



Infections virales émergentes

Comment et pourquoi naissent les variants ?

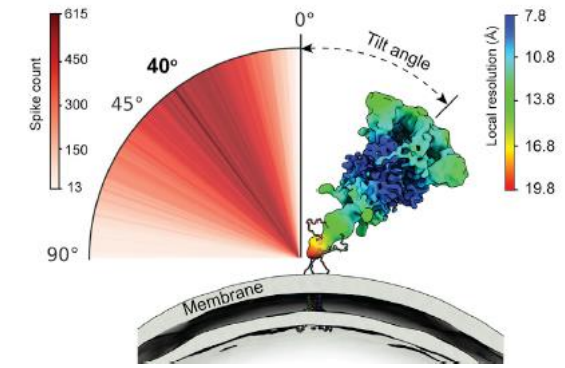
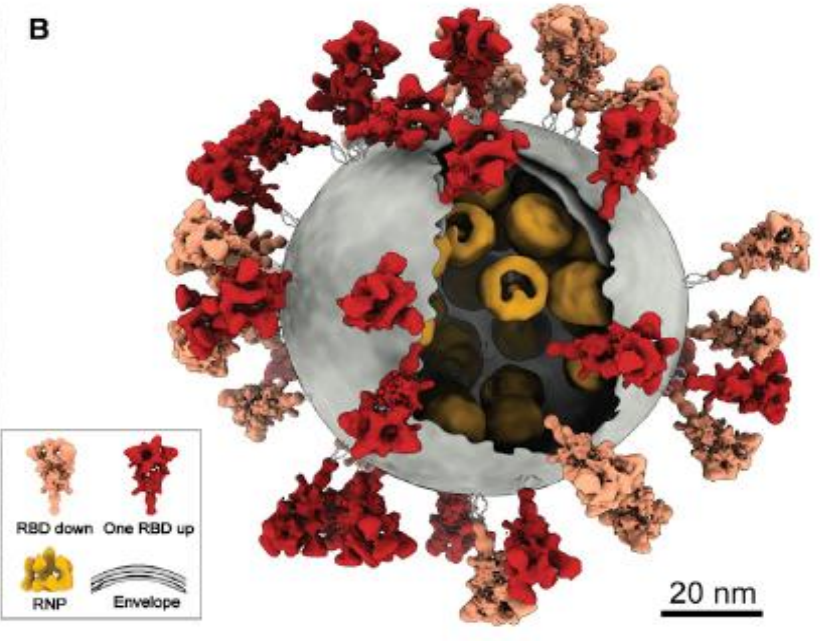
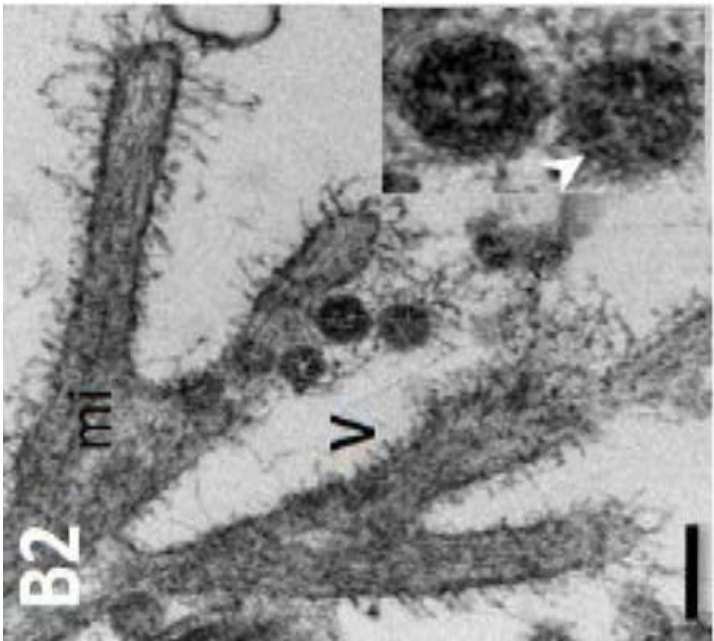
à propos du SARS-CoV2

Bruno Lina

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Le virus SARS-CoV-2



Phylogenie des precurseurs potentiels du SARS-CoV-2



- **New nearest bat precursor from Yunnan 2019 (high identity in Orf1ab, greatest difference in Spike protein, recombination or mixed viruses in metagenomic sample, not yet peer-reviewed)**
- **Nearest pangolin precursors from Guangdong (Southern China)**
- **Previous closest bat precursor also from Yunnan (Southern China) but sample from 2013**

Light Orange ... previous bat CoVs

Orange ... previous closest bat precursor (Yunnan 2013)

Red ... new bat CoVs (Yunnan 2019)

Light blue ... hCoV-19 2019-2020

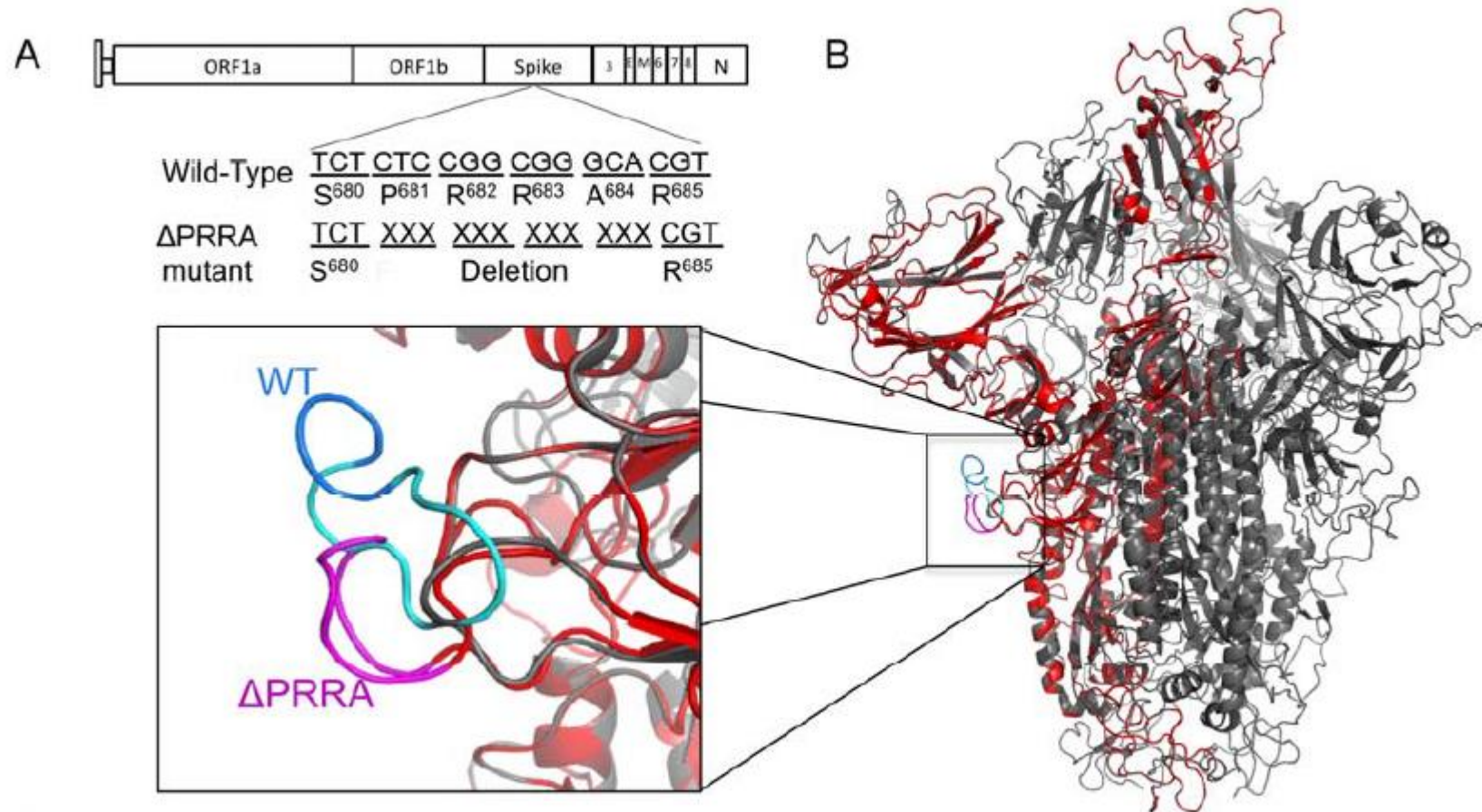
Green ... pangolin CoV (Southern China 2019)

Blue ... SARS CoV

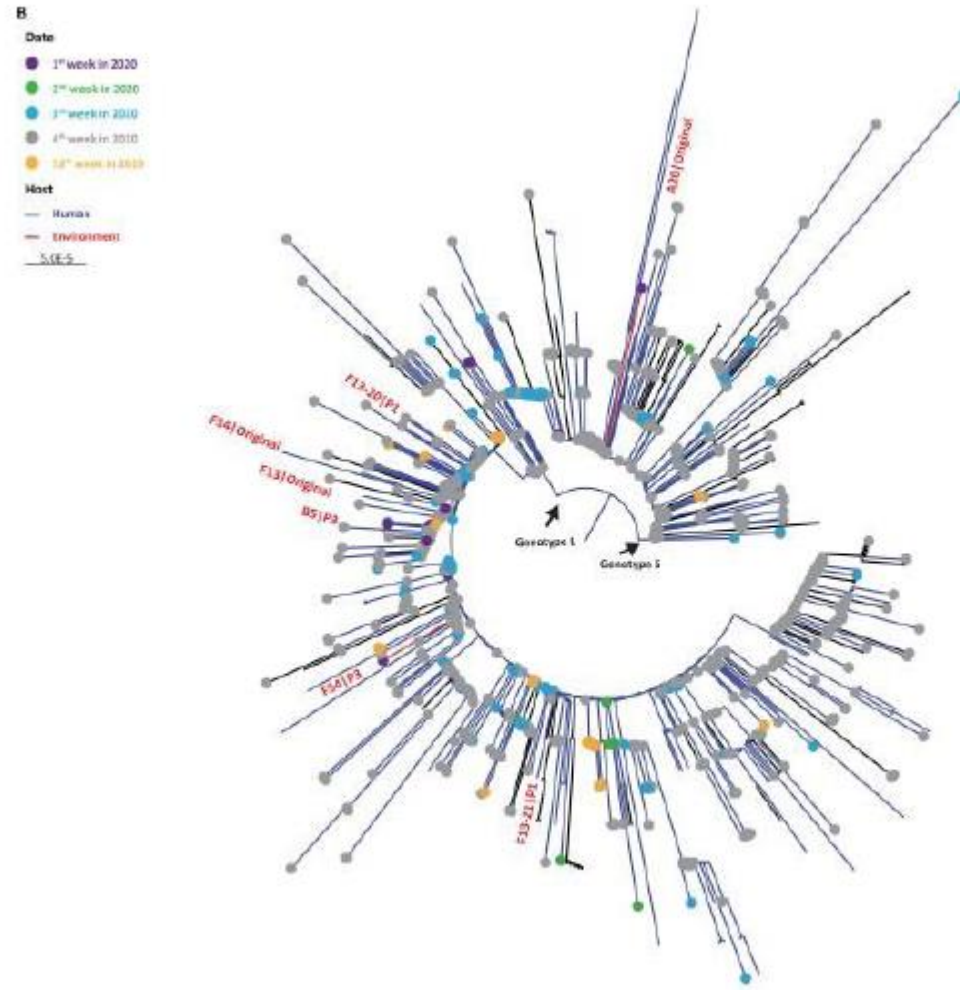
We gratefully acknowledge the Authors from Originating and Submitting laboratories of sequence data on which the analysis is based.



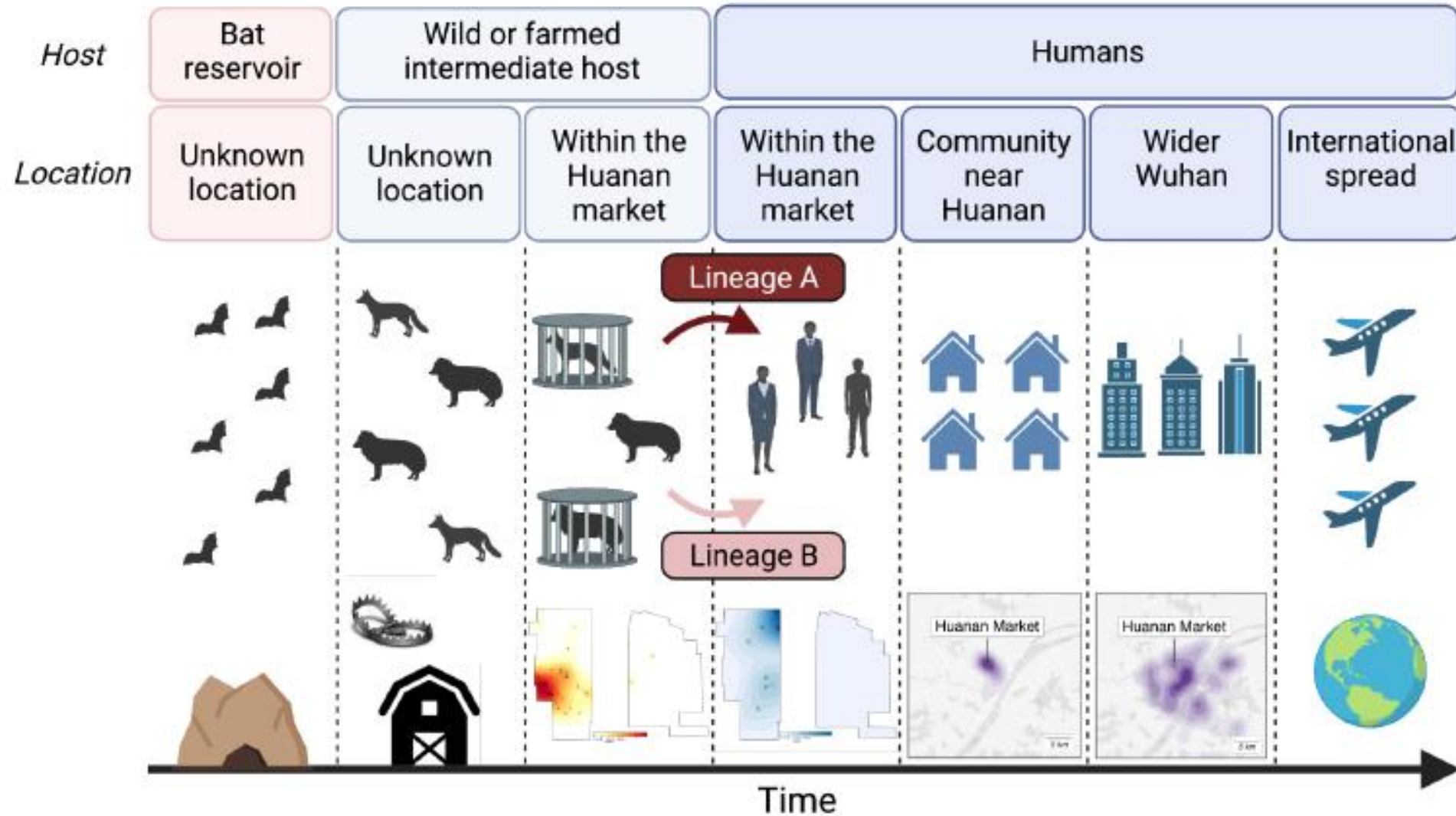
The furin cleavage site: adaptation step to its new host?



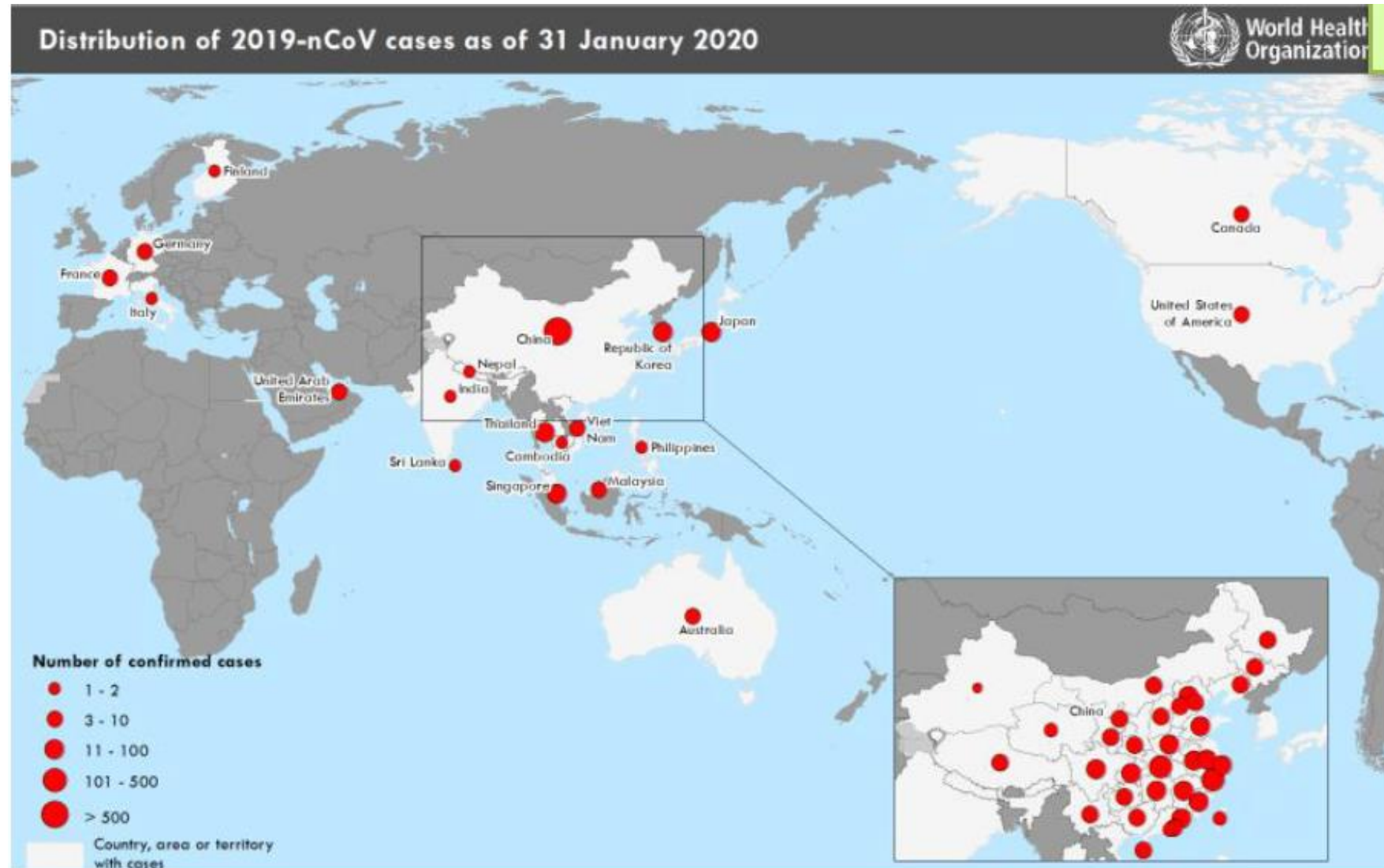
Deux genotypes distincts lors de l'émergence



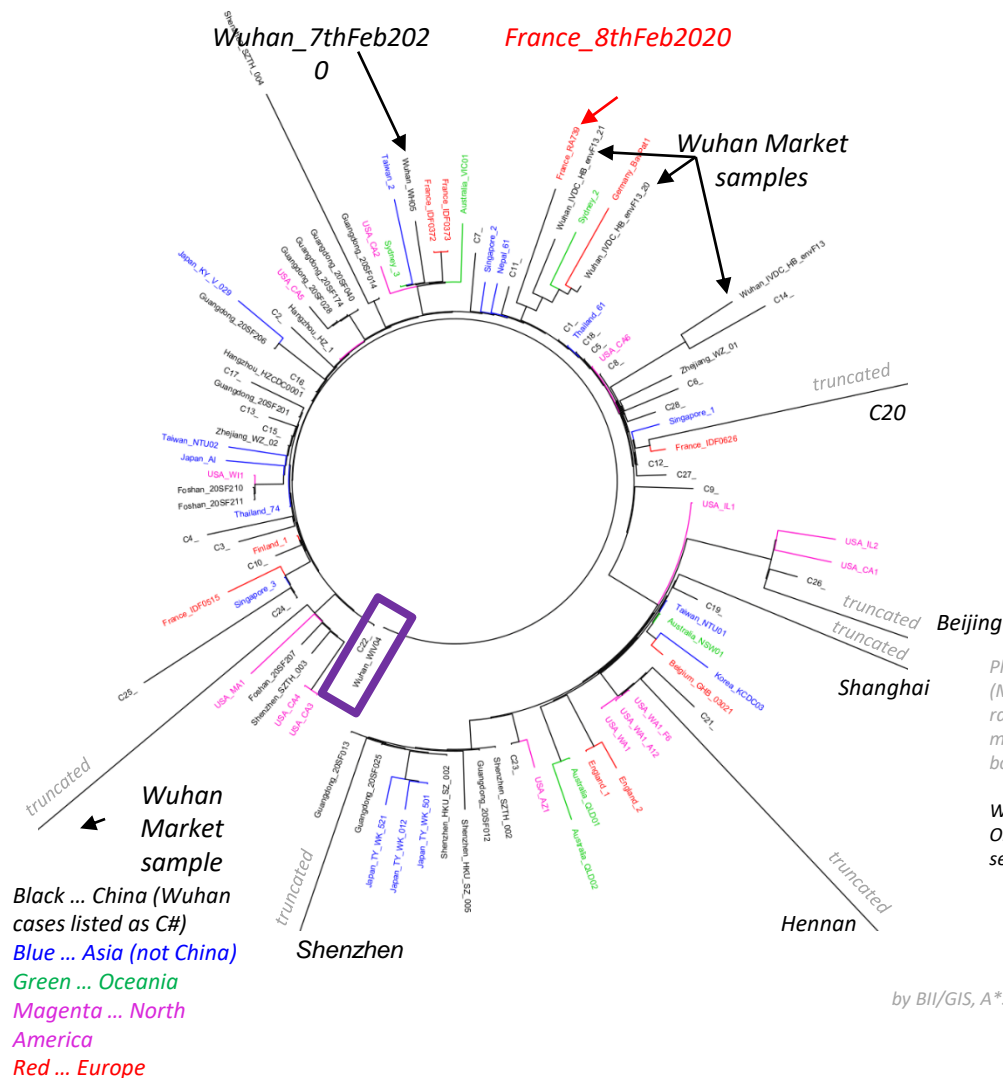
L'histoire du SARS-CoV-2



First steps of the dissemination (early January)



Virus du début de l' épidémie (fin janvier-début février)

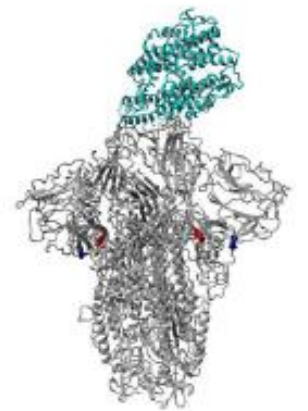


Phylogenetic tree created with RAXML-NG (Maximum Likelihood tree search, 10 randomized parsimony starting trees, GTR model, Gamma distributed rates, 500 bootstrap) and visualized in FigTree

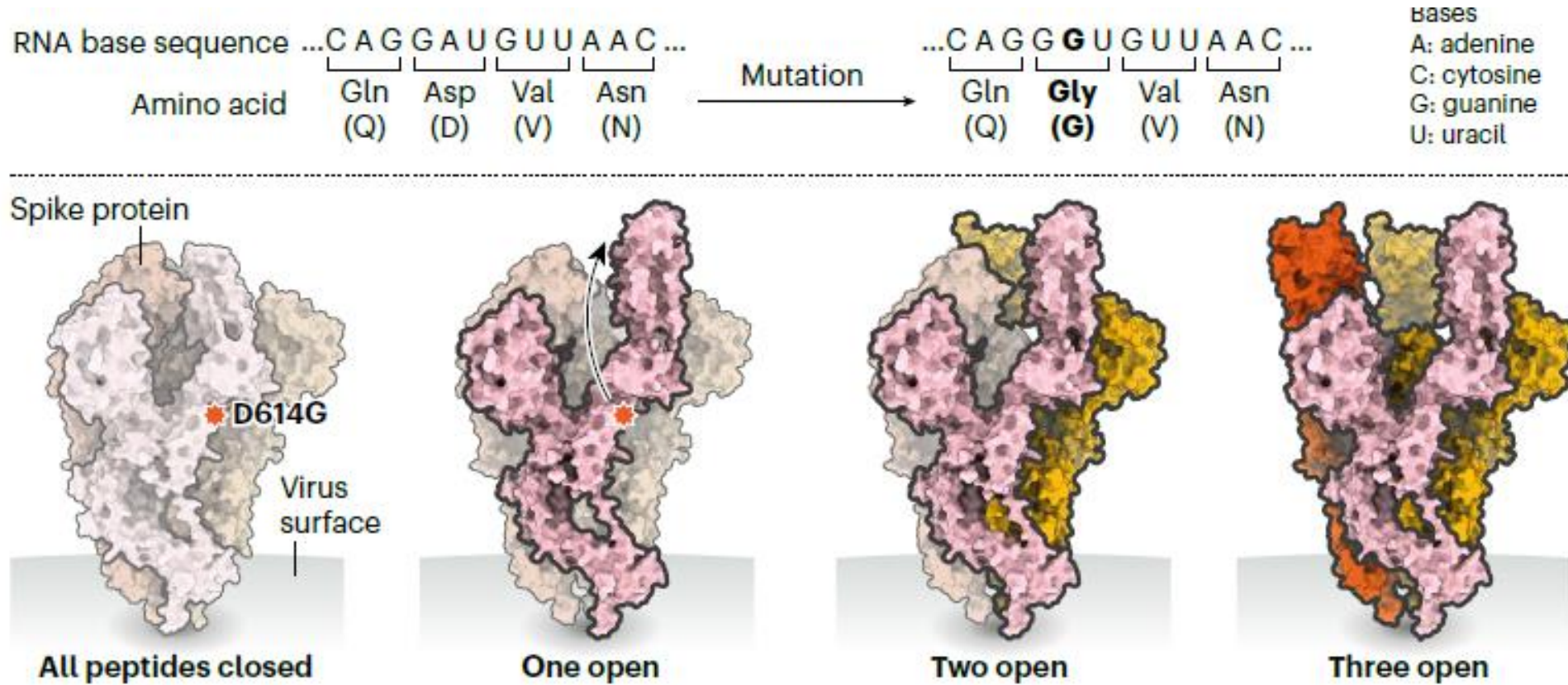
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by BII/GIS, A*STAR Singapore



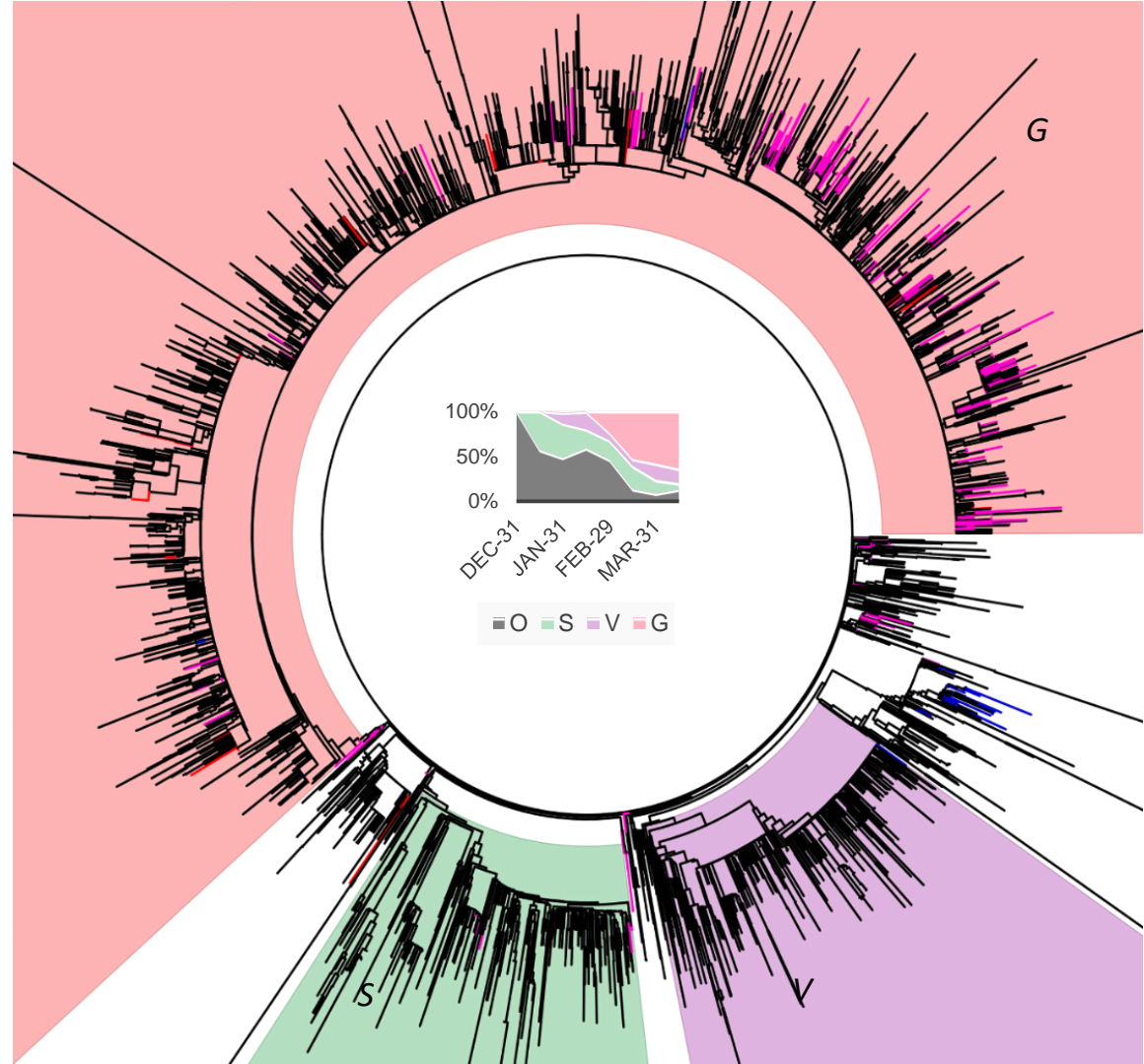
Impact de la substitution D614G : le premier pas evolutif



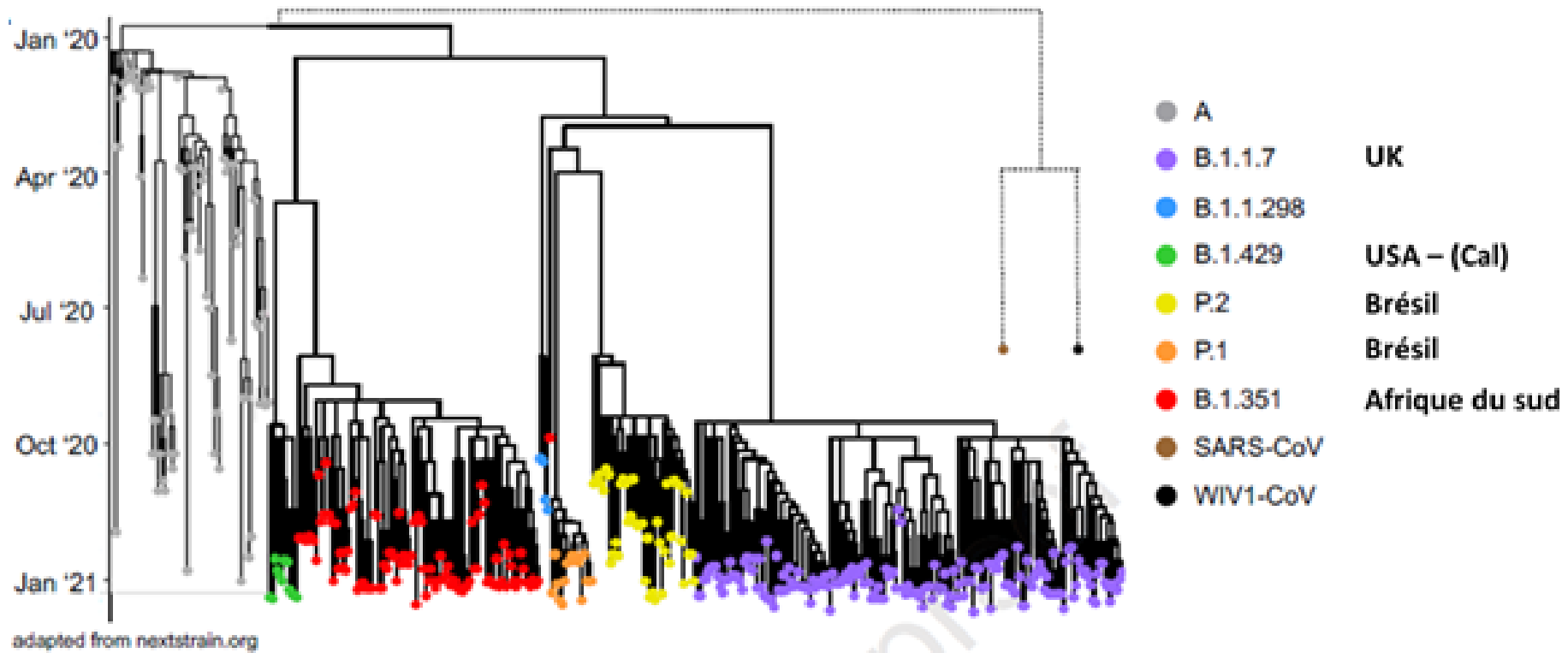
Phase d'extension avant l'apparition des variants (Avril-Mai 2020)

- 30-4-20
- Larger clades were named based on marker variants:
 - S ... ORF8-L84S*
 - G ... S-D614G*
 - V ... NS3-G251V*

We gratefully acknowledge the Authors from Originating and Submitting laboratories of sequence data on which the analysis is based.



Séquence d'apparition des variants avant émergence du delta

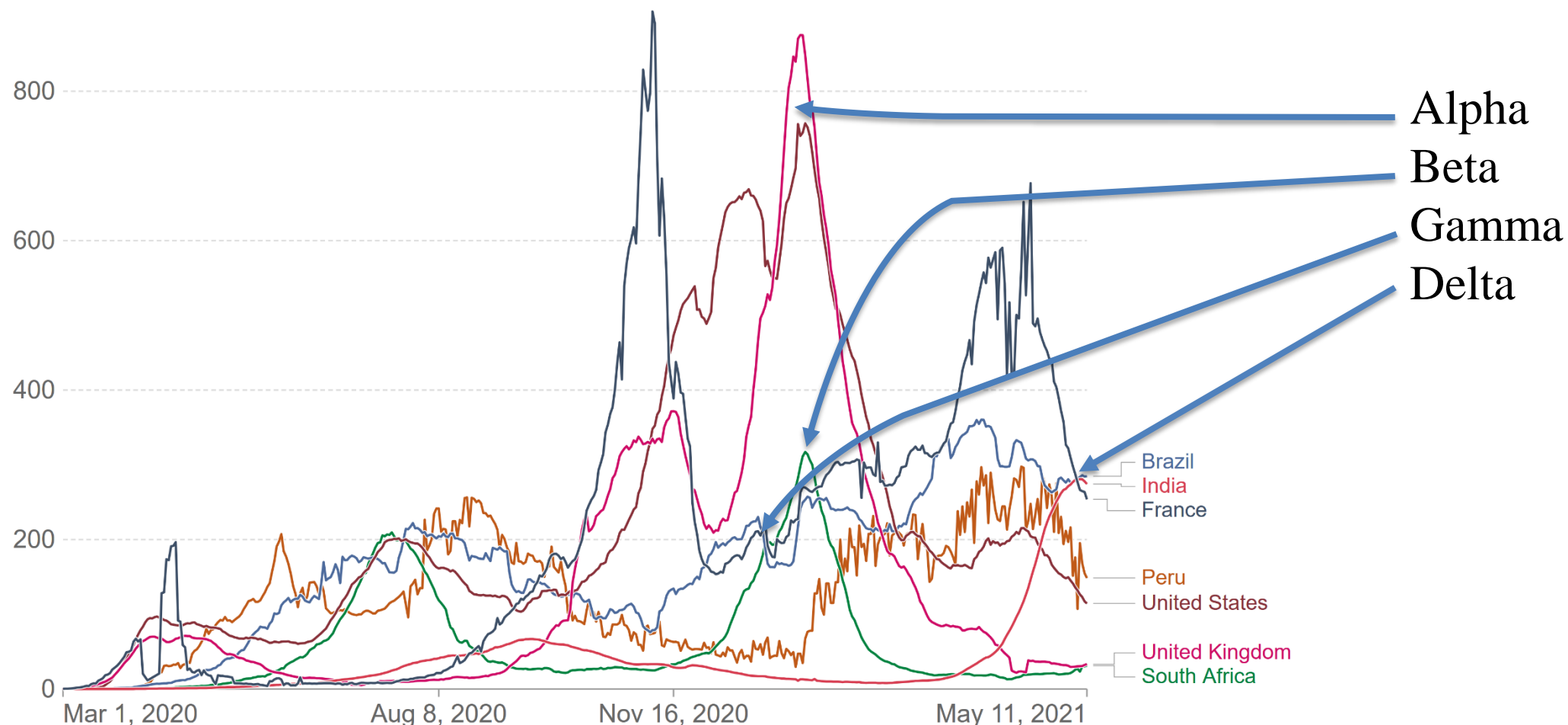


Troisième vague (avril - juin 2021)

Daily new confirmed COVID-19 cases per million people

7-day rolling average. Due to limited testing, the number of confirmed cases is lower than the true number of infections.

Our World
in Data



Source: Johns Hopkins University CSSE COVID-19 Data

CC BY

Source: www.covidtracker.fr

Transmissibilité augmentée (Obermeyer et al, 2021)

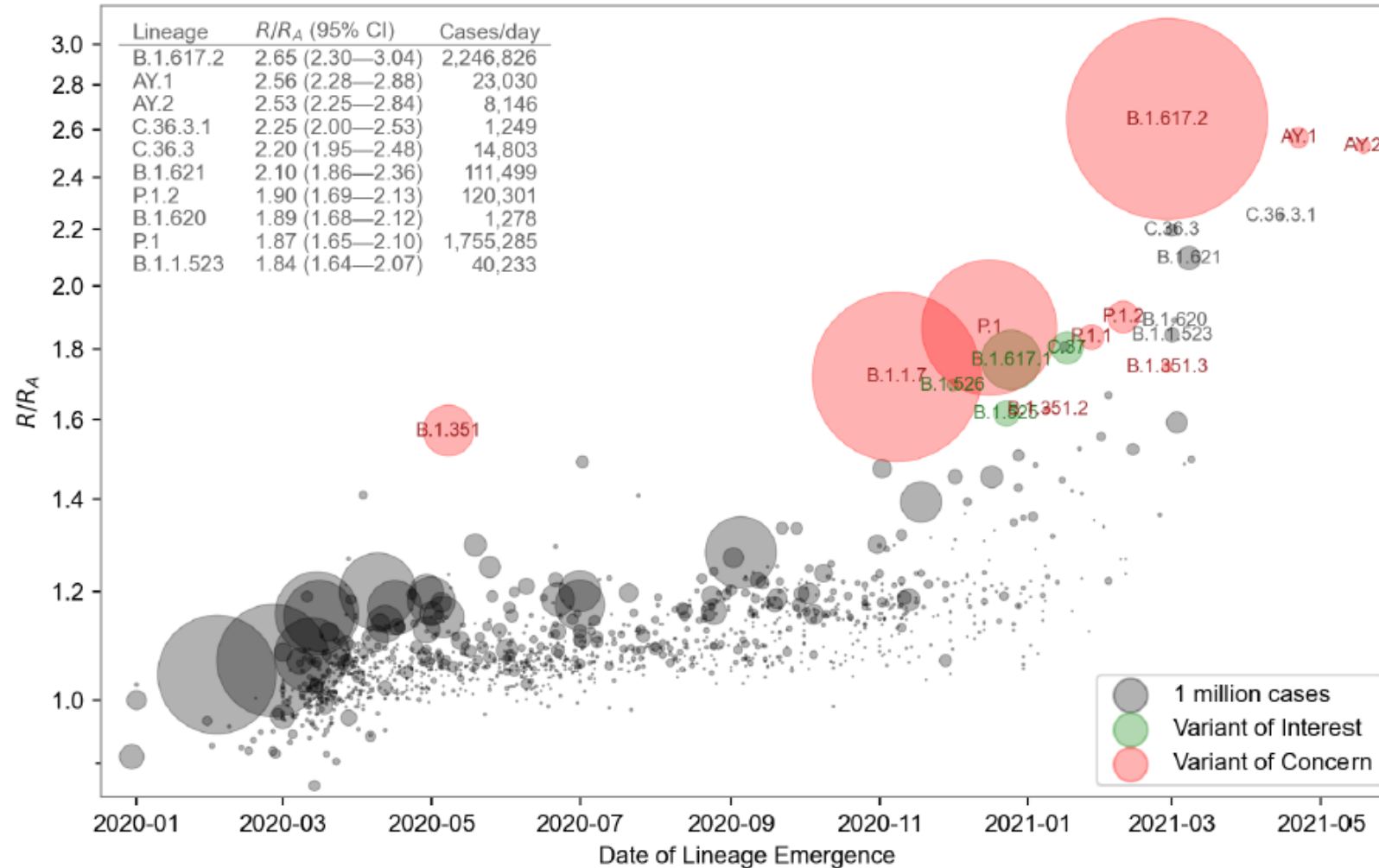


Figure 2. Growth rate versus date of lineage emergence. Circle size is proportional to cumulative case count inferred from lineage proportion estimates and confirmed case counts. Inset table lists the 10 most transmissible lineages inferred by the model. R/R_A : the fold increase in effective reproductive number over the Wuhan (A) lineage, assuming a fixed generation time of 5.5 days.

Que s'est il passé ?

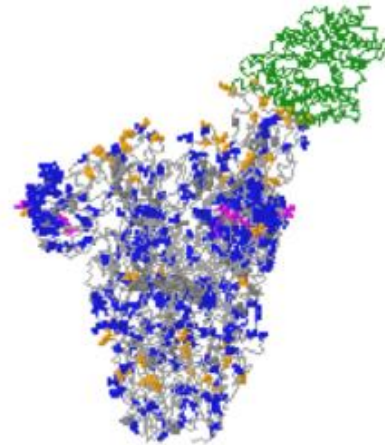
Tendance évolutive sur la Spike :

1 – modifications multiples

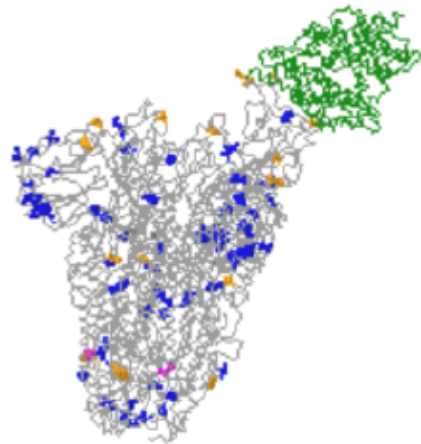
2 – évolution convergente

3 – grande dispersion des mutations

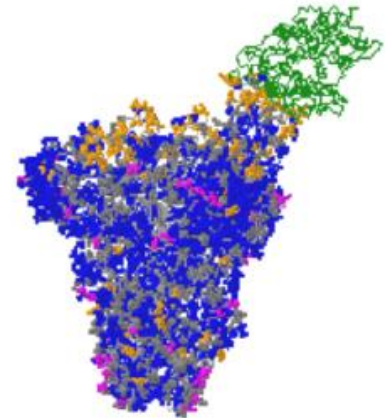
**K417T V445A N501Y E484K Y449H
T478K Y449S S494P F490S G485V**
in GR & GRY clade (B.1.1.1 & B.1.1.7)



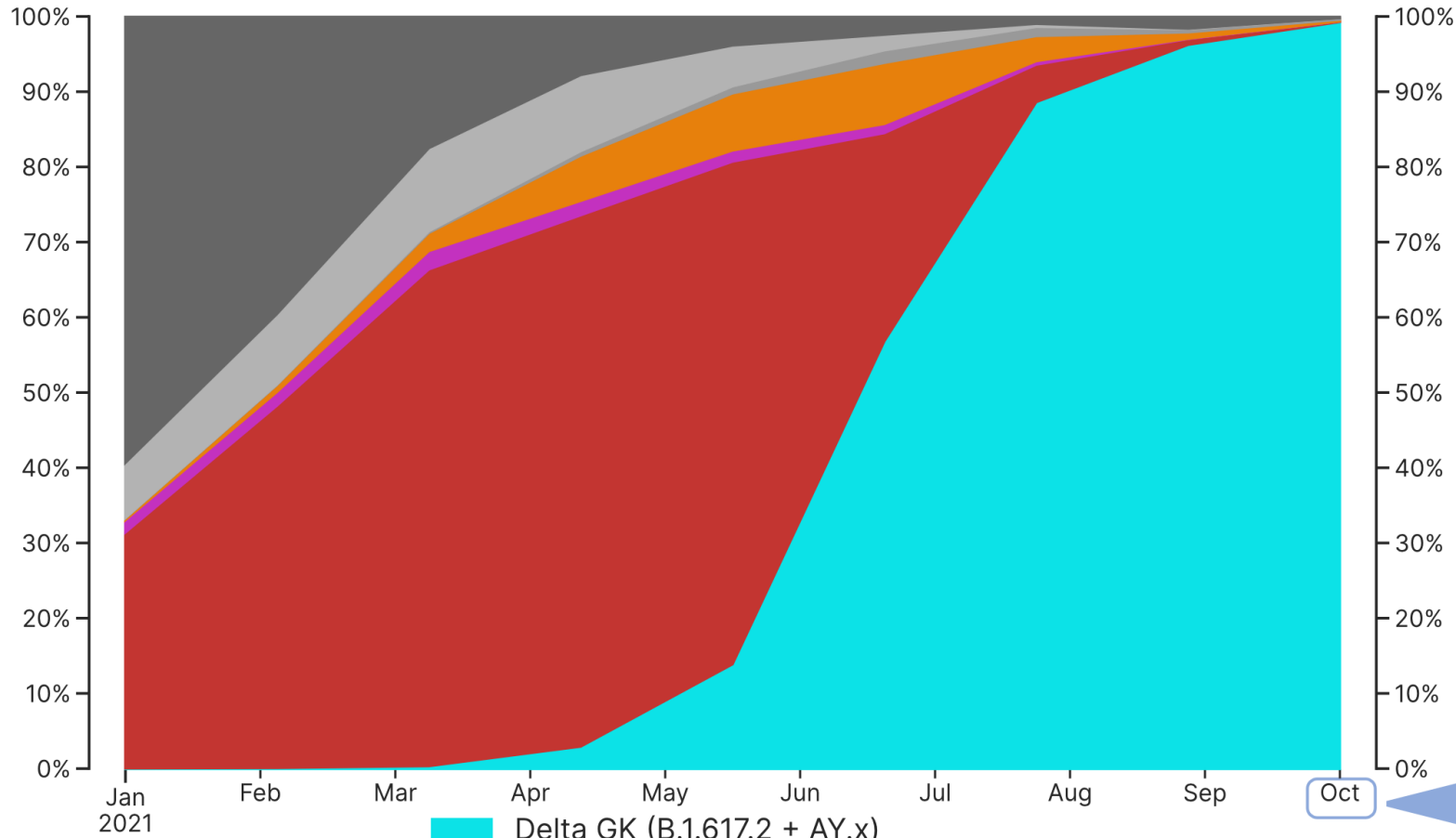
E484K T478K N501Y
in nonG clade (A, B & B.2)



**K458R G496V E484Q V445F V445A S494L
K458M F456L G446V S477N F490L G476S
N501T T478R G446A N501Y P499R E484K
E484V N437S G485R Q493L T478K S494P
E484G K417N N501I Q493E N439K S477G
A475V Q493P F490S S477I K417T R403K
L455F V445I G485S G446S E484D G446R**
in G, GK & GV clades (B.1, B.1.617.2, AY.* &
B.1.177)



Distribution temporelle des variants au 02-11-21



- Delta GK (B.1.617.2 + AY.x)
- Alpha GRY (B.1.1.7 + Q.x)
- Beta GH/501Y.V2 (B.1.351 + B.1.351.x)
- Gamma GR/501Y.V3 (P.1 + P.1.x)
- Variants of Interest
- Variants Under Monitoring
- Others

Le fitness viral compte!

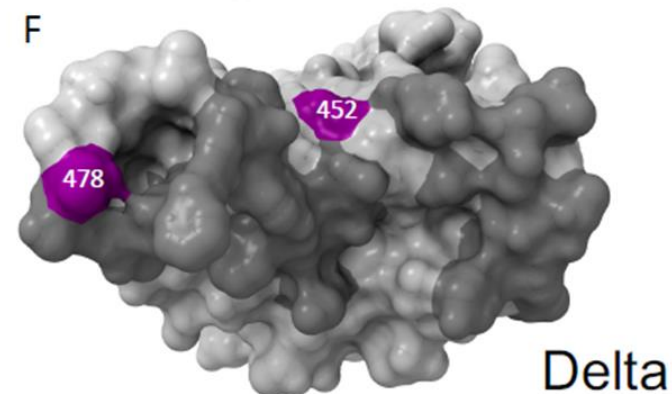
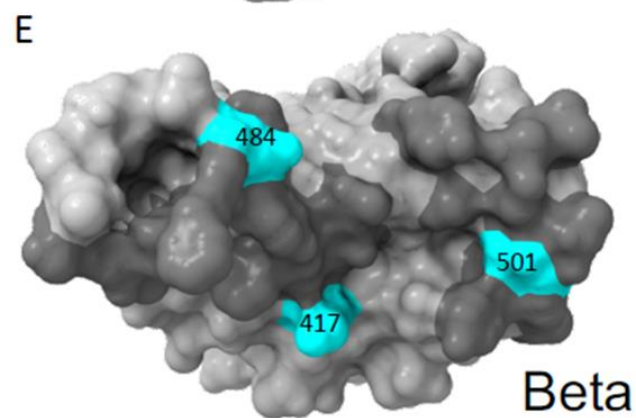
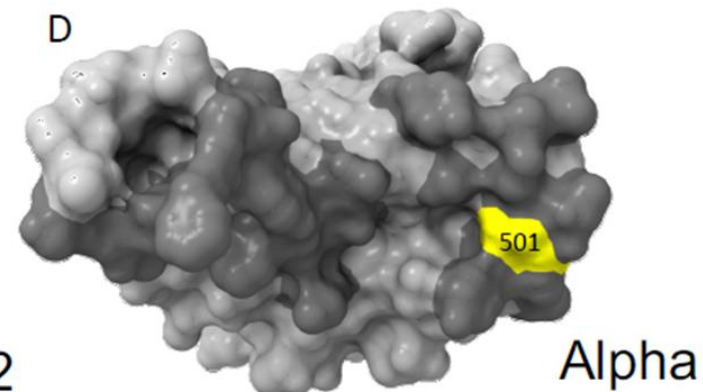
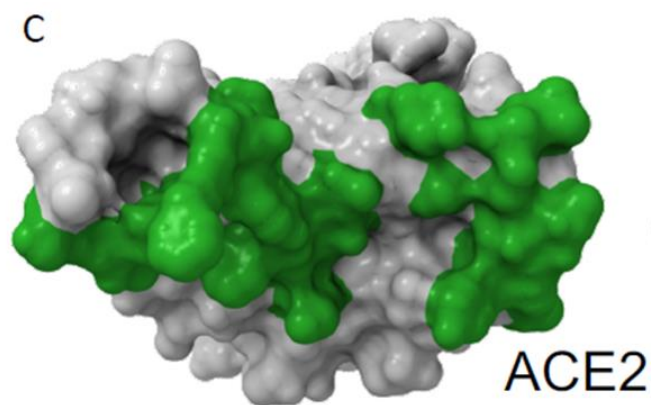
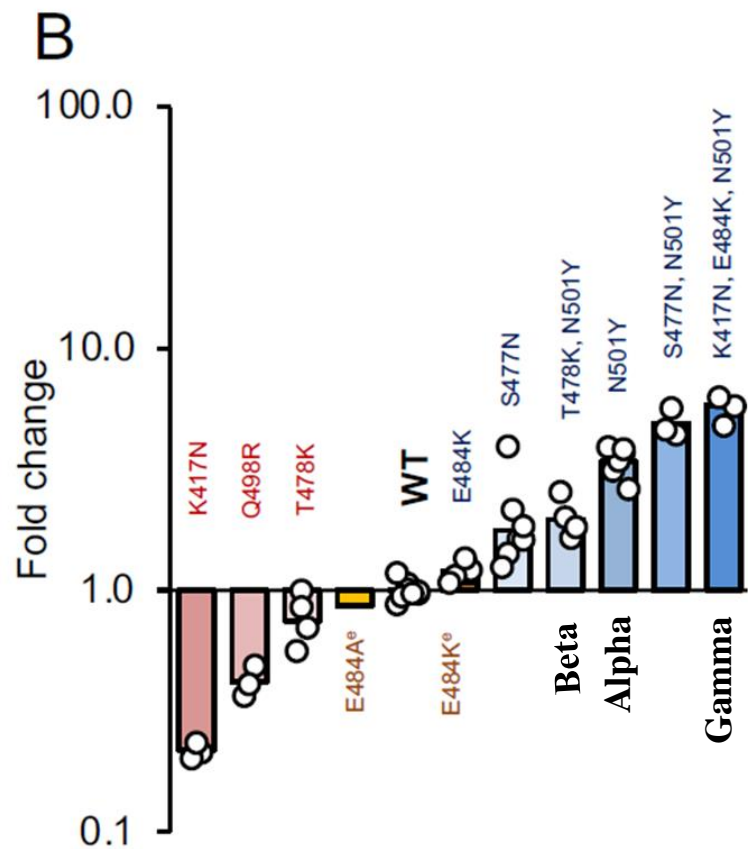
Small and/or
Variable Sample
Sizes

*We gratefully acknowledge
the Authors from Originating
and Submitting laboratories
of sequence data on which the
analysis is based.*



Pourquoi Alpha, Beta et Gamma sont plus transmissibles

Rôle du RBD de la spike



Données introduction Omicron (au 29 novembre 2021)

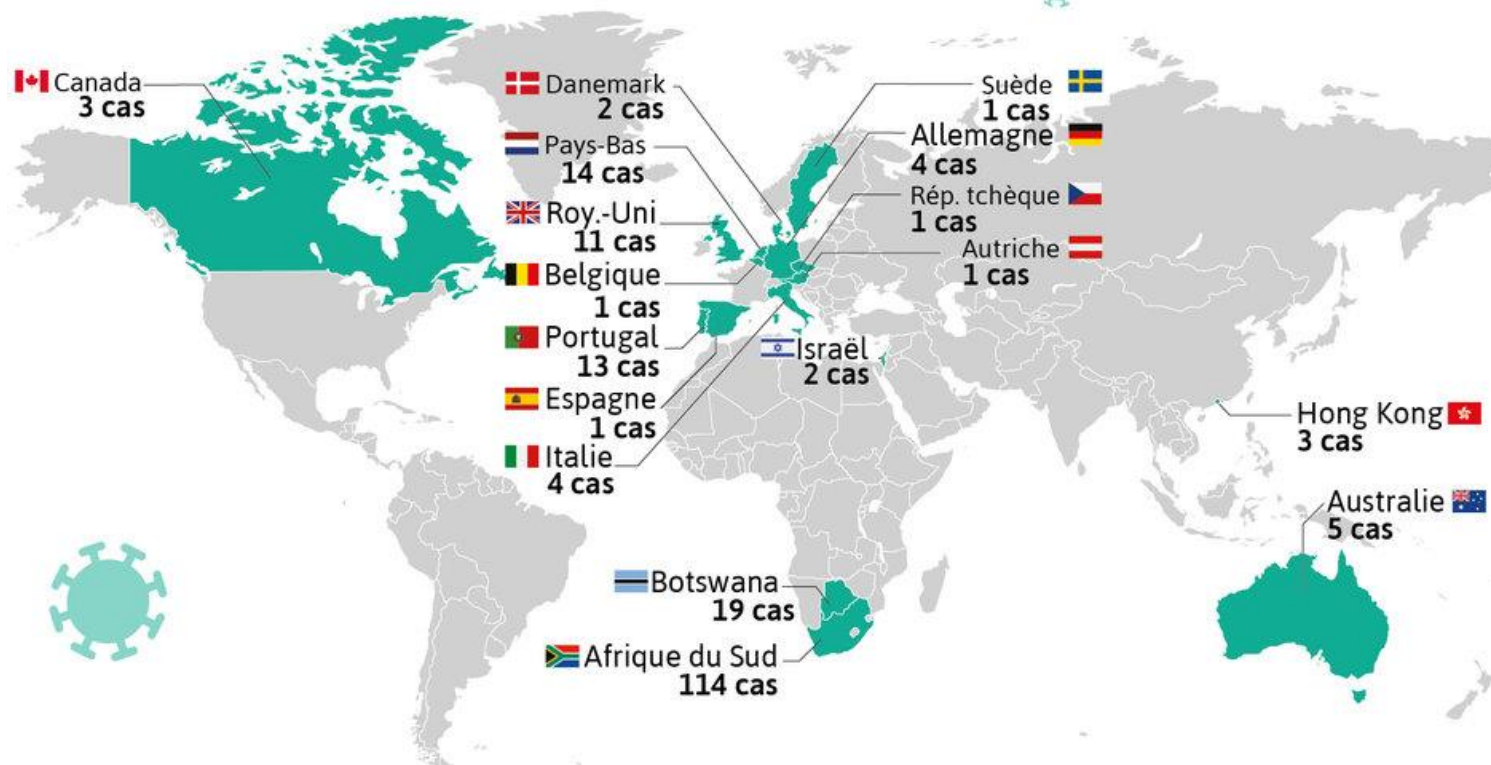
COVID-19

LE NOUVEAU VARIANT «OMICRON», B.1.1.529.

Les **17** pays et territoires
où un total de **199** cas ont été confirmés
par séquençage.

Au 29 novembre 2021

à 21h30*



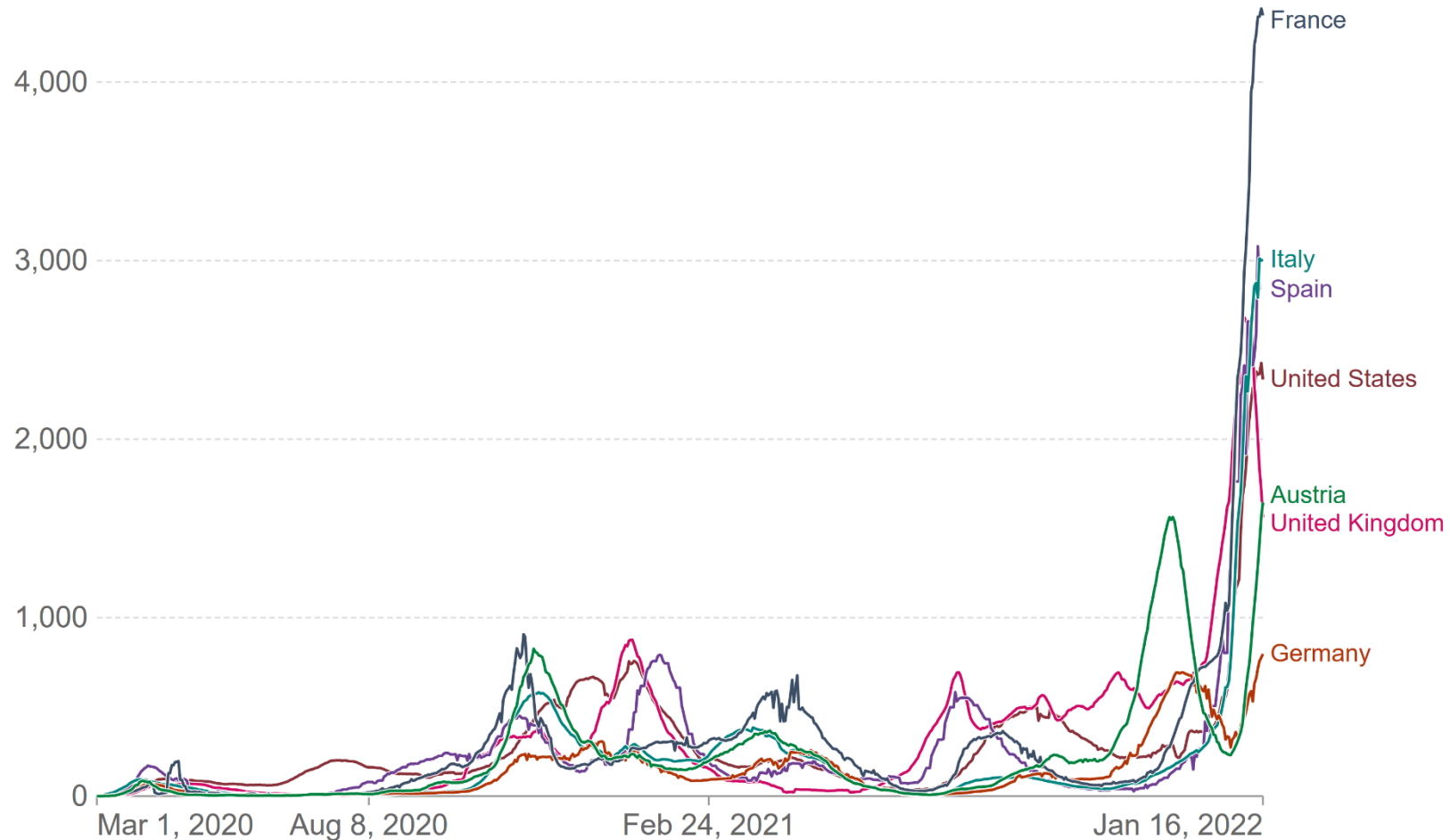
*heure française. Source: médias.

Et la 5^e vague avec Omicron...

Daily new confirmed COVID-19 cases per million people

7-day rolling average. Due to limited testing, the number of confirmed cases is lower than the true number of infections.

Our World
in Data

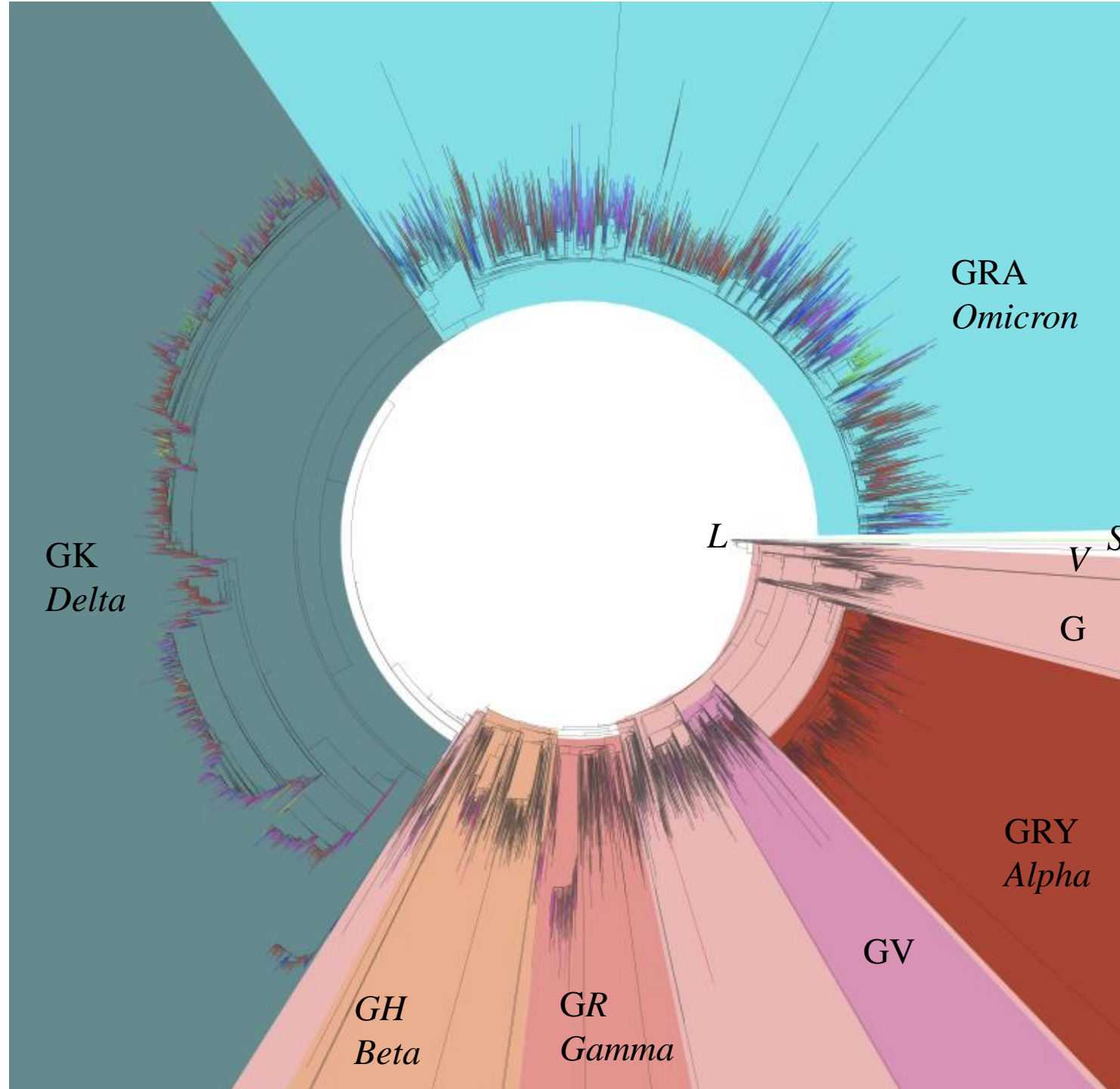


Source: Johns Hopkins University CSSE COVID-19 Data

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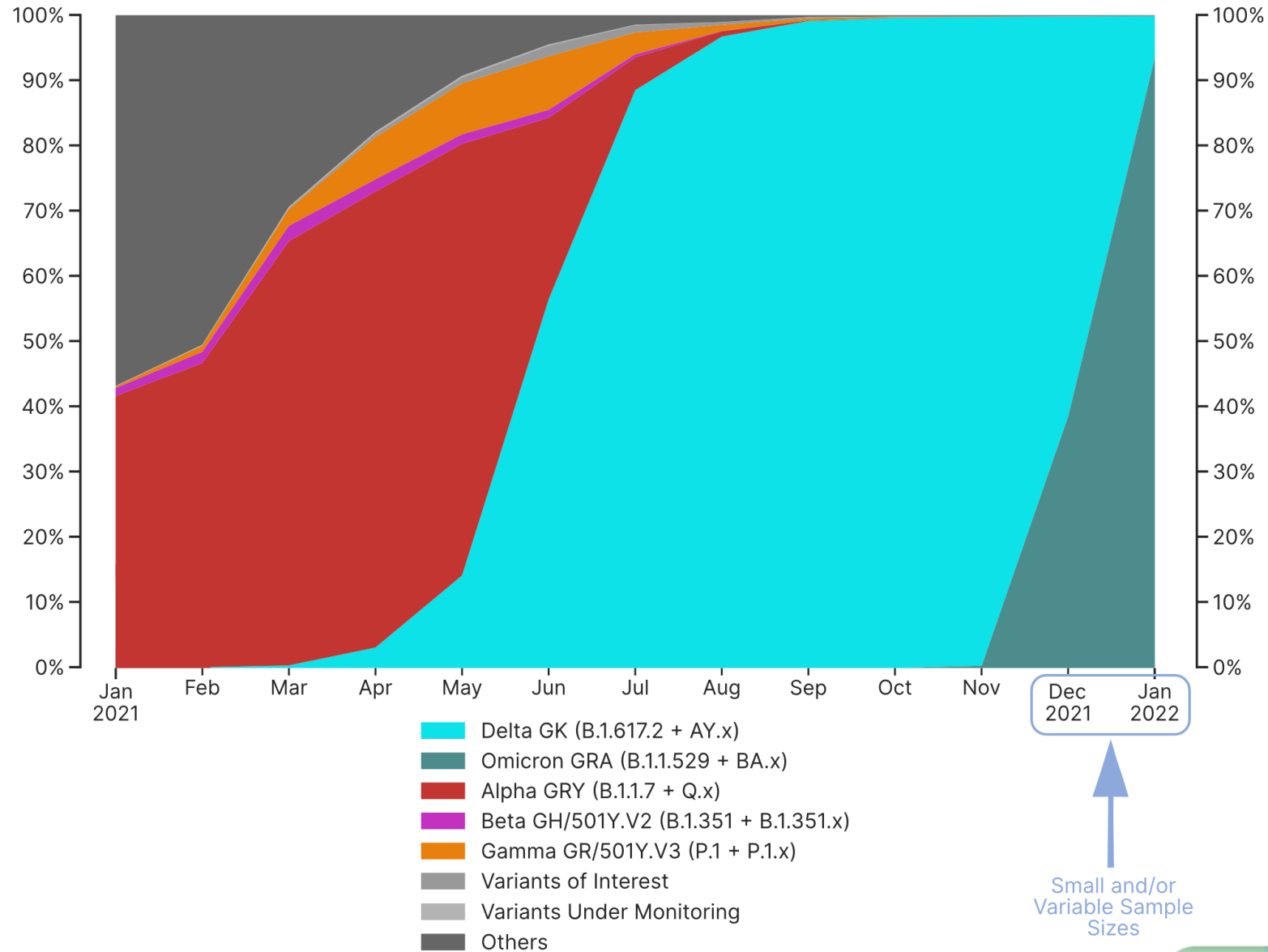
Source: www.covidtracker.fr

***Sampled genome
tree derived from all
outbreak sequences
2022-01-18***



Blue: Asia
Green: new from Oceania
Magenta: new from Americas
Red: new from Europe
Yellow: new from Africa
Grey: from previous updates

Timecourse of *variant* distribution in *all submitted sequences* 2022-01-18



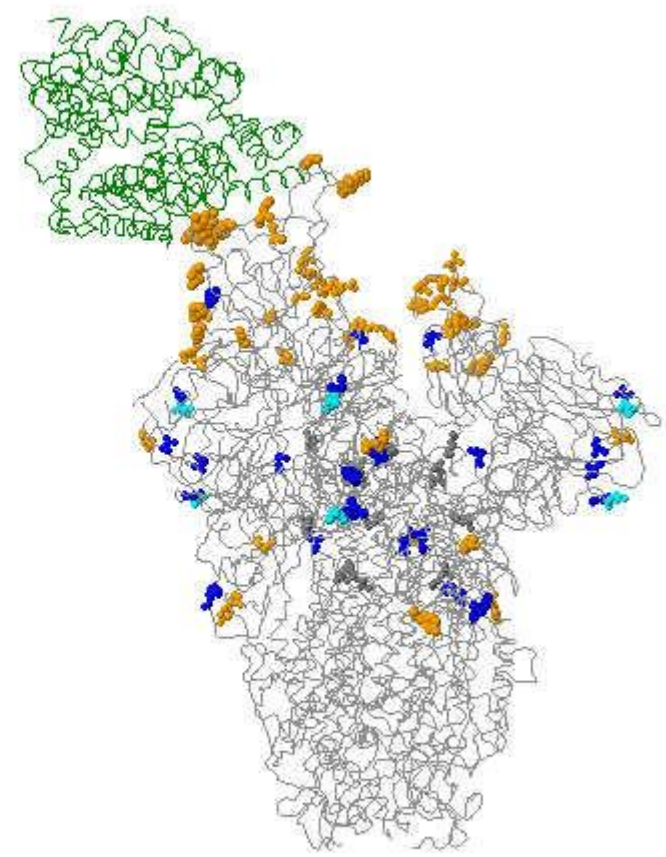
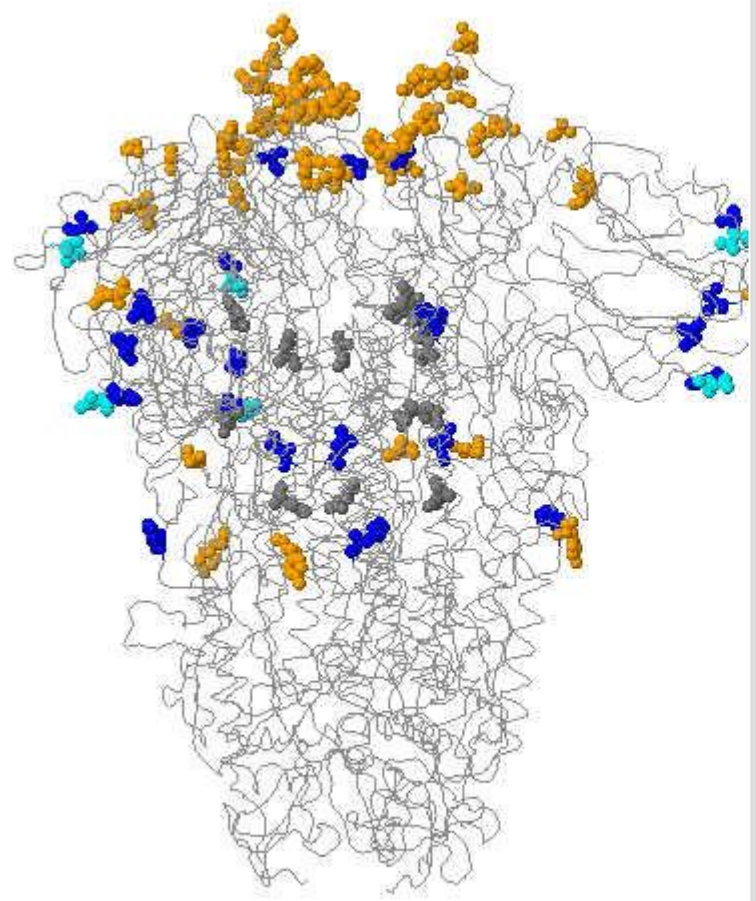
Dec 2021 Jan 2022

Small and/or Variable Sample Sizes

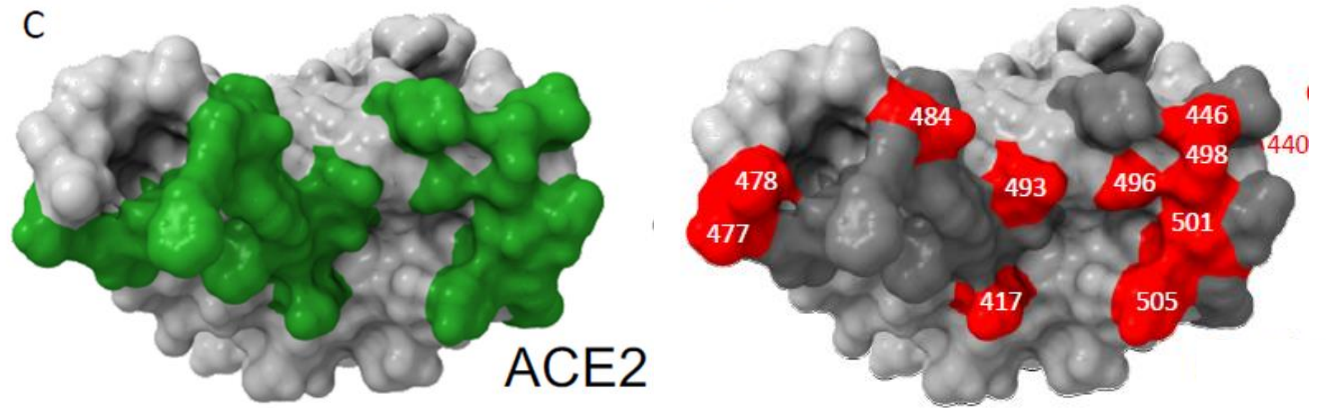
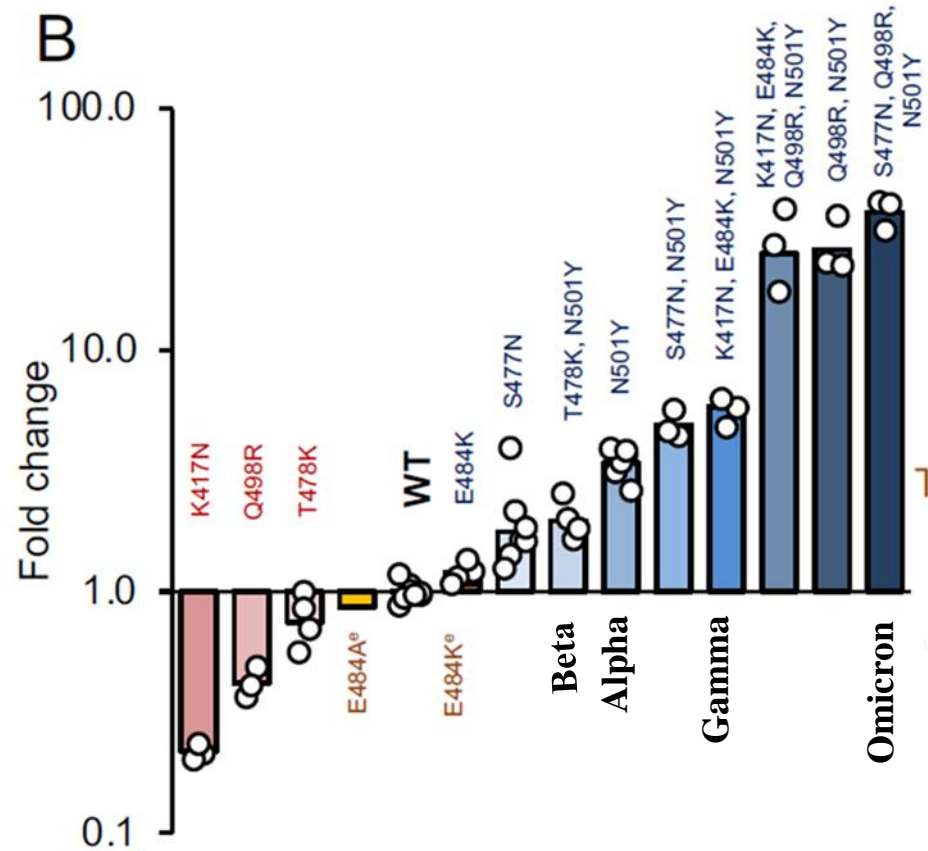
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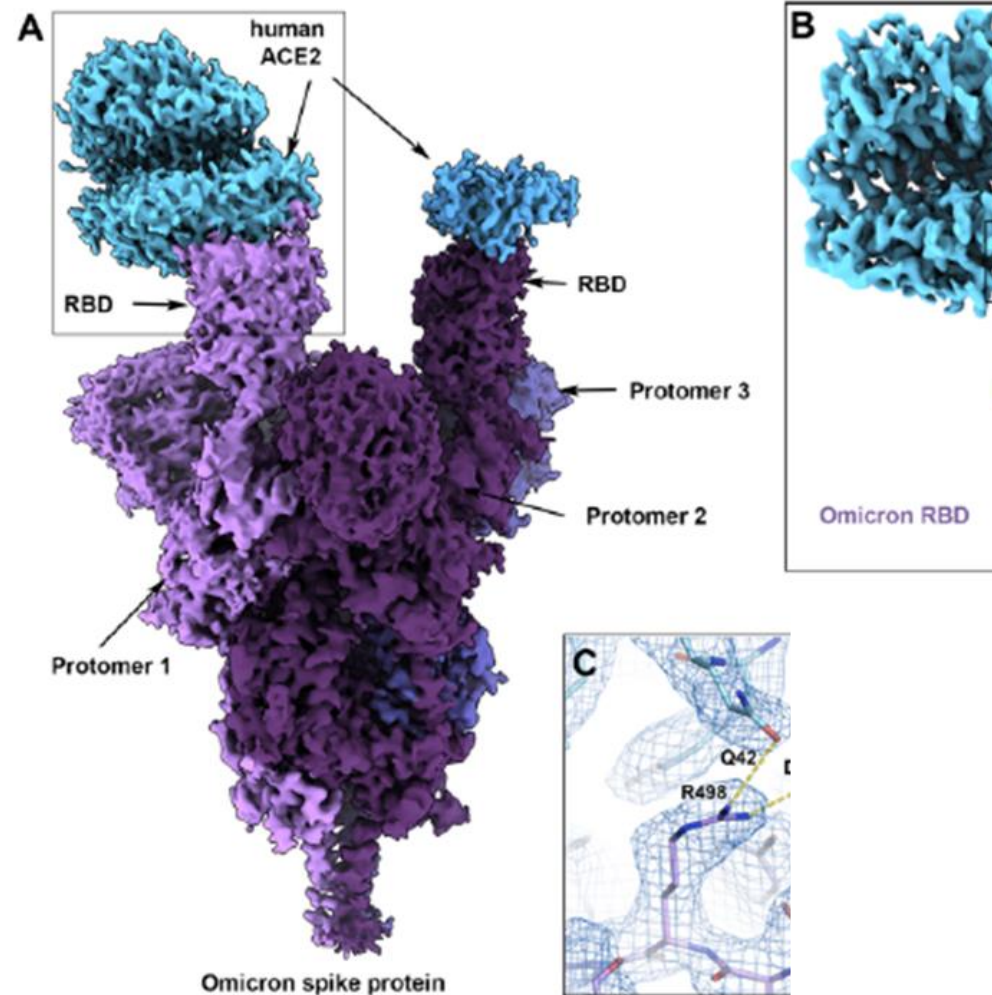
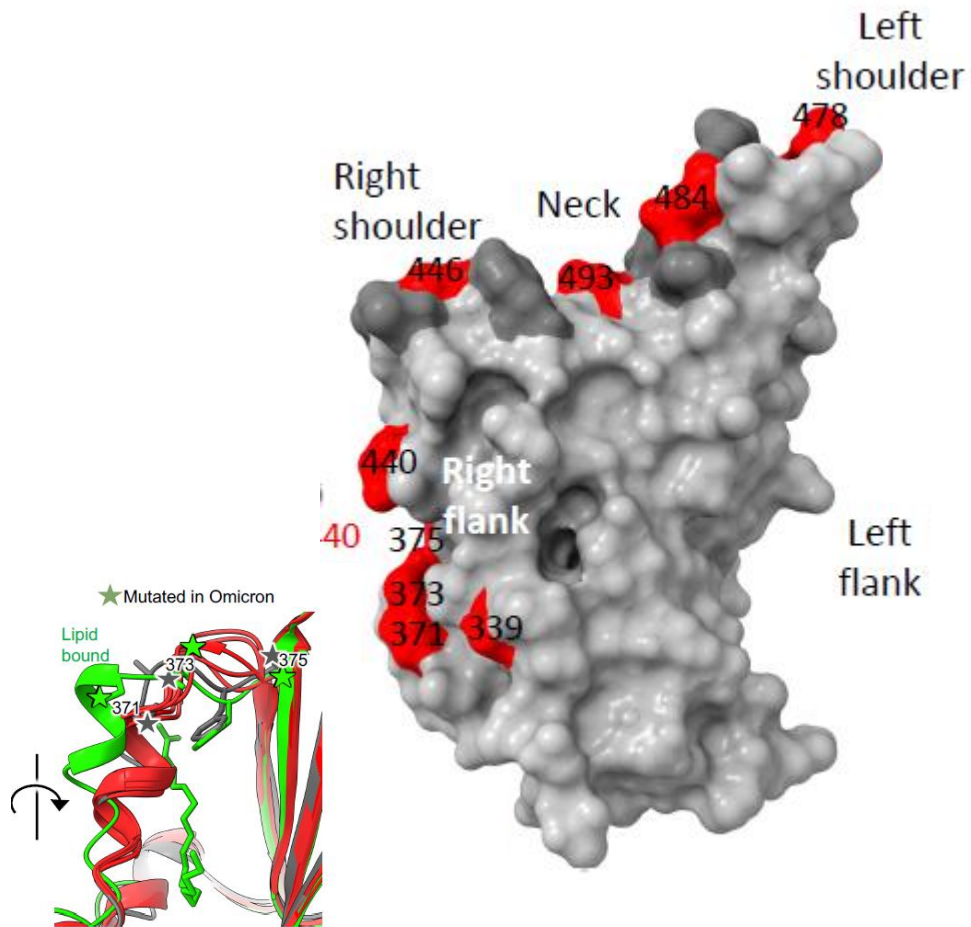
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Pourquoi Omicron est plus transmissible

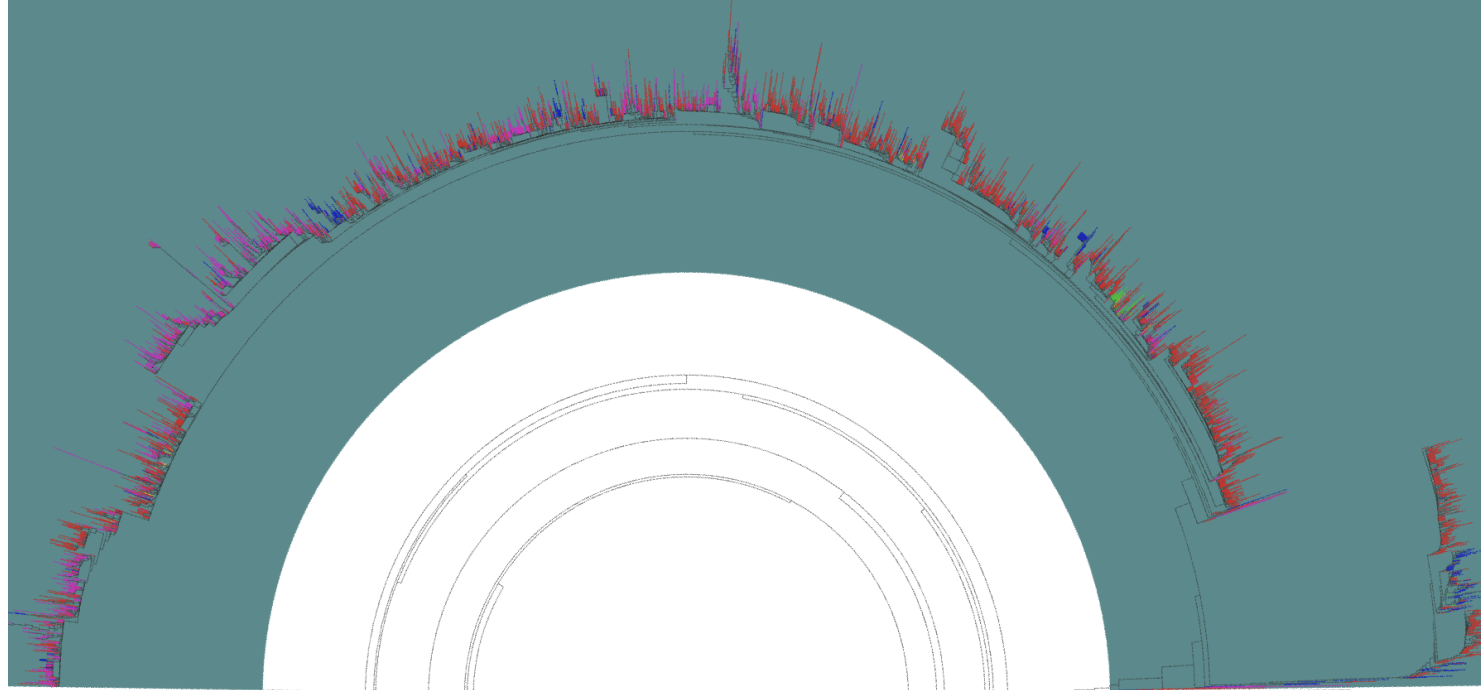


Pourquoi Omicron est plus transmissible : impact du RBD up



Phylogénie des virus (01-02-2022)

GRA
Omicron
BA.1



GRA
Omicron
BA.2

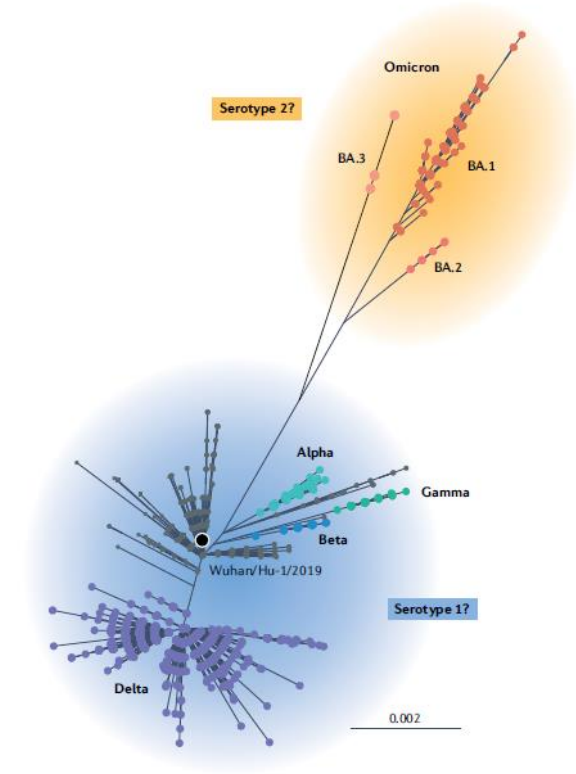
GR
Gamma

GRY
Alpha

GV

GH
Beta

G

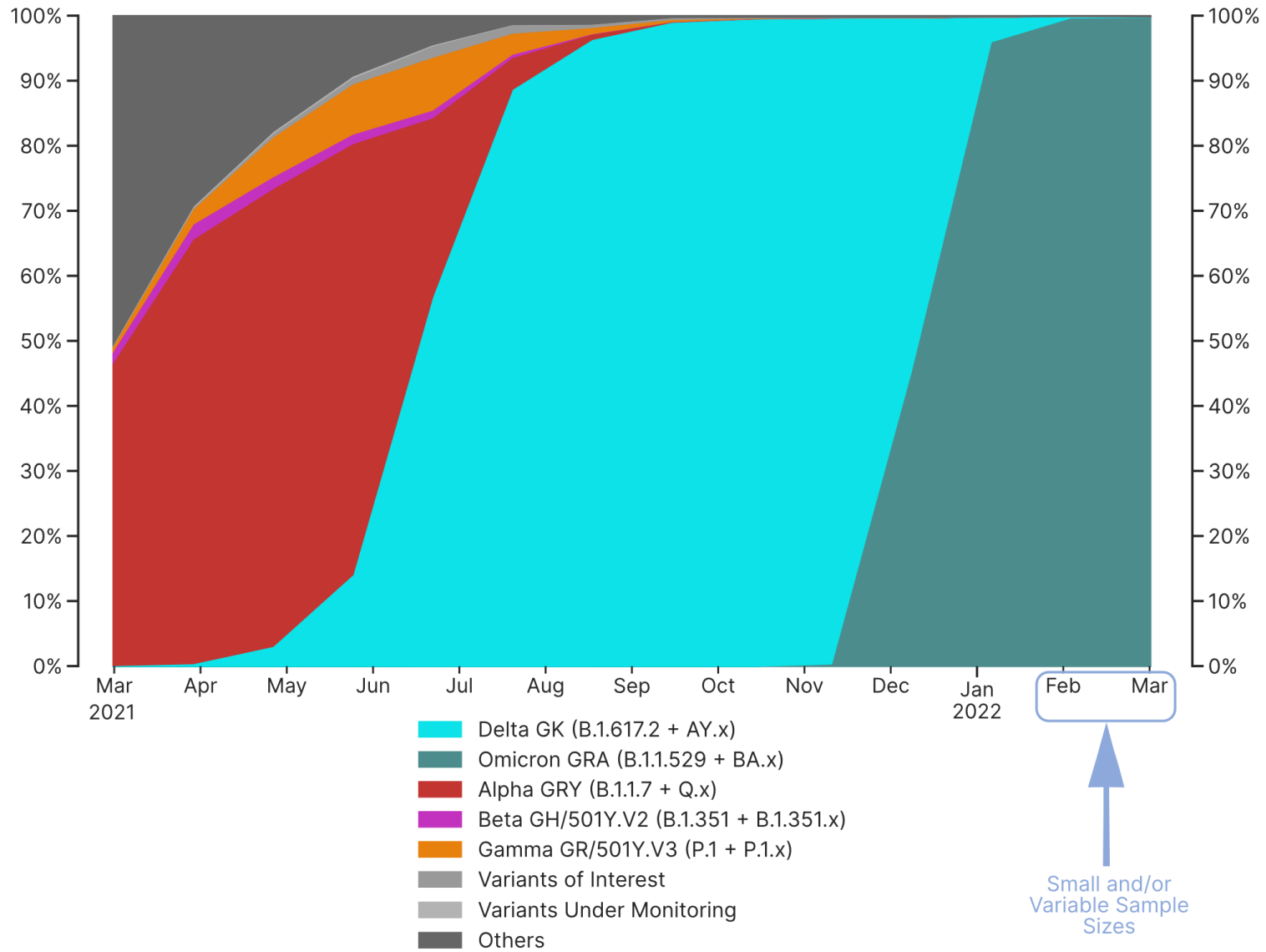


GK
Delta

Fig. 1 | SARS-CoV-2 global evolution and Omicron divergence. Maximum likelihood phylogenies inferred from spike nucleotide sequences; scale corresponding to number of substitutions per site.

Simon-Loriere E & Schwartz O, 2022

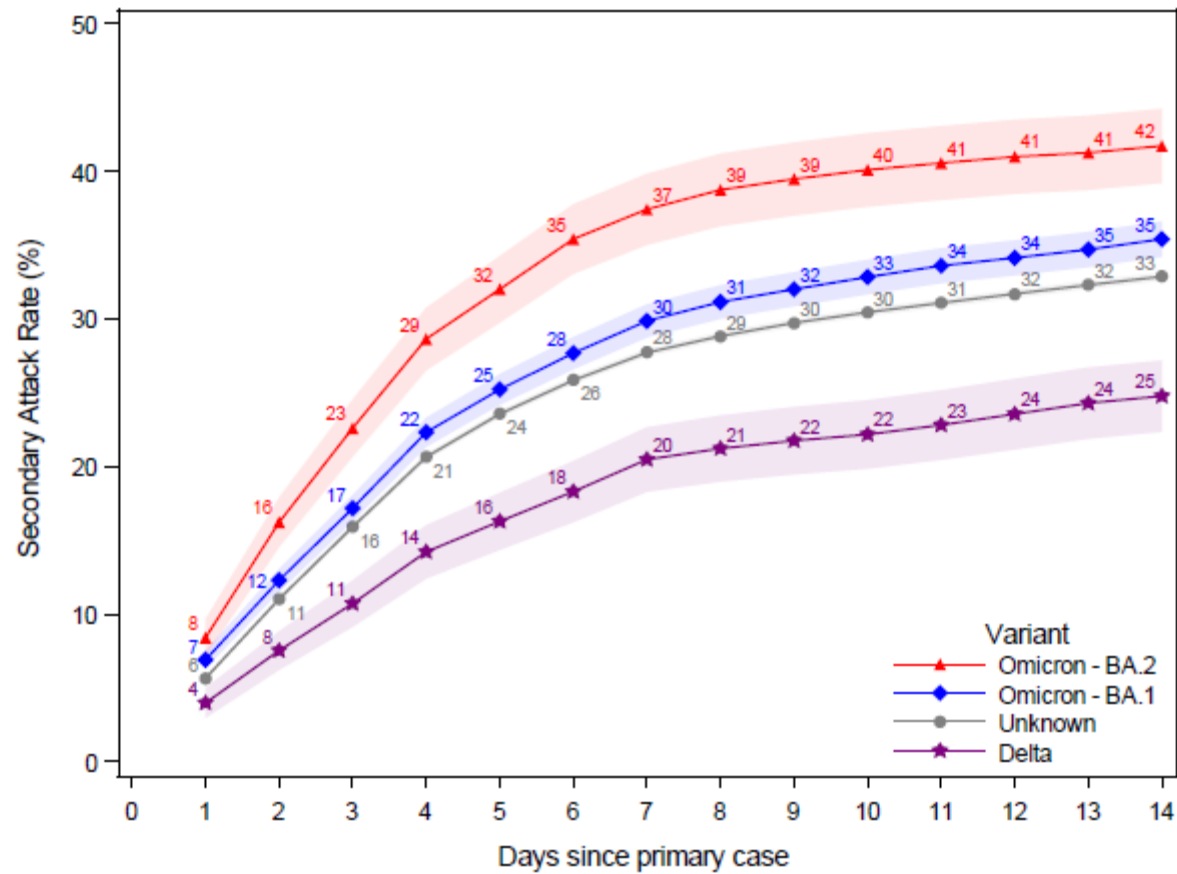




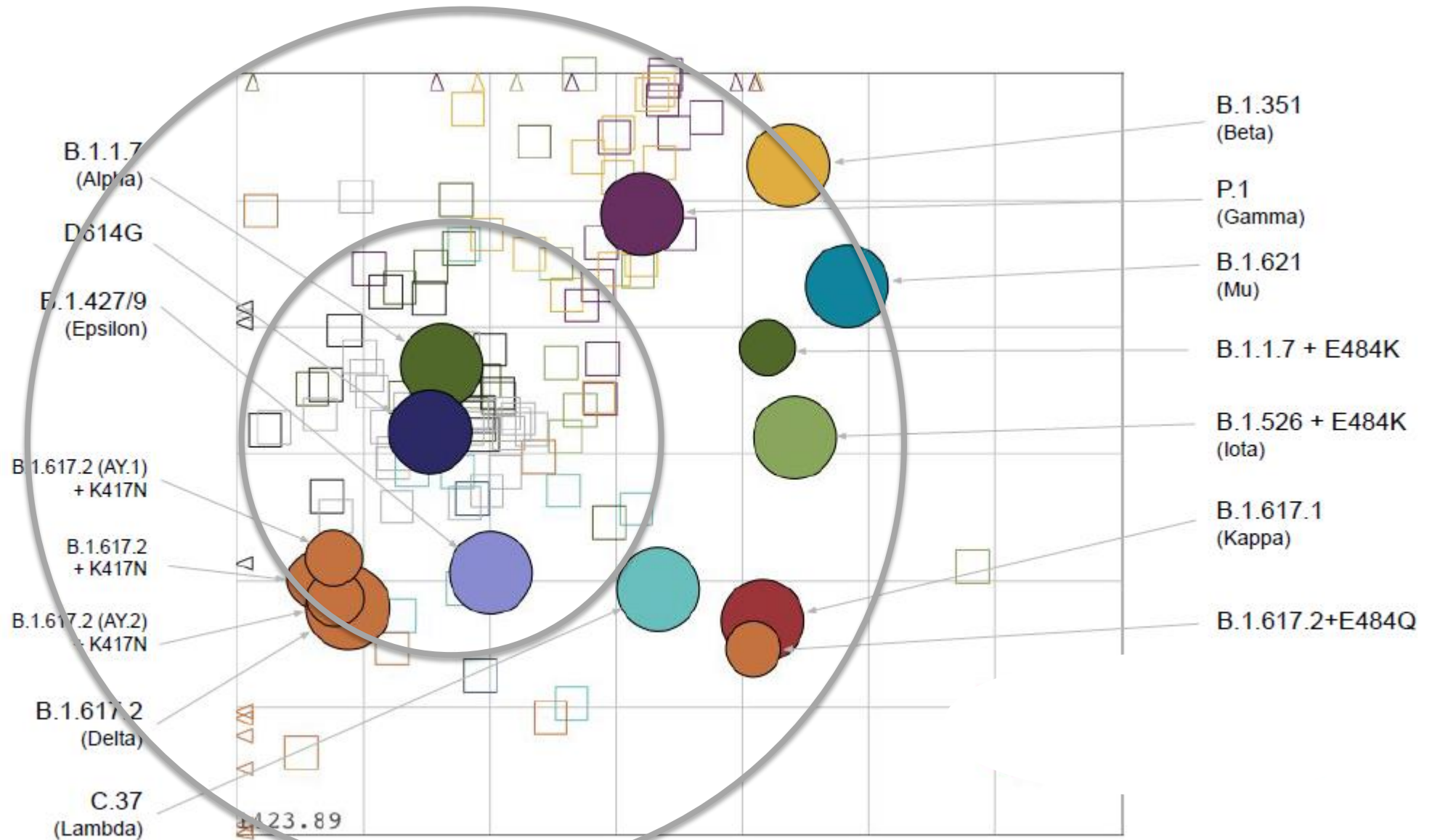
Transmission of SARS-CoV-2

Omicron VOC subvariants BA.1 and BA.2:

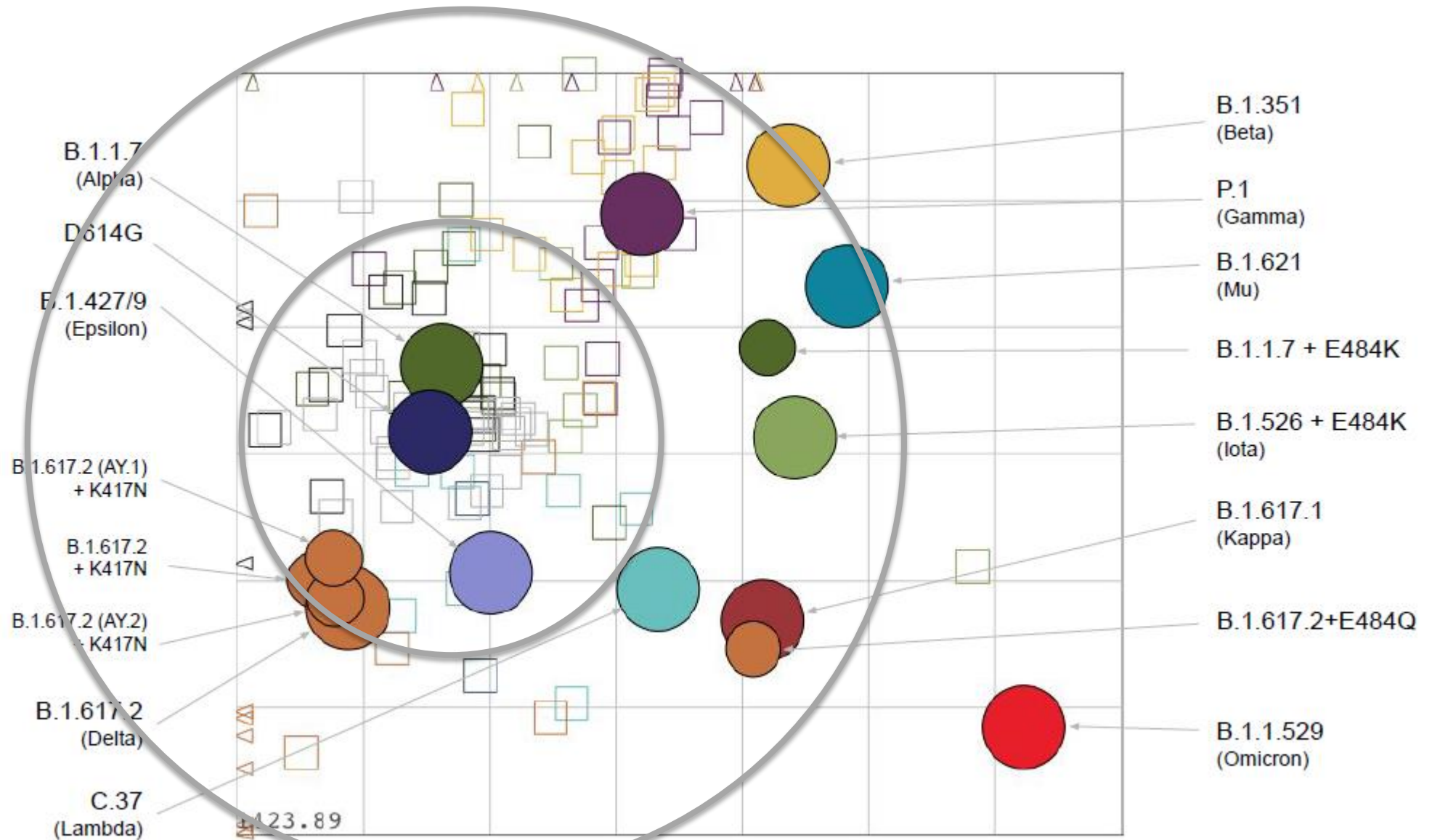
Evidence from Danish Households



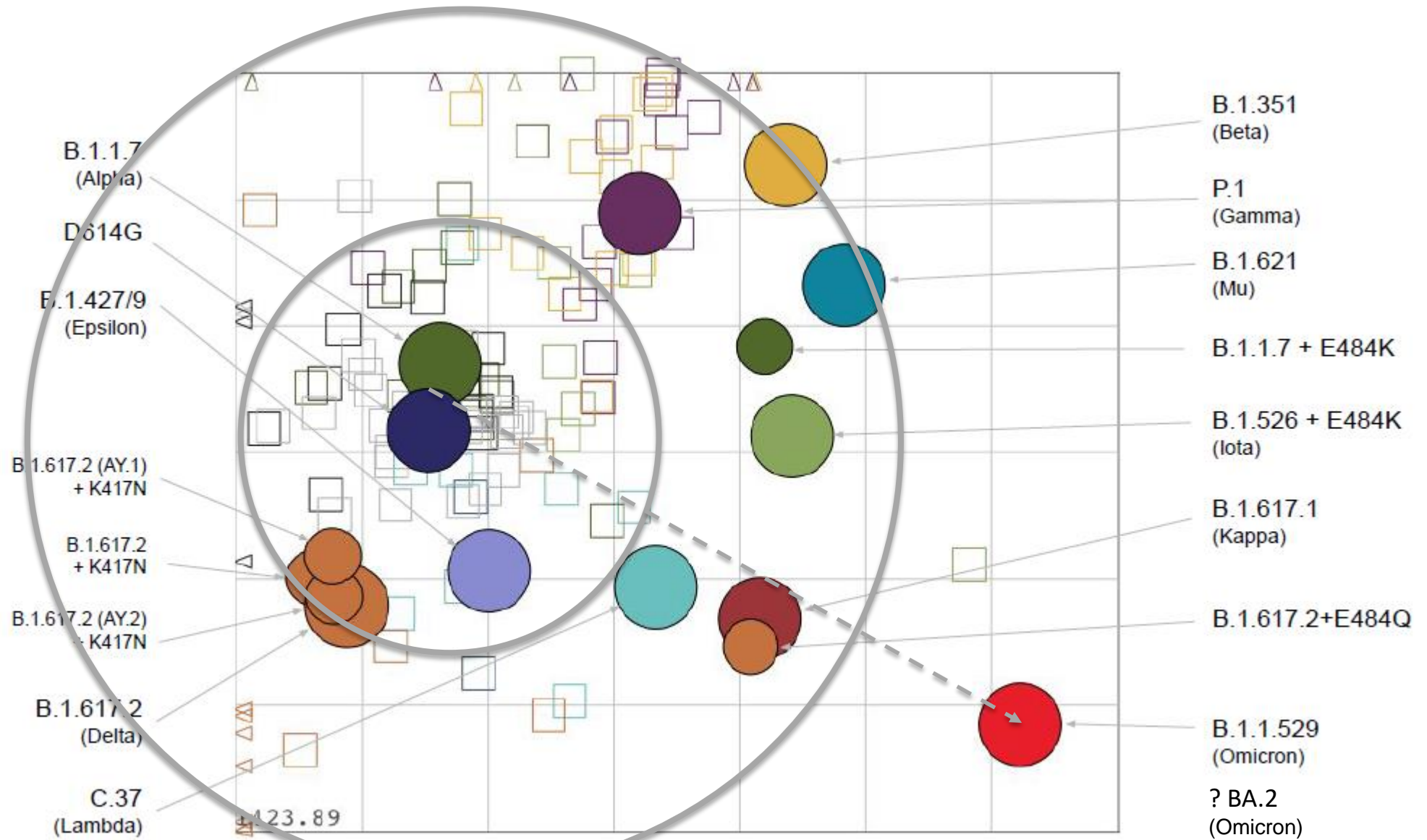
Données d'évolution antigénique



2021-12-20. Data: Shen & Montefiori (Duke). Omicron subject to change with more data. Method: Antigenic Cartography. Smith *et al*, Science, 2004.



2021-12-20. Data: Shen & Montefiori (Duke). Omicron subject to change with more data. Method: Antigenic Cartography. Smith *et al*, Science, 2004.

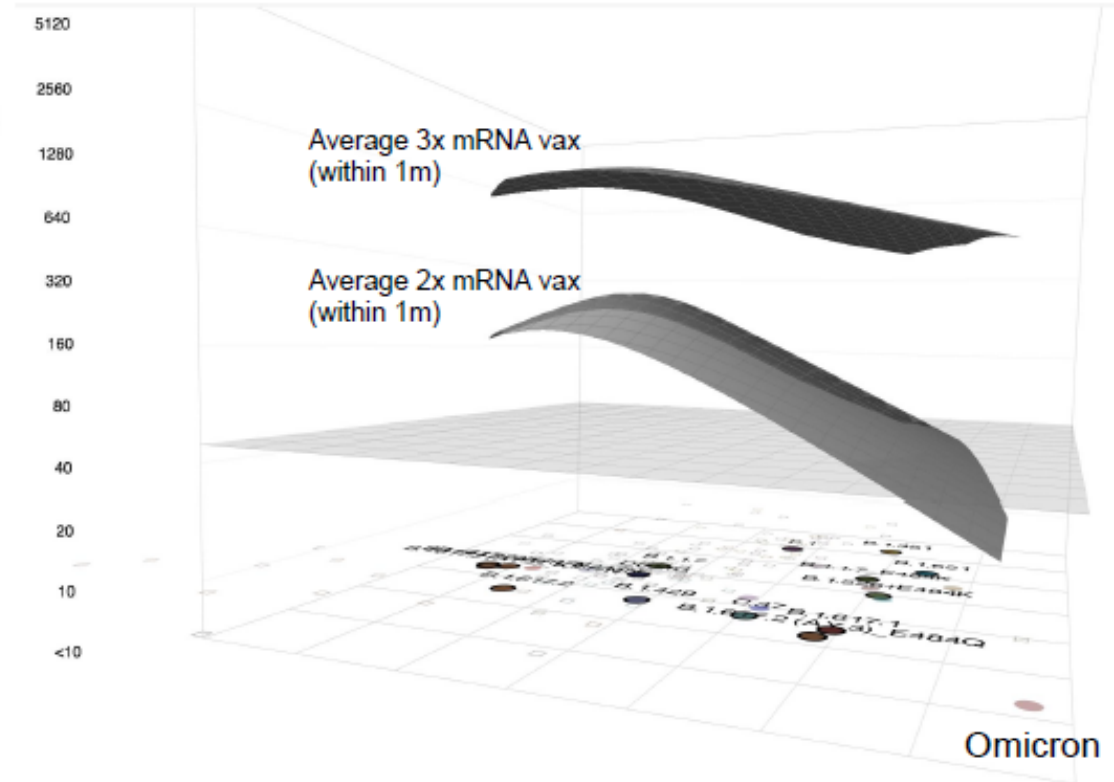
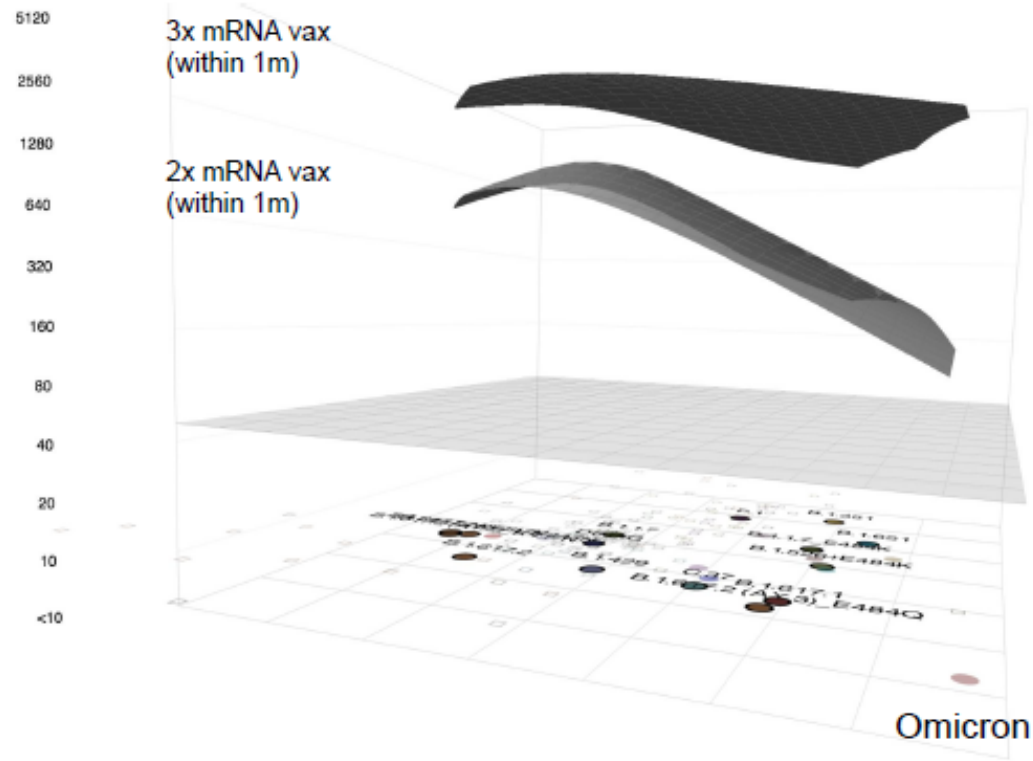


2021-12-20. Data: Shen & Montefiori (Duke). Omicron subject to change with more data. Method: Antigenic Cartography. Smith *et al*, Science, 2004.

Comparison of average 2x and 3x mRNA vax on estimated antibody landscapes

Shen, Montefiori and Doria-Rose

Average over 7 studies that did 2x and 3x vax

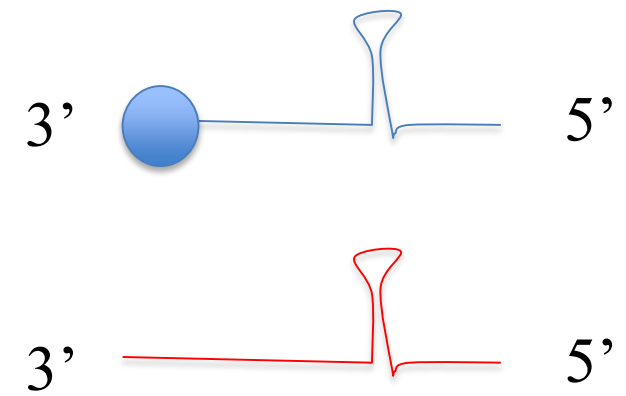
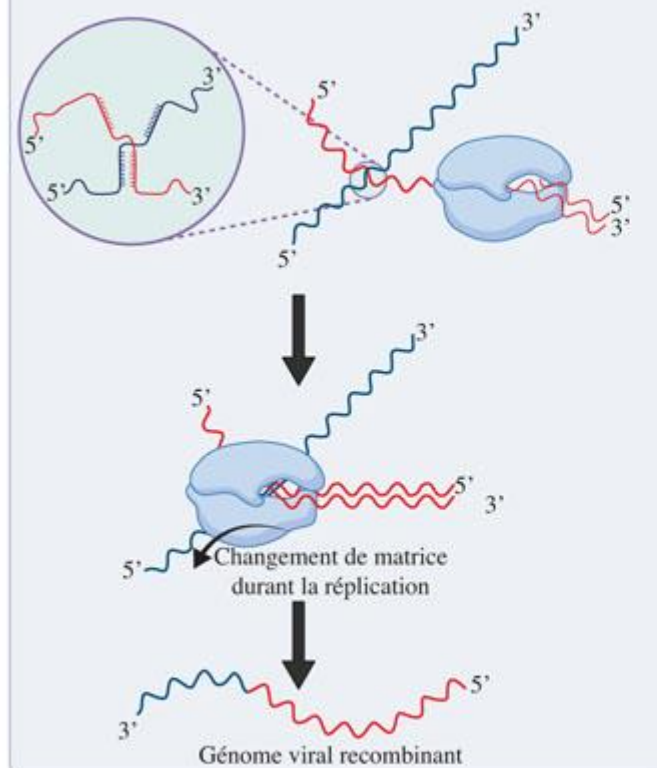


Les hypothèses pour la suite (mars 2022)

- Perspectives les plus probables :
 - Nouveau variant venant de la racine (circulation silencieuse ou immunodéprimés)
 - Evolution par dérive moléculaire / antigénique depuis BA.1
- Perspective a garder en tête
 - Recombinaison génétique entre le SARS-CoV-2 et un beta-coronavirus humain
 - Rétro-zoonose a partir d'animaux d'élevage
 - Histoire de Hamsters dorés
 - Histoire de visons
 - Cervidés en Amérique du Nord
 - Animaux de compagnie et de zoo infectés

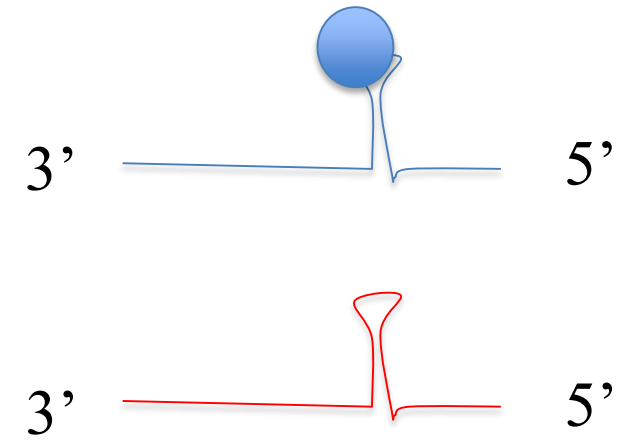
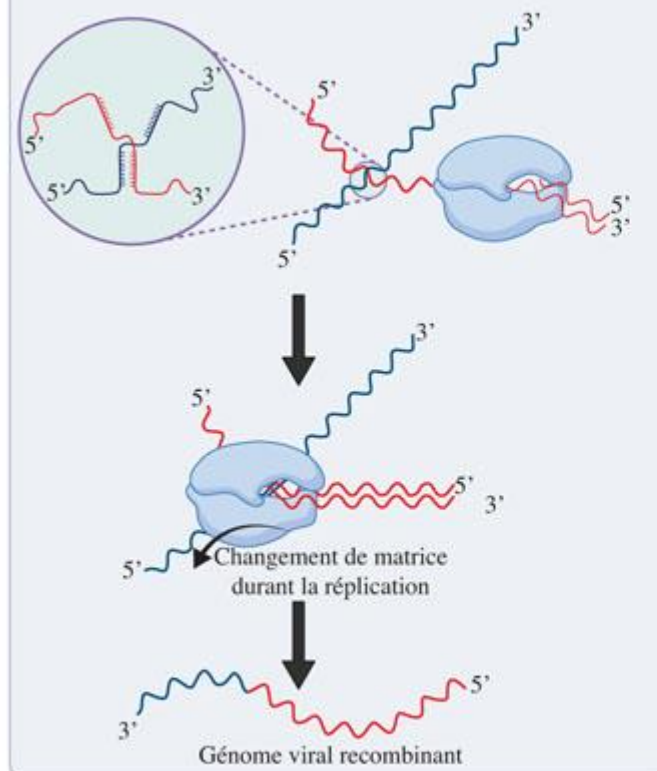
Emergence des recombinants

A Mécanisme du choix de copie (ou saut de matrice)



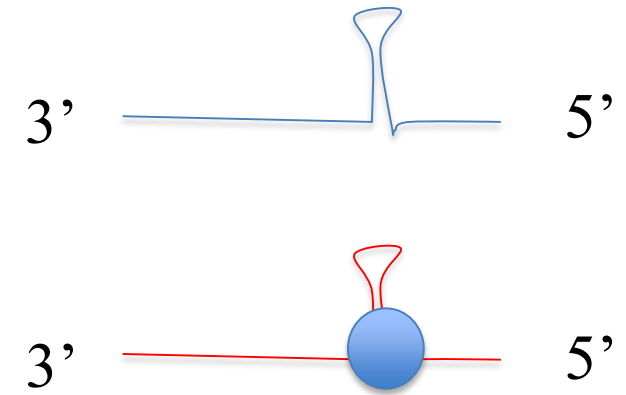
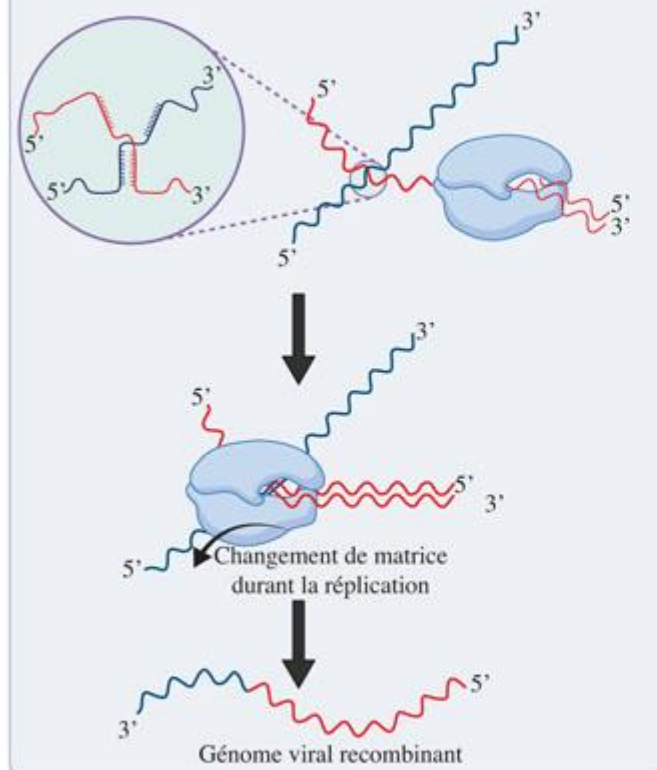
Emergence des recombinants

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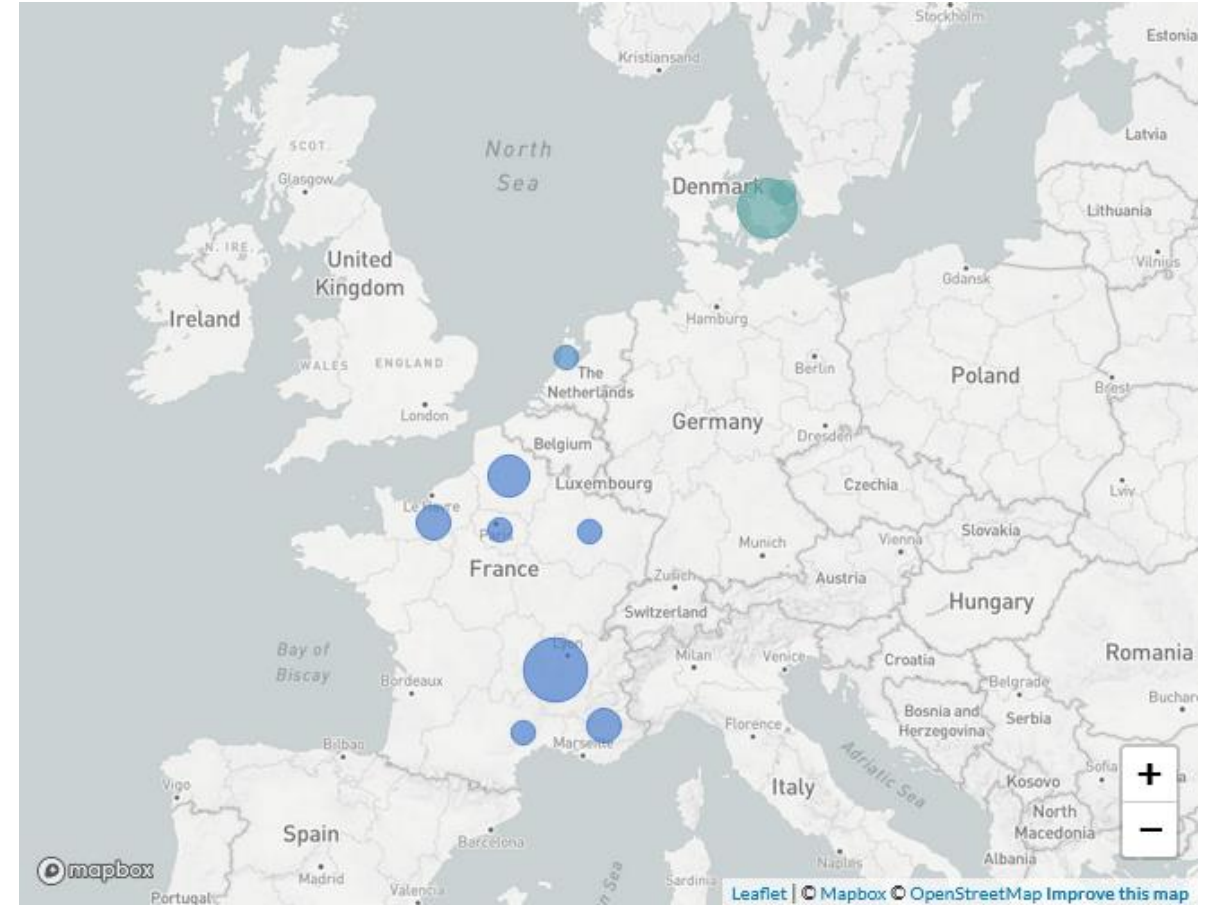
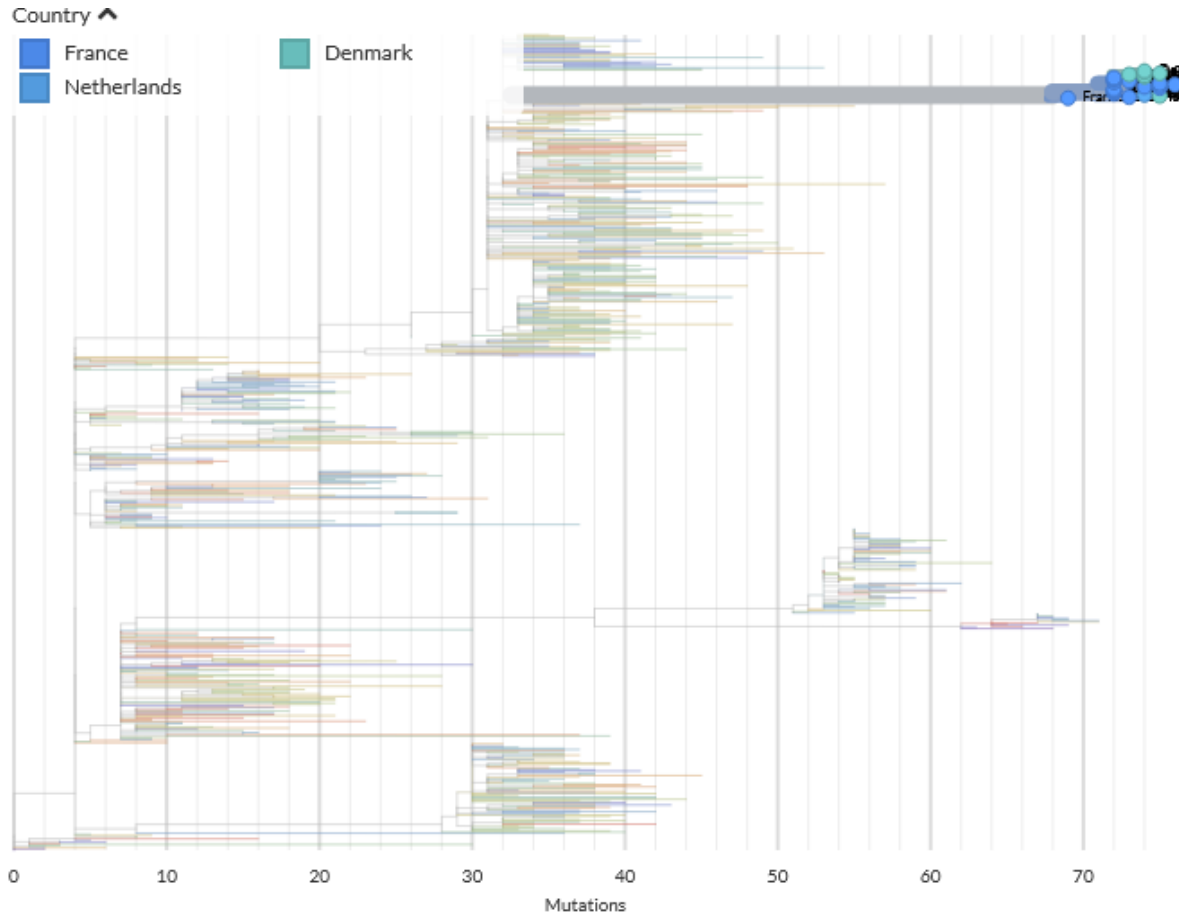


Emergence des recombinants

A Mécanisme du choix de copie (ou saut de matrice)



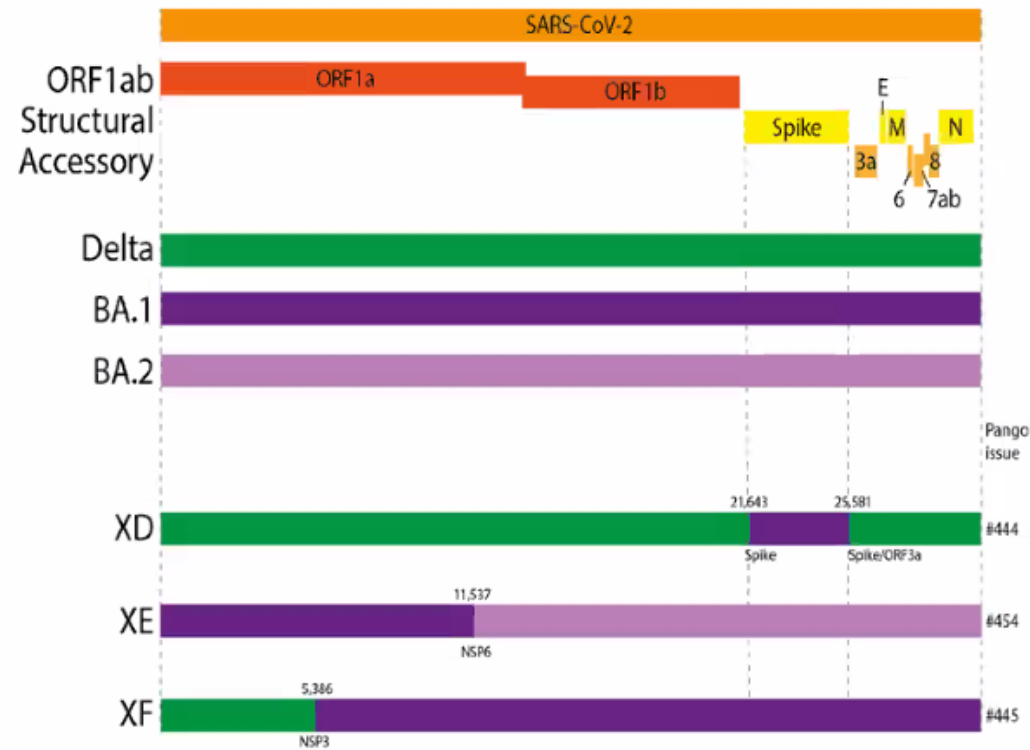
Emergence recombinant delta omicron (19-981) au 3 mars 2022



Panorama actuel des recombinants

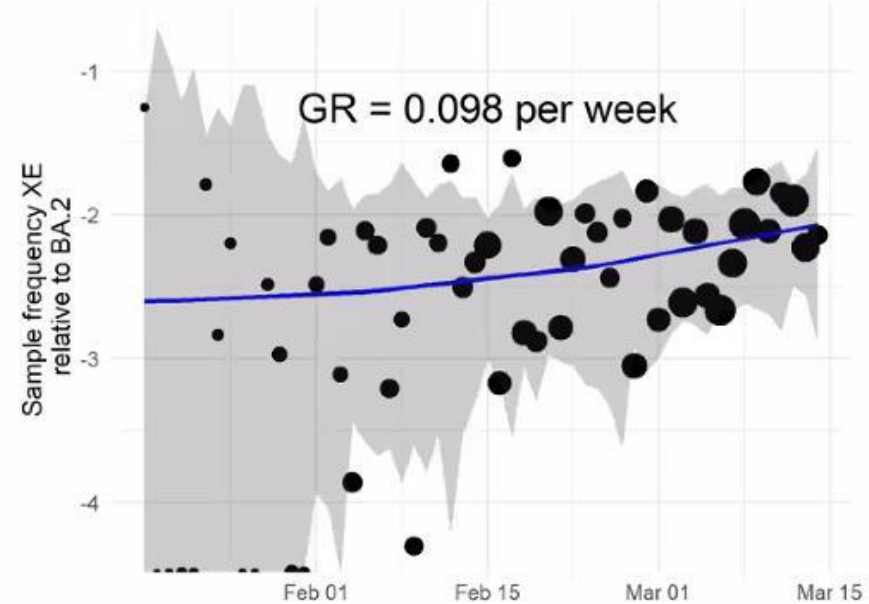
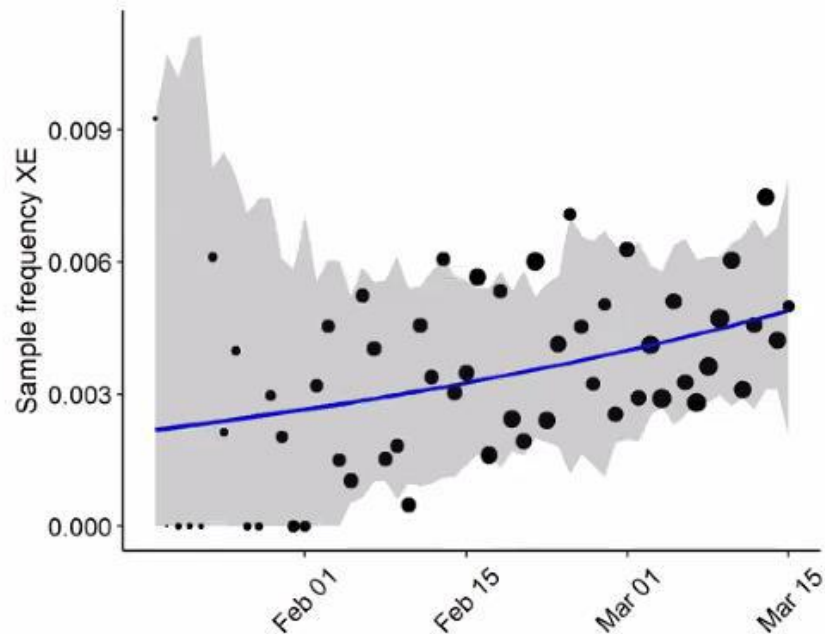
XD, XE and XF - newly designated recombinant lineages

- There are currently three recombinant lineages being monitored as part of horizon scanning: XD, XE, and XF.
- XD and XF are Delta and BA.1 recombinants.
- XE is a BA.1 and BA.2 recombinant.
- XF is associated with UK sequenced samples.
- XD is predominantly associated with France.
- Danish BA.1/BA.2 Recombinant



Consequences/inducteurs de l'apparition de recombinants

XE recombinant growth is 10% higher than BA.2 growth
(data to 16 March)



Note: sample frequency is shown as proportion of BA2s only

Conclusions

- La crise COVID est sans précédent dans le monde de la virologie moderne
- Cette situation exceptionnelle illustre le potentiel évolutif d'un virus pandémique
- Les connaissances sur l'évolution des coronavirus (et probablement des virus pandémiques respiratoires) se sont considérablement renforcées. Ces évolutions combinent
 - les modifications de fitness sélectionnées positivement avant le développement de la pression immunitaire,
 - puis survient la sélection de variants d'échappement immunitaire
- L'évolution reste imprévisible, mais le maintien du SARS-CoV-2 dans la population est certain
- L'évènement qui permettra la fin de la circulation du virus sur un mode « pandémique » reste inconnu
- Ce potentiel évolutif reste important
 - Dérive antigénique (diversité intra-hôte et inter-hôte)
 - Recombinaison
 - Retro-zoonose
 - Une combinaison des 3



MERCI

CNR des virus respiratoire et laboratoire de Virologie IAI des HCL:

NGS team (Dr Laurence Josset)

Antonin Bal

Grégory Destras

Grégory Quéromès

Hadrien Regue

Bruno Simon

Dr Alexandre Gaymard

Dr Emilie Frobert

Dr Martine Valette

Dr Vanessa Escuret

Dr Maude Bouscambert

Pr Florence Morfin

Virpath lab (Université de Lyon)

Dr Olivier Terrier

Dr Manuel Rosa-Calatrava

Dr Mario Andres Pizzorno



**GENomique
EPIdémiologique
des maladies
Infectieuses**



Public SARS-CoV-2 databases

GISAID

NextStrain

COV-GLUE

Covidtracker

ECDC

Ressource documentaire

Pr Derek Smith

HCL
**HOSPICES CIVILS
DE LYON**