



Maladies  
infectieuses

Inserm  
Institut national  
de la santé et de la recherche médicale



# Les différentes phases de l'évolution moléculaire et antigénique des SARS-CoV-2 au cours des 20 premiers mois suivant son émergence

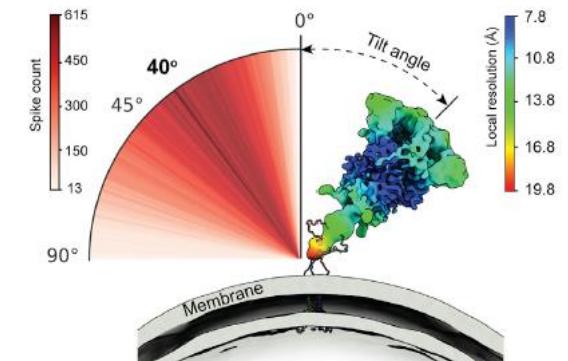
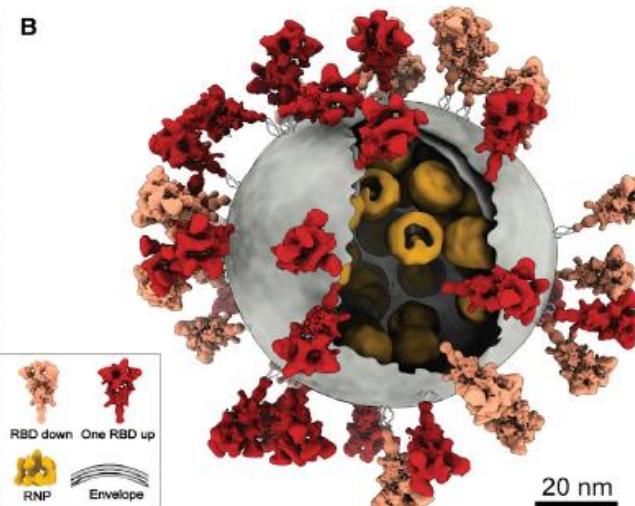
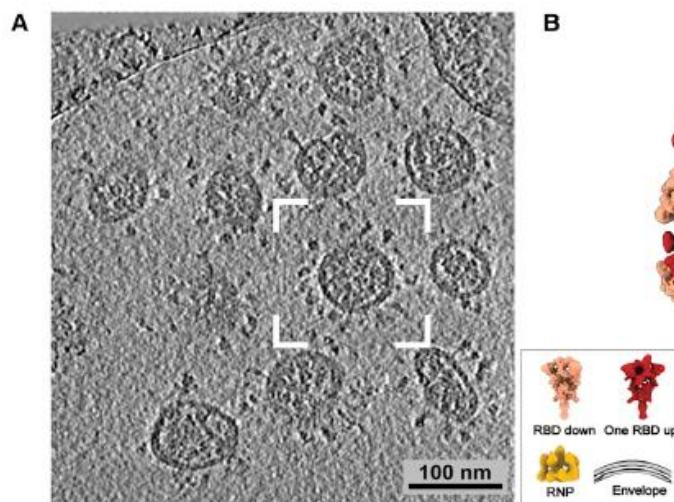
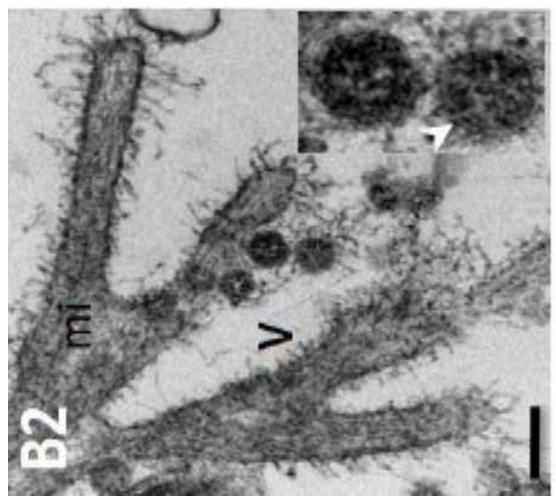
Bruno Lina

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Laboratoire Virpath, CIRI, INSERM U1111, CNRS 5308, ENS de Lyon, UCBL, Faculté de Médecine Lyon Est, Université de Lyon, F-69372, Lyon

*Les vaccins contre la Covid-19 : un état des lieux  
Groupe Vaccination et Prévention de la SPILF  
4 février 2022*

# Le virus SARS-CoV-2



# Phylogenie des précurseurs 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(high identity in Orf1ab, greatest difference in Spike protein, recombination or mixed viruses in metagenomic sample, not yet peer-reviewed)**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

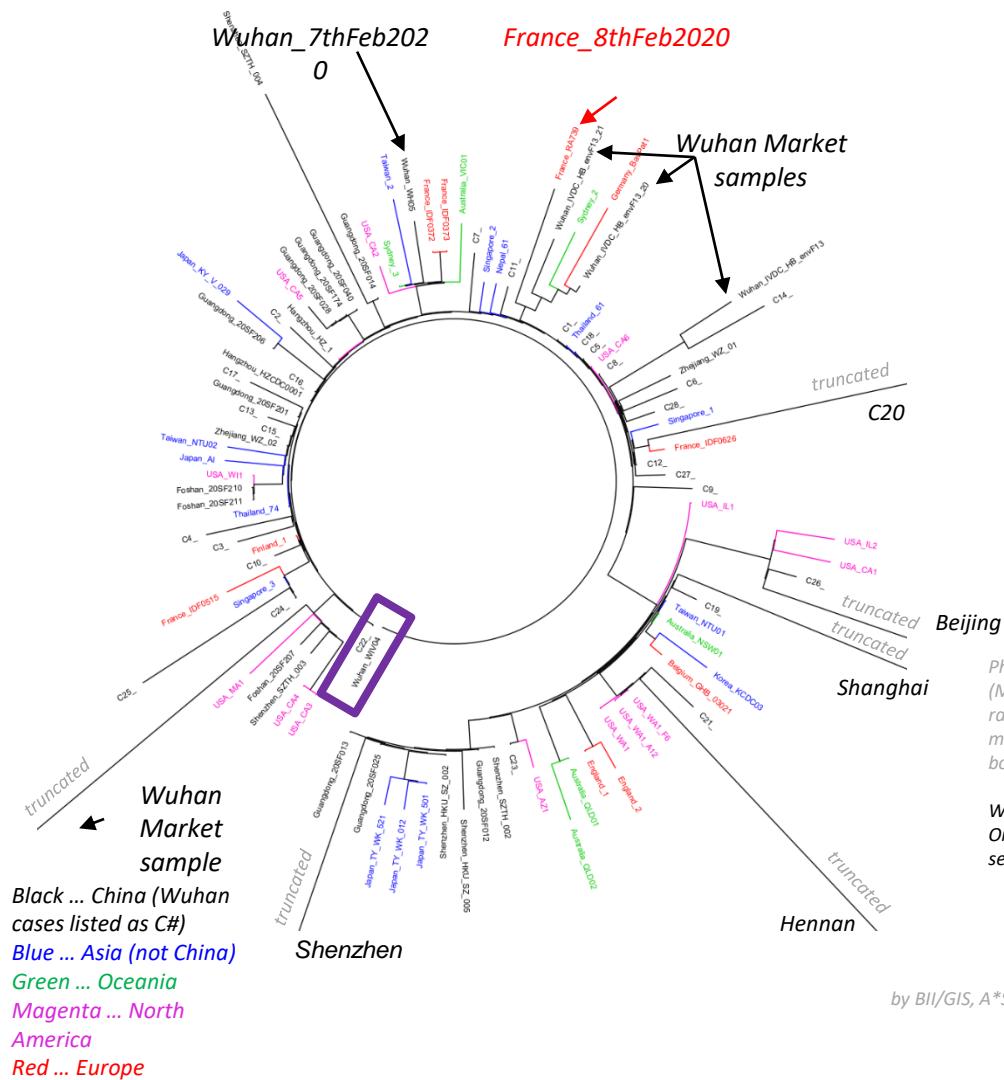
Green ... pangolin CoV (Southern China 2019)

Blue ... SARS CoV

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



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

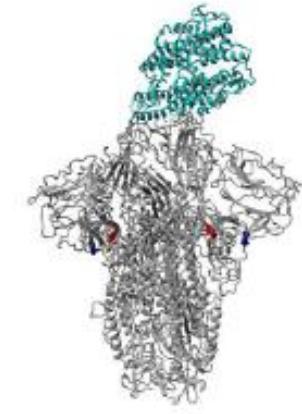


Phylogenetic tree created with RAXML-NG (Maximum Likelihood tree search, 10 randomized parsimony starting trees, GTR model, Gamma distributed rates, 500 bootstrap) and visualized in FigTree

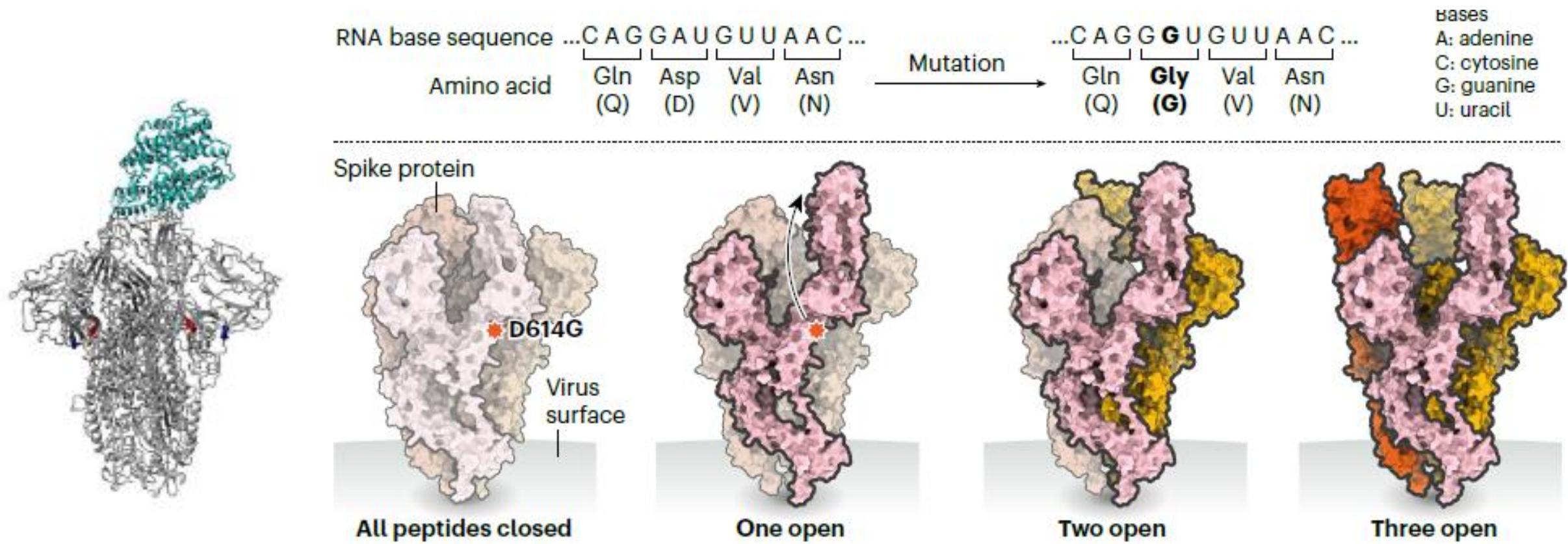
We gratefully acknowledge the Authors from Originating and Submitting laboratories of sequence data on which the analysis is based.



by BII/GIS, A\*STAR Singapore

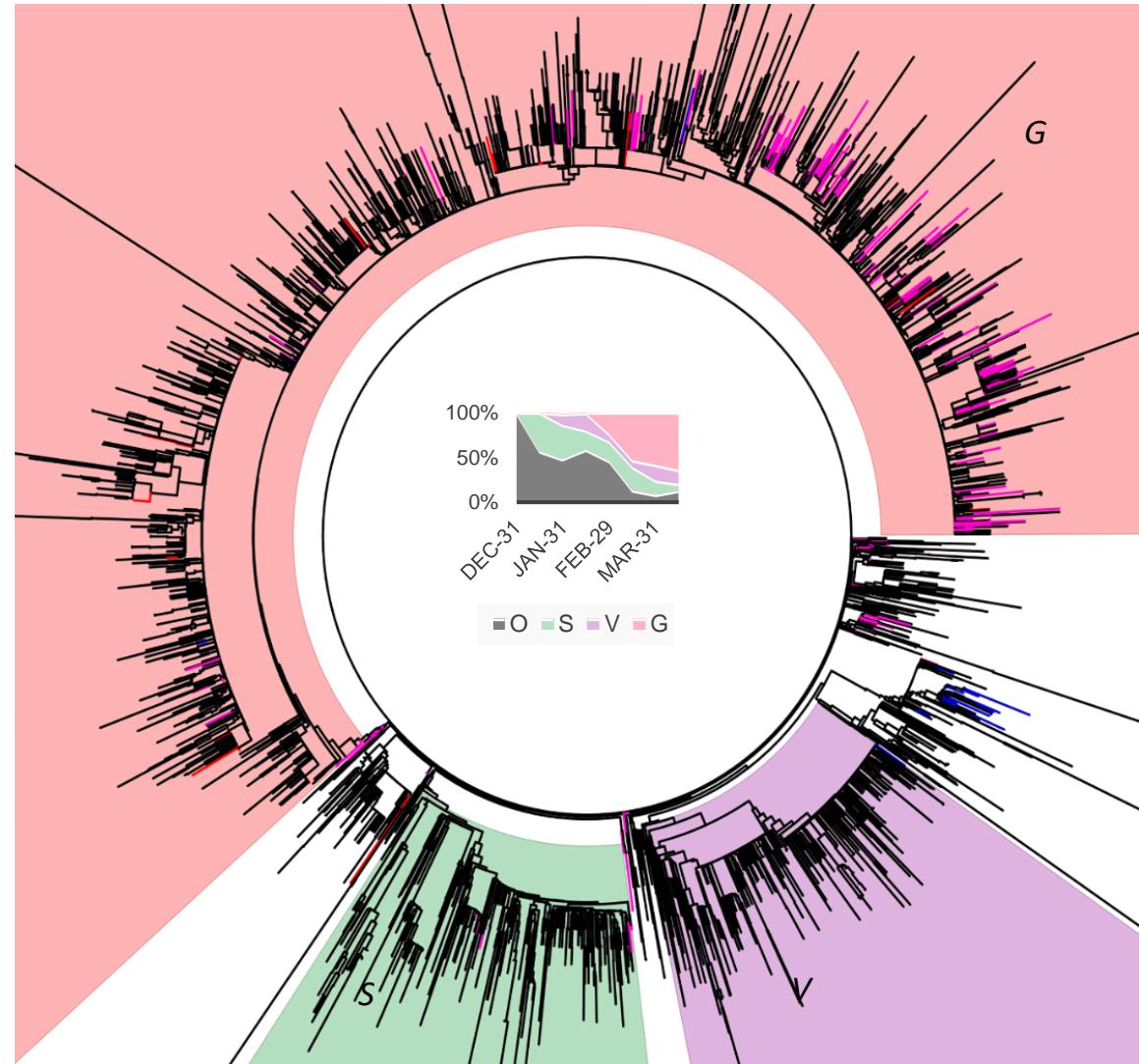


# Impact de la substitution D614G : le premier pas évolutif



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

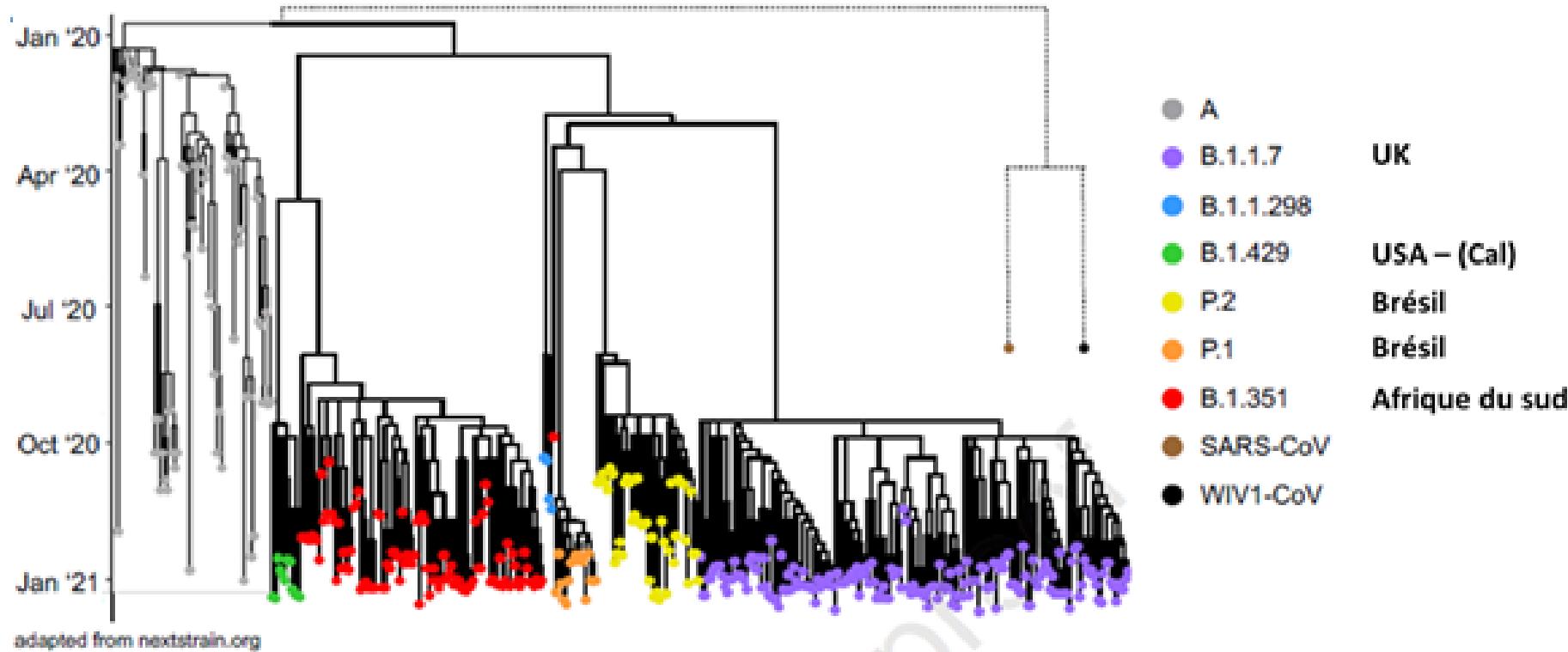
- 30-4-20
  - Larger clades were named based on marker variants:
    - S ... ORF8-L84S
    - G ... S-D614G
    - V ... NS3-G251V



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



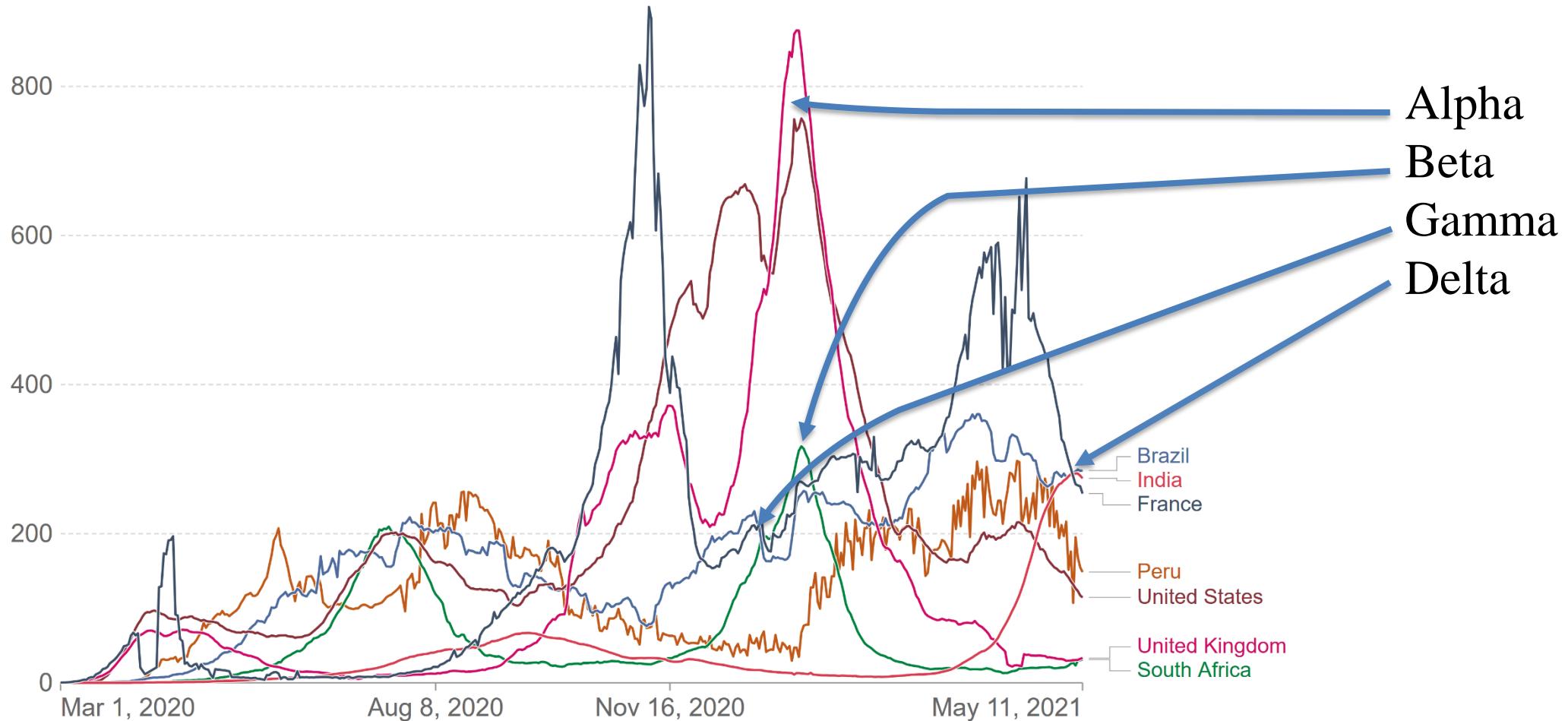
# Séquence d'apparition des variants avant émergence du delta



# 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.

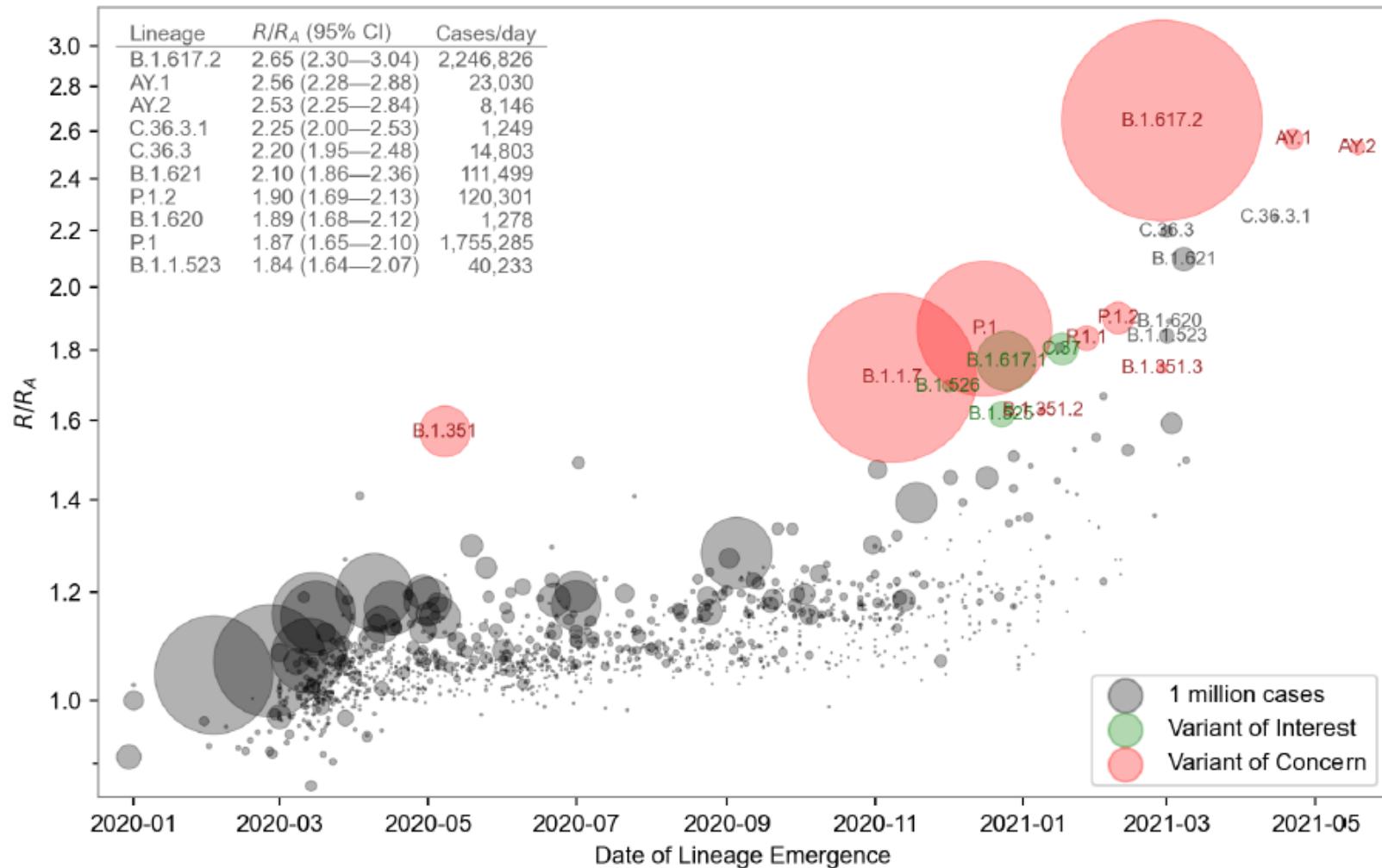


Source: Johns Hopkins University CSSE COVID-19 Data

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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 ?**

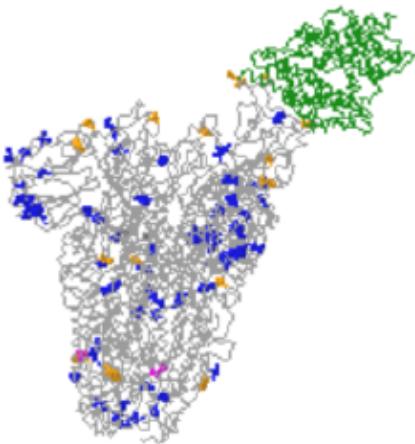
# Tendance évolutive sur la Spike :

1 – modifications multiples

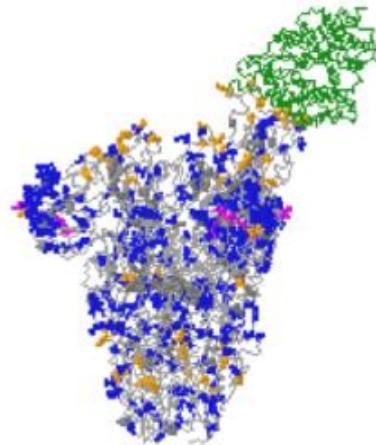
2 – évolution convergente

3 – grande dispersion des mutations

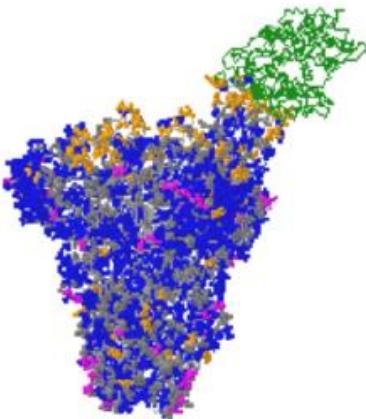
E484K T478K N501Y  
in nonG clade (A, B & B.2)



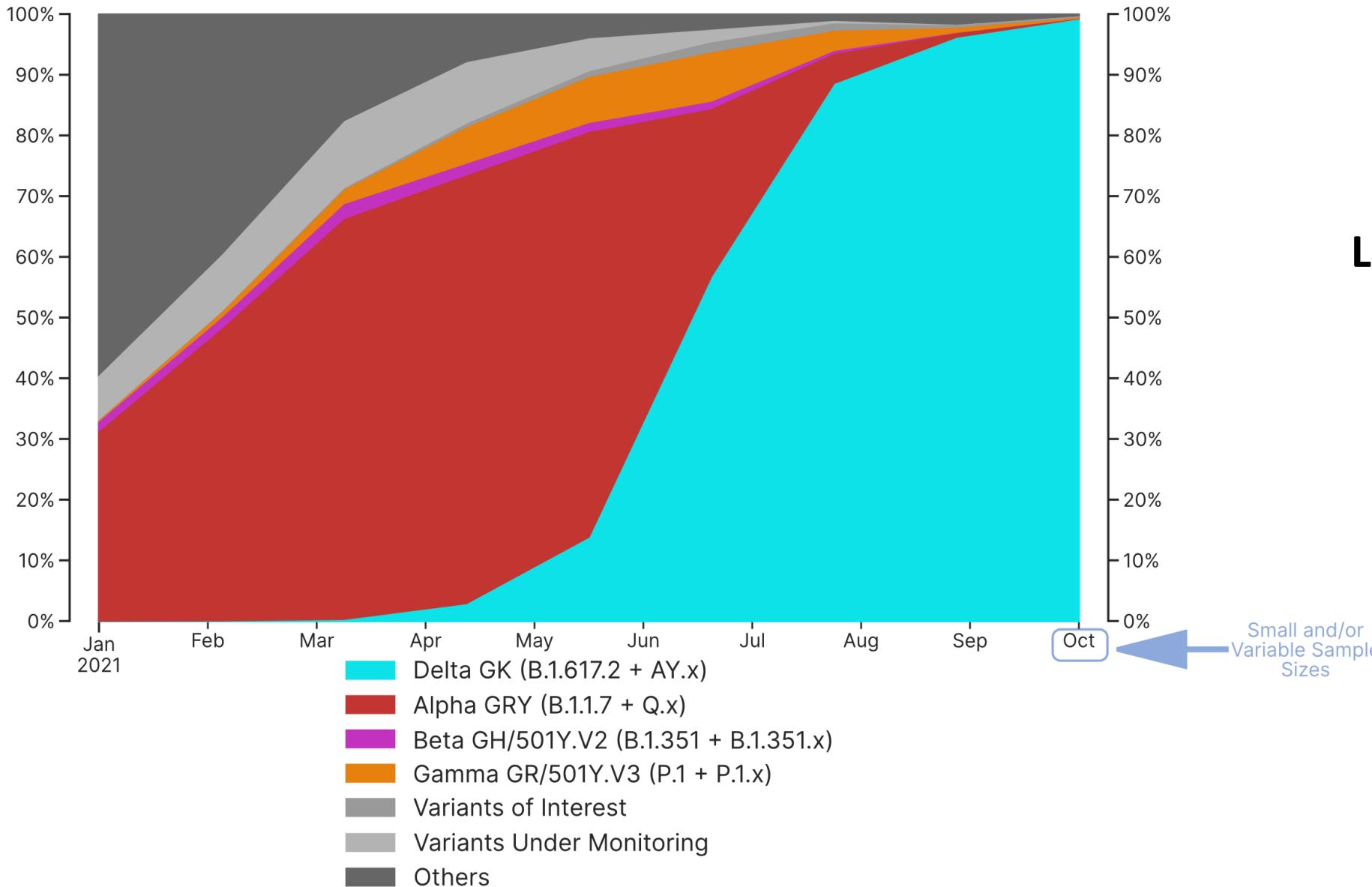
K417T V445A N501Y E484K Y449H  
T478K Y449S S494P F490S G485V  
in GR & GRY clade (B.1.1.1 & B.1.1.7)



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

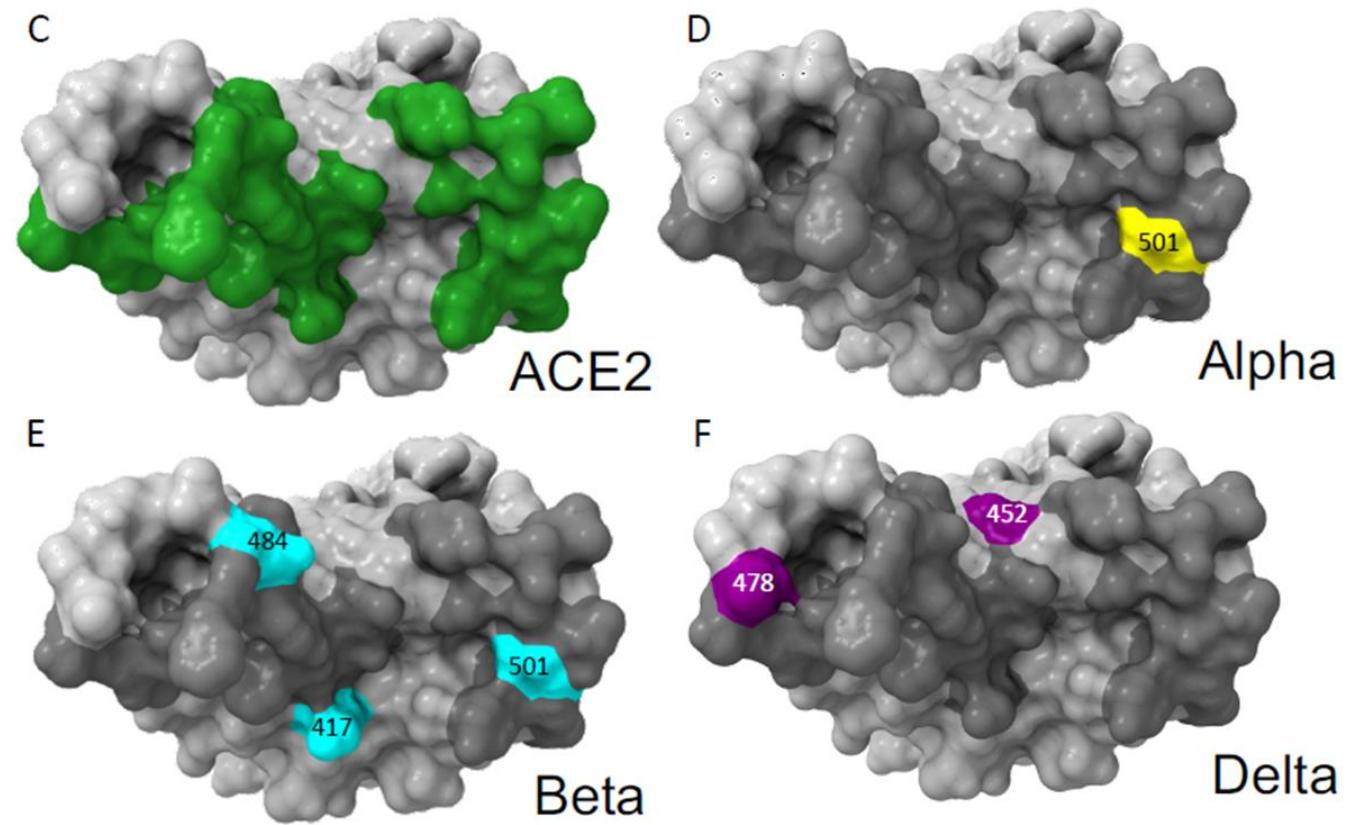
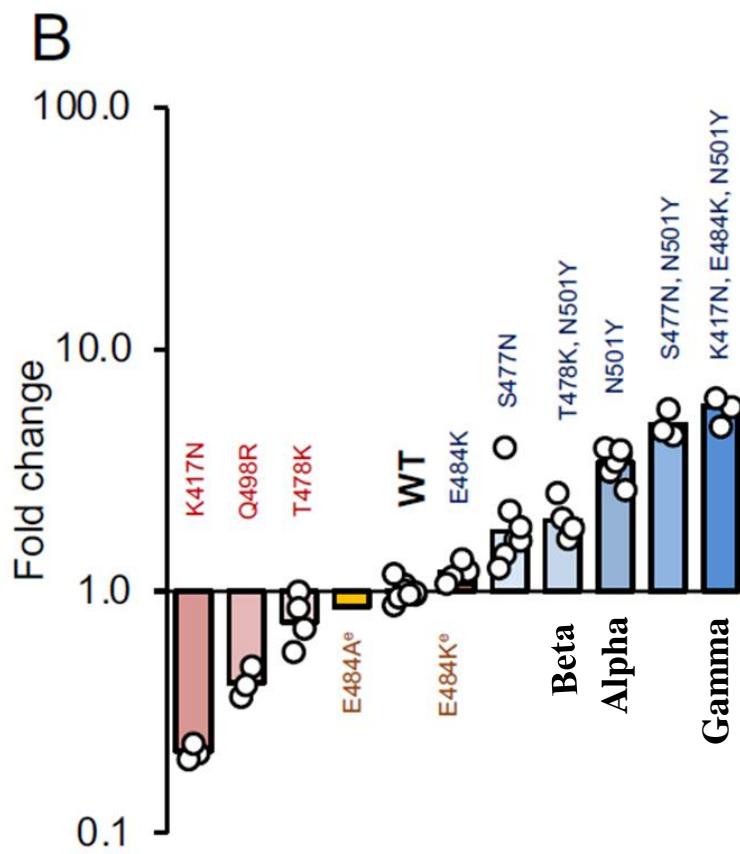


Le fitness viral compte!

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

# Pourquoi Alpha, Beta et Gamma sont plus transmissible

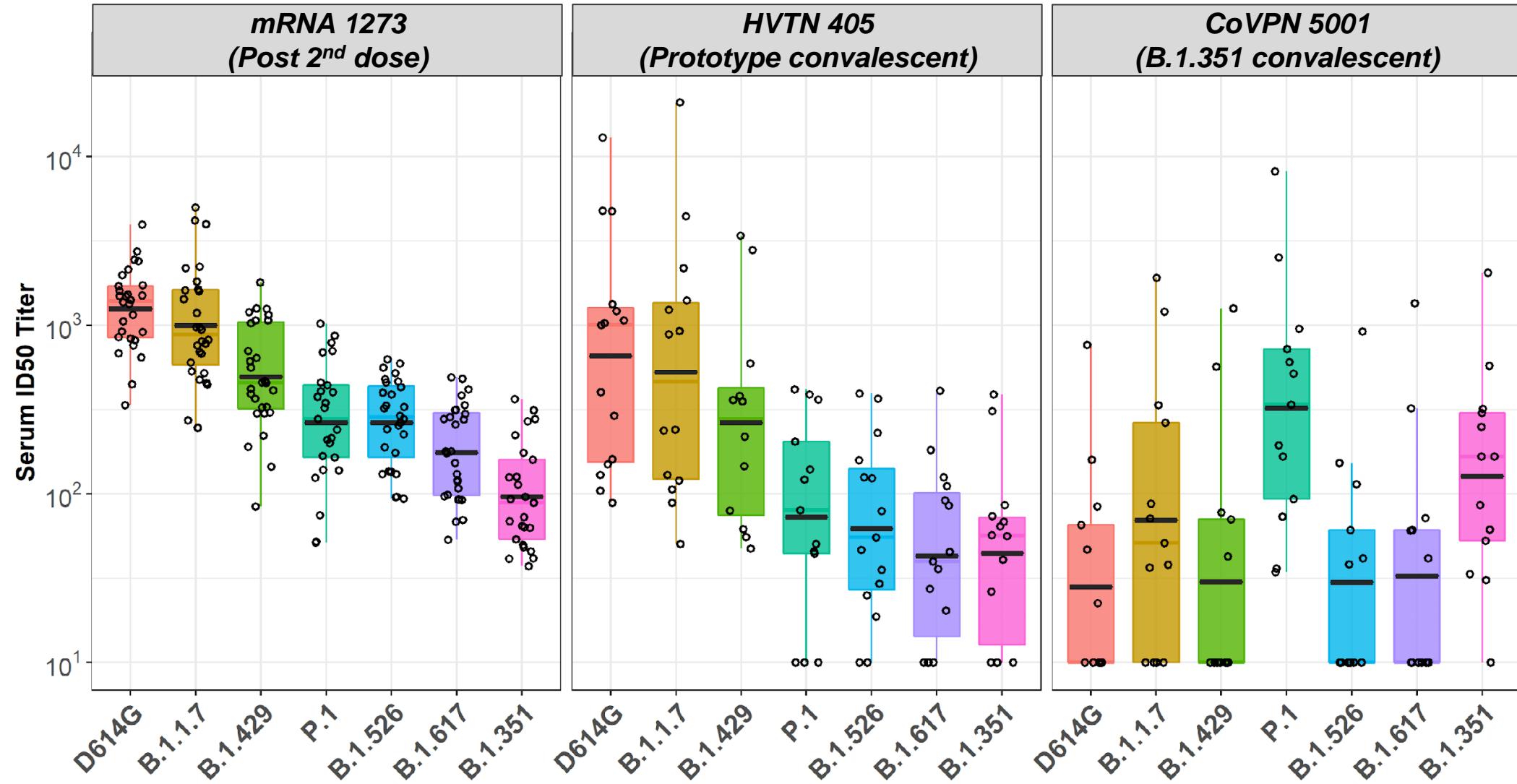
Rôle du RBD de la spike

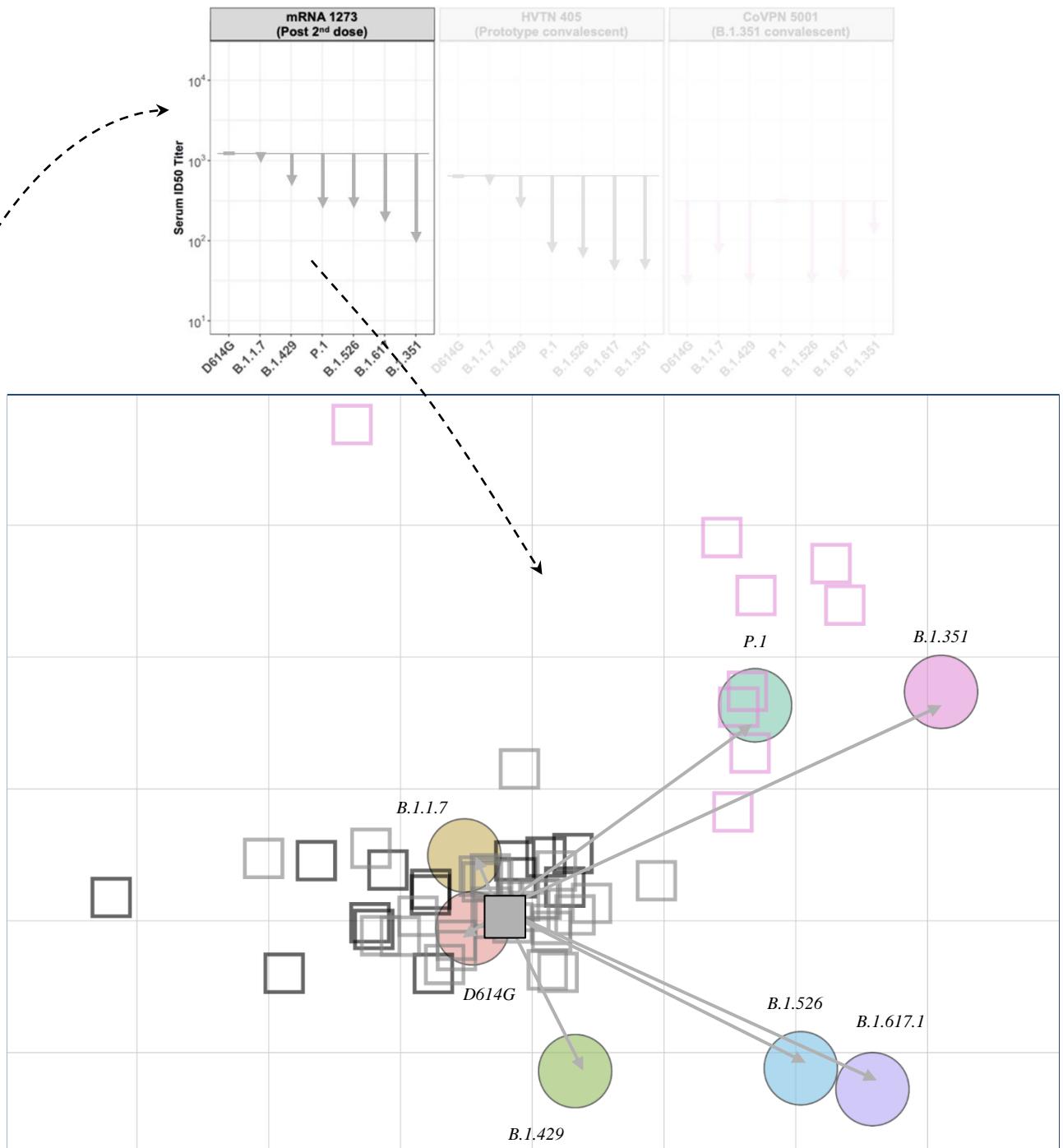
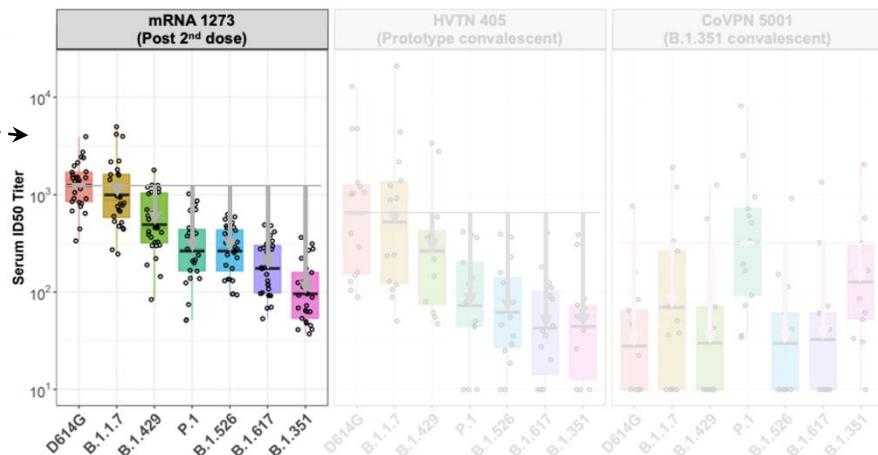
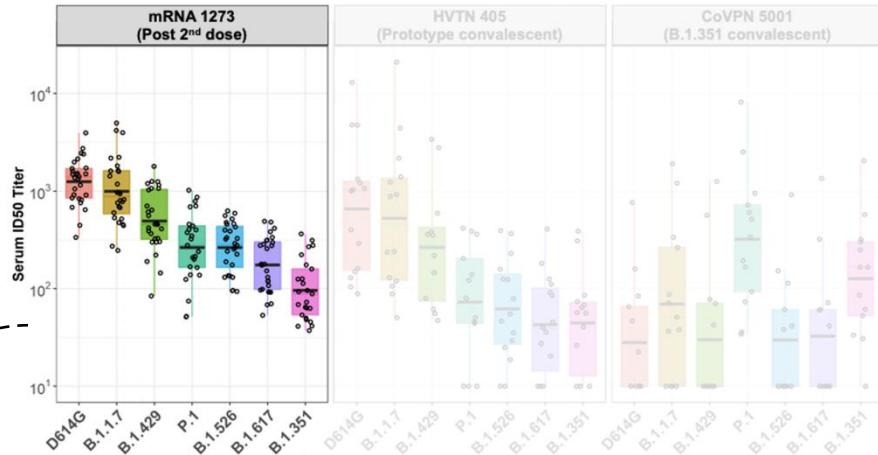


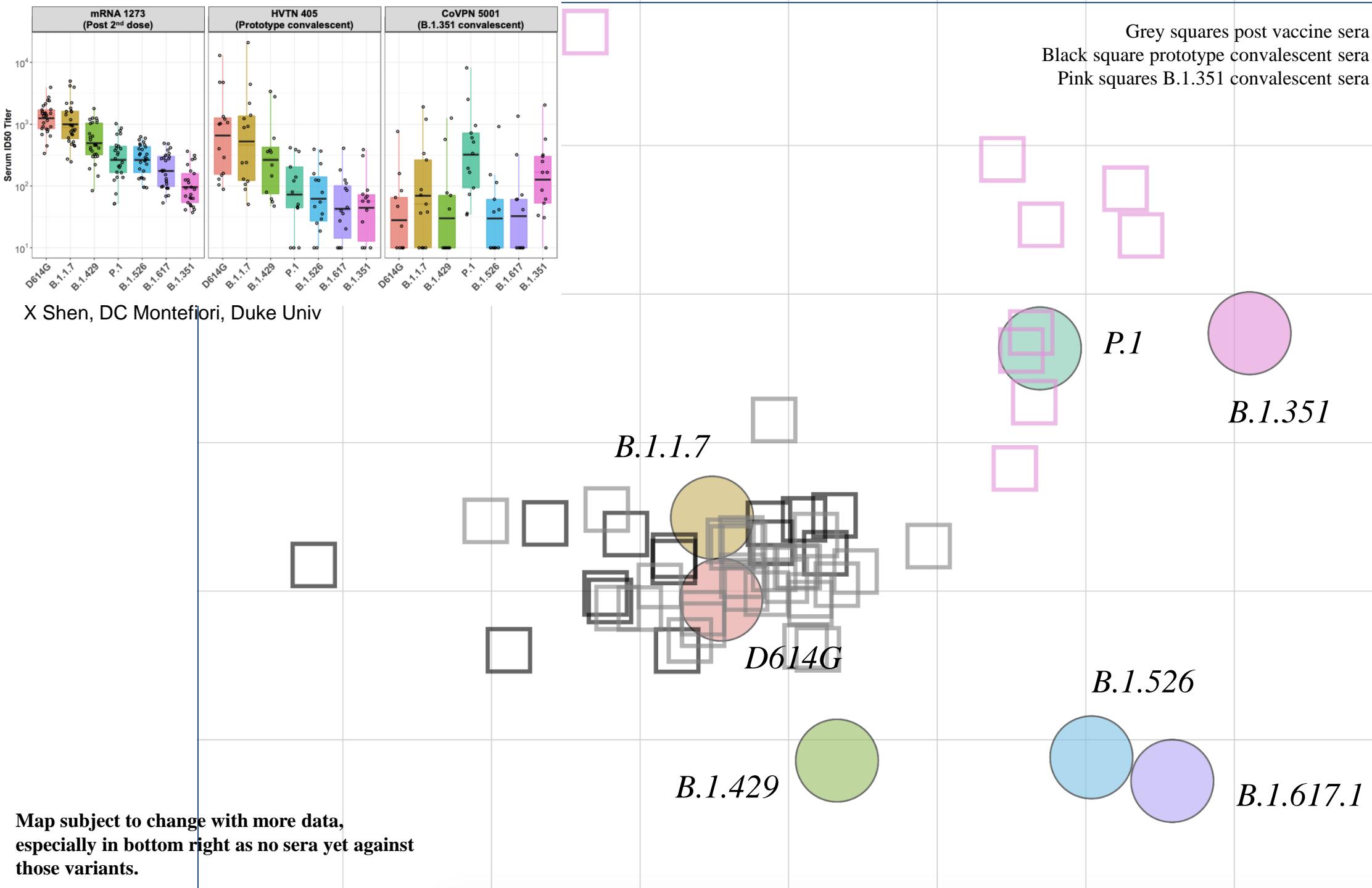
# **Impact des mutations sur l'échappement immunitaire : le concept de dérive antigénique et de couverture anticorps**

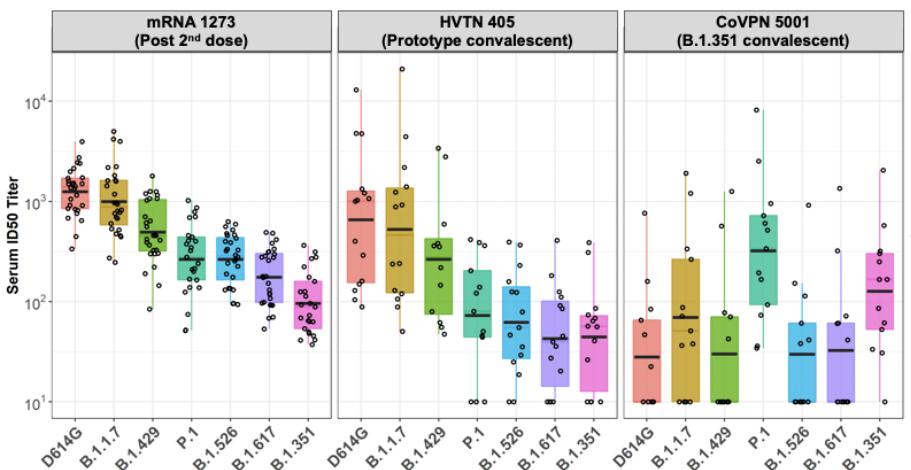
<b>Spike</b>	<b>Mutations in Spike Relative to Wuhan-1</b>
D614G	D614G
B.1.1.7	Δ69-70, Δ144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H
B.1.429	S13I, W152C, L452R, D614G
B.1.526	L5F, T95I, D253G, E484K, D614G, A701V
P.1	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I
B.1.617.1	G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H
B.1.351	L18F, D80A, D215G, Δ242-244, R246I, K417N, E484K, N501Y, D614G, A701V

# Neutralization of SARS-CoV-2 Variants: Convalescent Sera and Sera from Vaccine Recipients









X Shen, DC Montefiori, Duke Univ

Grey squares post vaccine sera  
Black square prototype convalescent sera  
Pink squares B.1.351 convalescent sera

### B.1.351

(L18F, D80A, D215G,  
Δ242-244, R246I, K417N,  
E484K, N501Y, D614G,  
A701V)

### P.1

(L18F, T20N, P26S,  
D138Y, R190S, K417T,  
E484K, N501Y, D614G,  
H655Y, T1027I)

### B.1.1.7

(Δ69-70, Δ144, N501Y, A570D,  
D614G, P681H, T716I, S982A,  
D1118H)

D614G

### B.1.617.1

(G142D, E154K,  
L452R, E484Q,  
D614G, P681R,  
Q1071H)

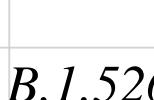
### B.1.429

(S13I, W152C, L452R,  
D614G)

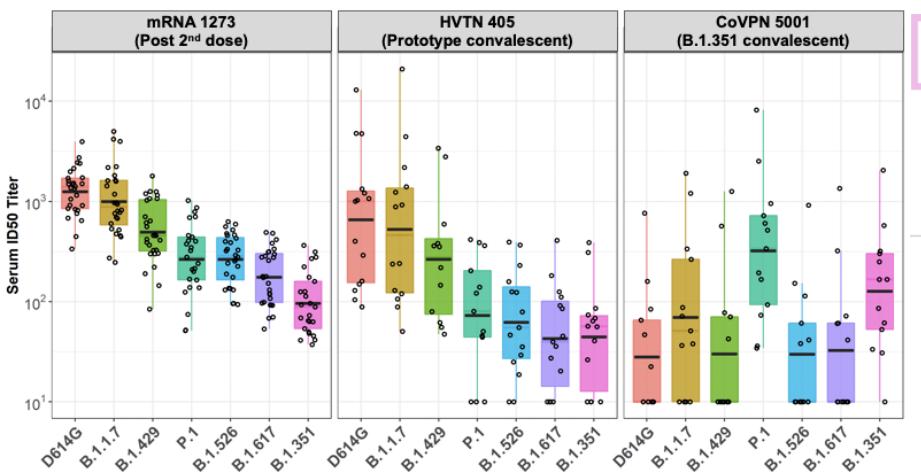


### B.1.526

(L5F, T95I, D253G,  
E484K, D614G,  
A701V)



Map subject to change with more data,  
especially in bottom right as no sera yet against  
those variants.



X Shen, DC Montefiori, Duke Univ

Grey squares post vaccine sera  
 Black square prototype convalescent sera  
 Pink squares B.1.351 convalescent sera

**B.1.351**  
 (L18F, D80A,  
 D215G, Δ242-244,  
 R246I, K417N,  
**E484K, N501Y**,  
 D614G, A701V)

**P.1**  
 (L18F, T20N,  
 P26S, D138Y,  
 R190S, **K417T**,  
**E484K, N501Y**,  
 D614G, H655Y,  
 T1027I)

**B.1.1.7**  
 (Δ69-70, Δ144, **N501Y**,  
 A570D, D614G, P681H,  
 T716I, S982A, D1118H)

D614G

**B.1.526**  
 (L5F, T95I,  
 D253G, **E484K**,  
 D614G, A701V)

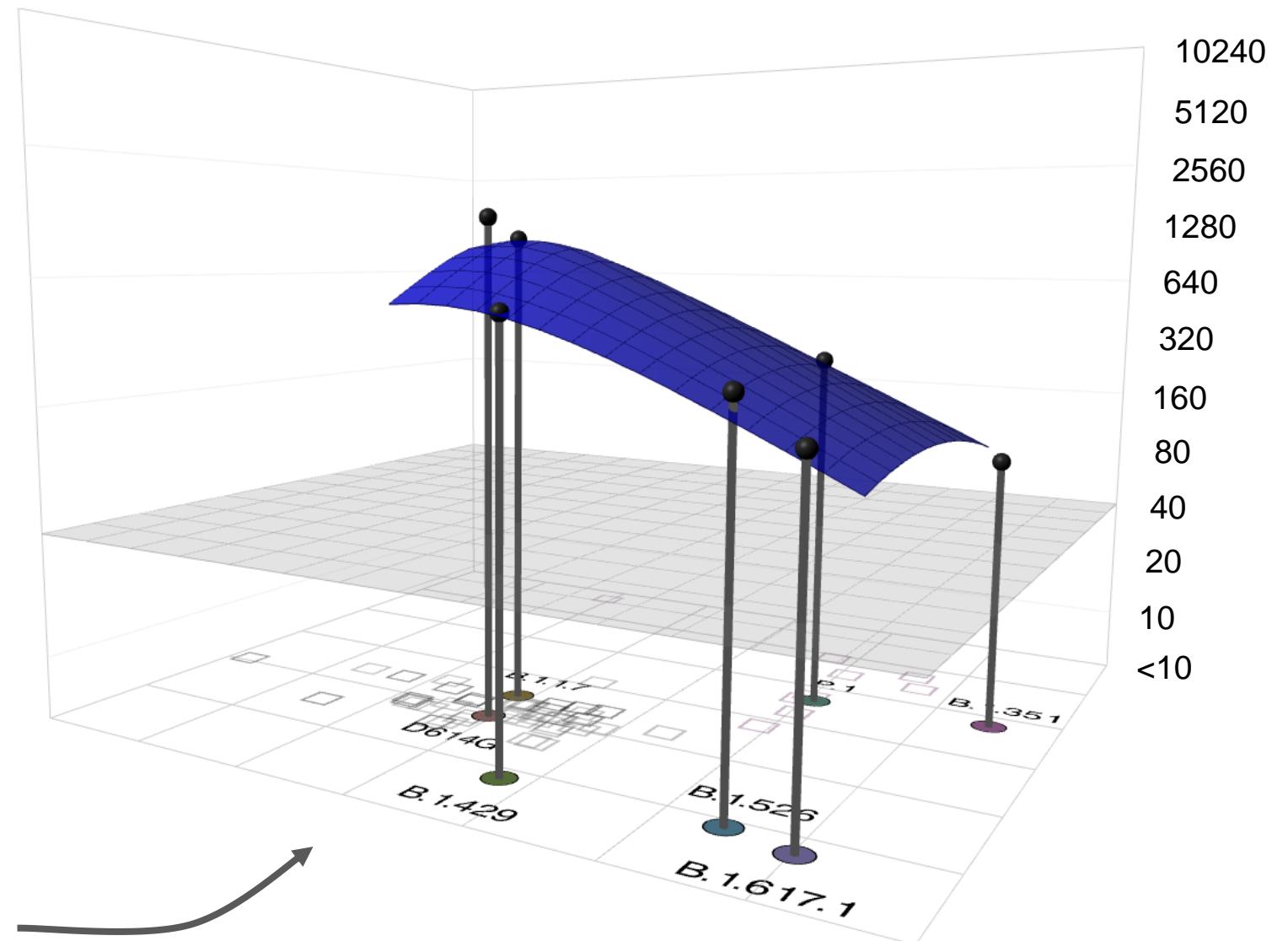
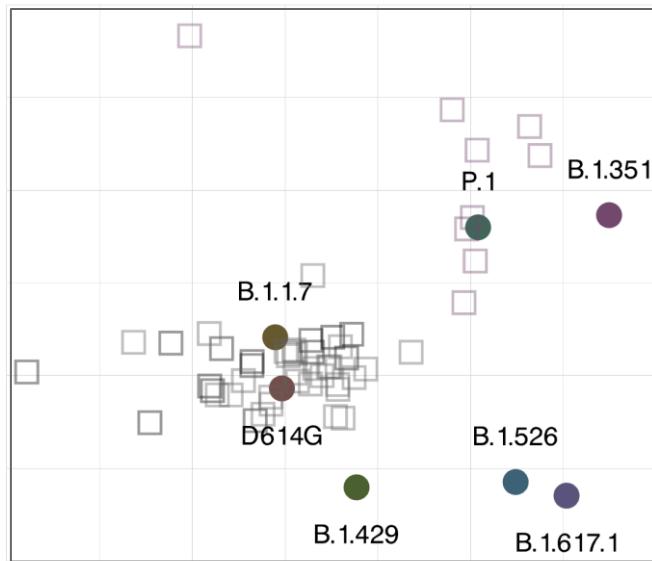
**B.1.617.1**  
 (G142D,  
 E154K, **L452R**,  
**E484Q**, D614G,  
 P681R,  
 Q1071H)

**B.1.429**  
 (S13I, W152C,  
**L452R**, D614G)

484?  
 484?  
 417?  
 with  
 immunodominance  
 switch?

Map subject to change with more data,  
 especially in bottom right as no sera yet against  
 those variants.

## “Antibody Landscapes” showing titers in the 3rd dimension

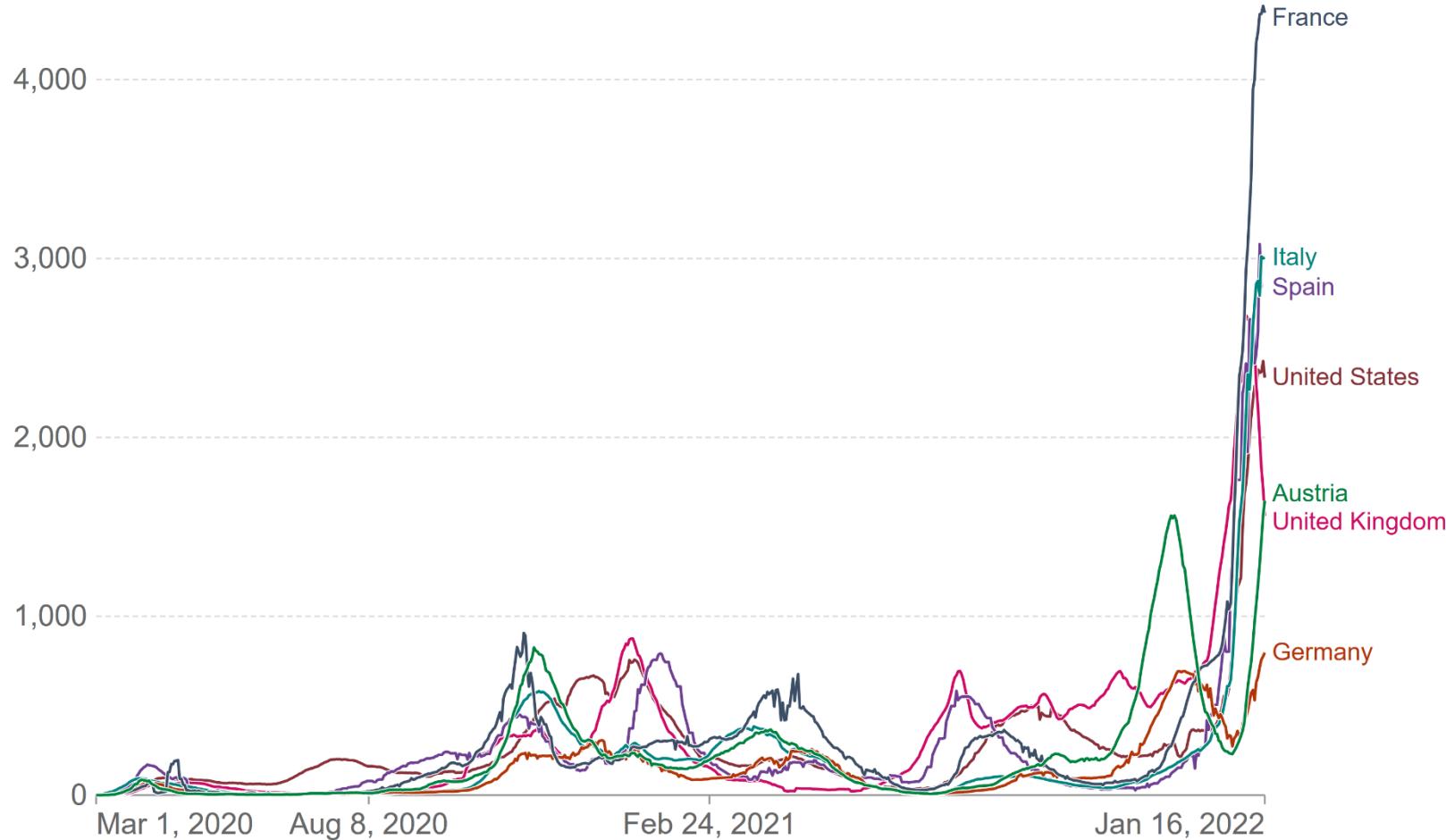


# Et la 5<sup>e</sup> vague avec Omicron...

## 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.

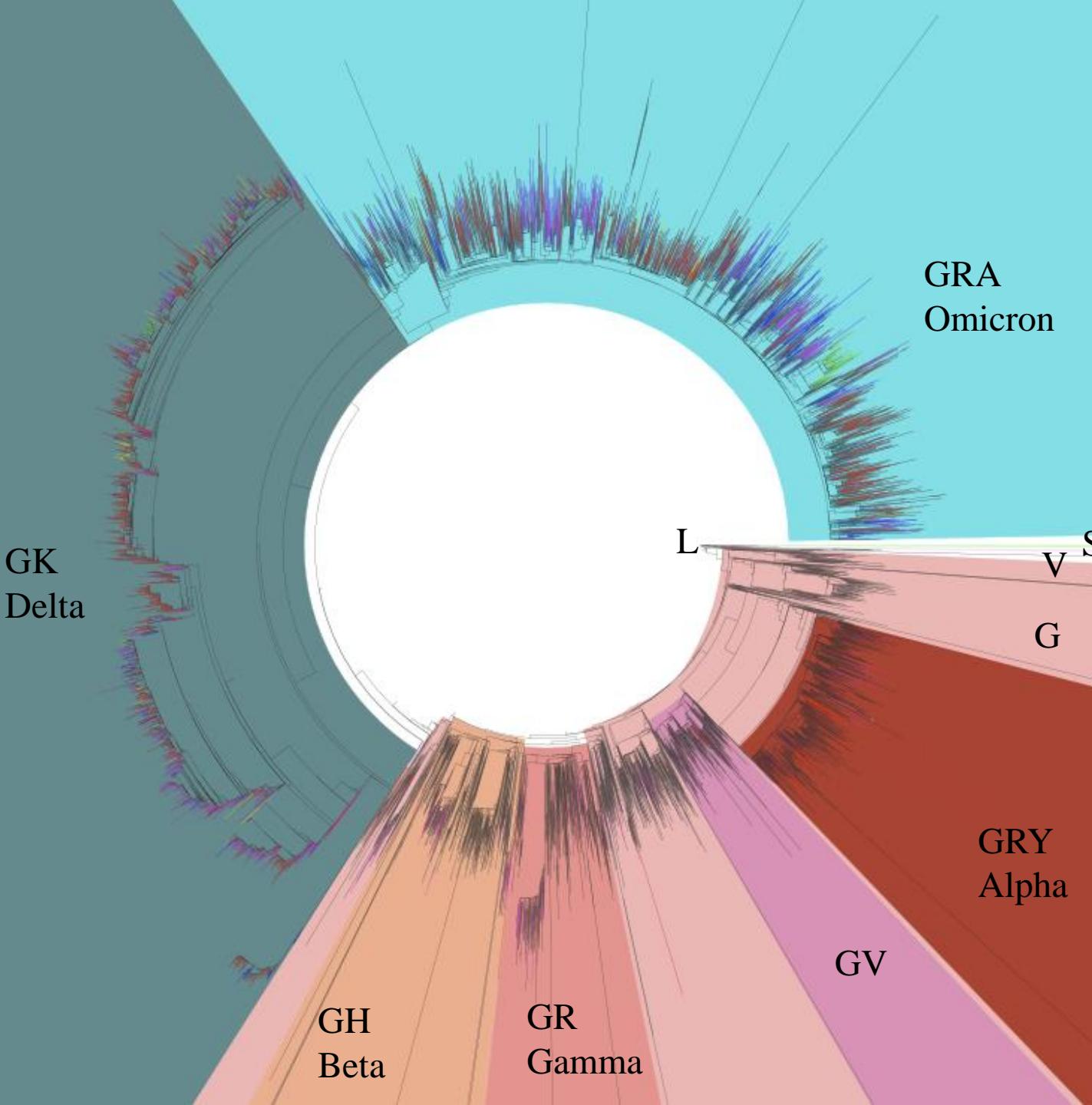
Our World  
in Data



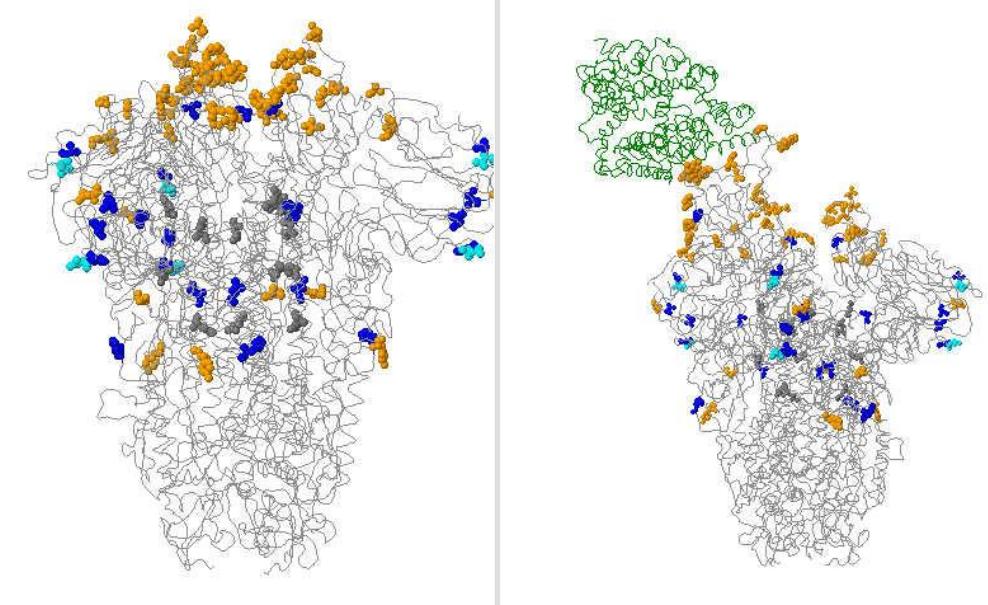
Source: Johns Hopkins University CSSE COVID-19 Data

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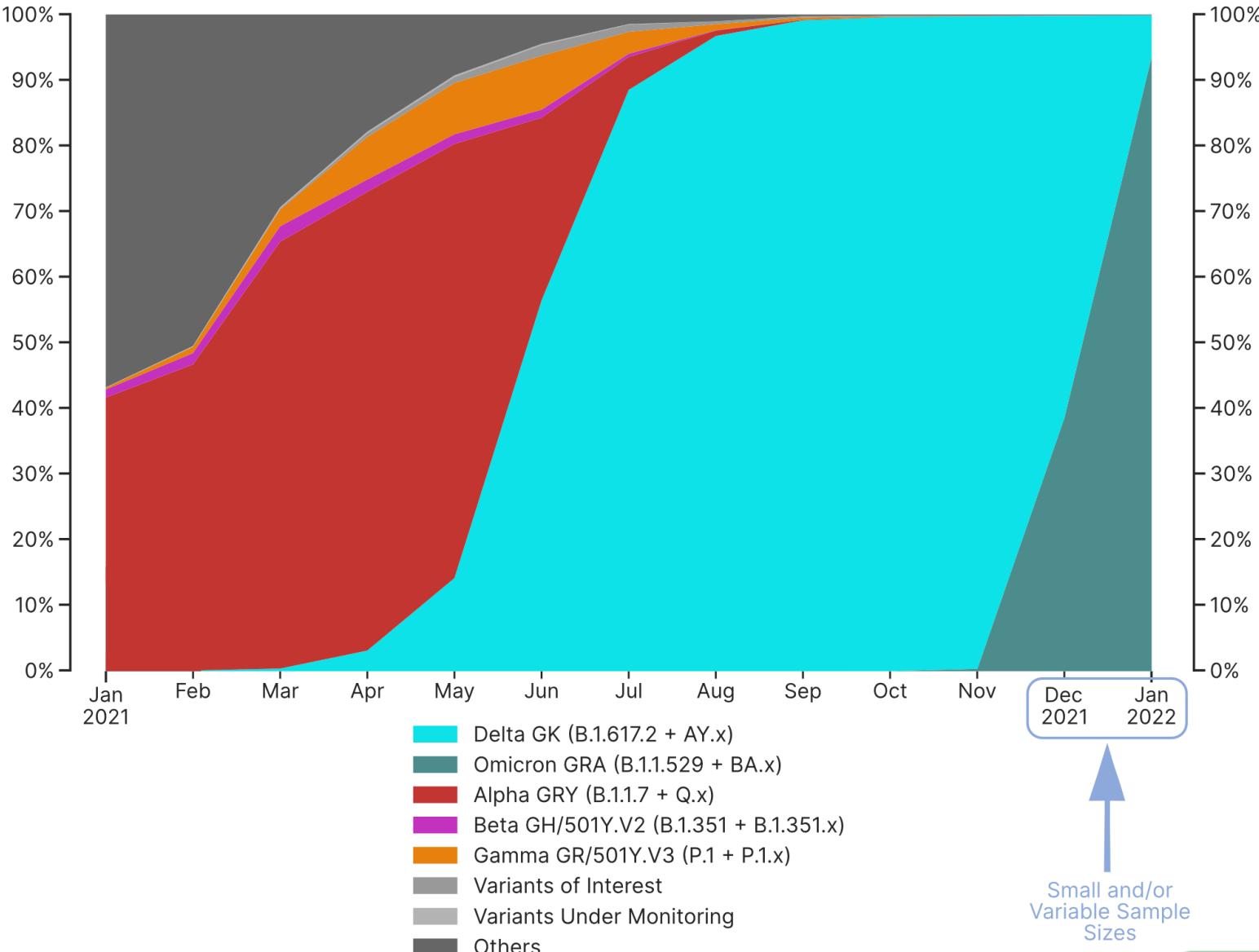
Source: [www.covidtracker.fr](http://www.covidtracker.fr)



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

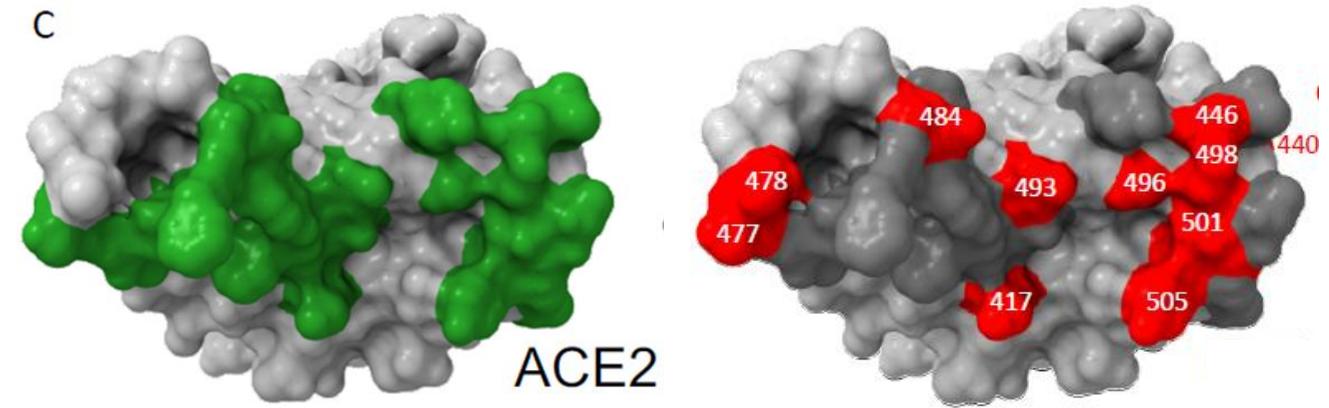
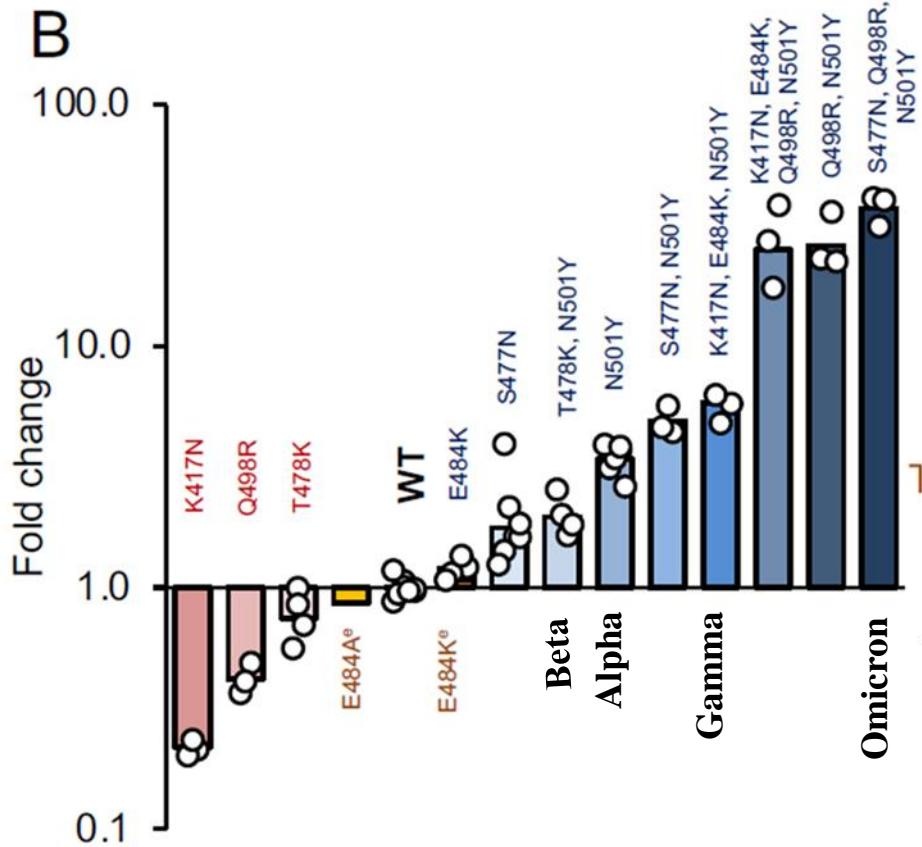


# Timecourse of variant distribution in all submitted sequences 2022-01-18

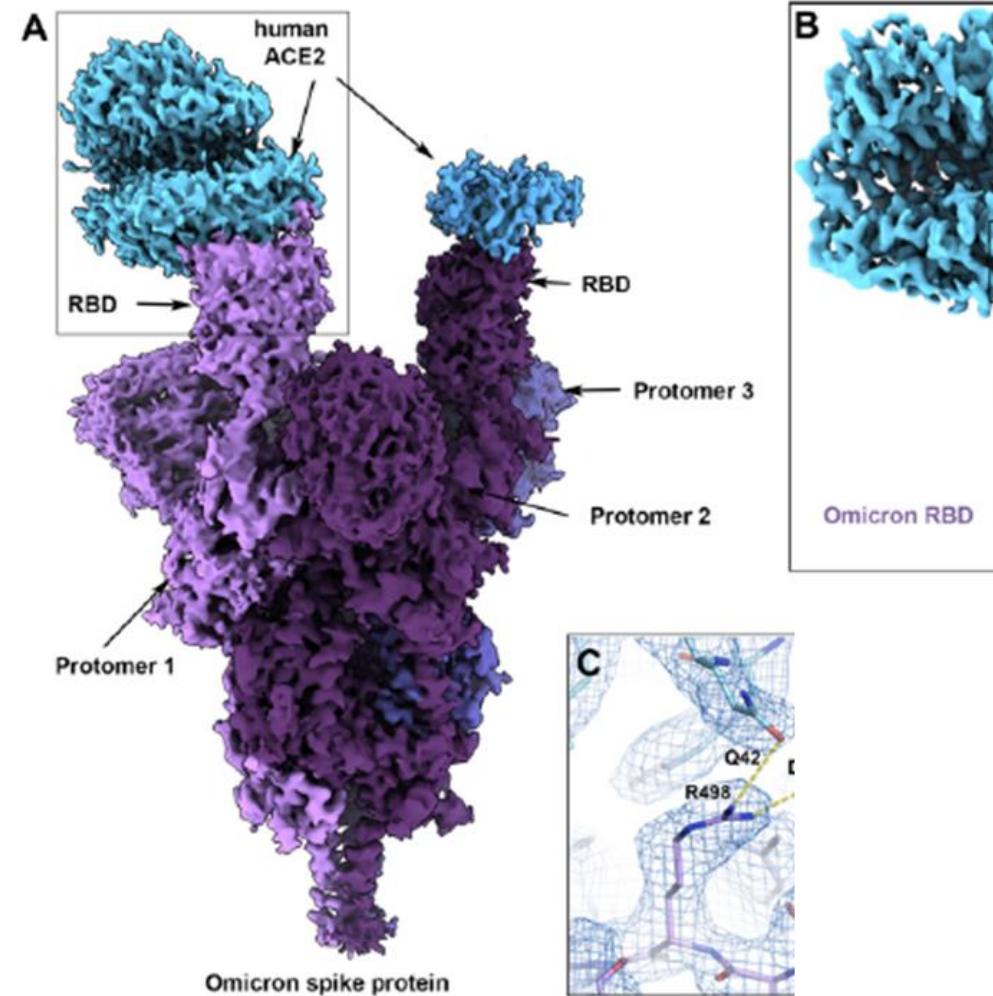
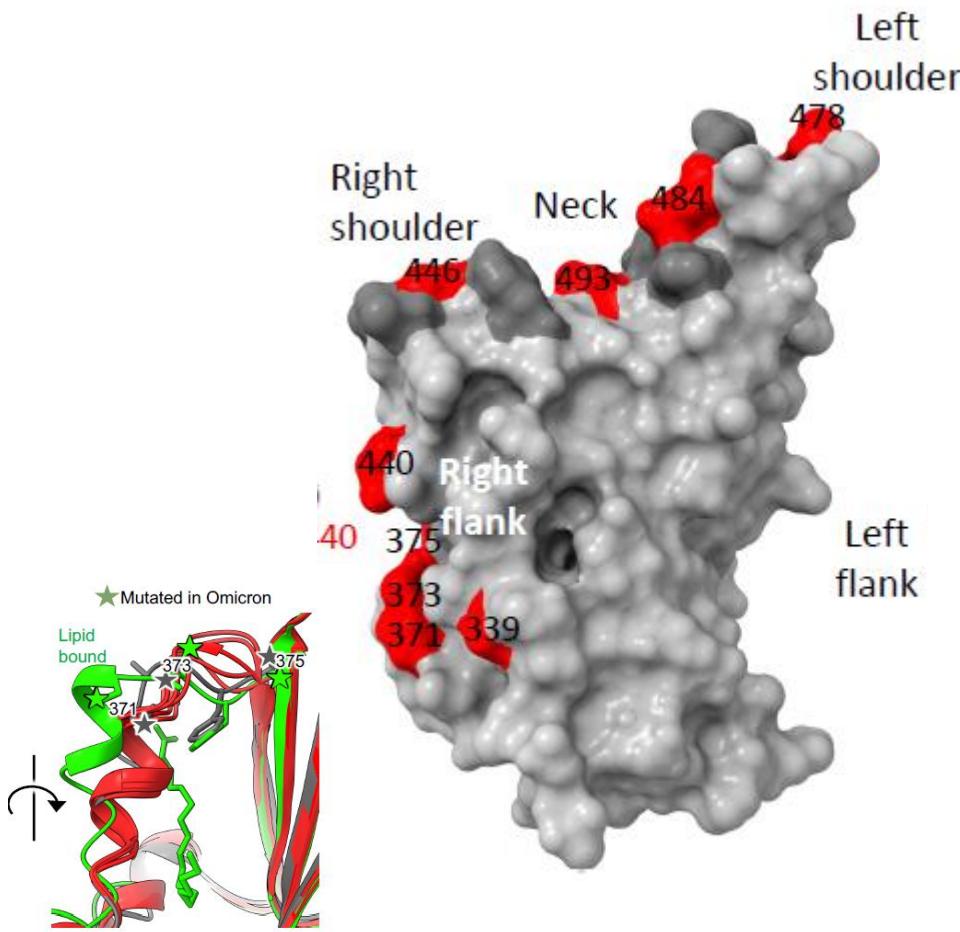


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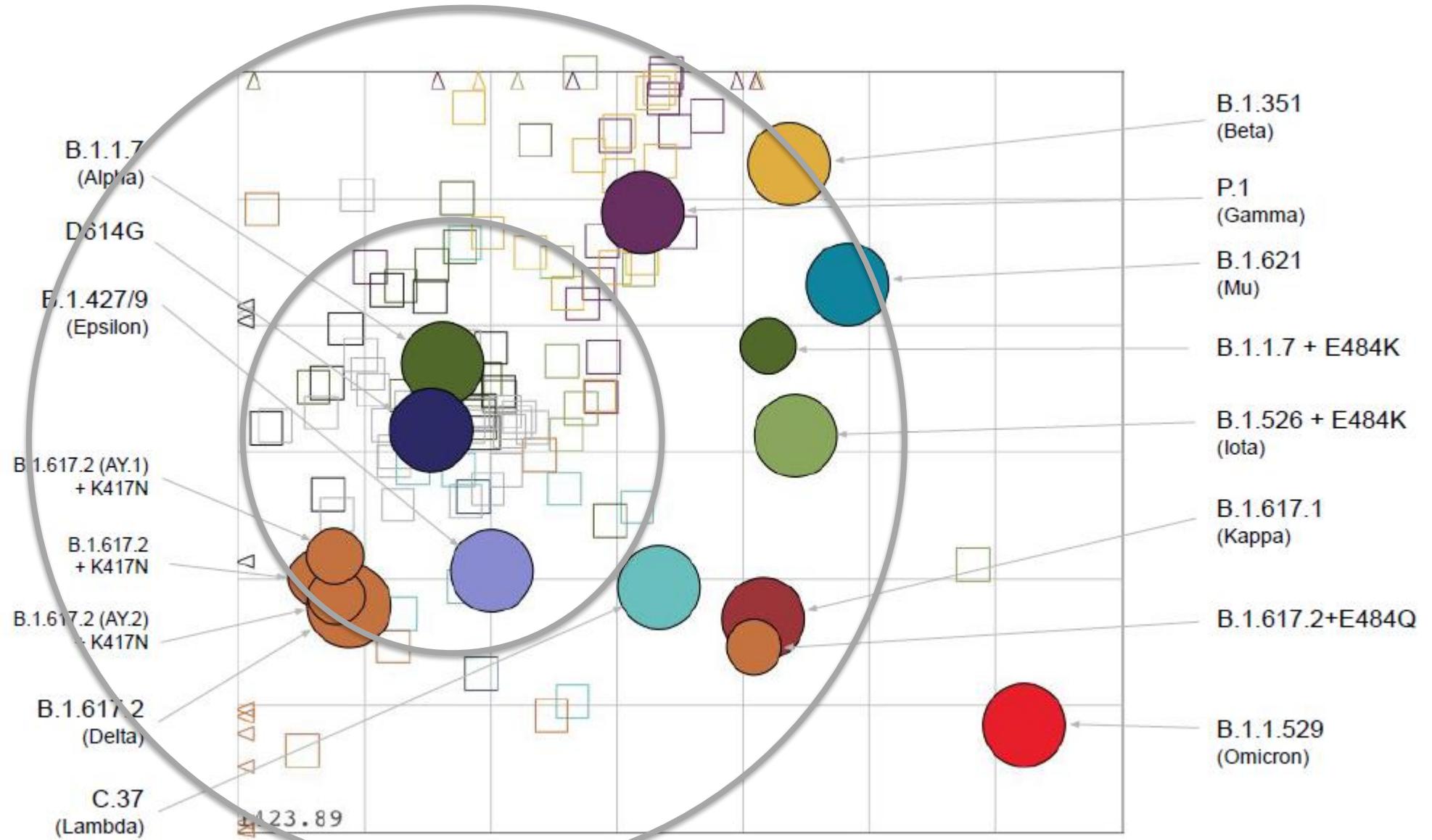
# Pourquoi Omicron est plus transmissible



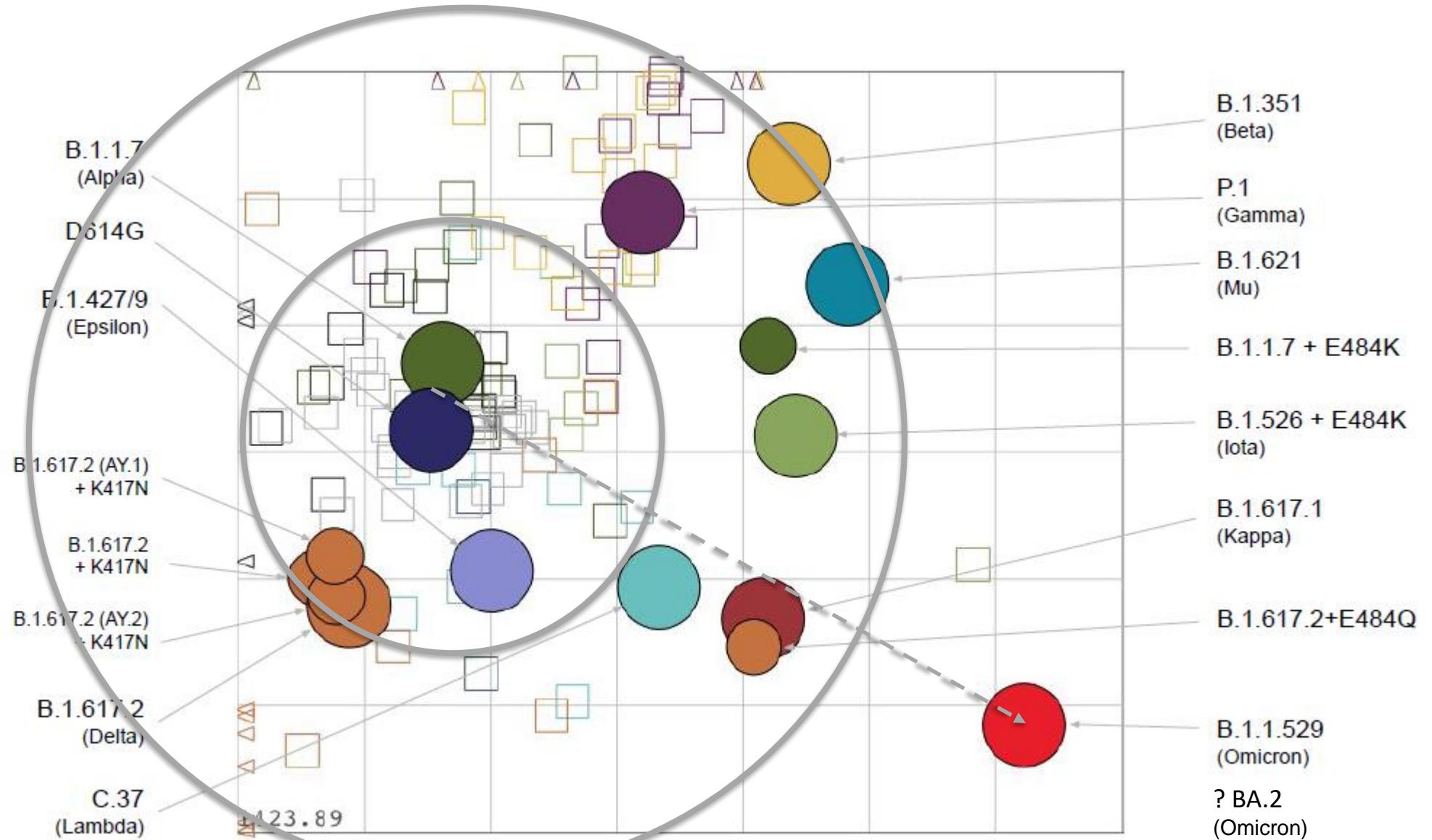
# Pourquoi Omicron est plus transmissible : impact du RBD up



# Données d'évolution antigénique



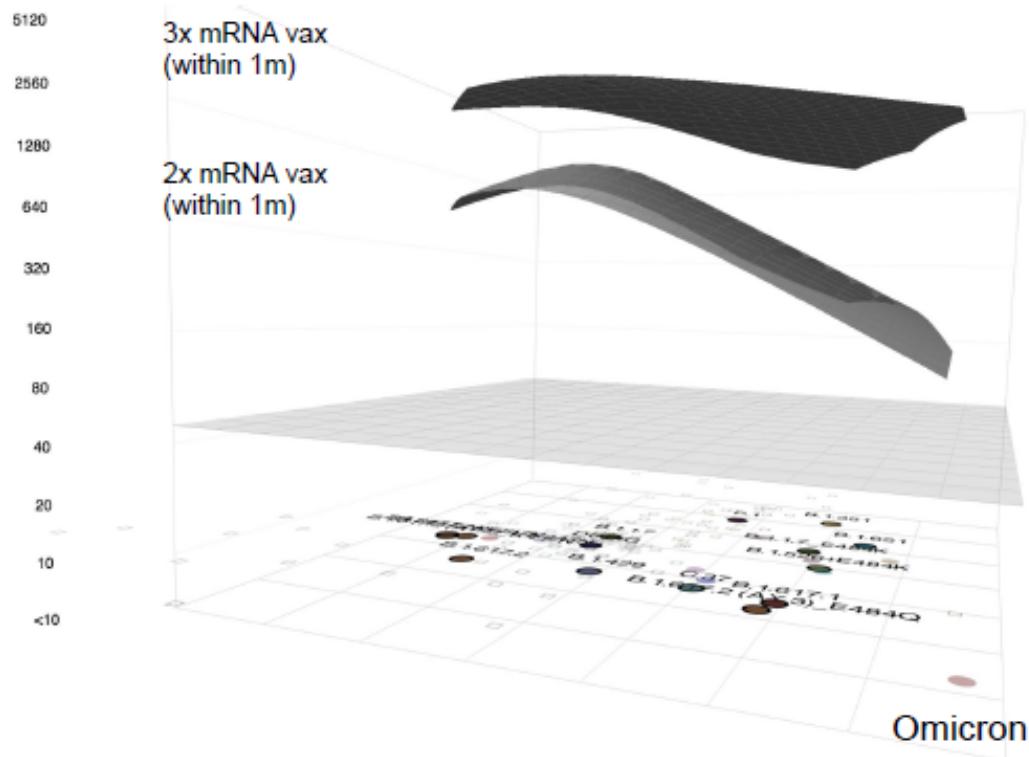
2021-12-20. Data: Shen & Montefiori (Duke). Omicron subject to change with more data. Method: Antigenic Cartography. Smith et al, Science, 2004.



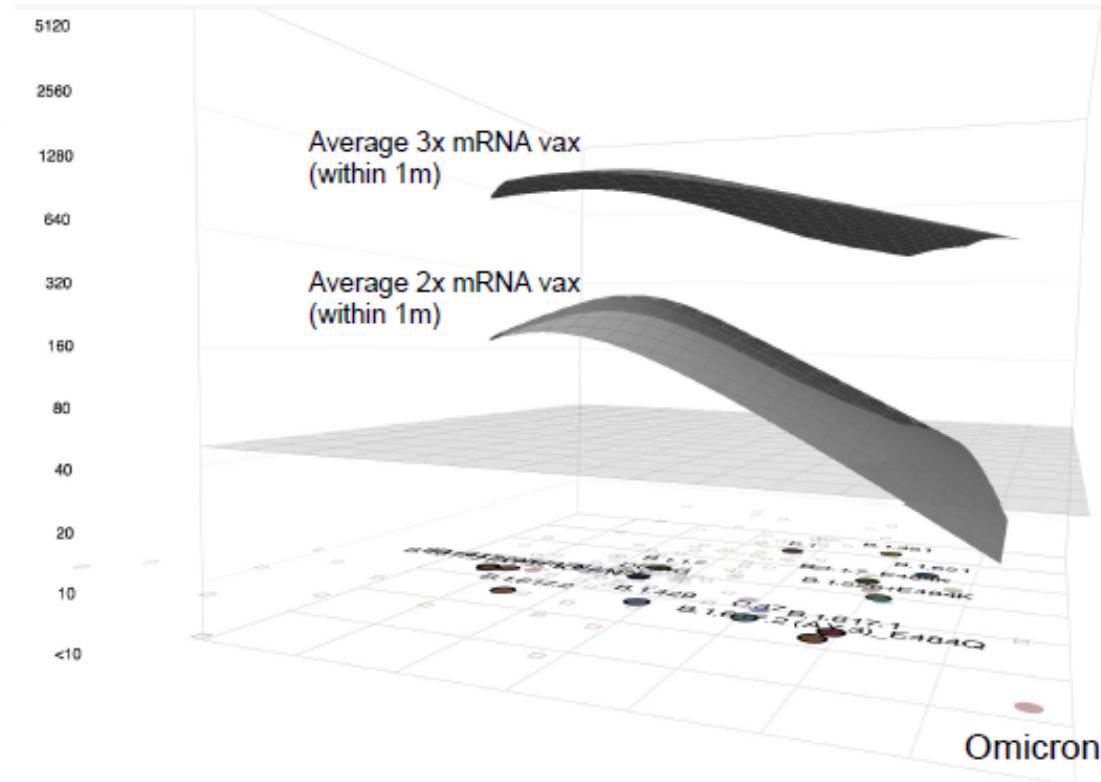
2021-12-20. Data: Shen & Montefiori (Duke). Omicron subject to change with more data. Method: Antigenic Cartography. Smith et al, Science, 2004.

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

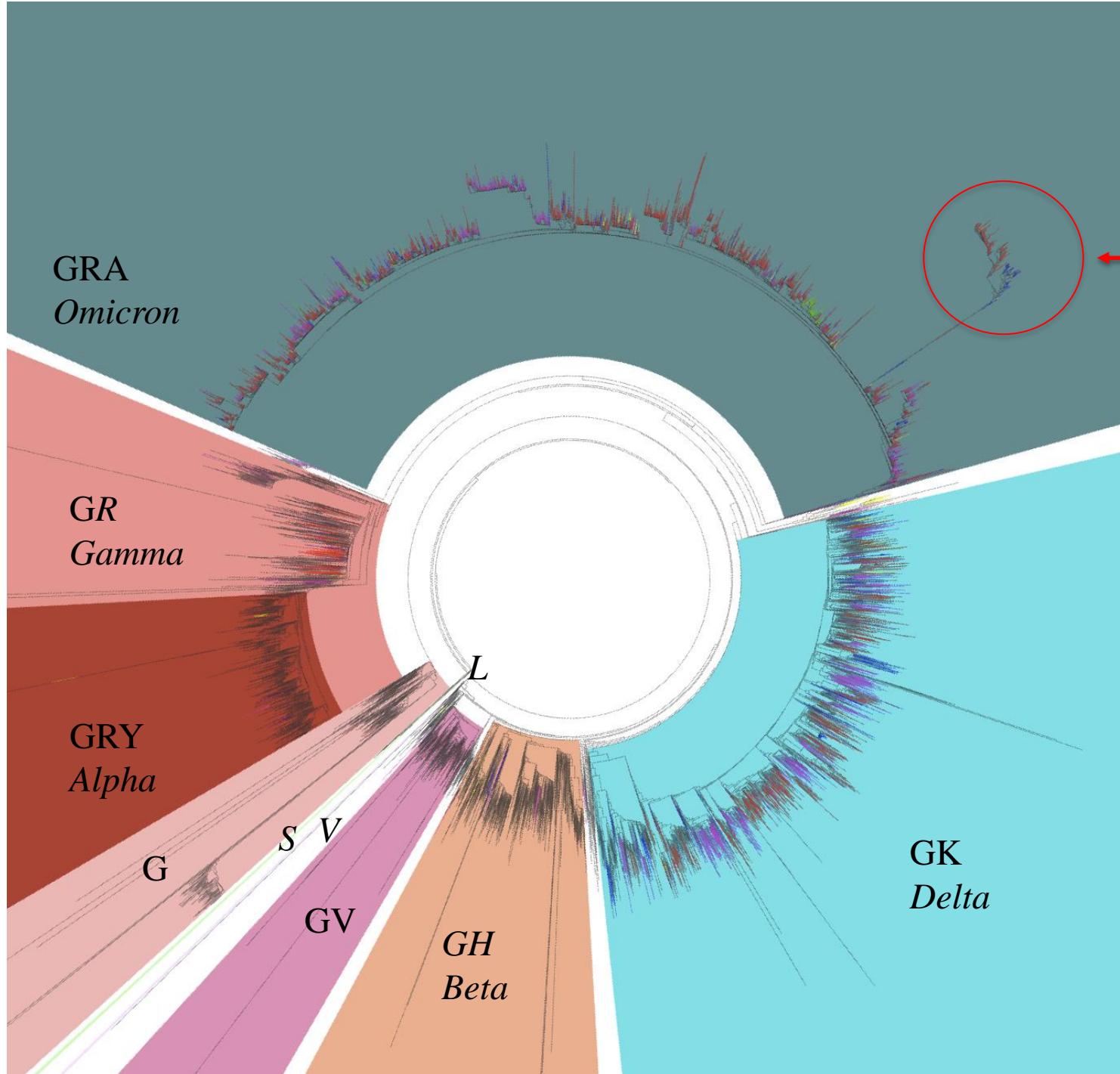
Shen, Montefiori and Doria-Rose



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



2021-12-22. Data: Shen & Montefiori (Duke), Doria-Rose (NIH). Method: Antibody Landscapes. Fonville, Wilks et al, Science, 2014.



Clade references and Pango lineages

GV B.1.177 20A.EU1 hCoV-19/Spain/CT-ISCIII-2013597/2020|EPI\_ISL\_539548|2020-06-26  
GH B.1. 20C hCoV-19/Canada/ON-PHL-8751/2020|EPI\_ISL\_418345|2020-02  
GR B.1.1.20B hCoV-19/England/20168037604/2020|EPI\_ISL\_466615|2020-02-16  
GRY Alpha B.1.1.7 20I hCoV-19/England/MILK-9E05B3/2020|EPI\_ISL\_601443|2020-09-20  
GRA Omicron B.1.5.29/BA.x 21K\_hCoV-19/South Africa/NICD-N21398/2021|EPI\_ISL\_7456440|2021-11-05  
GK Delta B.1.6.17.2/AY.x 21A\_hCoV-19/India/LSGS00941/2020|EPI\_ISL\_1663516|2020-12-12  
G B.1 20A hCoV-19/Germany/BY-ChVir-929/2020|EPI\_ISL\_406862|2020-01-28  
V B.2 19A hCoV-19/Italy/LAZ-INMI-SPL1/2020|EPI\_ISL\_412974|2020-01-29  
I B 19A hCoV-19/Wuhan/WIV04/2019|EPI\_ISL\_402124|2019-12-30  
S A 19B\_hCoV-19/Guangdong/20SF012/2020|EPI\_ISL\_403932|2020-01-14

# 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 reste important



# 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**