequences)
- Includes patient meta data & geographical locations
- Submitters retain rights over their data
- Easy upload of data
- Isolate based entry rather than sequence only
- Isolates can be updated by submitter in real-time
- Automated sequence annotation on upload
- Customised search function outputs
- Customised fasta headers with sequence downloads
- Meta-data can be downloaded in spreadsheet
- Workset function, worksets can be shared amongst users
- Analysis tools

Workflow of EpiFlu™ Database

Data

- Sequence data is organized into unique isolates assigned an EPI_ISL Accession (defined by virus name and passage history), and segment EPI Accession
- meta data fields include: Isolate name, virus type, HA and NA subtype, lineage (B; H1N1), host, collection date, location, patient data i.e.: age, gender, vax status..
- Originating Laboratory - collected the specimen (Lab ID)
- Submitting Laboratory - sequenced the virus

Upload

- Single Upload – using the webpage interface (5-10 min)
- Batch Upload – using a macro-enabled excel spreadsheet (necessary fields; time dependent on amount of data; automatic)
- Complimented with data from public-domain GenBank archive routinely imported

Curation

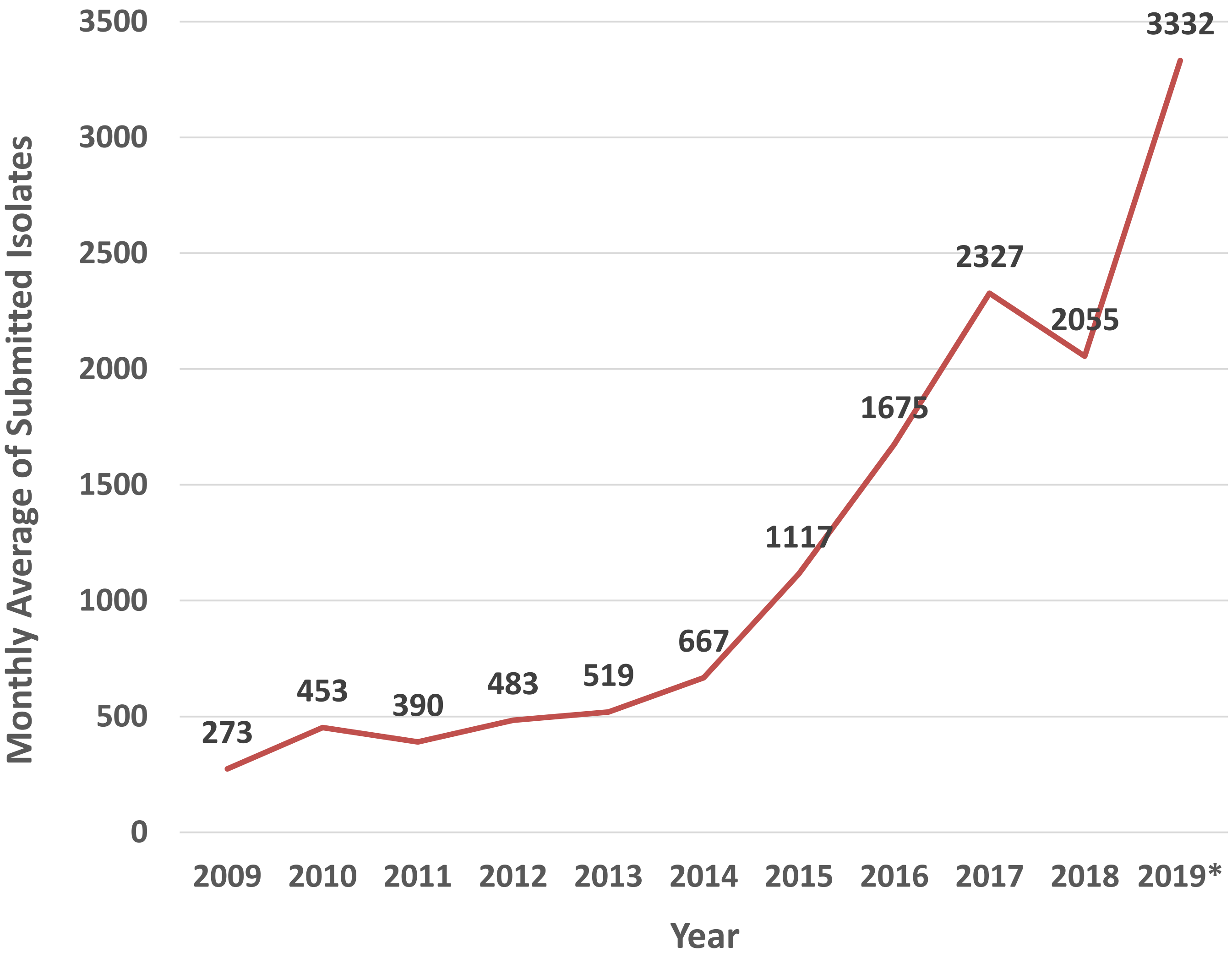
- Checks the correctness of sequence and meta data
- Flags errors

Data to Unreleased Files

- Pop-up message – errors, where and what type

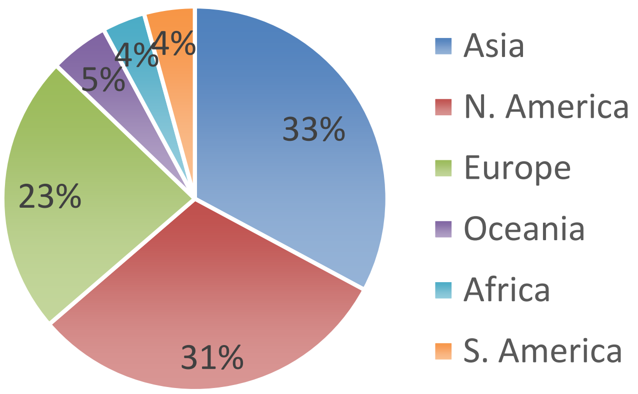
Release of corrected data

Increase in genetic sequence data published via GISAID



Geographical representativeness

- ~1,2m sequences of ~283,000 influenza viruses (70% human; 30% animal)
  - Data from >1,200 labs (incl. all 152 GISRS)
- Contains data from >2,000 influenza viruses with pandemic potential (IVPP)
  - >30,000 animal viruses (H4-H11)
  - Candidate vaccine viruses
- 8,700 active participants
  - Human and animal health
- 2017-18: sequence data of ~3,000 viruses (avg) uploaded monthly (70% directly to GISAID)
- Timely submission directly to GISAID: 94% of total within 3 months of collection; 83% (within 6 mo); 81% (within 12 mo); 77% (within 24 mo)

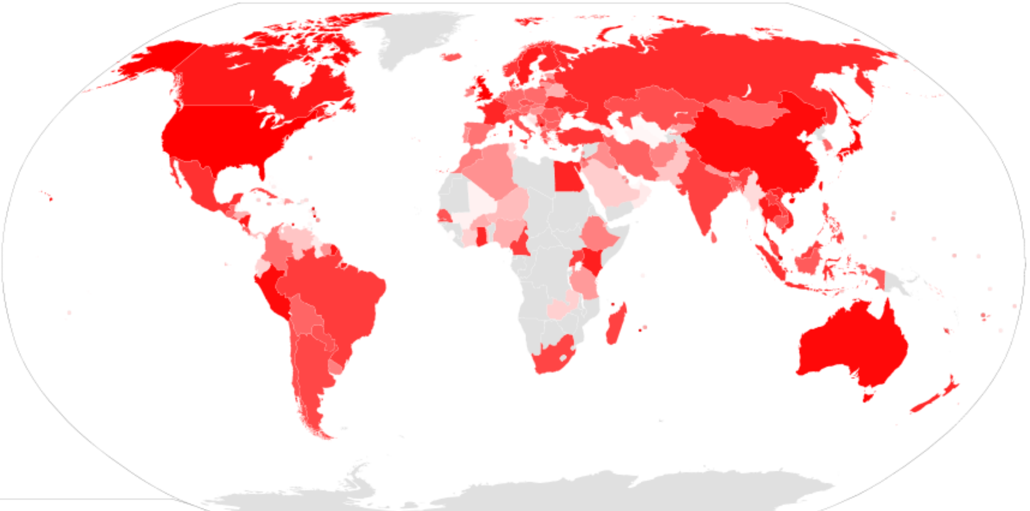


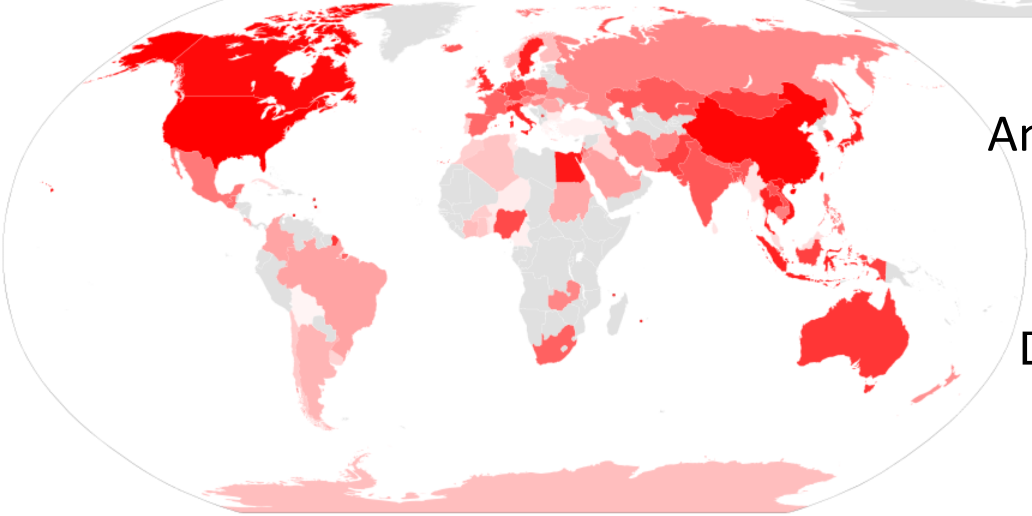
Geographical representativeness

(Hemispheres, Countries, Regions)

(282,481 viruses / 1,175,910 sequences; 9th Aug 2019)

Human-derived influenza virus sequences





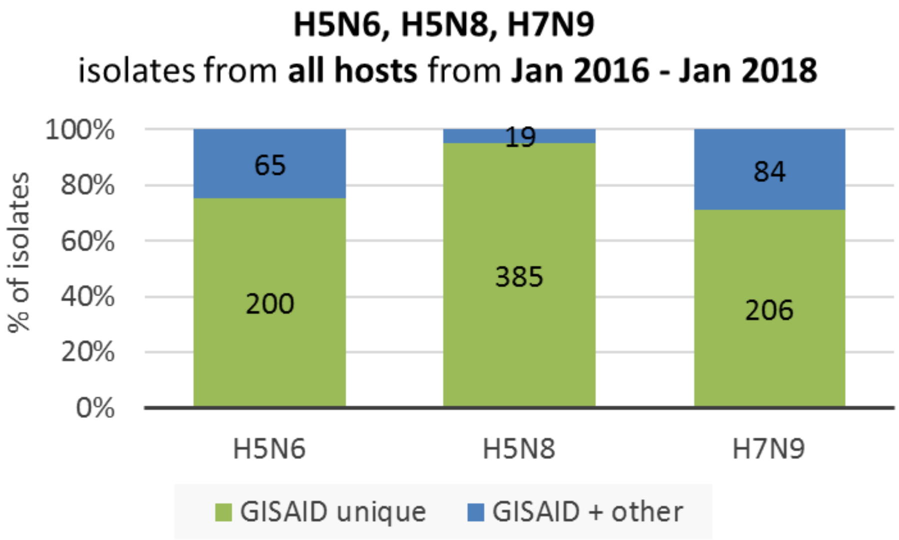
Animal-derived influenza virus sequences

Data in GISAID from >1,200 labs worldwide

Countries ranked by number of HA sequences in GISAID, colored by rank percentile from red (most) to white (least), gray (none)

(Analyses compiled by J. Büch (MPII, Germany) & S. Maurer-Stroh (A*STAR BII, Singapore)

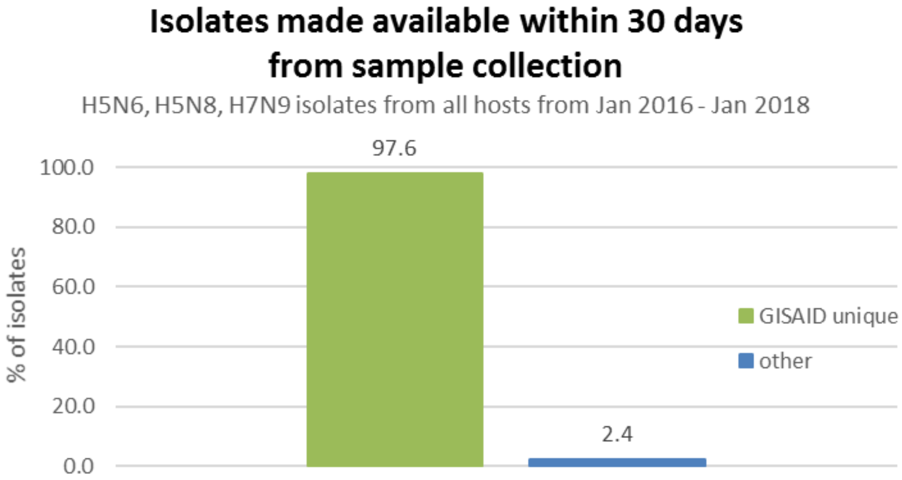
Rapid sharing of new avian influenza viruses with pandemic potential via GISAID



H5N6, H5N8, H7N9
isolates from **all hosts** from **Jan 2016 - Jan 2018**

The majority of isolates from new avian influenza subtypes with pandemic potential are **unique to GISAID.**

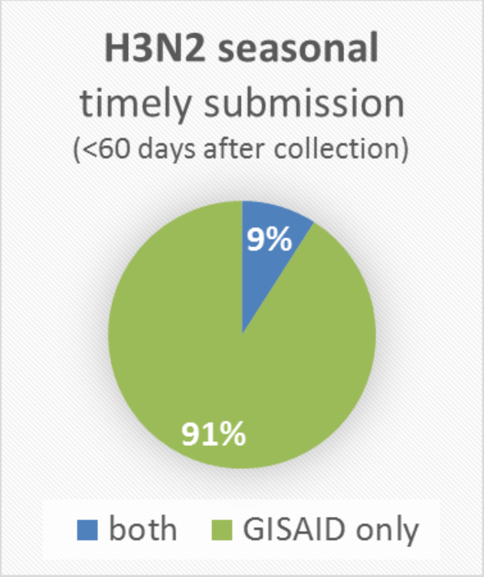
Timeliness:
98% of the strains submitted within 30 days from sample collection are **unique to GISAID**

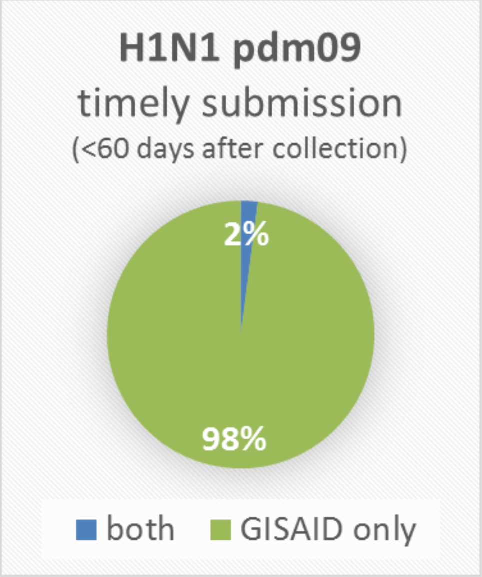


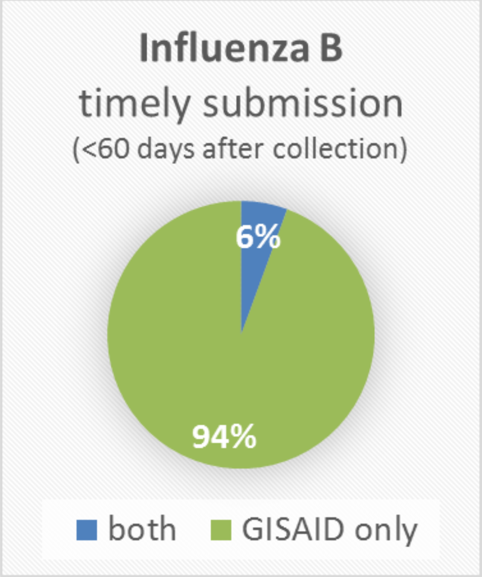
Isolates made available within 30 days from sample collection
H5N6, H5N8, H7N9 isolates from all hosts from Jan 2016 - Jan 2018

Timely submission of data to GISAID - human seasonal viruses

GISAID vs public-domain


H3N2 seasonal
timely submission
(<60 days after collection)


H1N1 pdm09
timely submission
(<60 days after collection)


Influenza B
timely submission
(<60 days after collection)

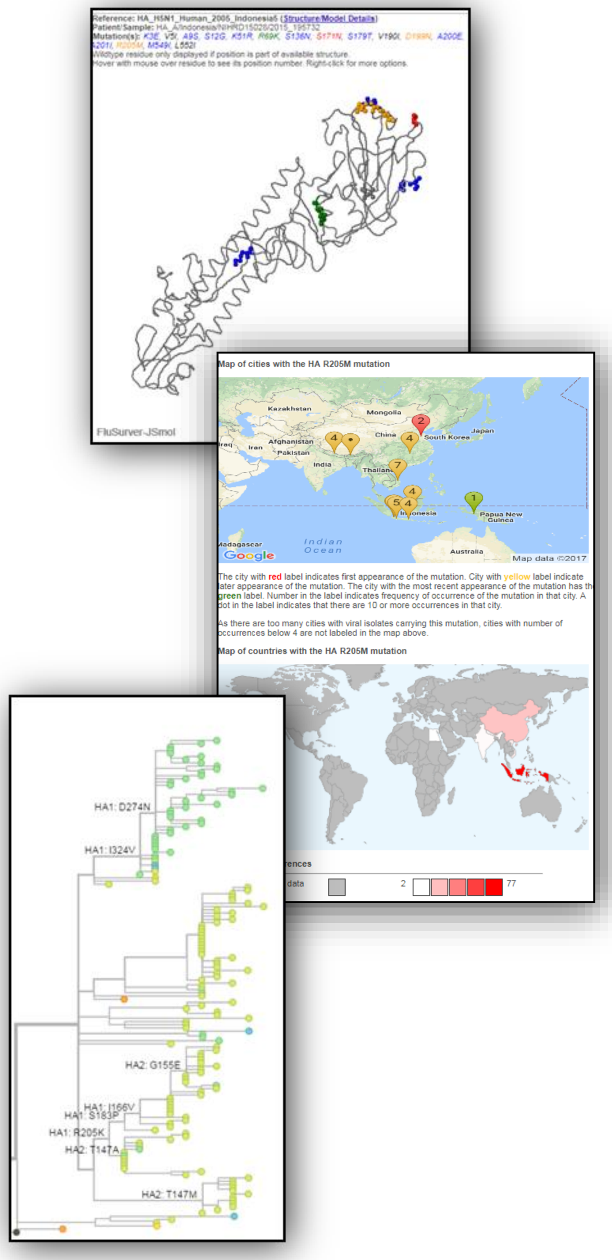
both … public-domain and GISAID

Proportion of unique sequence information in GISAID

Near real time data analysis

FluSurver:developed at the BII A*STAR, Singapore, assists the identification, analysis and interpretation of mutations in influenza sequences, providing mutation frequencies automatically kept up to date with the latest GISAID data.

Annotated Tree Tool: developed at the University of Basel, displays phylogenetic trees, along with alignments of nucleotide and amino acid sequences, showing the emergence of new clades in a temporal & geographical context



Reference: HA_H5N1_Human_2005_Indonesia5 (Structure/Model Details)
Patient/Sample: HA_A/Indonesia/NIHRD15026/2015_195732
Mutation(s): K3E, V5I, A9S, S12G, K51R, R69K, S136N, S171N, S179T, V190I, D199N, A200E, A201I, R205M, M549K, L552I
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.

Map of cities with the HA R205M 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 4 are not labeled in the map above.

Map of countries with the HA R205M mutation

Projects

- Global Server Resilience Strategy
- Expansion of Tools and Next Generation Sequencing
- Access via commercial lab applications
- Capacity building through educational program via GISAID’s series of workshops, webinars and seminars
- Realization of GISAID scientific retreat and school
- Application of GISAID sharing mechanism to other pathogens

  - *European Commission PREDEMICS*

Acknowledgements

GISAID

Database Technical Group

Bioinformatics Institute
A*STAR

CDC
Centers for Disease Control and Prevention

The Francis Crick Institute

mpi
max planck institut informatik

National Centre for Infectious Diseases

hosted by the Federal Republic of Germany

GISRS
GLOBAL INFLUENZA SURVEILLANCE & RESPONSE SYSTEM
Uniting the world in the fight against influenza

WHO Collaborating Centre for Reference and Research on Influenza
VIDRL

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The Melbourne WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Government Department of Health.

Searching and downloading data using GISAID EpiFlu™

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Introduction to GISAID EpiFlu™

Settings

- Customising settings to view search results

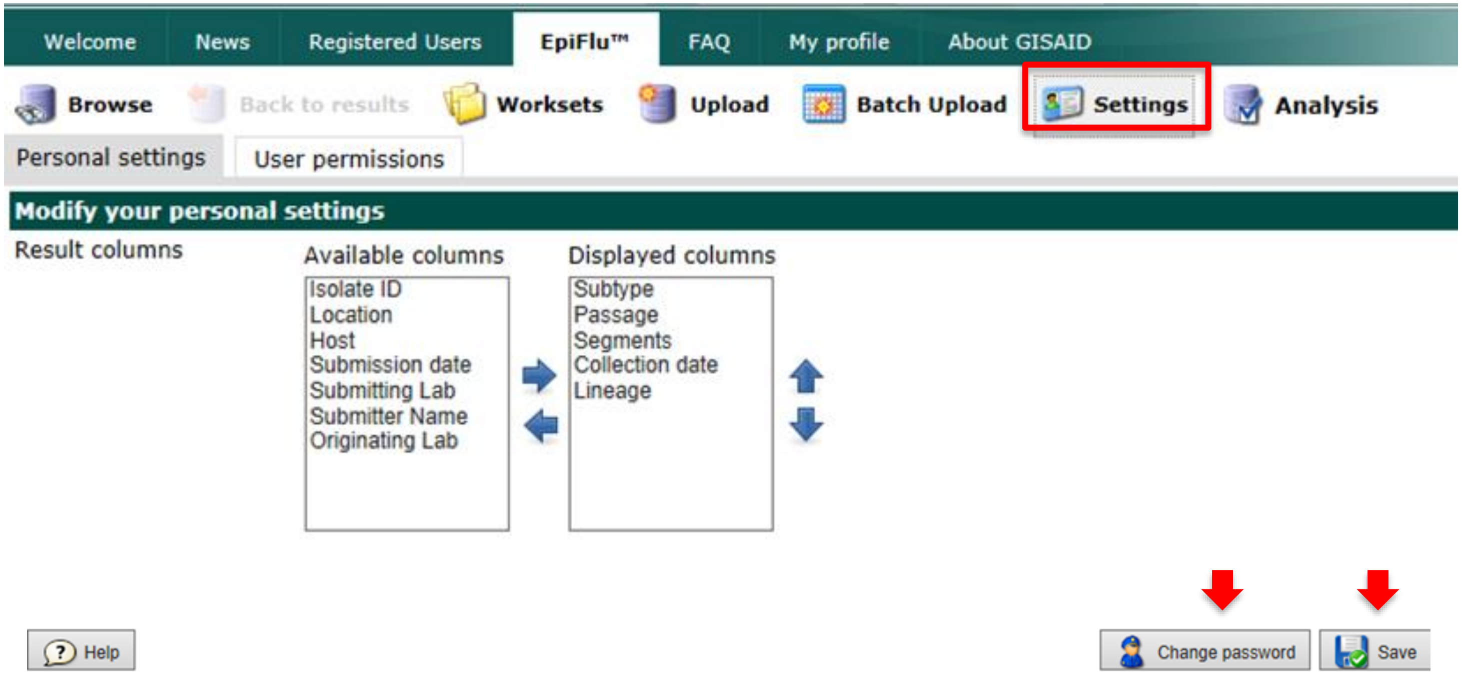
Searching for isolates

- Selecting database category to search
- Using the ‘Search Patterns’ field
- Searching by location, subtype, host
- Searching using Collection date or Submission date
- Selecting genes of interest
- Searching submitted to GISAID only or all siolates

Downloading data

- Setting fast headers
- Downloading protein or DNA sequences
- Downloading meta-data
- Downloading Acknowledgement Tables for publications

Customise Settings

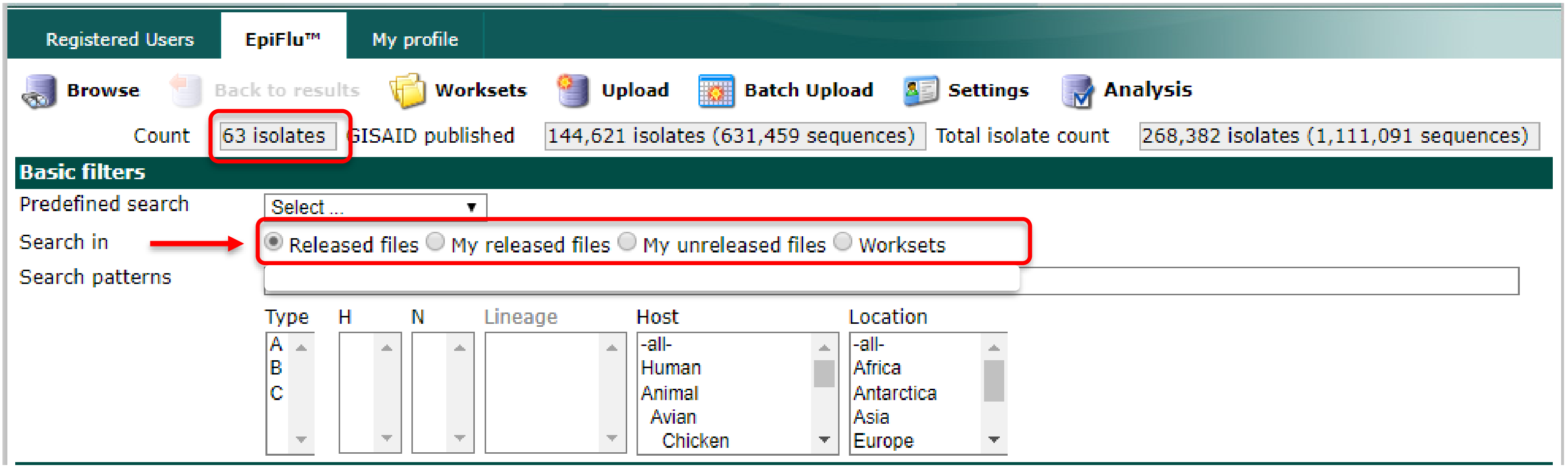


Modify your personal settings

Result columns

Available columns	Displayed columns
Isolate ID	Subtype
Location	Passage
Host	Segments
Submission date	Collection date
Submitting Lab	Lineage
Submitter Name	
Originating Lab	

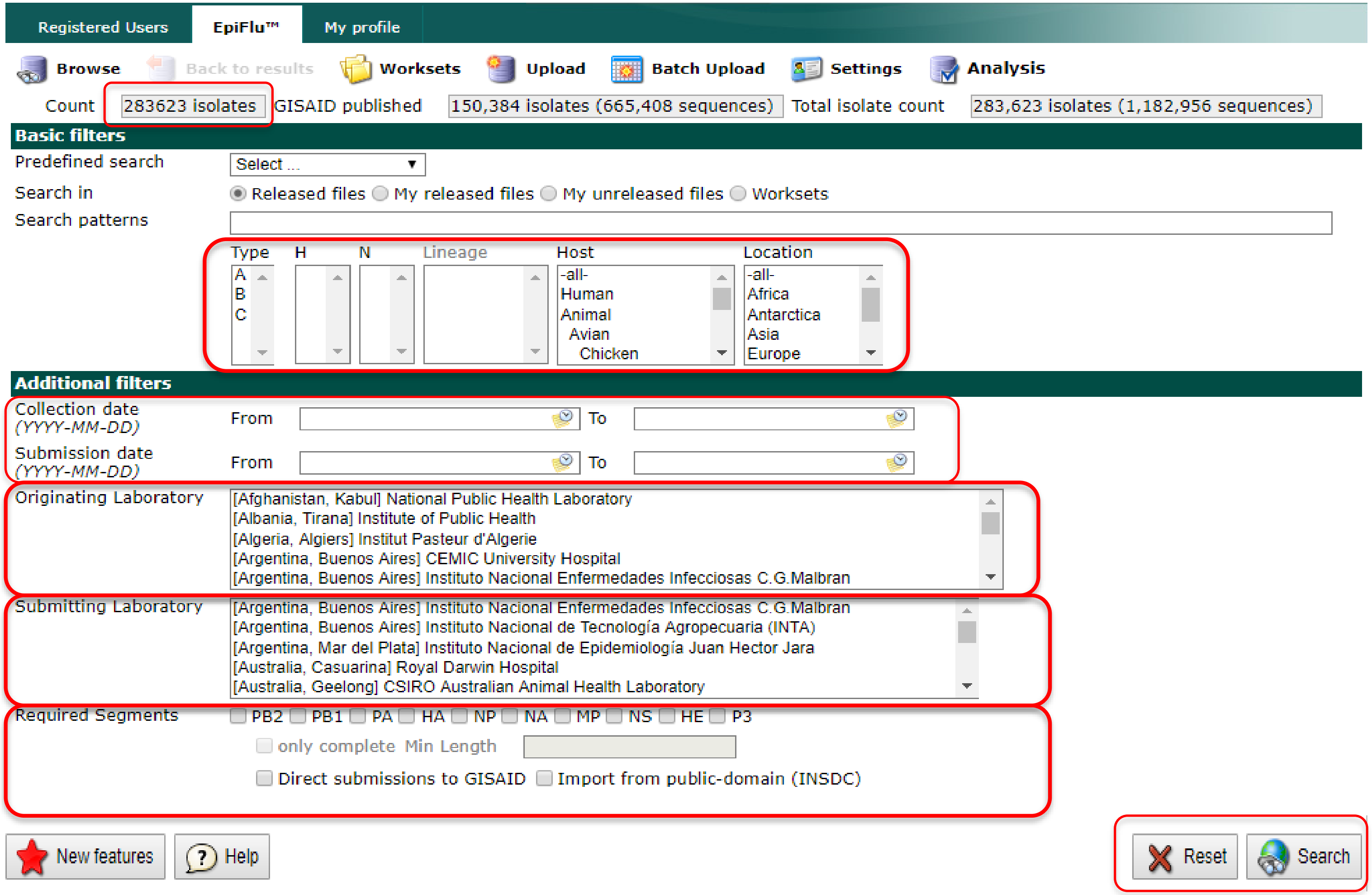
Database Selection & Search Patterns



Count: 63 isolates
GISAID published: 144,621 isolates (631,459 sequences)
Total isolate count: 268,382 isolates (1,111,091 sequences)
Predefined search: Select ...
Search in: ● Released files ○ My released files ○ My unreleased files ○ Worksets

Multiple subtypes can be searched for at the same time
Isolate name must be included in quotations ie: “ A/Brisbane/02 2018”
Wild cards can be used if searching for sequential isolates with a similar name
i.e A/Hong Kong/2670/2019 to A/Hong Kong/2679/2019 to search type in
“A/Hong Kong/26%%/2019

Available Search Parameters



Registered Users | EpiFlu™ | My profile

Browse | Back to results | Worksets | Upload | Batch Upload | Settings | Analysis

Count: 283623 isolates | GISAID published: 150,384 isolates (665,408 sequences) | Total isolate count: 283,623 isolates (1,182,956 sequences)

Basic filters

Predefined search: Select ... ▼

Search in: ● Released files ○ My released files ○ My unreleased files ○ Worksets

Search patterns:

Type	H	N	Lineage	Host	Location
A B C				-all- Human Animal Avian Chicken	-all- Africa Antarctica Asia Europe

Additional filters

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

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

Originating Laboratory:
- [Afghanistan, Kabul] National Public Health 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

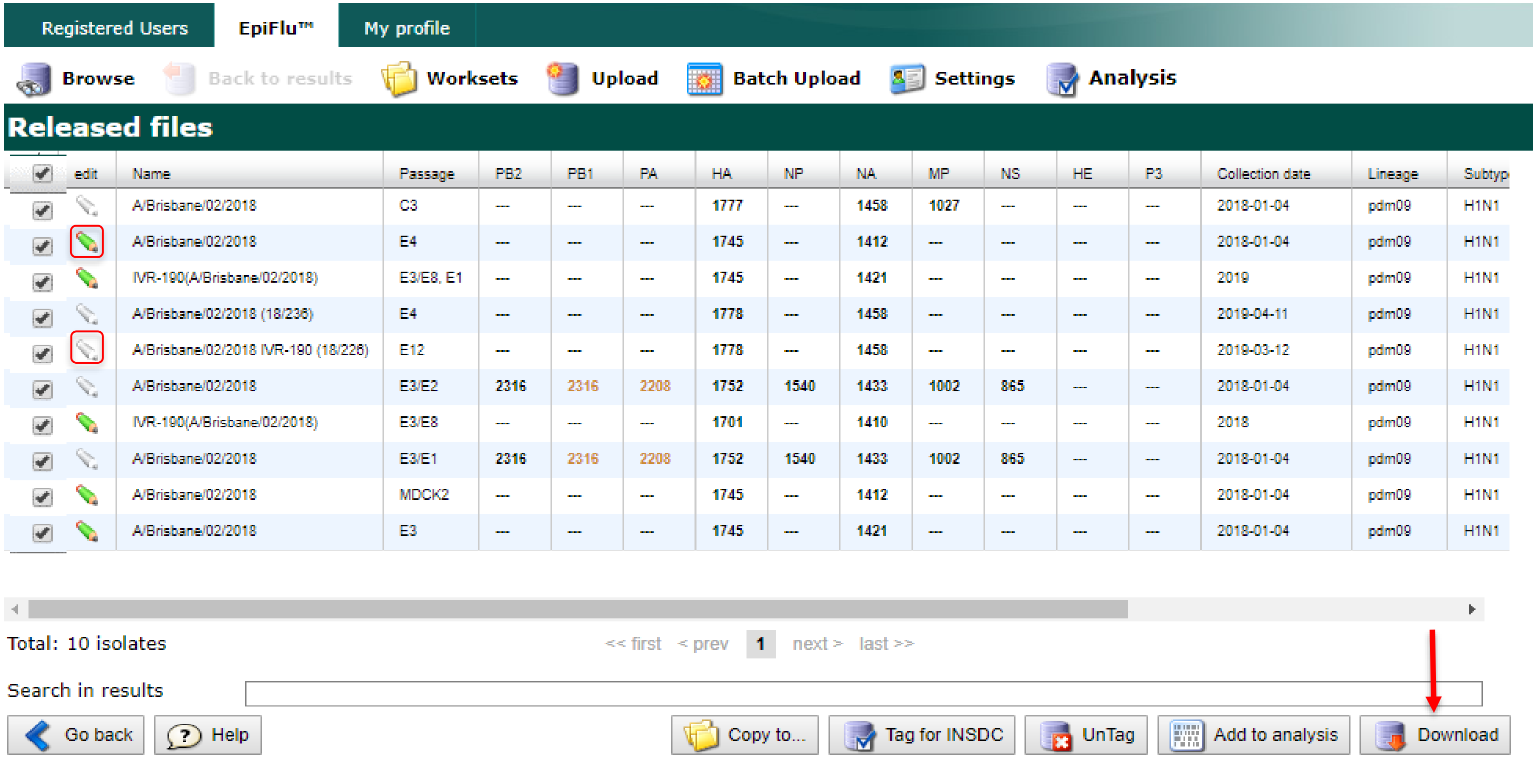
Submitting Laboratory:
- [Argentina, Buenos Aires] Instituto Nacional Enfermedades Infecciosas C.G.Malbran
- [Argentina, Buenos Aires] Instituto Nacional de Tecnología Agropecuaria (INTA)
- [Argentina, Mar del Plata] Instituto Nacional de Epidemiología Juan Hector Jara
- [Australia, Casuarina] Royal 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)

Search Results



Released files

☑	edit	Name	Passage	PB2	PB1	PA	HA	NP	NA	MP	NS	HE	P3	Collection date	Lineage	Subtyp
☑	✎	A/Brisbane/02/2018	C3	---	---	---	1777	---	1458	1027	---	---	---	2018-01-04	pdm09	H1N1
☑	✎	A/Brisbane/02/2018	E4	---	---	---	1745	---	1412	---	---	---	---	2018-01-04	pdm09	H1N1
☑	✎	IVR-190(A/Brisbane/02/2018)	E3/E8, E1	---	---	---	1745	---	1421	---	---	---	---	2019	pdm09	H1N1
☑	✎	A/Brisbane/02/2018 (18/236)	E4	---	---	---	1778	---	1458	---	---	---	---	2019-04-11	pdm09	H1N1
☑	✎	A/Brisbane/02/2018 IVR-190 (18/226)	E12	---	---	---	1778	---	1458	---	---	---	---	2019-03-12	pdm09	H1N1
☑	✎	A/Brisbane/02/2018	E3/E2	2316	2316	2208	1752	1540	1433	1002	865	---	---	2018-01-04	pdm09	H1N1
☑	✎	IVR-190(A/Brisbane/02/2018)	E3/E8	---	---	---	1701	---	1410	---	---	---	---	2018	pdm09	H1N1
☑	✎	A/Brisbane/02/2018	E3/E1	2316	2316	2208	1752	1540	1433	1002	865	---	---	2018-01-04	pdm09	H1N1
☑	✎	A/Brisbane/02/2018	MDCK2	---	---	---	1745	---	1412	---	---	---	---	2018-01-04	pdm09	H1N1
☑	✎	A/Brisbane/02/2018	E3	---	---	---	1745	---	1421	---	---	---	---	2018-01-04	pdm09	H1N1

Total: 10 isolates

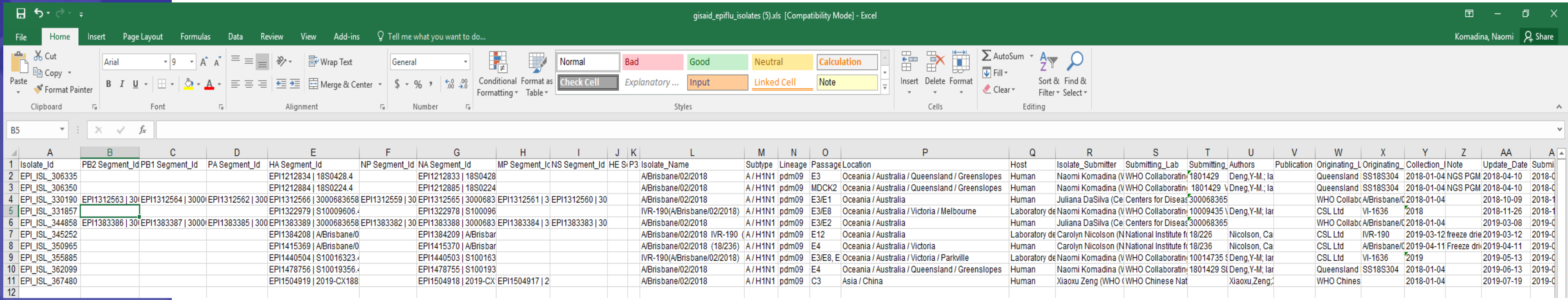
Download

10 isolates selected

Format
- ● Isolates as XLS (virus metadata only)
- ○ Sequences (DNA) as FASTA
- ○ Sequences (proteins) as FASTA
- ○ Acknowledgment table

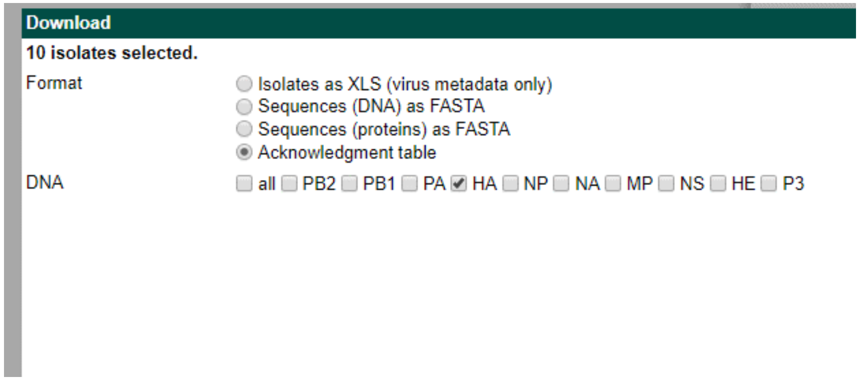
Date format: YYYY-MM-DD (2009-02-28) ▾

Dowloading Meta Data & Acknowledgement Tables



	A	B	C	D	E	F	G	H	I	J	K	L
1	Isolate_Id	PB2 Segment_Id	PB1 Segment_Id	PA Segment_Id	HA Segment_Id	NP Segment_Id	NA Segment_Id	MP Segment_Id	NS Segment_Id	HE S	P3	Isolate_Name
2	EPI_ISL_306335				EPI1212834 | 18S0428.4		EPI1212833 | 18S0428					A/Brisbane/02/2018
3	EPI_ISL_306350				EPI1212884 | 18S0224.4		EPI1212885 | 18S0224					A/Brisbane/02/2018
4	EPI_ISL_330190	EPI1312563 | 30	EPI1312564 | 3000	EPI1312562 | 300	EPI1312566 | 3000683658	EPI1312559 | 30	EPI1312565 | 3000683	EPI1312561 | 3	EPI1312560 | 30			A/Brisbane/02/2018
5	EPI_ISL_331857				EPI1322979 | S10009606.		EPI1322978 | S100096					IVR-190(A/Brisbane/02/2018)
6	EPI_ISL_344858	EPI1383386 | 30	EPI1383387 | 3000	EPI1383385 | 300	EPI1383389 | 3000683658	EPI1383382 | 30	EPI1383388 | 3000683	EPI1383384 | 3	EPI1383383 | 30			A/Brisbane/02/2018
7	EPI_ISL_345252				EPI1384208 | A/Brisbane/0		EPI1384209 | A/Brisbar					A/Brisbane/02/2018 IVR-190 (
8	EPI_ISL_350965				EPI1415369 | A/Brisbane/0		EPI1415370 | A/Brisbar					A/Brisbane/02/2018 (18/236)
9	EPI_ISL_355885				EPI1440504 | S10016323.		EPI1440503 | S100163					IVR-190(A/Brisbane/02/2018)
10	EPI_ISL_362099				EPI1478756 | S10019356.		EPI1478755 | S100193					A/Brisbane/02/2018
11	EPI_ISL_367480				EPI1504919 | 2019-CX188		EPI1504918 | 2019-CX	EPI1504917 | 2				A/Brisbane/02/2018
12												

	A	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	A
1	Isolate_Id	Subtype	Lineage	Passage	Location	Host	Isolate_Submitter	Submitting_Lab	Submitting_	Authors	Publication	Originating_L	Originating_	Collection_I	Note	Update_Date	Submi
2	EPI_ISL_306335	A / H1N1	pdm09	E3	Oceania / Australia / Queensland / Greenslopes	Human	Naomi Komadina (V	WHO Collaborating	1801429	Deng,Y-M.; Ia		Queensland	SS18S304	2018-01-04	NGS PGM	2018-04-10	2018-0
3	EPI_ISL_306350	A / H1N1	pdm09	MDCK2	Oceania / Australia / Queensland / Greenslopes	Human	Naomi Komadina (V	WHO Collaborating	1801429 V	Dneg,Y-M.; Ia		Queensland	SS18S304	2018-01-04	NGS PGM	2018-04-10	2018-0
4	EPI_ISL_330190	A / H1N1	pdm09	E3/E1	Oceania / Australia	Human	Juliana DaSilva (Ce	Centers for Diseas	300068365			WHO Collabo	A/Brisbane/0	2018-01-04		2018-10-09	2018-1
5	EPI_ISL_331857	A / H1N1	pdm09	E3/E8	Oceania / Australia / Victoria / Melbourne	Laboratory de	Naomi Komadina (V	WHO Collaborating	10009435 V	Deng,Y-M; Iar		CSL Ltd	VI-1636	2018		2018-11-26	2018-1
6	EPI_ISL_344858	A / H1N1	pdm09	E3/E2	Oceania / Australia	Human	Juliana DaSilva (Ce	Centers for Diseas	300068365			WHO Collabo	A/Brisbane/0	2018-01-04		2019-03-08	2019-0
7	EPI_ISL_345252	A / H1N1	pdm09	E12	Oceania / Australia	Laboratory de	Carolyn Nicolson (N	National Institute fo	18/226	Nicolson, Ca		CSL Ltd	IVR-190	2019-03-12	freeze drie	2019-03-12	2019-0
8	EPI_ISL_350965	A / H1N1	pdm09	E4	Oceania / Australia / Victoria	Human	Carolyn Nicolson (N	National Institute fo	18/236	Nicolson, Ca		CSL Ltd	A/Brisbane/0	2019-04-11	Freeze dri	2019-04-11	2019-0
9	EPI_ISL_355885	A / H1N1	pdm09	E3/E8, E	Oceania / Australia / Victoria / Parkville	Laboratory de	Naomi Komadina (V	WHO Collaborating	10014735 S	Deng,Y-M; Iar		CSL Ltd	VI-1636	2019		2019-05-13	2019-0
10	EPI_ISL_362099	A / H1N1	pdm09	E4	Oceania / Australia / Queensland / Greenslopes	Human	Naomi Komadina (V	WHO Collaborating	1801429 SI	Deng,Y-M; Iar		Queensland	SS18S304	2018-01-04		2019-06-13	2019-0
11	EPI_ISL_367480	A / H1N1	pdm09	C3	Asia / China	Human	Xiaoxu Zeng (WHO (	WHO Chinese Nat		Xiaoxu,Zeng;		WHO Chines		2018-01-04		2019-07-19	2019-0
12																	



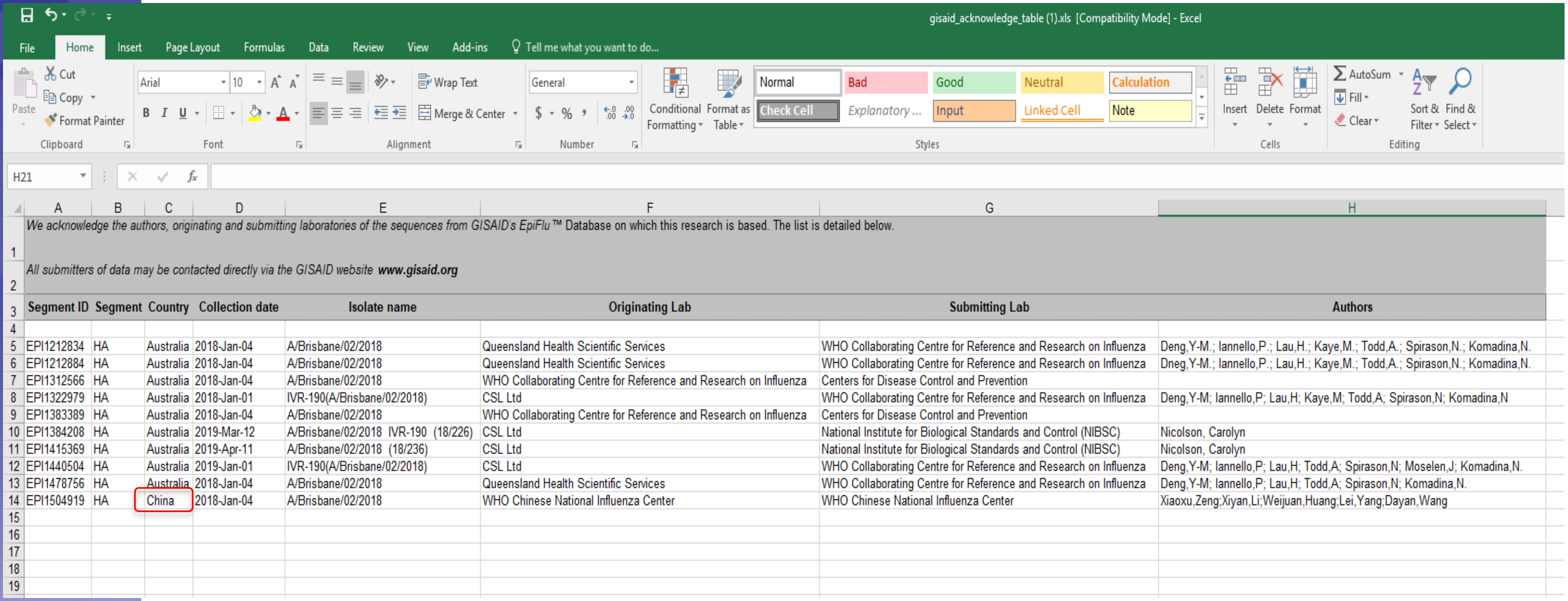
Download

10 isolates selected.

Format
○ Isolates as XLS (virus metadata only)
○ Sequences (DNA) as FASTA
○ Sequences (proteins) as FASTA
● Acknowledgment table

DNA ☐ all ☐ PB2 ☐ PB1 ☐ PA ☑ HA ☐ NP ☐ NA ☐ MP ☐ NS ☐ HE ☐ P3

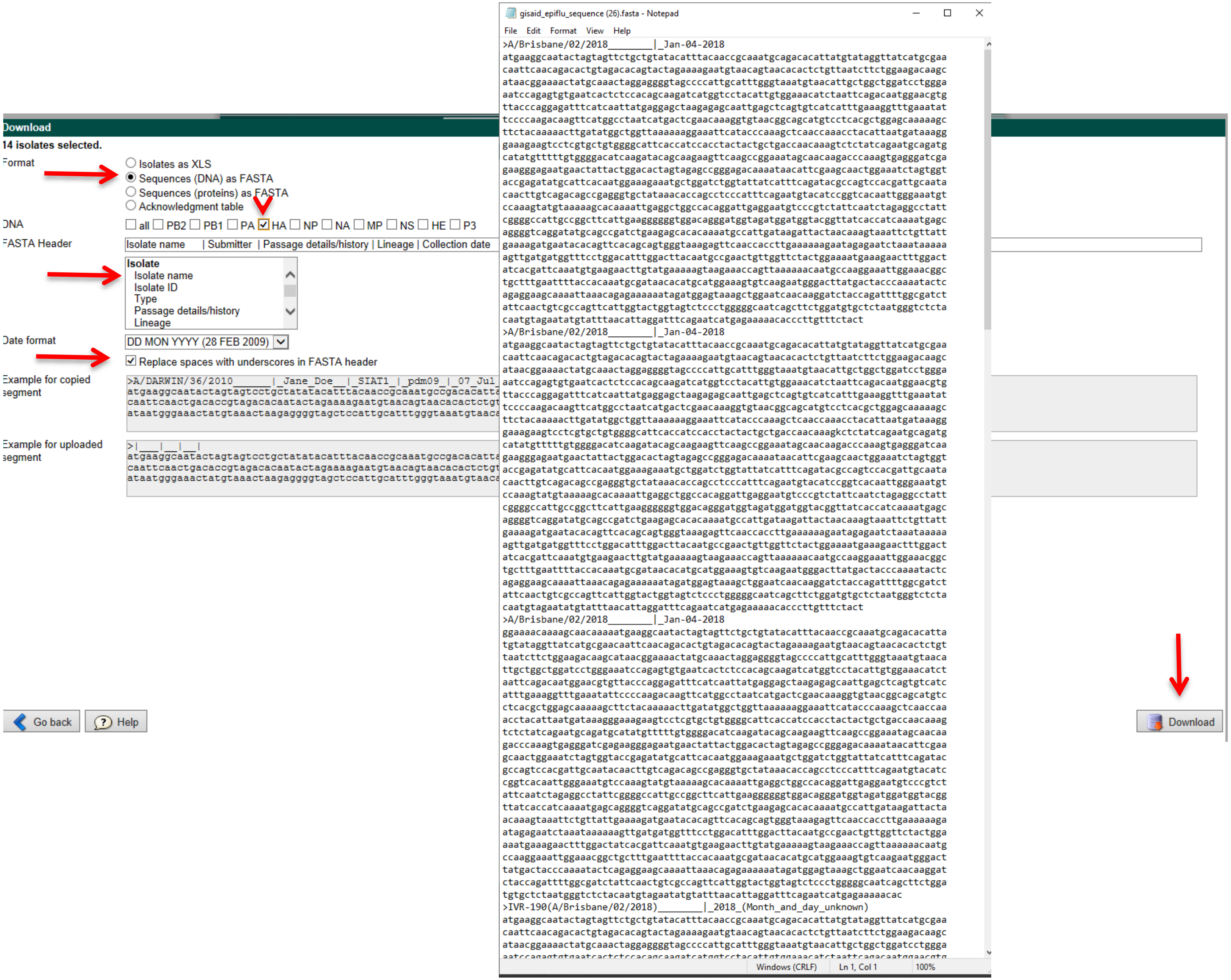
Acknowledgement Table



We acknowledge the authors, originating and submitting laboratories of the sequences from GISAID's EpiFlu™ Database on which this research is based. The list is detailed below.

All submitters of data may be contacted directly via the GISAID website ***www.gisaid.org***

Segment ID	Segment	Country	Collection date	Isolate name	Originating Lab	Submitting Lab	Authors
EPI1212834	HA	Australia	2018-Jan-04	A/Brisbane/02/2018	Queensland Health Scientific Services	WHO Collaborating Centre for Reference and Research on Influenza	Deng,Y-M.; Iannello,P.; Lau,H.; Kaye,M.; Todd,A.; Spirason,N.; Komadina,N.
EPI1212884	HA	Australia	2018-Jan-04	A/Brisbane/02/2018	Queensland Health Scientific Services	WHO Collaborating Centre for Reference and Research on Influenza	Dneg,Y-M.; Iannello,P.; Lau,H.; Kaye,M.; Todd,A.; Spirason,N.; Komadina,N.
EPI1312566	HA	Australia	2018-Jan-04	A/Brisbane/02/2018	WHO Collaborating Centre for Reference and Research on Influenza	Centers for Disease Control and Prevention	
EPI1322979	HA	Australia	2018-Jan-01	IVR-190(A/Brisbane/02/2018)	CSL Ltd	WHO Collaborating Centre for Reference and Research on Influenza	Deng,Y-M; Iannello,P; Lau,H; Kaye,M; Todd,A; Spirason,N; Komadina,N
EPI1383389	HA	Australia	2018-Jan-04	A/Brisbane/02/2018	WHO Collaborating Centre for Reference and Research on Influenza	Centers for Disease Control and Prevention	
EPI1384208	HA	Australia	2019-Mar-12	A/Brisbane/02/2018 IVR-190 (18/226)	CSL Ltd	National Institute for Biological Standards and Control (NIBSC)	Nicolson, Carolyn
EPI1415369	HA	Australia	2019-Apr-11	A/Brisbane/02/2018 (18/236)	CSL Ltd	National Institute for Biological Standards and Control (NIBSC)	Nicolson, Carolyn
EPI1440504	HA	Australia	2019-Jan-01	IVR-190(A/Brisbane/02/2018)	CSL Ltd	WHO Collaborating Centre for Reference and Research on Influenza	Deng,Y-M; Iannello,P; Lau,H; Todd,A; Spirason,N; Moselen,J; Komadina,N.
EPI1478756	HA	Australia	2018-Jan-04	A/Brisbane/02/2018	Queensland Health Scientific Services	WHO Collaborating Centre for Reference and Research on Influenza	Deng,Y-M; Iannello,P; Lau,H; Todd,A; Spirason,N; Komadina,N.
EPI1504919	HA	China	2018-Jan-04	A/Brisbane/02/2018	WHO Chinese National Influenza Center	WHO Chinese National Influenza Center	Xiaoxu,Zeng;Xiyan,Li;Weijuan,Huang;Lei,Yang;Dayan,Wang



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14 isolates selected.

Format
○ Isolates as XLS
● Sequences (DNA) as FASTA
○ Sequences (proteins) as FASTA
○ Acknowledgment table

DNA ☐ all ☐ PB2 ☐ PB1 ☐ PA ☑ HA ☐ NP ☐ NA ☐ MP ☐ NS ☐ HE ☐ P3

FASTA Header: Isolate name | Submitter | Passage details/history | Lineage | Collection date

Isolate
Isolate name
Isolate ID
Type
Passage details/history
Lineage

Date format: DD MON YYYY (28 FEB 2009)

☑ Replace spaces with underscores in FASTA header

Example for copied segment

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Example for uploaded segment

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```

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A*STAR

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and Agriculture

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informatik

WHO Collaborating Centre
for Reference and
Research on Influenza
VIDRL

Doherty
Institute

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