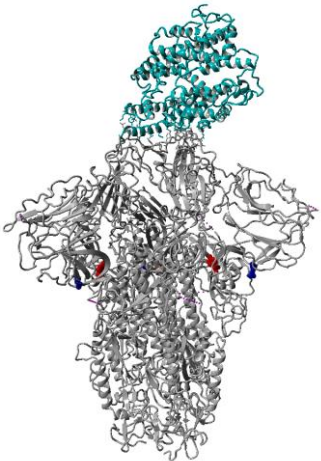# Real-time Surveillance of Pathogen Evolution and Global Transmission

Dr. Sebastian Maurer-Stroh, ED (D) BII

Bioinformatics Institute, A*STAR
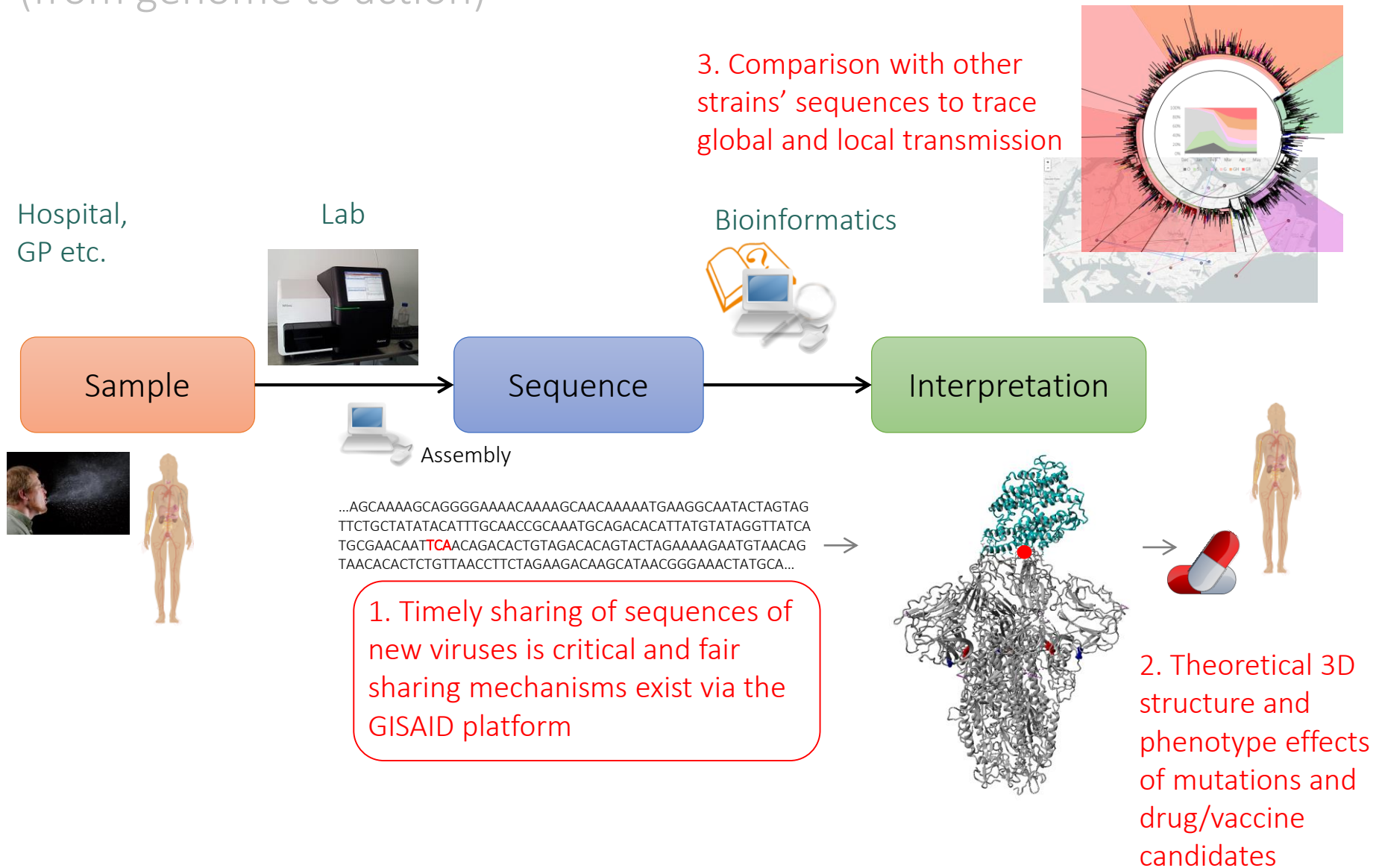
ID Labs, A*STAR

GISAID

Real-time Surveillance of Pathogen Evolution and Global Transmission
(from genome to action)

3. Comparison with other strains' sequences to trace global and local transmission

Hospital, GP etc.

Lab

Bioinformatics

Sample → Sequence → Interpretation

Assembly

...AGCAAAAGCAGGGGAAAACAAAAGCAACAAAAATGAAGGCAATACTAGTAG
TTCTGCTATATACATTTGCAACCGCAAATGCAGACACATTATGTATAGGTTATCA
TGCGAACAATTCAACAGACACTGTAGACACAGTACTAGAAAAGAATGTAACAG
TAACACACTCTGTTAACCTTCTAGAAGACAAGCATAACGGGAAACTATGCA...

1. Timely sharing of sequences of new viruses is critical and fair sharing mechanisms exist via the GISAID platform

2. Theoretical 3D structure and phenotype effects of mutations and drug/vaccine candidates

Real-time data sharing is not achieved by governmental Regulations
... it is incentivized by the confidence in transparent sharing mechanisms
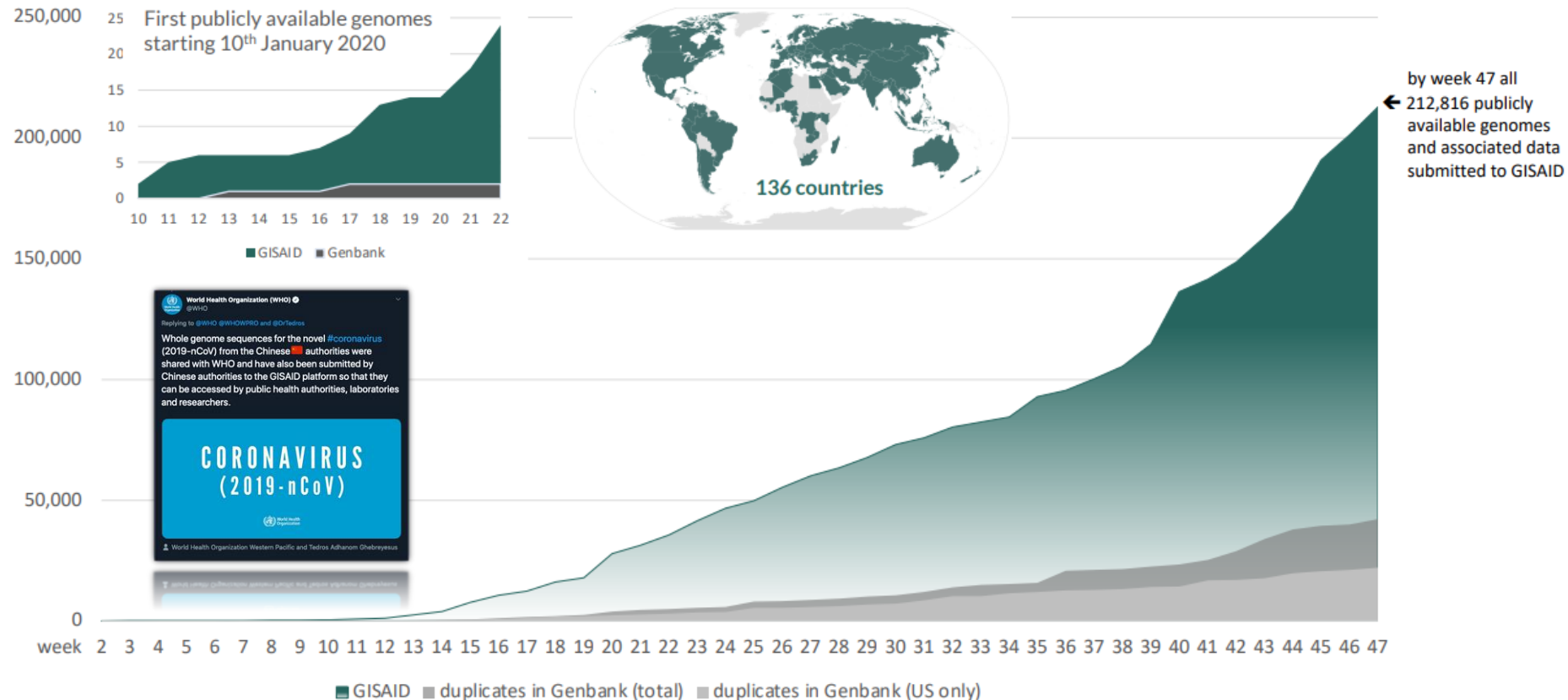
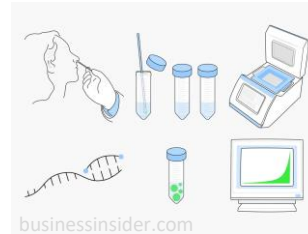
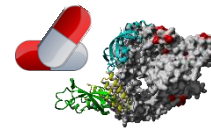"GISAID was a well-oiled machine when the Coronavirus hit"
BBC and PRI the World
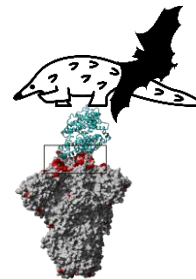
Genome use for first response

- ## How can you detect it?

Enabling first PCR and antigen-based diagnostic kits

- How can you treat it?

Repurposed and new drugs, e.g. Remdesivir, mAbs, Vaccine candidates
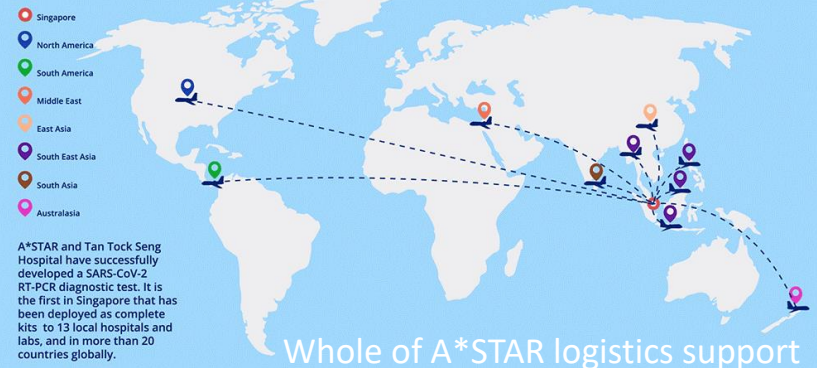
- Where did it come from?

Likely animal source, understanding animal to human jump

GISAID

Team Fortitude – an ongoing collaboration from SARS to flu to MERS to ZIKA to COVID
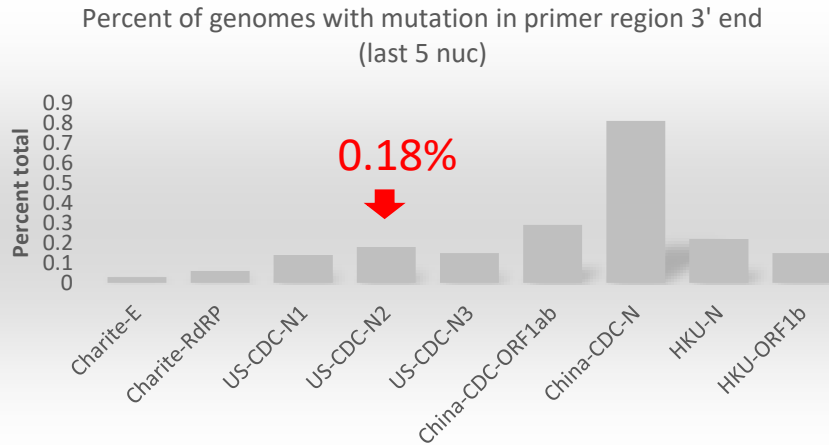

Whole of A*STAR logistics support

Real-time Surveillance of Primer Diagnostic Kit Mutations

Percent of genomes with mutation in primer region 3' end (last 5 nuc)

Aug 7th — 0.18%

Aug 21st — 1.01%
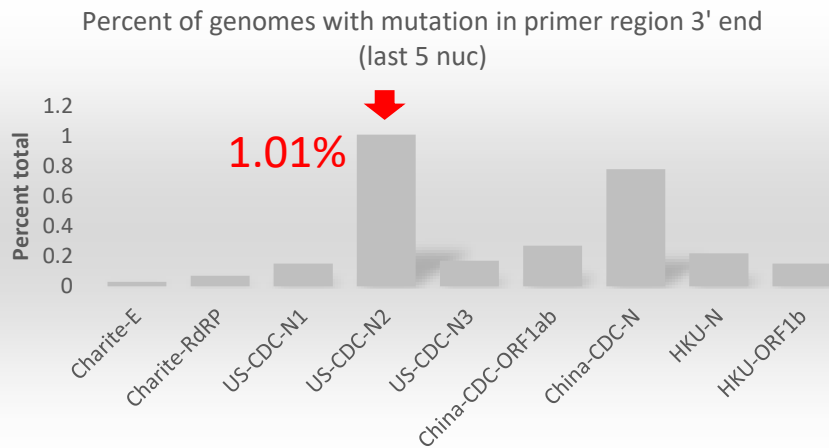
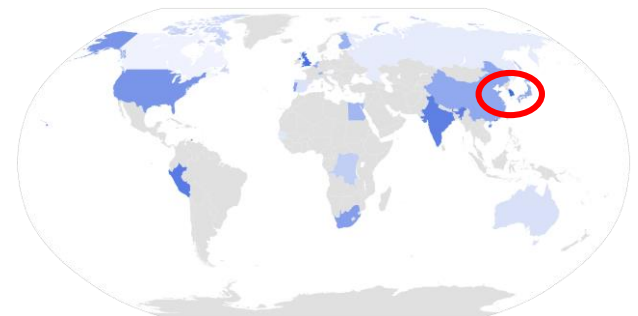## PCR-based (RNA amplification)

Target regions need to be specific (not conserved with other viruses) but also evolutionary stable
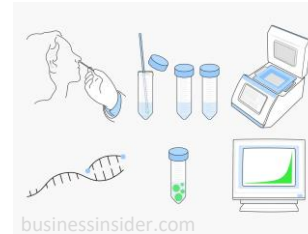
Mutations can occur and primers/probes may need to be updated

by BII/GIS, A*STAR Singapore

Genome use for first response

GISAID

- How can you detect it?

Enabling first PCR and antigen-based diagnostic kits

- How can you treat it?
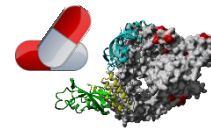
Repurposed and new drugs, e.g. Remdesivir, mAbs, Vaccine candidates

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

F.P. Polack, et al.   DOI: 10.1056/NEJMoa2034577

CLINICAL PROBLEM

Safe and effective vaccines to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 are urgently needed. No vaccines that protect against betacoronaviruses are currently available, and mRNA-based vaccines have not been widely tested.

Lipid nanoparticle — mRNA

Spike protein (prefusion conformation)

CELL
Ribosome
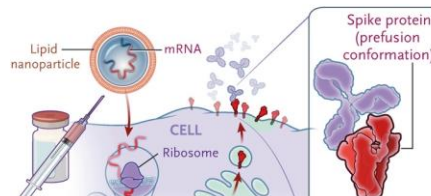
The Food and Drug Administration (FDA) announced Dec 11th it has issued an emergency use authorization (EUA) for the Pfizer-BioNTech COVID-19 vaccine, allowing shipments to begin and marking a significant milestone in the battle against the virus.

investment of resources. The development of BNT162b2 was initiated on January 10, 2020, when the SARS-CoV-2 genetic sequence was released by the Chinese Center for Disease Control and Prevention and disseminated globally by the GISAID (Global Initiative on Sharing All Influenza Data) initiative.

Genome use for first response
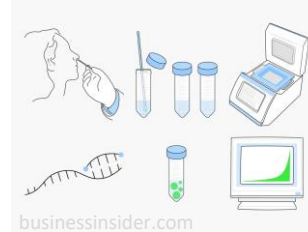
- How can you detect it?

Enabling first PCR and antigen-based diagnostic kits

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Repurposed and new drugs, e.g. Remdesivir, mAbs, Vaccine candidates

- **Where did it come from?**

Likely animal source, understanding animal to human jump

GISAID
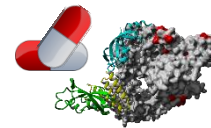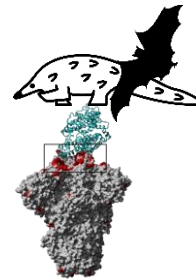
Genome can point to zoonotic source

Light Orange ... previous bat CoVs
Orange ... previous closest bat precursor (Yunnan 2013)
Red ... new bat CoVs (Yunnan 2019)
Light blue ... hCoV-19 2019-2020
Green ... pangolin CoV (Southern China 2019)
Blue ... SARS CoV
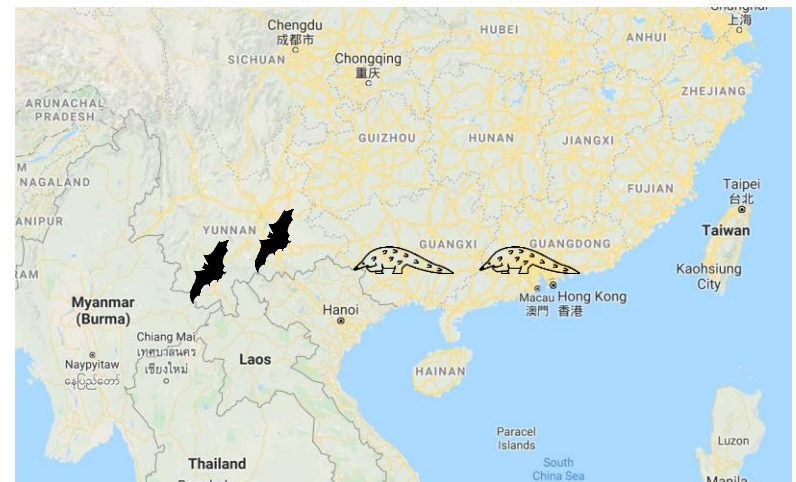
Southern China 2019: precursors in 2 species

by BII/GIS, A*STAR Singapore

How can a virus jump from animals to humans?
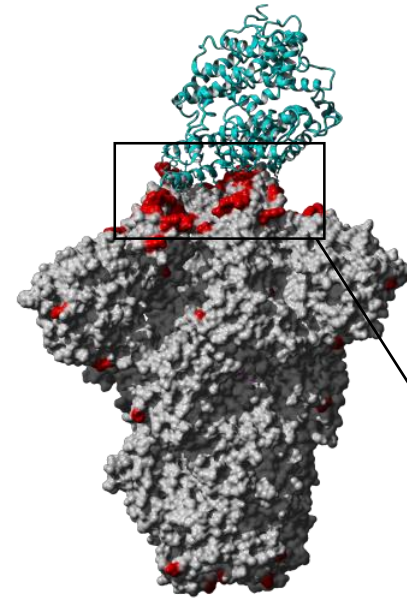
Cyan … ACE2 human host receptor
Gray … CoV spike glycoprotein
Red … mutations between bat precursor
RaTG13 vs human outbreak WIV04 CoV

bat RaTG13 vs hCoV-19

- Surface proteins are 98% identical

- Bat precursor differences in receptor
  binding interface indicative of changes
  that allowed host switch

by BII/GIS, A*STAR Singapore

GISAID

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TGCGAACAATTCAACAGACACTGTAGACACAGTACTAGAAAAGAATGTAACAG
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1. Timely sharing of sequences of new viruses is critical and fair sharing mechanisms exist via the GISAID platform

2. Theoretical 3D structure and phenotype effects of mutations and drug/vaccine candidates

From the **sequence** and **structure** we can partially deduce important **properties** of the virus

- Infect different hosts
- More or less severe
- Spread more easily
- Antigenic drift, drug resistance

Body   Organ/Tissue   Cell

Virion
Viral Particle

RNA

Primary Structure
Amino Acid Sequence

Met Asn Ile Phe Glu Met Leu Arg Ile Asp Glu Gly Leu Arg Leu Lys Ile Tyr Lys Asp

β-sheet

Secondary Structure
Regular Sub-Structures

α-helix

E119G
H275Y
T466I
E259K
S28G
I99V
D451N

Protein Tertiary Structure
3D Structure
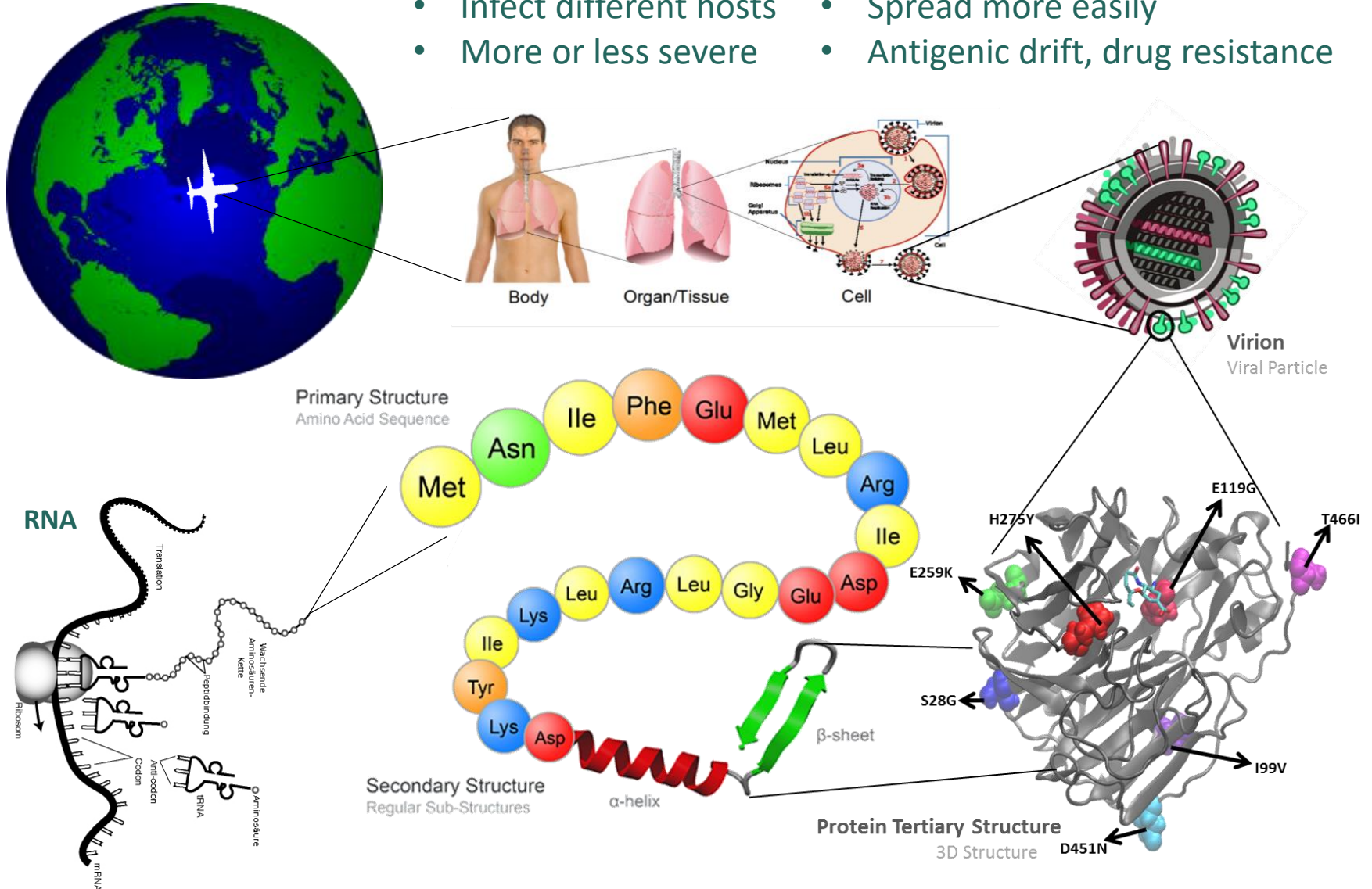
The virus is mutating into different strains and what does this mean?

All viruses naturally mutate resulting in many different but **highly similar variants** (also called **strains**) which most often do not cause any change in severity but this can be used to track movement of the virus. Virus mutations can also be seen as changes creating a barcode of a virus allowing its identification.

Strain = 1 virus barcode
Lineage = several related strains
Clade = many strains/lineages

License plate = Founder/marker mutations

Italy 1

USA 4

2.0
1.6

Engine size = Phenotypic mutations
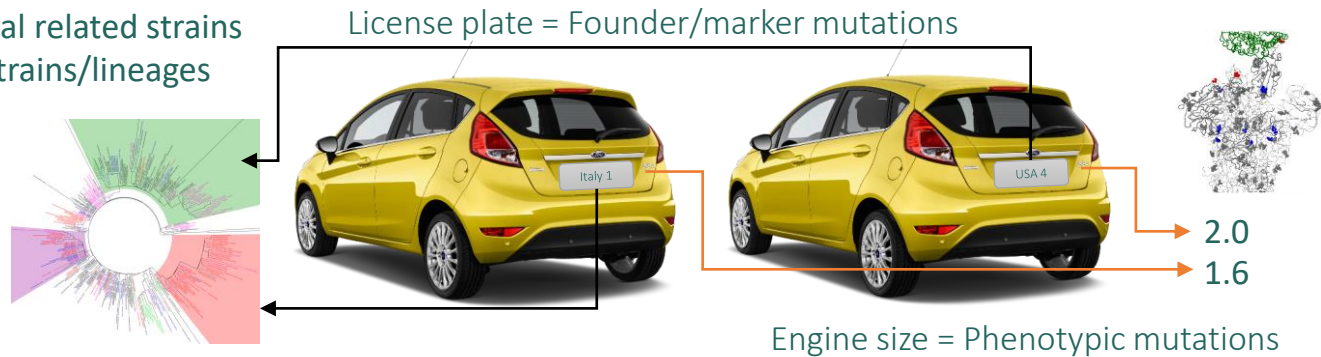
Mutant virus strains are highly similar and can be imagined like this:
- same car model, same car color, **different license plate = no change in severity** but can be used to track virus (clusters, imports, transmission)
- same car model, same car color, **different engine size = possible change in severity**

Estimated frequency:

>99.99%

<0.01%

So far no mutation linked to severity identified, S-D614G not linked to severity

CoVsurver:

New analysis tool released on GISAID developed by BII A*STAR

Capabilities:

Identification and interpretation of mutations including 3D structure and database with curated literature links for 166 mutation reports
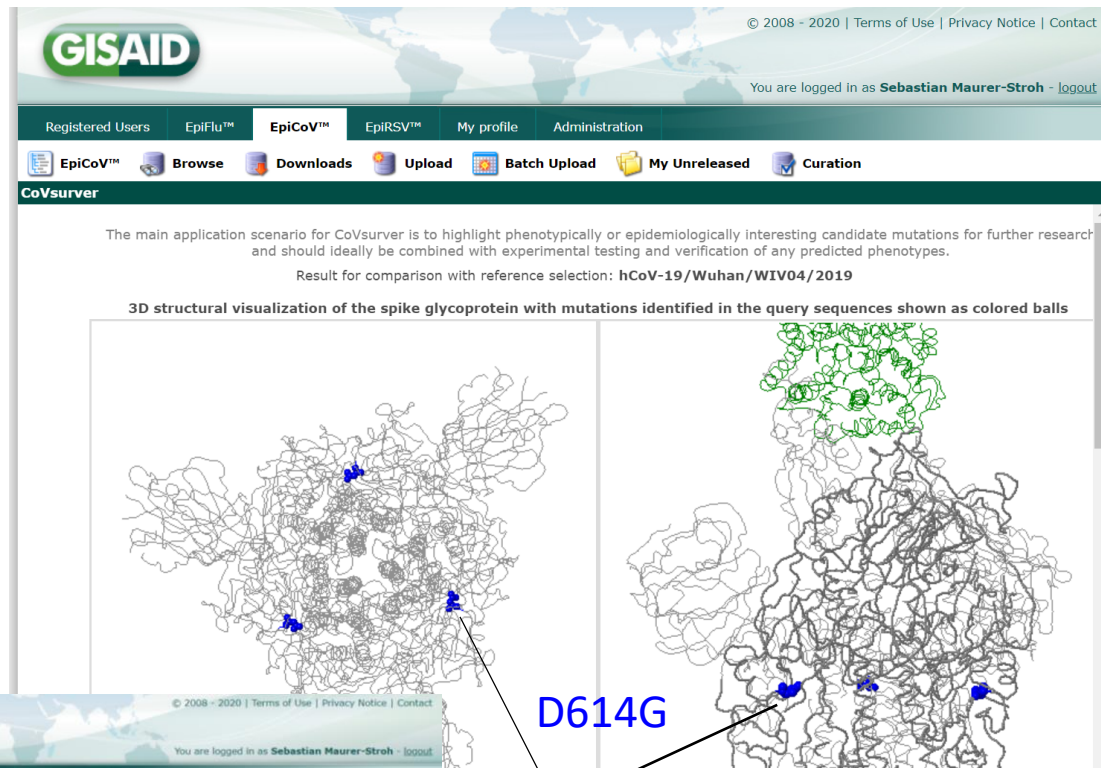
Example D614G:

- Structural position not near receptor binding site, not in RBD antigenic sites, **at oligomer interface (can indirectly affect stability of complex)**
- Phylogenetic distribution points to founder-like effect and is accompanied with multiple other mutations

D614G

Alternate numberings, Occurrence statistics, Literature links

and view in phylogenetic tree
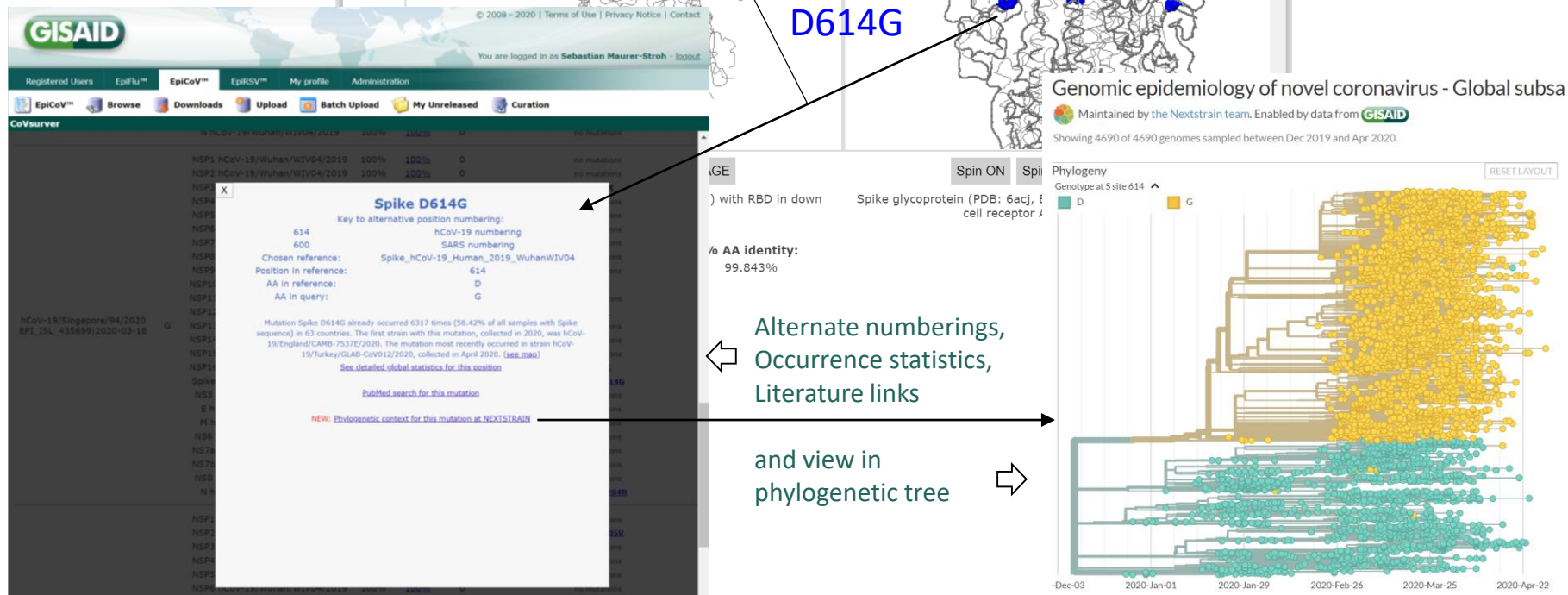
Spike-D614G: License plate or engine size mutation?

CoVsurver:
New analysis tool released on GISAID developed by BII A*STAR

Article

Cell

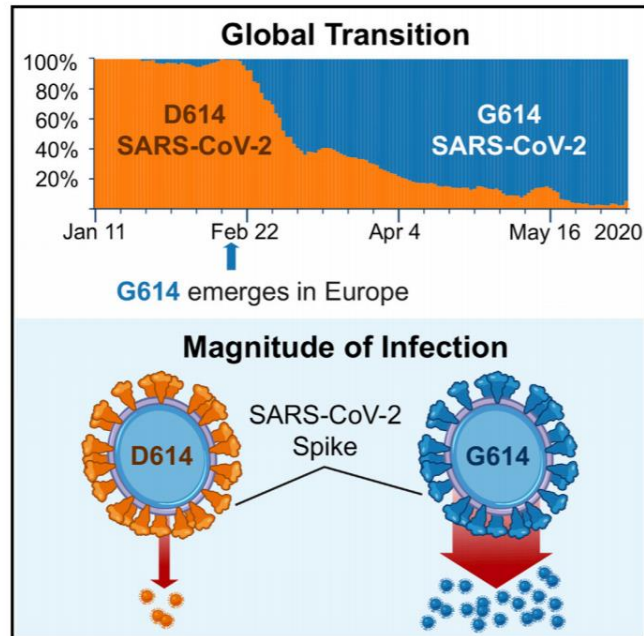**Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus**

Graphical Abstract

Authors

Bette Korber, Will M. Fischer, Sandrasegaram Gnanakaran, ..., Celia C. LaBranche, Erica O. Saphire, David C. Montefiori

Correspondence

btk@lanl.gov

In Brief

Korber et al. present evidence that there are now more SARS-CoV-2 viruses circulating in the human population globally that have the G614 form of the Spike protein versus the D614 form that was originally identified from the first human cases in Wuhan, China. Follow-up studies show that patients infected with G614 shed more viral nucleic acid compared with those with D614, and G614-bearing viruses show significantly higher infectious titers *in vitro* than their D614 counterparts.
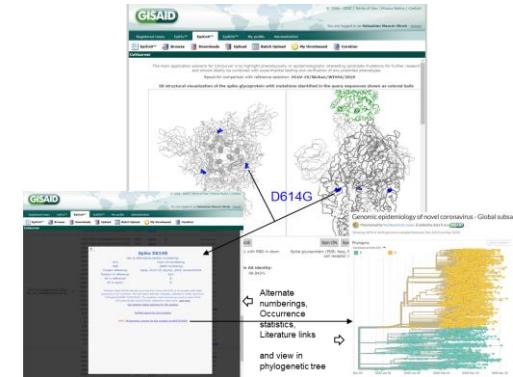
Evidence for/against founder effect (license plate):
- Variant present in 3+ major Chinese cities in Feb but did not cause big outbreak
- Europe where big increase occurred was not prepared to contain virus
- Spain is example where different virus was more successful (first import wins)
- Some regions where 614G outperformed the D variant (COG-UK paper)

Evidence for/against phenotype (engine size):
- Increased infectivity in cells (higher titres in vitro)
- Increased spike stability (other paper)
- Hamster transmission (other paper)
- No clinical correlation with severity (also confirmed in SG data)

Verdict: Probably a bit of both... effect on cell infectivity/titre plausible, increased transmissibility claim partially disputed, consensus that there is **no correlation with clinical severity**

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January: Early outbreak genomes showed very low diversity, only a handful of mutations over 30,000 bases

Nucleotide (base) differences among early outbreak strains

- Thailand: First full genomes outside of China were still identical to the Wuhan consensus

	WH-01	HB-01	WH-02	WH-03	WH-04	IVDC-HB-01	HB-05	WIV02	WIV04	WIV05	WIV06	WIV07	IVDC-HB-04	Nonth/61	Nonth/74	20SF012	20SF013	20SF014	20SF025	WZ-01	20SF028	WZ-02
2019-12-24 Wuhan/IPBCAMS-WH-01																						
2019-12-30 Wuhan/HBCDC-HB-01	4																					
2019-12-30 Wuhan/IPBCAMS-WH-02	9	7																				
2019-12-30 Wuhan/IPBCAMS-WH-03	4	2	7																			
2019-12-30 Wuhan/IPBCAMS-WH-04	3	1	6	1																		
2019-12-30 Wuhan/IVDC-HB-01	3	1	6	1	0																	
2019-12-30 Wuhan/IVDC-HB-05	5	3	8	3	2	2																
2019-12-30 Wuhan/WIV02	5	3	8	3	2	2	4															
2019-12-30 Wuhan/WIV04	3	1	6	1	0	0	2	2														
2019-12-30 Wuhan/WIV05	5	3	8	3	2	2	4	4	2													
2019-12-30 Wuhan/WIV06	3	1	6	1	0	0	2	2	0	2												
2019-12-30 Wuhan/WIV07	5	3	8	3	2	2	4	4	2	4	2											
2020-01-01 Wuhan/IVDC-HB-04	6	4	9	4	3	3	5	5	3	5	3	5										
2020-01-08 Nonthaburi/61	3	1	6	1	0	0	2	2	0	2	0	2	3									
2020-01-13 Nonthaburi/74	3	1	6	1	0	0	2	2	0	2	0	2	3	0								
2020-01-14 Guangdong/20SF012	6	4	9	4	3	3	5	5	3	5	3	5	6	3	3							
2020-01-15 Guangdong/20SF013	6	4	9	4	3	3	5	5	3	5	3	5	6	3	3	0						
2020-01-15 Guangdong/20SF014	4	2	7	2	1	1	3	3	1	3	1	3	4	1	1	4	4					
2020-01-15 Guangdong/20SF025	6	4	9	4	3	3	5	5	3	5	3	5	6	3	3	0	0	4				
2020-01-16 Zhejiang/WZ-01	5	3	8	3	2	2	4	3	2	4	2	4	5	2	2	5	5	3	5			
2020-01-17 Guangdong/20SF028	4	2	7	2	1	1	3	3	1	3	1	3	4	1	1	4	4	2	4	3		
2020-01-17 Zhejiang/WZ-02	3	1	6	1	0	0	2	2	0	2	0	2	3	0	0	3	3	1	3	2	1	
2020-01-18 Guangdong/20SF040	4	2	7	2	1	1	3	3	1	3	1	3	4	1	1	4	4	2	4	3	0	1

GISAID

by BII/GIS, A*STAR Singapore

Feb/March: Split into genetic groups (clades)

Black ... China
Blue ... Asia (not China)
Green ... Oceania
Magenta ... Americas
Red ... Europe
Light Blue ... Africa

USA cruise ship

S

L+S already around in Dec

L

Scotland

Switzerland

Brazil

V

England

England

Scotland

Brazil

Scotland

England

Position in tree shows source of global import or local transmission

G

England

GISAID

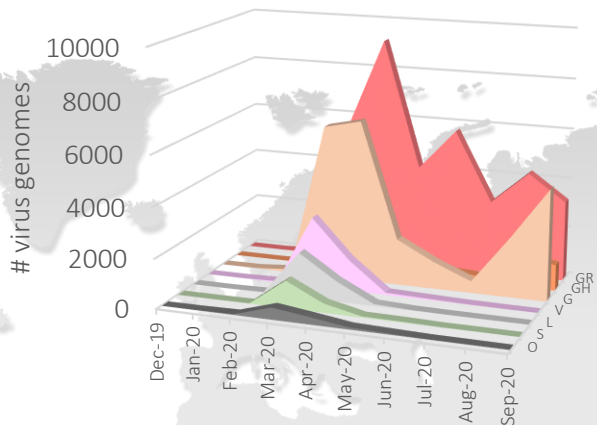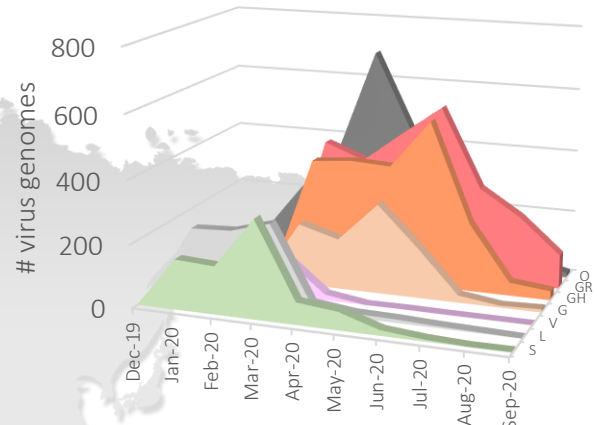by BII/GIS, A*STAR Singapore
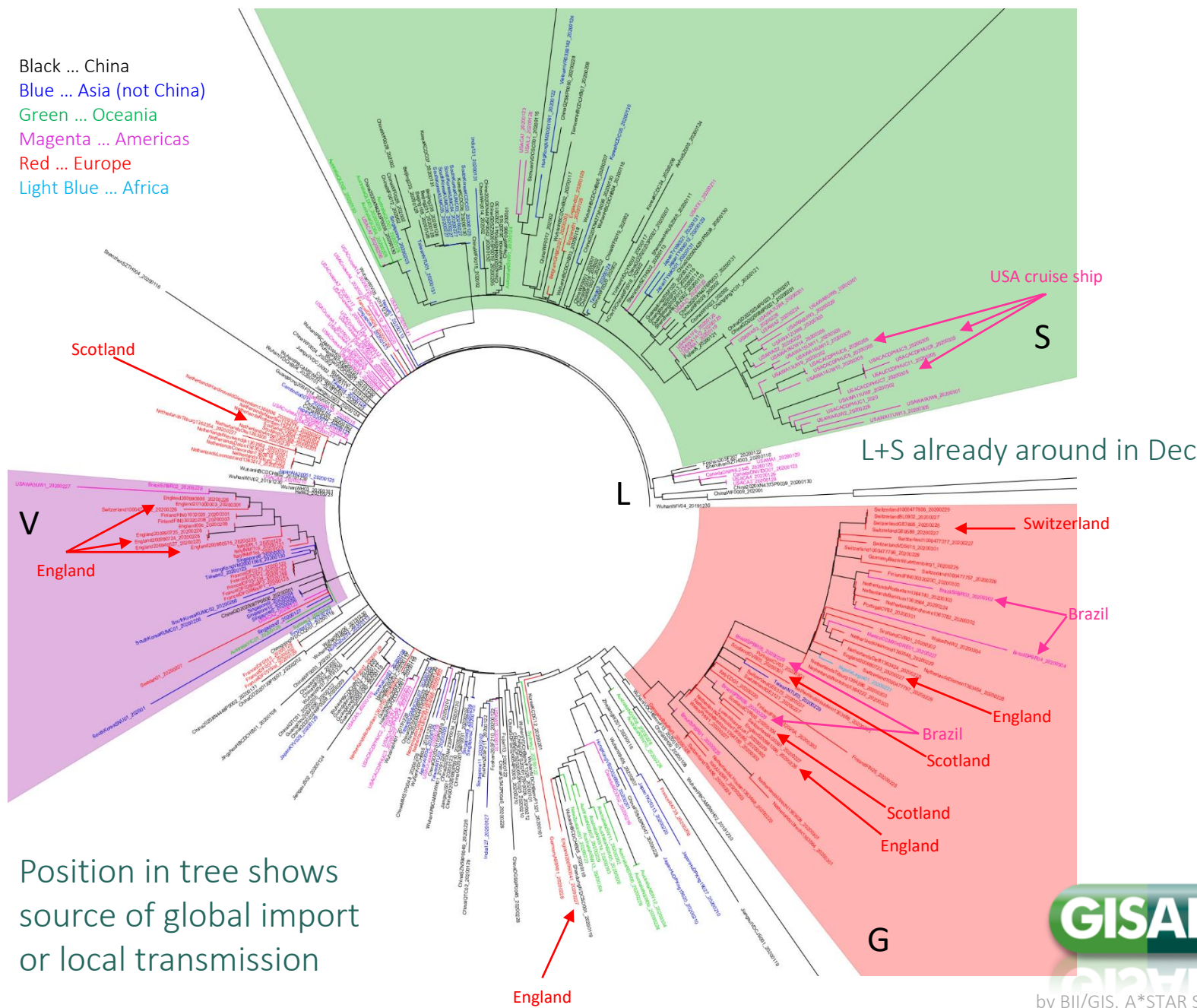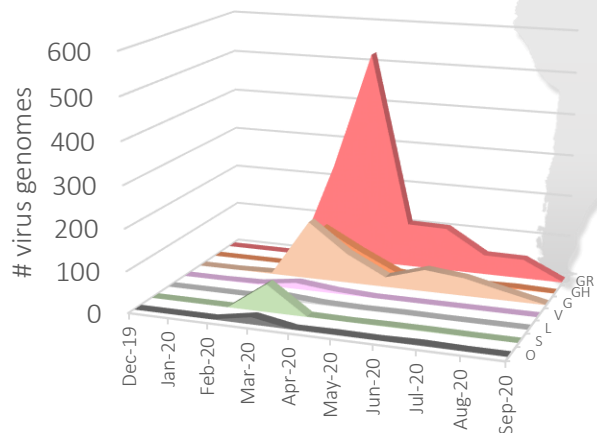
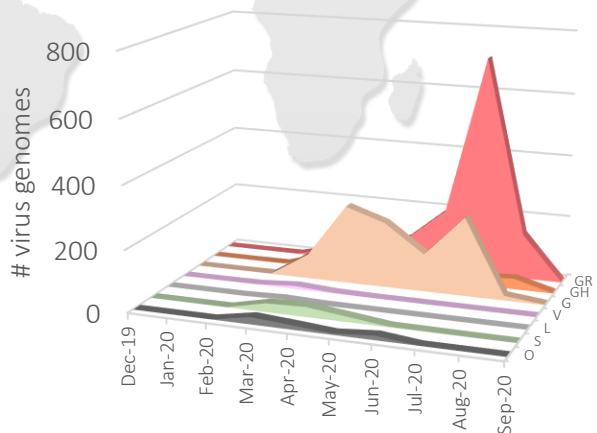# October: Temporal and regional distribution of clades

North America
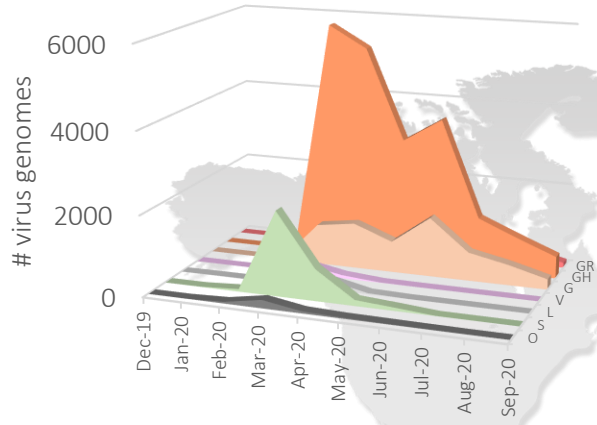
Europe

Asia

South America

Africa

Oceania
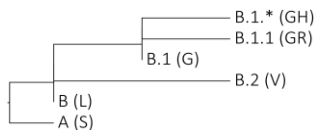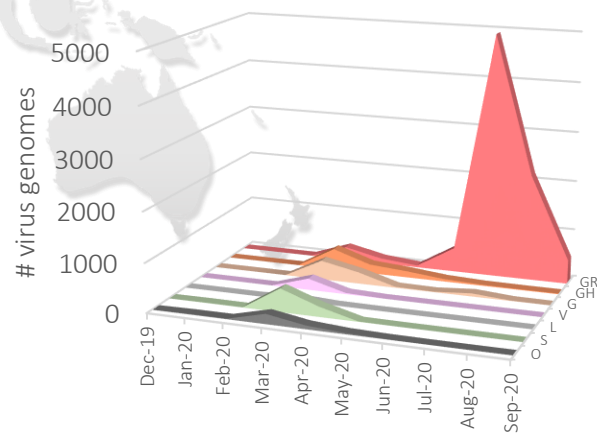
GISAID clades and PANGOLIN lineages

B.1.* (GH)
B.1.1 (GR)
B.1 (G)
B.2 (V)
B (L)
A (S)

O S L V G GH GR

by BII/GIS, A*STAR Singapore

GISAID

Genetic markers for contact tracing

Kenema Government Hospital, Ministry of Health and Sanitation

GR

Sierra Leone

S

G

L

5x Sierra Leone

Sierra Leone

Sierra Leone

Sierra Leone

Sierra Leone

Sierra Leone

GH

Goba,A., Momoh,M., Sandi,J., Tomkins-Tinch,C., Siddle,K., Mehta,S., Oluniyi,P., Jalloh,S., Park,D., Andersen,K., Garry,R., Happi,C., Grant,D., Olawoye,I.

Genomic Epidemiology of COVID-19 in Sierra Leone enabled by GISAID suggests 7 independent imports with one local outbreak with possible link to Saudi Arabia.

GISAID

by BII/GIS, A*STAR Singapore

Global to local

Global

Global

Singapore
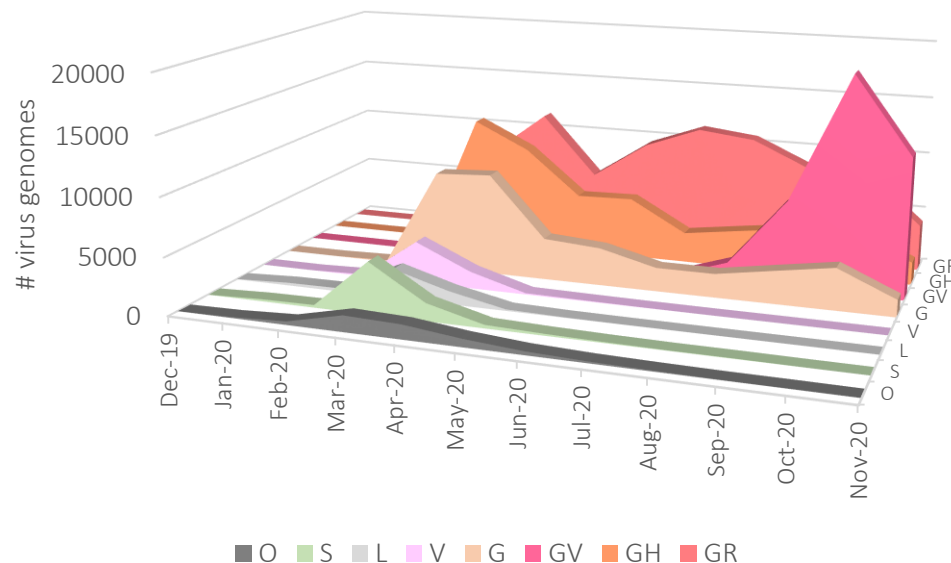
GV (B.1.177) hCoV-19 Spain CT-ISCIII-2013597 2020

GR (B.1.1.1) hCoV-19 England 20168037604 2020 EPI IS

GH (B.1.*) hCoV-19 Canada ON-PHL-8751 2020 EPI ISL 41834

G (B.1) hCoV-19 Germany BY-ChVir-929 2020 EPI ISL 406862 2020

V (B.2) hCoV-19 Italy LAZ-INMI-SPL1 2020 EPI ISL 412974 2020-01-

L (B) hCoV-19 Wuhan WIV04 2019 EPI ISL 402124 2019-12-30

S (A) hCoV-19 Guangdong 20SF012 2020 EPI ISL 403932 2020-01-1

0.000050

GISAID

Genetic markers for contact tracing

Contact network from epidemiological (left) and genetic (right) data
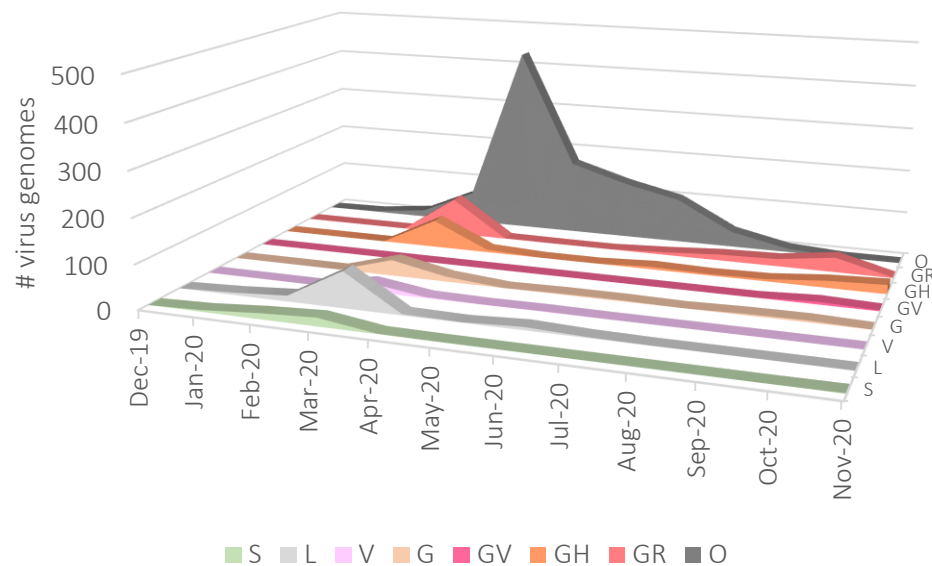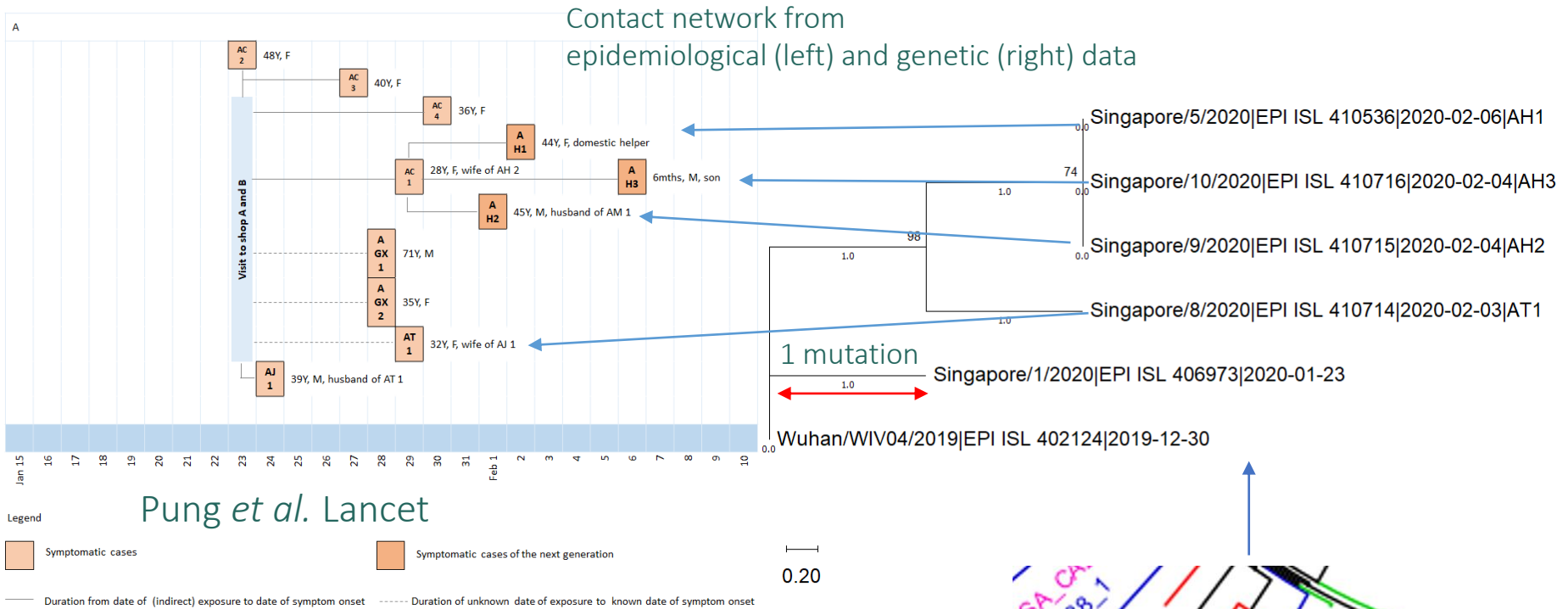
Pung *et al.* Lancet

Not all local sequences can be connected easily but linkage can be significant if they are identical or share unique mutations or deletions (SG 382bp deletion: Young *et al.*, Lancet). Full genomes needed for interpretation.

Genetic markers for contact tracing

One variant has a unique 3bp deletion in nsp2 that allows to follow a detailed transmission chain and spread of a single variant

(Source: Public Health England)

Slide prepared by Shannon Low (Imperial UK) under supervision of Maria Zambon and Sebastian Maurer-Stroh

October Qingdao sequences are new imports, possibly over cold chain products

Huilai Ma,
Zhaoguo Wang,
Xiang Zhao, Jun
Han, Yong
Zhang, Hong
Wang, Cao
Chen, Ji Wang,
Jingdong Song,
Yao Meng,
Yuchao Wu,
Zhixiao Chen,
Dayan Wang,
Ruqin Gao,
George F.Gao,
Wenbo Xu

Phylogenetic tree labels:

100
- hCoV-19_Qingdao_IVDC-02-10_2020_EPI_ISL_591271
- hCoV-19_env_Qingdao_IVDC-07-10_2020_EPI_ISL_591276
- hCoV-19_env_Qingdao_IVDC-08-10_2020_EPI_ISL_591277
- hCoV-19_env_Qingdao_IVDC-010-10_2020_EPI_ISL_591279
- hCoV-19_env_Qingdao_IVDC-011-10_2020_EPI_ISL_591280
- hCoV-19_Qingdao_IVDC-01-10_2020_EPI_ISL_591270
85
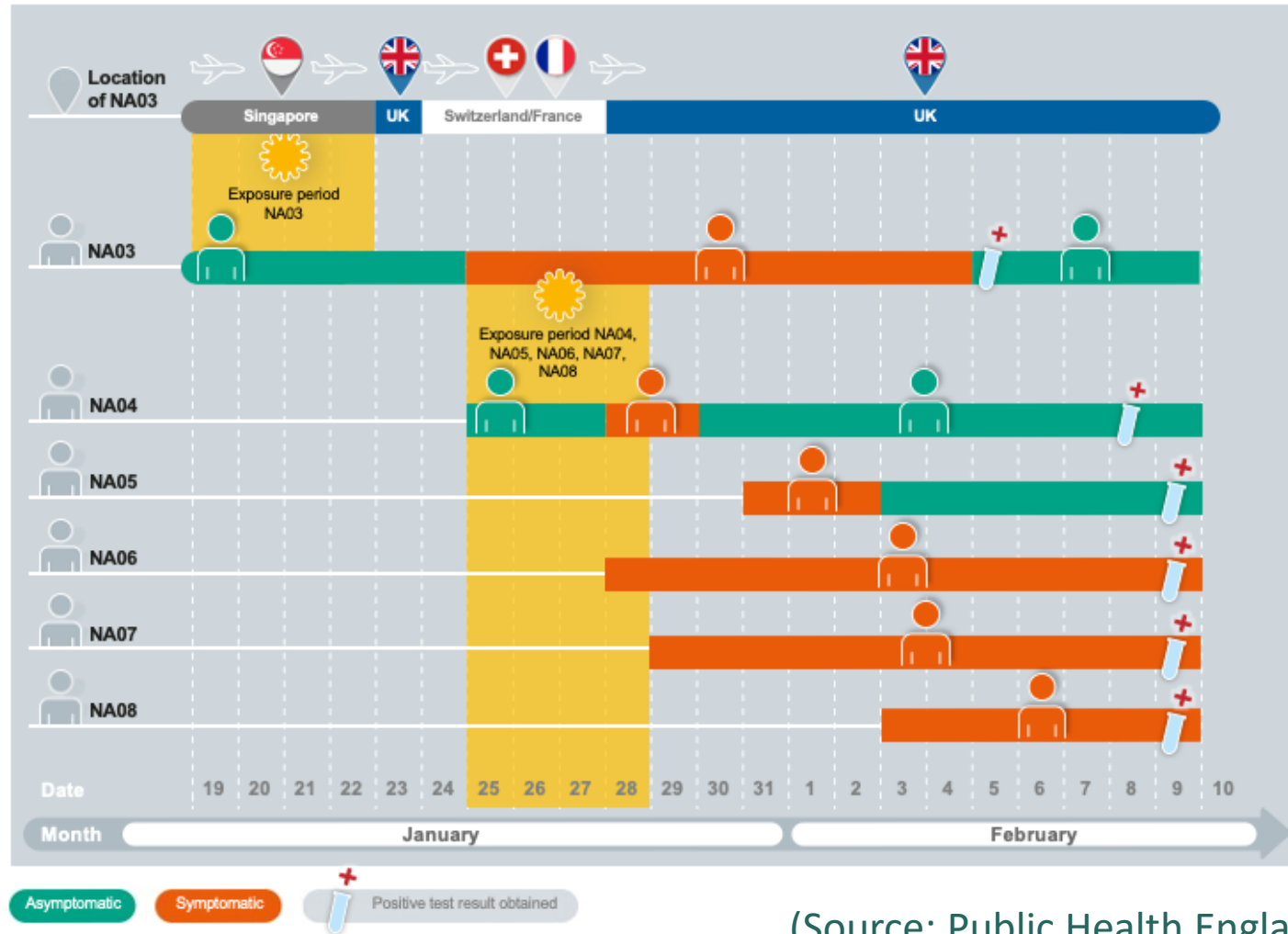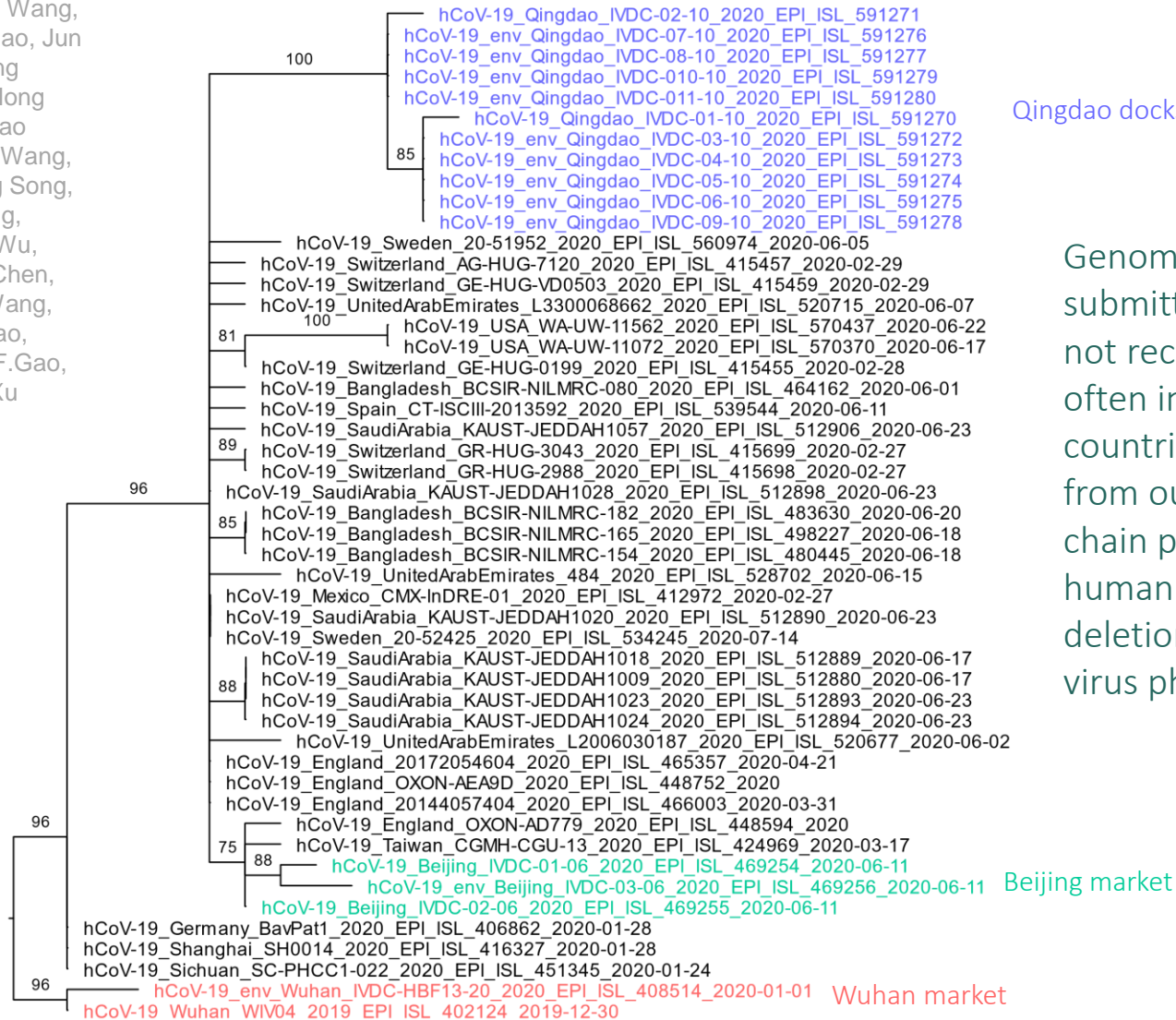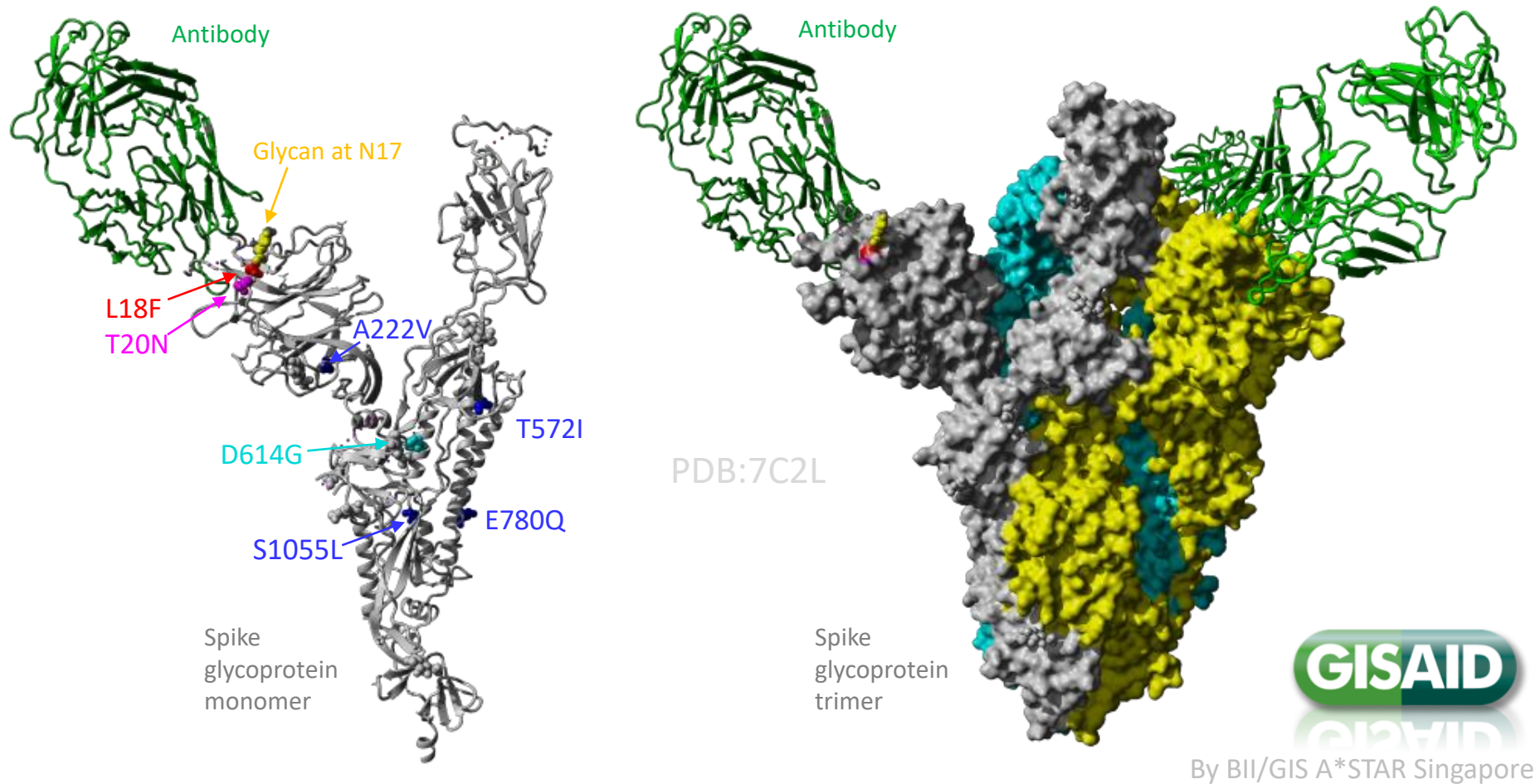- hCoV-19_env_Qingdao_IVDC-03-10_2020_EPI_ISL_591272
- hCoV-19_env_Qingdao_IVDC-04-10_2020_EPI_ISL_591273
- hCoV-19_env_Qingdao_IVDC-05-10_2020_EPI_ISL_591274
- hCoV-19_env_Qingdao_IVDC-06-10_2020_EPI_ISL_591275
- hCoV-19_env_Qingdao_IVDC-09-10_2020_EPI_ISL_591278

Qingdao docks

- hCoV-19_Sweden_20-51952_2020_EPI_ISL_560974_2020-06-05
- hCoV-19_Switzerland_AG-HUG-7120_2020_EPI_ISL_415457_2020-02-29
- hCoV-19_Switzerland_GE-HUG-VD0503_2020_EPI_ISL_415459_2020-02-29
- hCoV-19_UnitedArabEmirates_L3300068662_2020_EPI_ISL_520715_2020-06-07
81 / 100
- hCoV-19_USA_WA-UW-11562_2020_EPI_ISL_570437_2020-06-22
- hCoV-19_USA_WA-UW-11072_2020_EPI_ISL_570370_2020-06-17
- hCoV-19_Switzerland_GE-HUG-0199_2020_EPI_ISL_415455_2020-02-28
- hCoV-19_Bangladesh_BCSIR-NILMRC-080_2020_EPI_ISL_464162_2020-06-01
- hCoV-19_Spain_CT-ISCIII-2013592_2020_EPI_ISL_539544_2020-06-11
- hCoV-19_SaudiArabia_KAUST-JEDDAH1057_2020_EPI_ISL_512906_2020-06-23
89
- hCoV-19_Switzerland_GR-HUG-3043_2020_EPI_ISL_415699_2020-02-27
- hCoV-19_Switzerland_GR-HUG-2988_2020_EPI_ISL_415698_2020-02-27
- hCoV-19_SaudiArabia_KAUST-JEDDAH1028_2020_EPI_ISL_512898_2020-06-23
85
- hCoV-19_Bangladesh_BCSIR-NILMRC-182_2020_EPI_ISL_483630_2020-06-20
- hCoV-19_Bangladesh_BCSIR-NILMRC-165_2020_EPI_ISL_498227_2020-06-18
- hCoV-19_Bangladesh_BCSIR-NILMRC-154_2020_EPI_ISL_480445_2020-06-18
- hCoV-19_UnitedArabEmirates_484_2020_EPI_ISL_528702_2020-06-15
- hCoV-19_Mexico_CMX-InDRE-01_2020_EPI_ISL_412972_2020-02-27
- hCoV-19_SaudiArabia_KAUST-JEDDAH1020_2020_EPI_ISL_512890_2020-06-23
- hCoV-19_Sweden_20-52425_2020_EPI_ISL_534245_2020-07-14
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- hCoV-19_SaudiArabia_KAUST-JEDDAH1018_2020_EPI_ISL_512889_2020-06-17
- hCoV-19_SaudiArabia_KAUST-JEDDAH1009_2020_EPI_ISL_512880_2020-06-17
- hCoV-19_SaudiArabia_KAUST-JEDDAH1023_2020_EPI_ISL_512893_2020-06-23
- hCoV-19_SaudiArabia_KAUST-JEDDAH1024_2020_EPI_ISL_512894_2020-06-23
- hCoV-19_UnitedArabEmirates_L2006030187_2020_EPI_ISL_520677_2020-06-02
- hCoV-19_England_20172054604_2020_EPI_ISL_465357_2020-04-21
- hCoV-19_England_OXON-AEA9D_2020_EPI_ISL_448752_2020
- hCoV-19_England_20144057404_2020_EPI_ISL_466003_2020-03-31
96
- hCoV-19_England_OXON-AD779_2020_EPI_ISL_448594_2020
75
- hCoV-19_Taiwan_CGMH-CGU-13_2020_EPI_ISL_424969_2020-03-17
88
- hCoV-19_Beijing_IVDC-01-06_2020_EPI_ISL_469254_2020-06-11
- hCoV-19_env_Beijing_IVDC-03-06_2020_EPI_ISL_469256_2020-06-11
- hCoV-19_Beijing_IVDC-02-06_2020_EPI_ISL_469255_2020-06-11

Beijing market

- hCoV-19_Germany_BavPat1_2020_EPI_ISL_406862_2020-01-28
- hCoV-19_Shanghai_SH0014_2020_EPI_ISL_416327_2020-01-28
- hCoV-19_Sichuan_SC-PHCC1-022_2020_EPI_ISL_451345_2020-01-24
96
- hCoV-19_env_Wuhan_IVDC-HBF13-20_2020_EPI_ISL_408514_2020-01-01
- hCoV-19_Wuhan_WIV04_2019_EPI_ISL_402124_2019-12-30

Wuhan market

5.0E-5

Genomes from Qingdao submitted to GISAID. Genotype not recently seen in China but often in Europe and other countries. Samples taken from outer packaging of cold chain products match the human samples (share unique deletion marker not linked to virus phenotype).
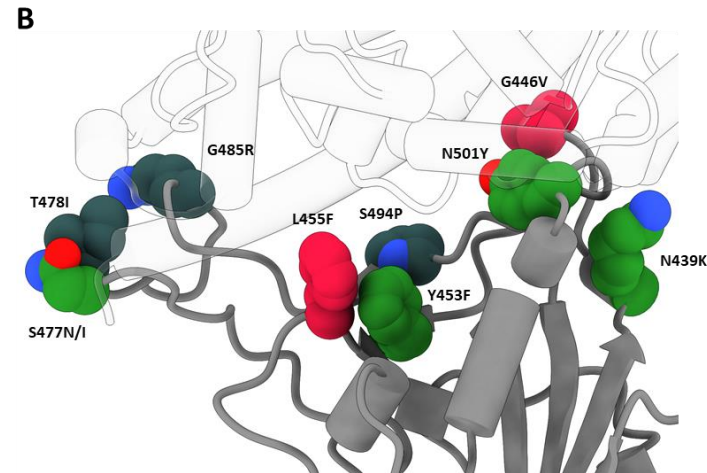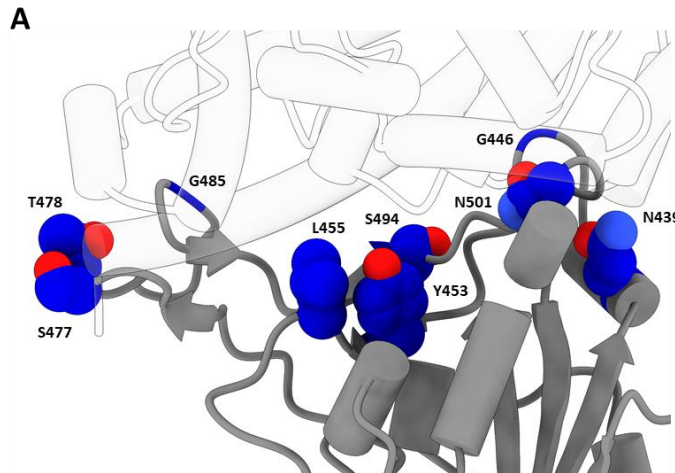
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Mutations and potential vaccine/immunity escape: reinfection cases

Antibody

Glycan at N17

L18F
T20N
A222V
D614G
T572I
S1055L
E780Q

Spike glycoprotein monomer

PDB:7C2L

Antibody

Spike glycoprotein trimer

GISAID

By BII/GIS A*STAR Singapore

2 of 4 reinfection cases have mutations possibly interfering with the structural conformation of glycosylation sites in a region that is also broadly recognized by antibodies which would provide a hypothetical mechanism for immune escape potentially contributing to permitting second infection. However, this doesn't apply to all cases and many other factors could play a role too. Importantly, these mutations are rare and occur sporadically without causing large clusters so far.

Real-time Surveillance of receptor binding pocket mutations

MS in preparation

AA	Frequency	Location counts
S477N	**12115**	**8427 Australia/VIC**, 1300 England, 1032 Denmark, 425 Australia/NSW, 303 Switzerland, 153 France, 92 Belgium, 80 Netherlands, 66 Scotland, 44 Norway, 44 Australia/QLD, 37 Wales, 27 Australia/WA, 18 Sweden, 11 Northern Ireland, 9 USA/FL, 8 Australia/SAP, 5 Australia/ACT, 4 CotedIvoire, 4 Germany, 4 Slovakia, 3 New Zealand, 2 Australia/TAS, 2 Tunisia, 2 Australia/NT, 2 Spain, 1 Hong Kong, 1 Lebanon, 1 Canada, 1 Thailand, 1 Gibraltar, 1 USA/MA, 1 Singapore, 1 USA/CA, 1 USA/WA, 1 Japan, 1 India
N439K	3344	1277 England, 772 Denmark, 726 Scotland, 251 Wales, 140 Ireland, 47 Switzerland, 35 Northern Ireland, 26 Czech Republic, 16 France, 12 Norway, 11 Netherlands, 8 Faroe Islands, 5 Germany, 3 Italy, 3 Belgium, 3 USA/IL, 2 Australia/SAP, 1 Sweden, 1 New Zealand, 1 USA/WI, 1 Australia/NSW, 1 Singapore, 1 Australia/WA, 1 Romania
Y453F	343	329 Denmark, 6 Netherlands, 3 Switzerland, 2 South Africa, 1 Faroe Islands, 1 Russia, 1 USA/UT
N501Y	220	140 Wales, 37 Australia/VIC, 33 England, 5 USA/MA, 1 USA/OR, 1 USA/NY, 1 USA/IL, 1 Denmark, 1 Brazil
T478I	116	113 England, 1 Northern Ireland, 1 South Africa, 1 Spain
S477I	100	70 England, 11 USA/NM, 5 Wales, 3 USA/CA, 3 Scotland, 1 South Africa, 1 Singapore, 1 Indonesia, 1 USA/SC, 1 India, 1 Colombia, 1 Luxembourg, 1 Australia/VIC
S494P	89	34 England, 26 USA/CA, 7 USA/MA, 4 USA/MI, 3 Scotland, 2 Sweden, 2 India, 2 Denmark, 1 CotedIvoire, 1 Australia/VIC, 1 France, 1 Wales, 1 Singapore, 1 Nigeria, 1 USA/UT, 1 USA/MD, 1 Spain
G485R	37	37 Australia/VIC
L455F	36	17 Australia/VIC, 7 England, 3 Scotland, 2 South Africa, 2 South Korea, 2 USA/CA, 1 Italy, 1 USA/WA, 1 USA/MO
G446V	31	9 England, 5 Australia/VIC, 2 USA/VA, 2 USA/TX, 2 South Korea, 1 USA/MN, 1 Italy, 1 Scotland, 1 Australia/NSW, 1 Wales, 1 USA/CA, 1 USA/WA, 1 Israel, 1 Finland, 1 Portugal, 1 Denmark

Collaboration with DSO and VIDRL and Uni Melb

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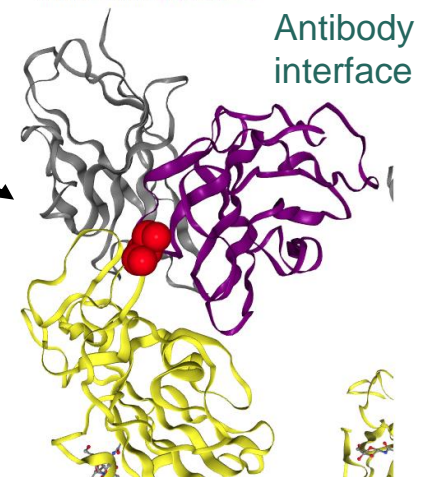by BII/GIS, A*STAR Singapore

CoVsurver tool to analyse mutations –spike S477N

by BII/GIS, A*STAR Singapore

Real-time Surveillance of Pathogen Evolution and Global Transmission
(from genome to action)

1. Development of first diagnostics kits and refinement through ongoing surveillance for mutations

2. Identification of potential drug and vaccine targets on hCoV-19 through repurposing

3. Genomic epidemiology of hCoV-19, allows analysis of the exportation and importation events of viruses between countries, contact-tracing in countries, or identification of transmission chains

4. Evidence that the virus has not drifted to significant strain difference, with in particular the cell receptor binding pocket being followed closely

5. Identification of animal precursors of hCoV-19 (in bats and pangolins)
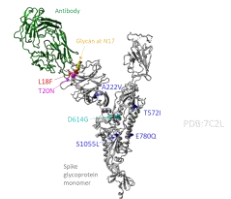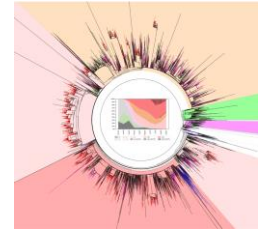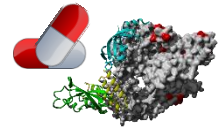
We gratefully acknowledge the Authors from Originating and Submitting laboratories of sequence and meta data.

GISAID

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Fernanda
Yi Hong, Shilpa
Niranjan (GIS)
Shawn (IMCB)

BII – drug-related modelling
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Sam

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GIS, SIgN/ID labs, IMCB, EDDC, DxD, Duke-NUS, DSO, NUS, NPHL, NCID, MOH, TTSH, NUH, SGH …and many more!

THANK YOU!