

COVID an 2 : où en sommes-nous ?

Le SARS-CoV-2 : un virus qui mute

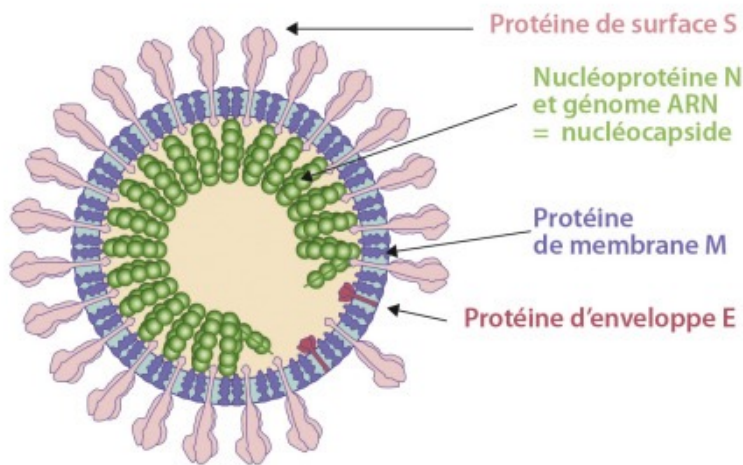
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Déclaration publique d'intérêts

Anne-Geneviève Marcelin a reçu des subventions pour participations à des conférences scientifiques, des honoraires pour des travaux d'expertise et bourses de recherches de différentes firmes pharmaceutiques : Gilead Sciences, Merck, ViiV Healthcare, Theratechnologies, Roche diagnostics, Biorad

SARS-CoV-2

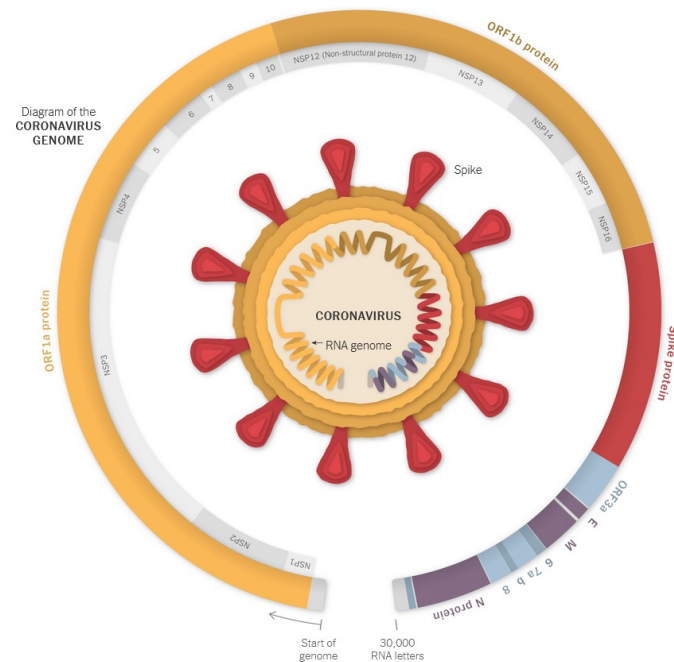


Virus enveloppé, 80 et 200 nm

ARN monocaténaire linéaire non segmenté, polarité positive

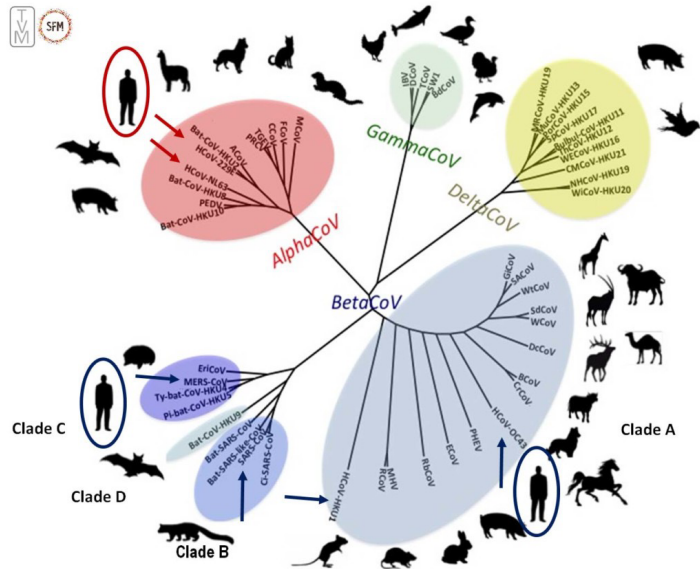
30 000 pb

- Les **protéines S (spike)** forment une large couronne à leur surface → préfixe latin corona
- Protéines N, étroitement liées à l'acide ribonucléique (ARN) génomique → **Nucléocapside**
- Protéines M et E → matrice et enveloppe



Classification

Famille Coronaviridae, sous-famille Coronavirinae
Genre Beta coronavirus

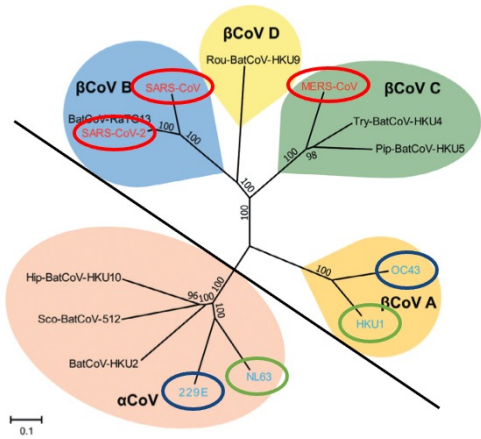


Les 7 coronavirus humains (HCoV)

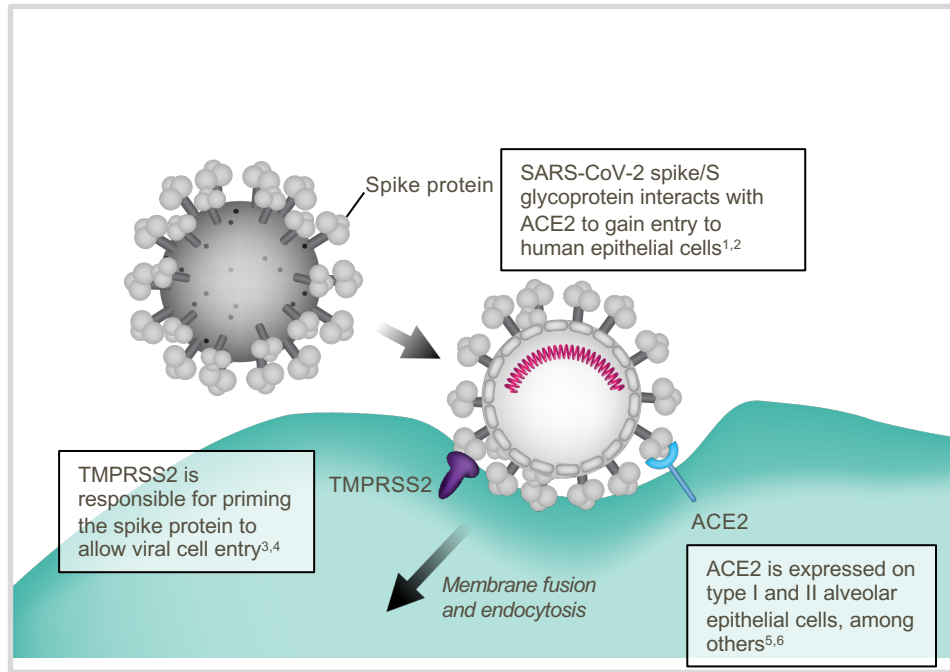
- HCoV « classiques »**
 - HCoV 229E
 - HCoV OC43
- HCoV « nouveaux »**
 - HCoV NL63
 - HCoV HKU1
- HCoV « émergents »**
 - SARS-CoV (2002-2003)
 - MERS-CoV (2012-...)
 - SARS-CoV-2 (2019-...)

Infections respiratoires hautes

Infections respiratoires basses



SARS-CoV-2 viral infection depends on the spike protein



ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, type 2 transmembrane serine protease

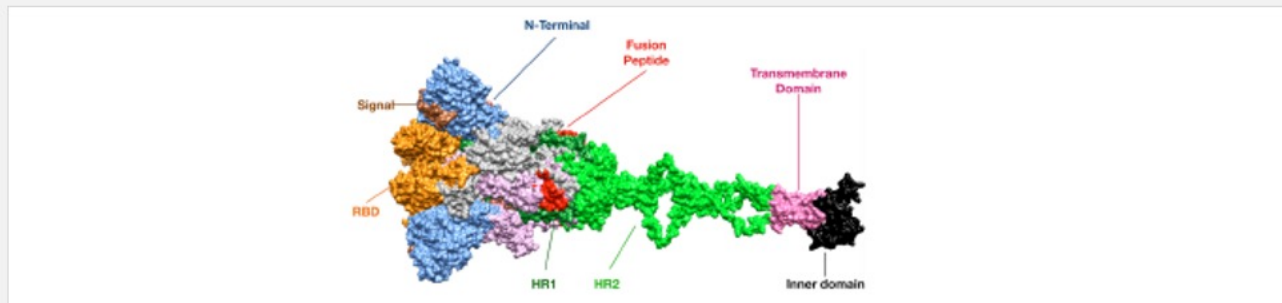
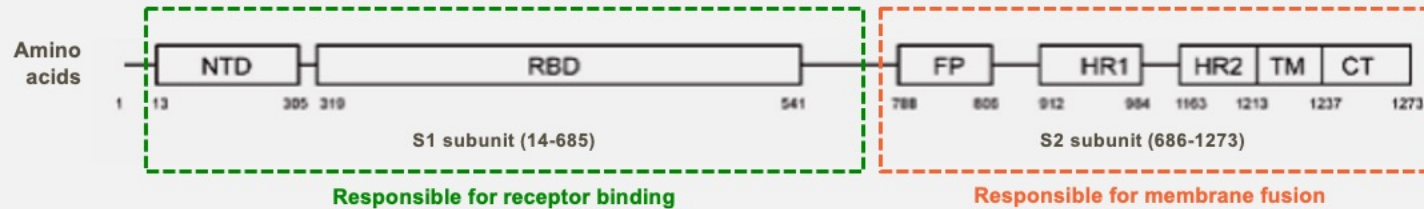
- > Spike protein plays an essential role in attachment to and infection of the target host cells¹
 - Mediates recognition of ACE2, viral attachment, and entry into host cells¹
- > Considered to be the prime targets for antibodies against SARS-CoV-2; by blocking the interaction between the spike protein and human cells, infection may be prevented⁷
- > Changes in the spike protein may help the virus to evade neutralizing antibodies^{8,9}

Figure adapted from: Bergmann CC & Silverman RH. *Cleve Clin J Med* 2020;87:321–7 and Jiang S, et al. *Trends Immunol* 2020;41:355–9

1. Bergmann CC & Silverman RH. *Cleve Clin J Med* 2020;87:321–7; 2. Jiang S, et al. *Trends Immunol* 2020;41:355–9; 3. Elshabrawy HA. *Vaccines* 2020;8:335; 4. Hoffman M, et al. *Cell* 2020;181:271–280; 5. Sun P, et al. *J Med Virol* 2020;92:548–51; 6. Zhao Y, et al. *Am J Resp Crit Care Med* 2020;202:756–9; 7. Pinto D, et al. *Nature* 2020;583:290–5; 8. Starr TN, et al. *Science* 10.1126/science.abf9302 (2021); 9. Li et al. *Cell* 2020;182:1284–94

SARS-CoV-2 spike structure and function

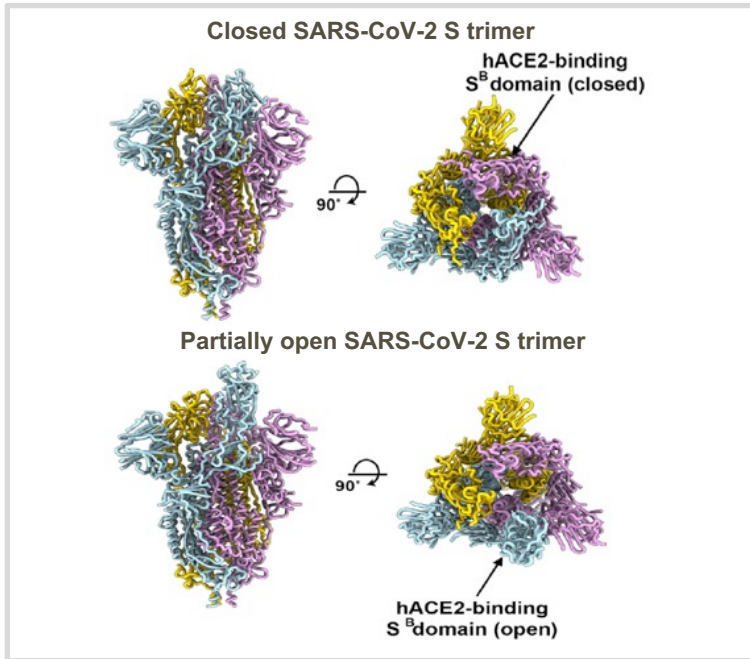
Genetic structure of SARS-CoV-2 Spike protein^{1,2}



CT, cytoplasm [inner] domain; fusion peptide; HR, heptapeptide repeat sequence; NTD, N-terminal domain; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TM, transmembrane;

Figure (top) adapted with permission from Calcagnile M, et al. bioRxiv preprint doi: <https://doi.org/10.1101/2021.01.12.426365>; (bottom) reprinted with permission from Calcagnile M, et al. bioRxiv preprint doi: <https://doi.org/10.1101/2021.01.12.426365>

SARS-CoV-2 spike protein conformation



Three spike protein monomers join forming a trimer, which, together form the characteristic protrusions on the virus surface¹



The spike normally exists in a metastable, prefusion conformation. Following receptor binding, structural rearrangement takes place enabling viral fusion with the host cell membrane^{1,2}



The NTD and RBD can exist in an open or closed conformation. In the closed conformation the RBD is largely hidden whereas in the open conformation it points upward, and the receptor binding site is exposed. Binding of ACE2 to the open conformation appears to stimulate the spike protein to adopt the post-fusion state²


ACE2, angiotensin-converting enzyme 2; hACE2, human ACE2; NTD, N-terminal domain; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Figure: adapted with permission from 1. Walls AC, et al. *Cell* 2020;181:281–92

1. Huang Y, et al. *Acta Pharmacologica Sinica* 2020;41:1141–9; 2. Xiong X, et al. *Nature Structural Molecular Biol* 2020;27:934–41

Mutations within the spike protein can affect its activity and function

Variations in the spike protein can lead to:

 Increased transmissibility¹

 Avoid immunity via mAb treatment or vaccination¹

 Higher viral loads^{1,2}

 Increased mortality¹

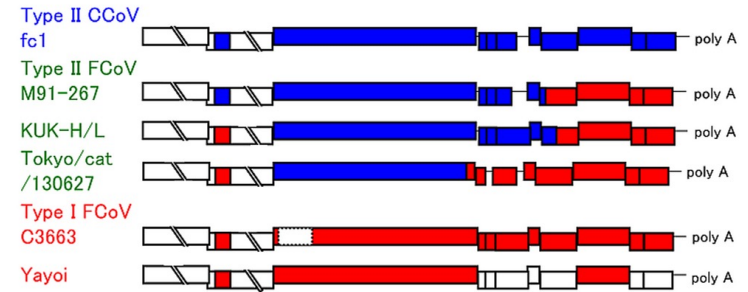
mAb, monoclonal antibody

1. Li Q, et al. *Cell* 2020;182:1284–94; 2. Baric RS; *The New England Journal Of Medicine*;2020;383;2684-2686

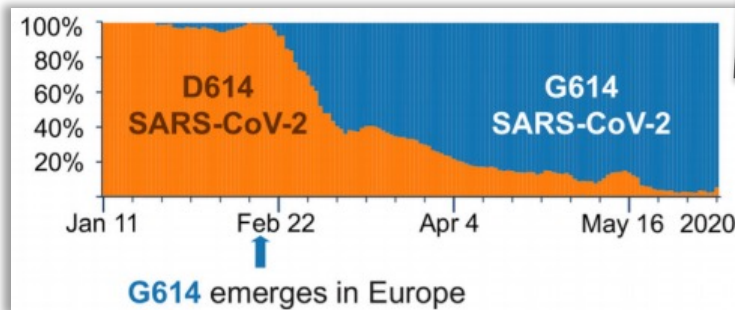
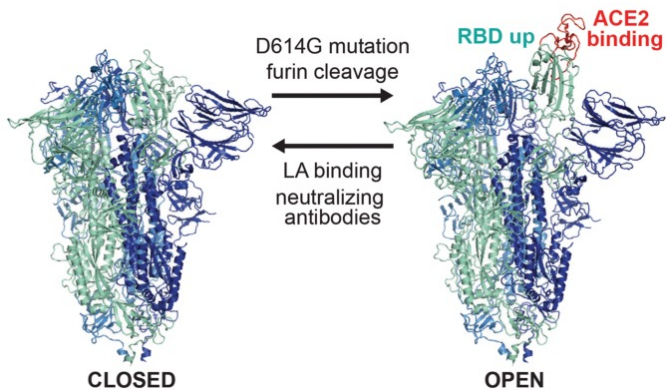
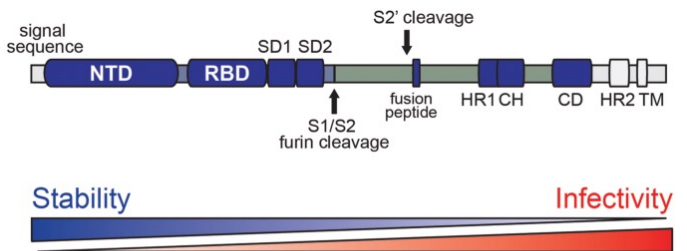
Mécanismes de variabilité génétique

- Erreur incorporation de l'ARN polymérase virale. Fonction correctrice d'erreur unique (exoribonuclease NSP14)
 - Faible taux de mutation viral (10-6 nt/ cycle viral)
 - Estimation du taux de mutation viral à 1 à 2 nt par mois
- Recombinaison homologue (exceptionnelle entre deux genres de coronavirus différents : ex. alpha et bêta)
- Edition génomique par facteurs de restriction cellulaire (APOBEC3) ?

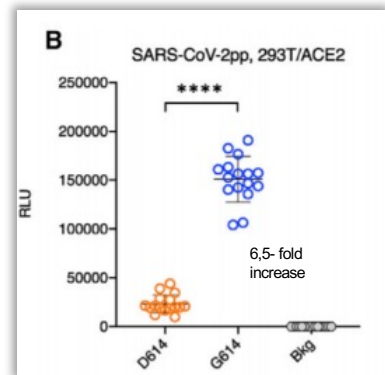
■ Coronavirus félin
■ Coronavirus canin



Adaptation du SARS-CoV-2

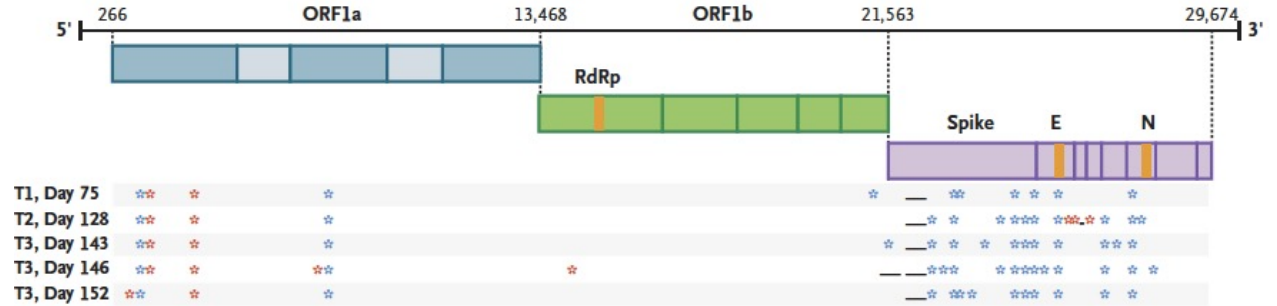


D614G de la protéine Spike



Sélection *in vivo* des mutations E484K et N501Y chez des patients immunodéprimés

Locations of SARS-CoV-2 Sequence Polymorphisms over Time



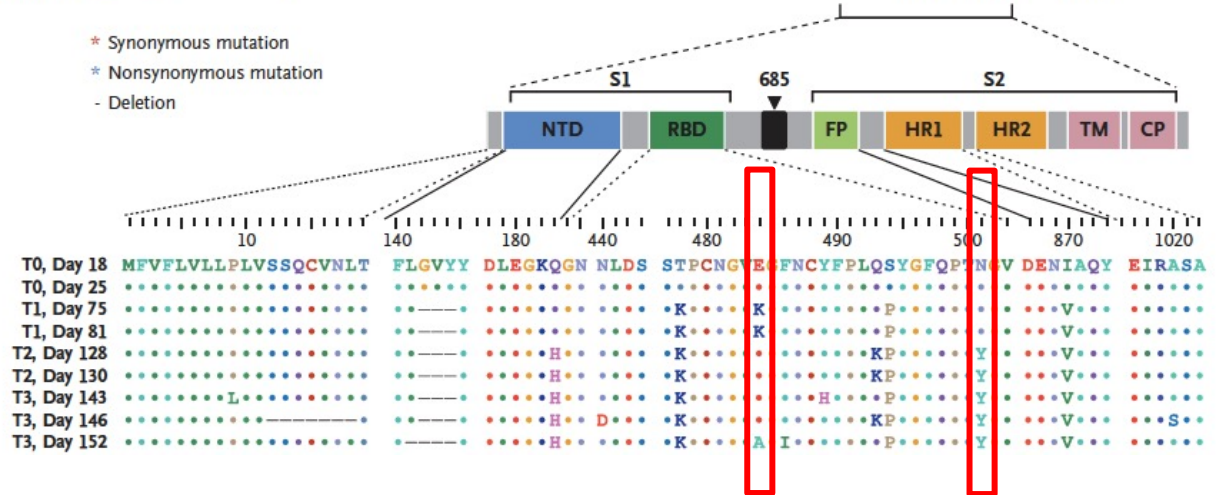
THE NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE



Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host

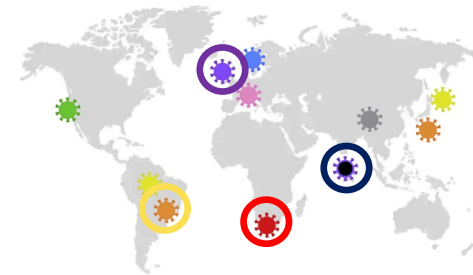
- * Synonymous mutation
- * Nonsynonymous mutation
- Deletion



Emergence de variants

- **Variant préoccupant, ou VOC (« variant of concern ») : variant pour lequel il a été démontré :**
 - une augmentation de la transmissibilité ou un impact défavorable sur l'épidémiologie du COVID-19
 - une augmentation de la gravité ou un changement de présentation clinique
 - une diminution de l'efficacité des mesures de contrôle mises en place (mesures de prévention, tests diagnostiques, vaccins, molécules thérapeutiques)

WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I/S:501Y.V1	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H/S:501Y.V2	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J/S:501Y.V3	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2	G/452R.V3	21A/S:478K	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021



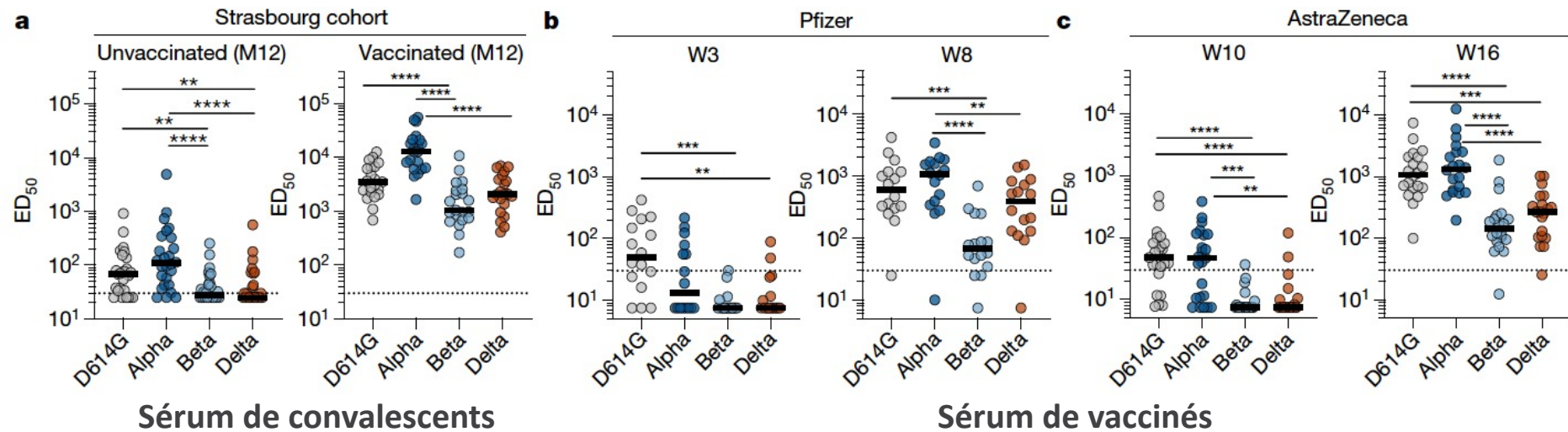
Variants préoccupants

Nom nomenclature Nextstrain (Lignage PANGO)	Alpha (UK) 20I/501Y (B.1.1.7)	Beta (SA) 20H/501Y (B.1.351)	Gamma (BR) 20J/501Y (P.1)	Delta (IN) 20A/452R (B.1.617.2)
Première détection	Royaume Uni Septembre 2020 France 09/2020	Afrique du Sud Mai 2020 France 12/2020	Brésil Novembre 2020 France 01/2021	Inde Octobre 2020 France 04/2021
Diffusion dans le monde	172 pays (> 900 000 séquences GISAID)	120 pays (26 000 seq)	72 pays (40 000 seq)	>100 pays (90 000 seq)
Fréquence en France (Aout 2021)	< 1%	< 1%	< 1%	> 95%
Transmissibilité	↑ (43-90%)	↑ (50%)	↑ (à consolider : 40 à 120%)	↑↑ (environ 40 à 60% plus transmissible que VOC Alpha)
Sévérité	Débatte: probable ↑ Risque hospitalisation (40-64%) et de décès (30-70%)	Débatte : probable ↑ mortalité hospitalière (20%)	?	A confirmer: probable ↑ Risque hospitalisation et forme sévère (X2 VOC Alpha)
Impact sur échappement immunitaire	Non significatif Del69/70 + 501Y	Significatif +++ 417N + 501Y + 484K	Significatif < SA 417T + 501Y + 484K	Limité 452R + 478K

Variant Delta

- **Augmentation de la transmissibilité : 40-60% par rapport à Alpha et 97% par rapport aux non-VOC**
- **Données préliminaires en faveur d'une charge virale plus élevée par rapport à Alpha**
- **Données préliminaires en faveur d'un impact sur l'échappement immunitaire post-vaccinal supérieur à celui de Alpha, surtout si vaccination incomplète (1 seule des 2 doses)**

Neutralisation du variant Delta



X 4 Delta versus Alpha

1 dose Pfizer et Astra: Peu/pas de neutralisation du Delta

2 doses du vaccin Pfizer: X3 Delta versus Alpha

2 doses du vaccin Astra: X5 Delta versus Alpha

Efficacité des vaccins sur le variant Delta

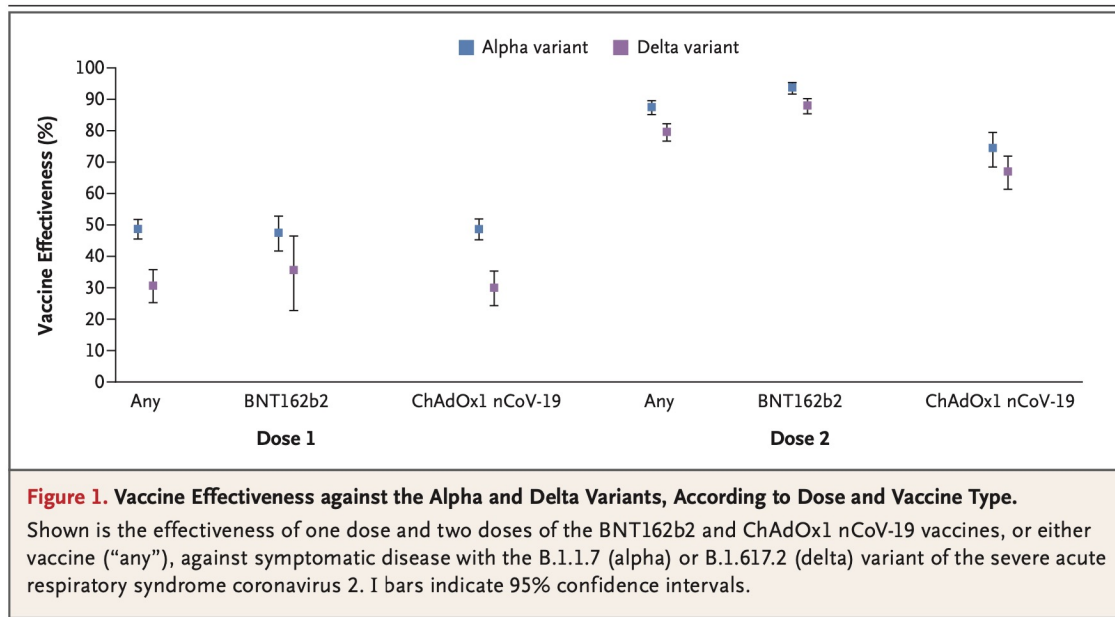
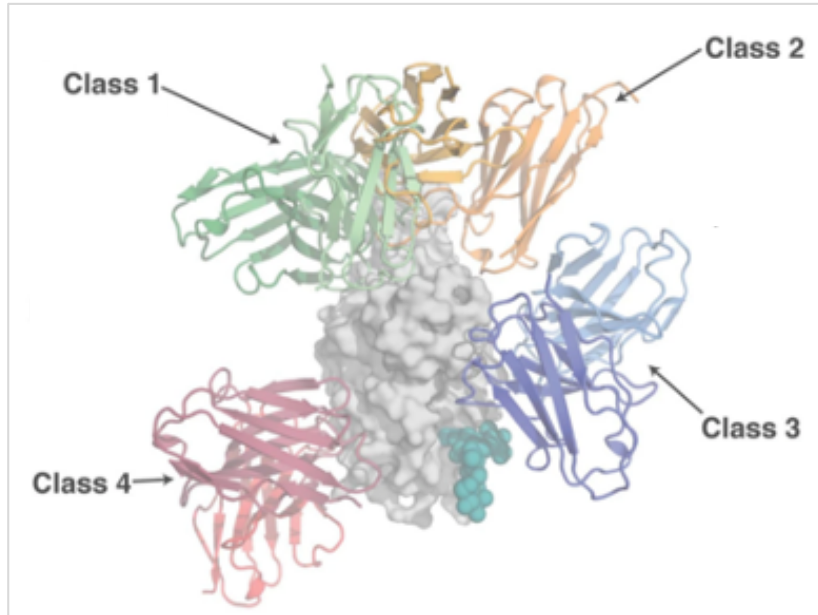


Figure 1. Vaccine Effectiveness against the Alpha and Delta Variants, According to Dose and Vaccine Type.

Shown is the effectiveness of one dose and two doses of the BNT162b2 and ChAdOx1 nCoV-19 vaccines, or either vaccine (“any”), against symptomatic disease with the B.1.1.7 (alpha) or B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2. I bars indicate 95% confidence intervals.

Only modest differences in vaccine effectiveness against symptomatic disease were noted with the delta variant as compared with the alpha variant after the receipt of two vaccine doses

Antibodies against the SARS-CoV-2 spike protein are classified according to their binding site



Classification	Structural characteristics
Class 1	<ul style="list-style-type: none">• Blocks ACE2• Binds only to 'up' RBDs
Class 2	<ul style="list-style-type: none">• Blocks ACE2• Binds both 'up' and 'down' RBDs• Can contact adjacent RBDs
Class 3	<ul style="list-style-type: none">• Binds outside the RBM (ACE2 binding site)• Recognises both 'up' and 'down' RBDs
Class 4	<ul style="list-style-type: none">• Does not block ACE2• Binds only to 'up' RBDs

ACE2, angiotensin-converting enzyme 2; RBD, receptor binding domain; RBM, receptor binding motif

Current mAbs for treatment of COVID-19 differ in their classification

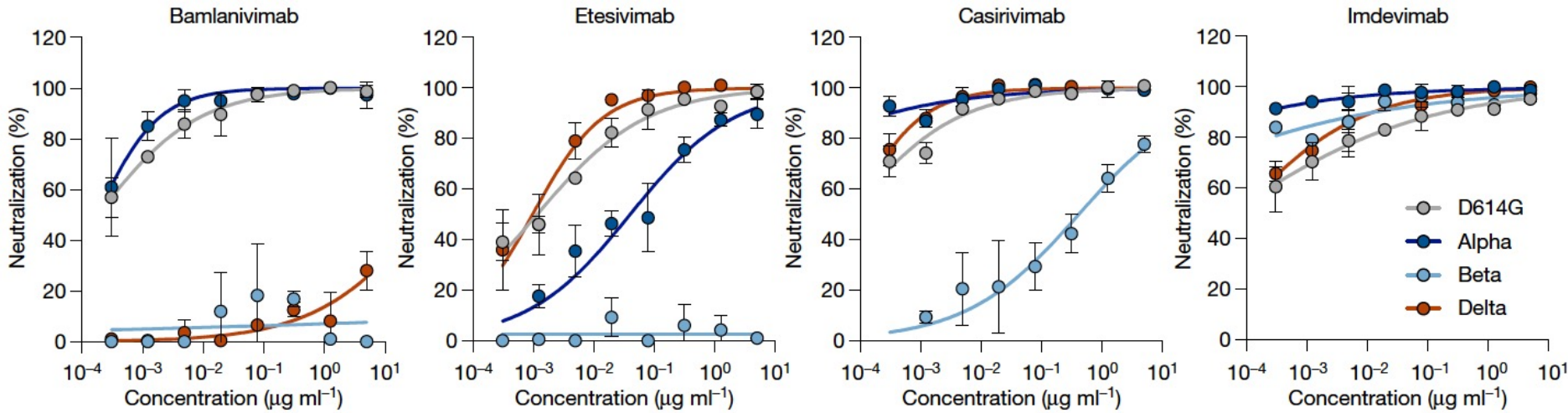
Name	RBD site
Sotrovimab (VIR-7831)^{1,2} VIR-7832^{1,2}	Class 3
REGN-COV2 (REGN10933 and REGN10987) ^{3,4,5}	Class 1 Class 2
LY-CoV555 and LY-CoV16^{6,7}	Class 2
AZD7442⁸ (cocktail of AZD8895 and AZD1061)	Class 1 Class 2

Only sotrovimab† binds to a Class 3 RBD site, distinct from the RBM (ACE2 binding site)^{1,2}

*mAbs selected according to progression in their development plan; †and VIR-7832
ACE2, angiotensin-converting enzyme 2; mAbs, monoclonal antibodies; RBD, receptor binding domain; RBM, receptor binding motif

1. Barnes CO, et al. *Nature* 2020;588:682–7; 2. Pinto D, et al. *Nature* 2020;583:290–5; 3. Baum A, et al. *Science* 2020;369:1014–18; 4. Baum A, et al. *Science* 2020;370:1110–5; 5. Hansen J, et al. *Science* 2020;369:1010–14; 6. Jones BE, et al. *bioRxiv preprint* 2020; doi: <https://doi.org/10.1101/2020.09.30.318972>; 7. Shi R, et al. *Nature* 2020;584:120–4; 8. Zost SJ, et al. *Nature* 2020;584:443–9.

Reduced sensitivity of SARS-CoV-2 variant Delta to antibody neutralization



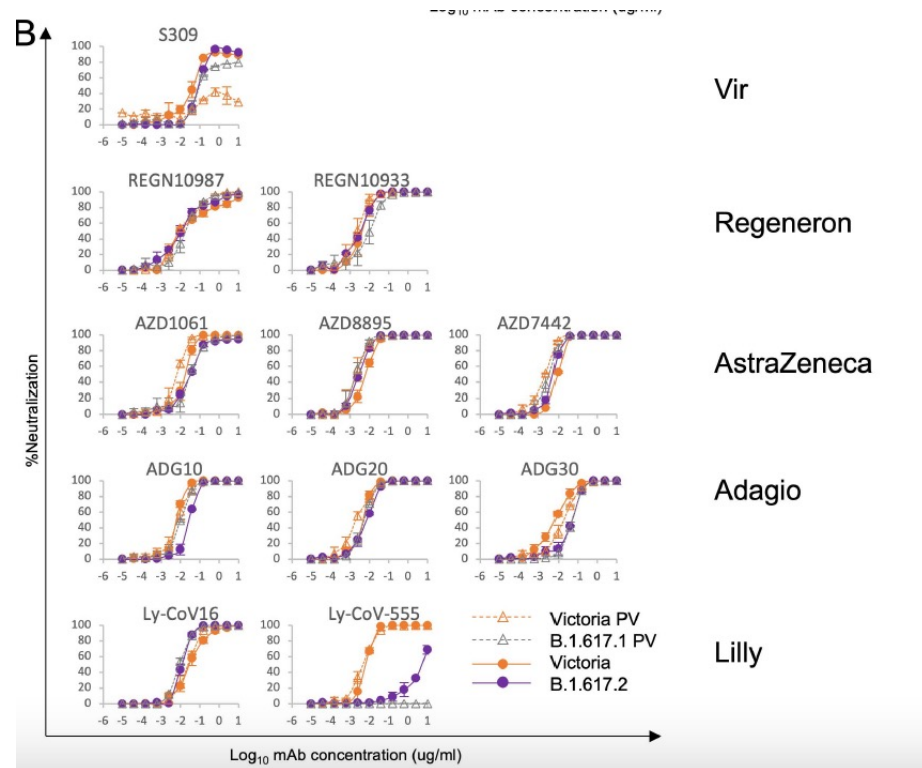
Beta et Delta résistants

X200 Alpha
Beta résistant

Beta résistant



Activité *in vitro* de différents mAbs sur le variant Delta



Variant	Spike Mutations	Fold-Change in VIR-7831 IC ₅₀ vs. Wild-type	Fold-Change in VIR-7832 IC ₅₀ vs. Wild-type
Alpha (B.1.1.7)	H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H	2.3	2.5
Beta (B.1.351)	L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V	0.6	0.7
Gamma (P.1)	D138Y, D614G, E484K, H655Y, K417T, L18F, N501Y, P26S, R190S, T1027I, T20N, V1176F	0.4	0.4
Delta (B.1.617.2)	T19R, G142D, E156G, F157-, R158-, L452R, T478K, D614G, P681R, D950N	1	NT

Vir

Regeneron

AstraZeneca

Adagio

Lilly

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<https://doi.org/10.1101/2021.03.09.43460>



<https://doi.org/10.1016/j.cell.2021.06.020>

22^{es} JN1, Montpellier du 30/08 au 1^{er}/09/2021

Conclusions

- **Variabilité génétique du SARS-CoV-2**
 - Facteurs: ARN, fitness, circulation, pression immune, vaccination, mAbs
- **Mutations dans Spike**
 - Impact: transmissibilité, charge virale, efficacité vaccination/mAbs (variant Beta), mortalité
- **Variant Delta**
 - Transmissibilité +++
 - Mortalité?
 - Efficacité de la vaccination
 - Efficacité des mAbs sauf Bam