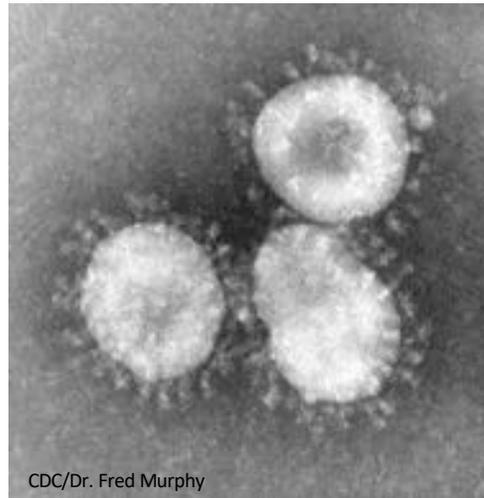


SARSCOV2 – Saison 2

Variants of Concern (VOC)

Mylene Ogliastro

mylene.ogliasro@gmail.com



CDC/Dr. Fred Murphy

Evolution des maladies virales chez l'Homme

- Les hommes vivaient initialement en groupes isolés, ayant peu de contacts les uns avec les autres.
- L'invention de l'agriculture (12000 ans) puis de l'élevage et le développement de l'urbanisation ont considérablement augmenté la taille des populations humaines.
- Ces 1000 dernières années, les contacts se sont intensifiés et ont conduit à la dissémination des virus à des échelles beaucoup plus larges.
- Ces 100 dernières années, les pratiques sanitaires ont changé le "profil" des maladies causées par certains virus en raison d'un allongement de l'Espérance de vie.
- Des changements environnementaux locaux, régionaux, mondiaux, générés par l'Homme ont profondément modifié l'écologie des virus

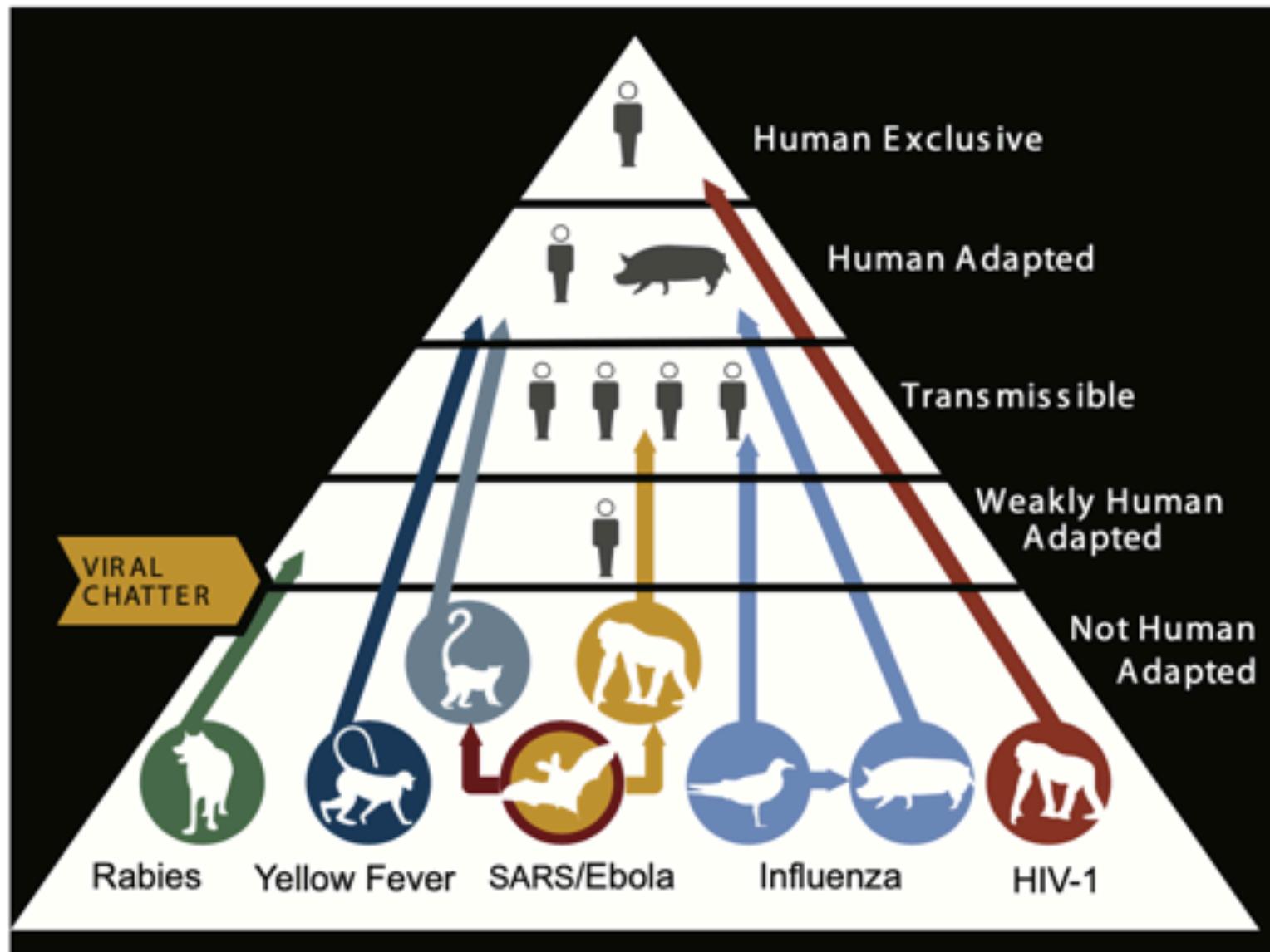


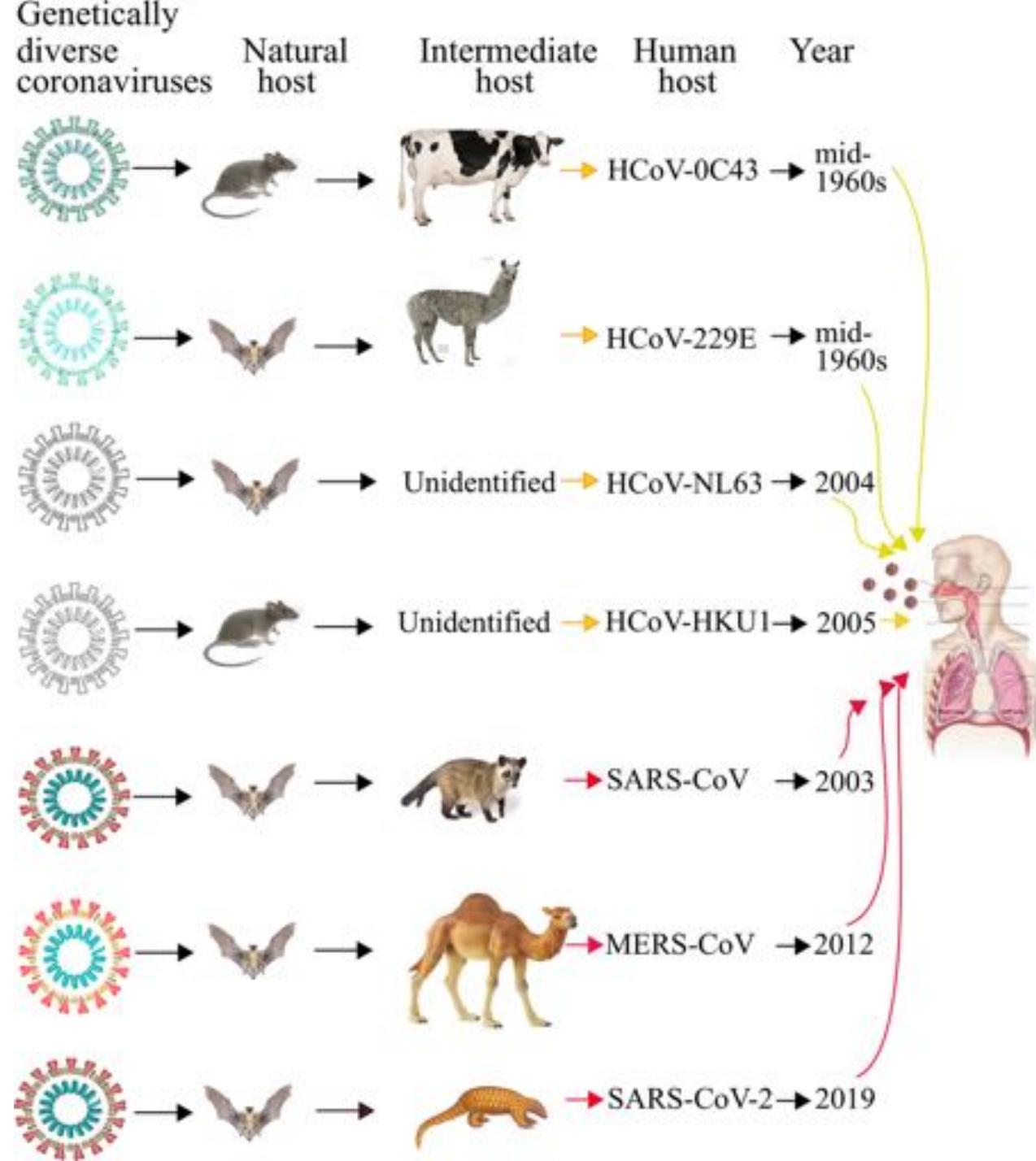
FIGURE WO-24 Human viruses have animal origins.
 SOURCES: Wolfe (2011); adapted from Wolfe et al. (2007).

D'une épidémie à une pandémie

International Agro-Food Trade Network

Ercsey-Ravasz et al., (2012), PLoS ONE

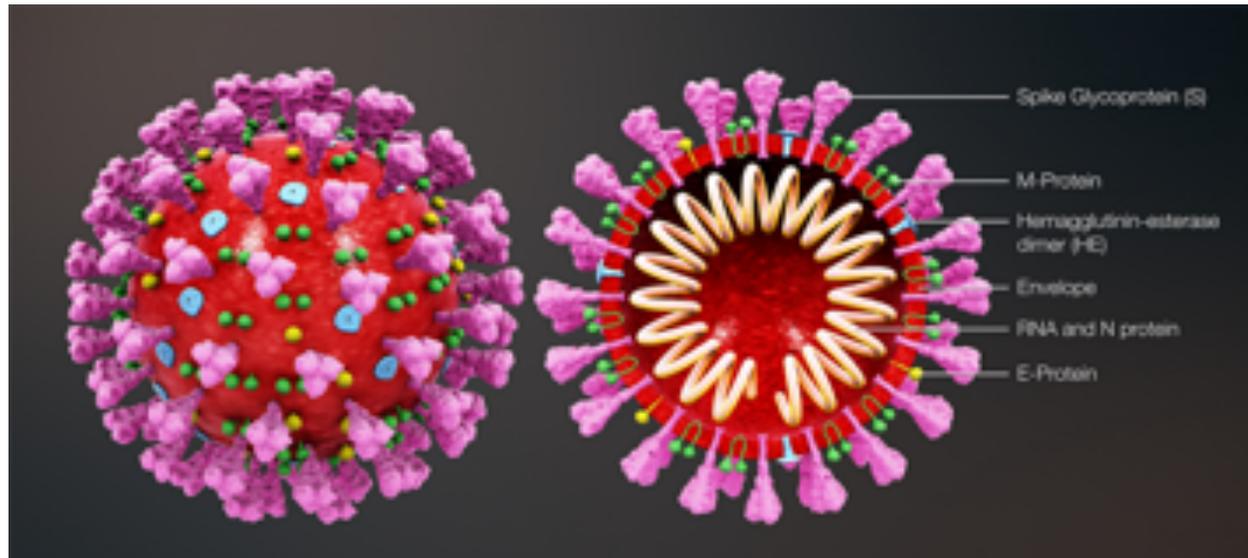




Découverte du SARSCOV2

Zhou et al., publié le 23 Janvier 2020

Family *Coronaviridae*



- **Virus enveloppés**
- **Nucleocapsides hélicoïdale ou tubulaire**
- **Genome RNA « + » (27-32kb)**

Découverte du SARSCOV2

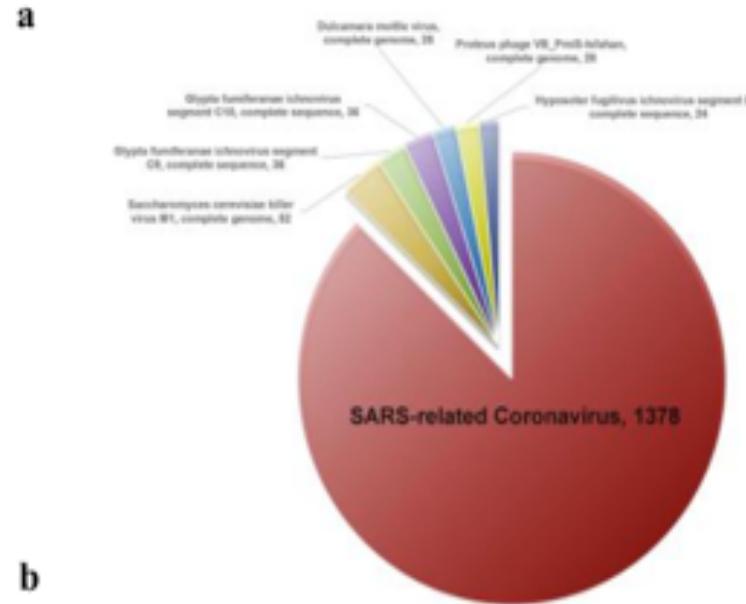
Zhou et al., publié le 23 Janvier 2020

Séquencage:
déterminer la carte génétique du virus

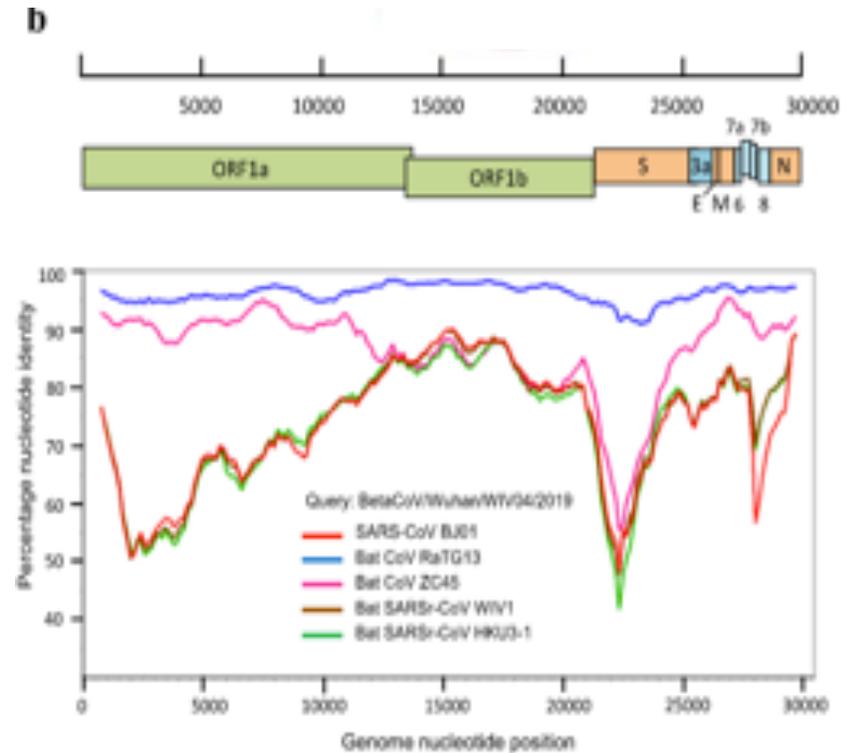
ADN <- ARN



Analyses bioinformatiques



b



Découverte du SARSCOV2

Séquence publiée le 23 Janvier 2020

Nucleotide

GenBank Ser

Wuhan seafood market pneumonia virus isolate Wuhan-Hu-1, complete genome

GenBank: MN908947.3

[FASTA](#) [Graphics](#)

Go to:

LOCUS MN908947 29903 bp ss-RNA linear **VRL 23-JAN-2020**

DEFINITION Wuhan seafood market pneumonia virus isolate Wuhan-Hu-1, complete genome.

ACCESSION MN908947

VERSION MN908947.3

KEYWORDS -

SOURCE Wuhan seafood market pneumonia virus

ORGANISM [Wuhan seafood market pneumonia virus](#)
 Viruses; Riboviria; Nidovirales; Coronaviridae; Orthocoronavirinae; Betacoronavirus; unclassified Betacoronavirus.

REFERENCE 1 (bases 1 to 29903)

AUTHORS Wu, F., Zhao, S., Yu, B., Chen, Y.-M., Wang, W., Hu, Y., Song, Z.-G., Tao, Z.-W., Tian, J.-H., Pei, Y.-Y., Yuan, M. L., Zhang, Y.-L., Dai, F.-H., Liu, Y., Wang, Q.-M., Zheng, J.-J., Xu, L., Holmes, E. C. and Zhang, Y.-Z.

TITLE A novel coronavirus associated with a respiratory disease in Wuhan of Hubei province, China

JOURNAL Unpublished

REFERENCE 2 (bases 1 to 29903)

AUTHORS Wu, F., Zhao, S., Yu, B., Chen, Y.-M., Wang, W., Hu, Y., Song, Z.-G.,

FASTA

SARS: 30 000 bases (30 kb)

Send to:

Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome

GenBank: MN908947.3

[GenBank](#) [Graphics](#)

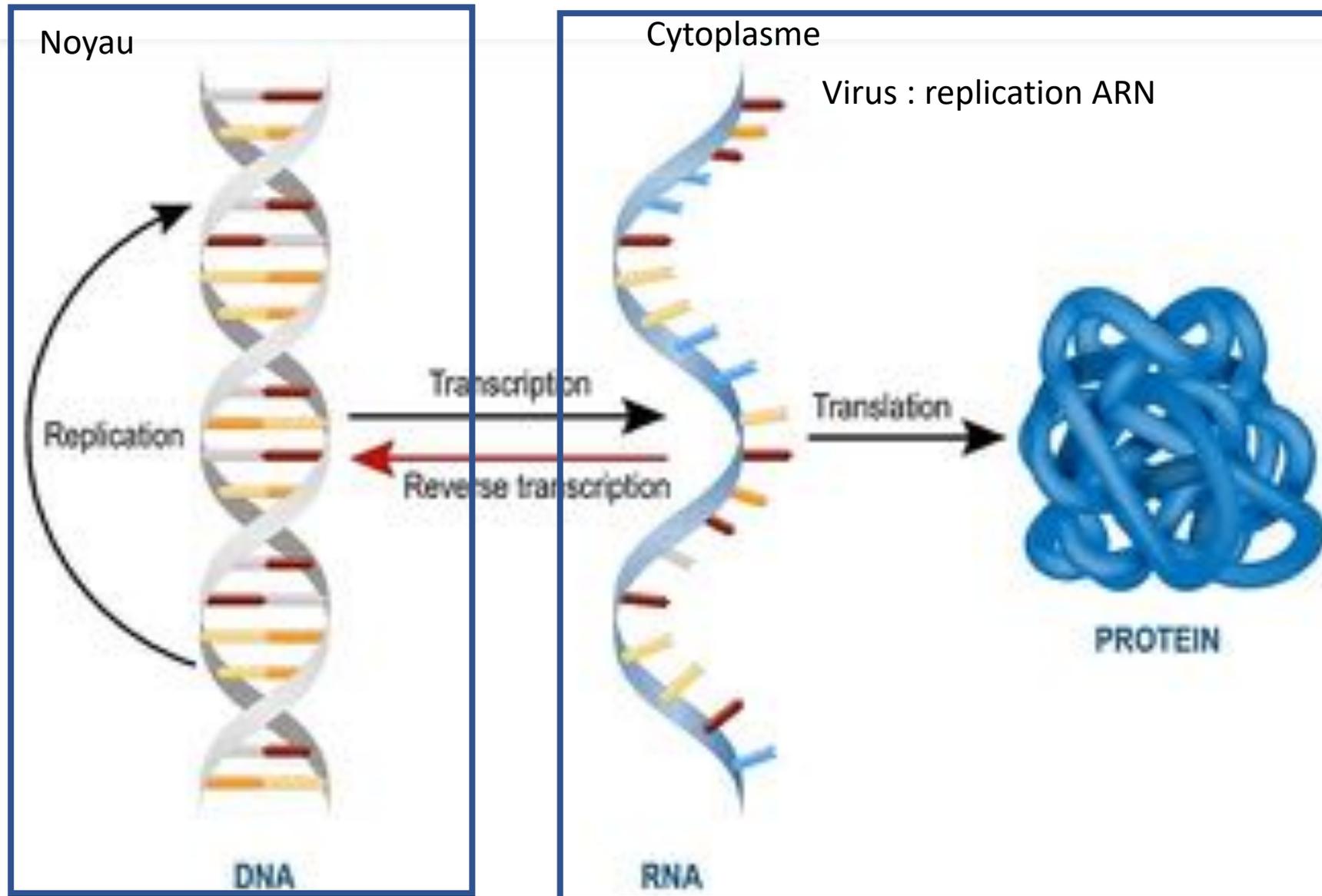
>MN908947.3 Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome

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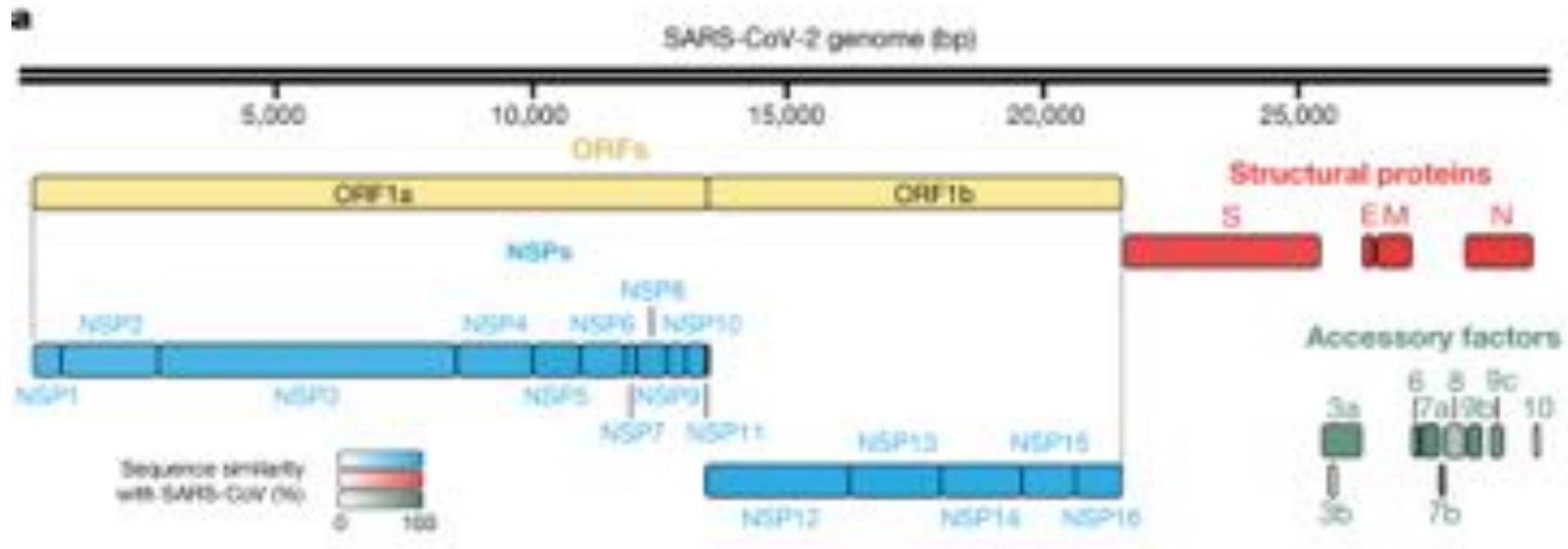
Le "Dogme Central" en Biologie



Découverte du SARSCOV2

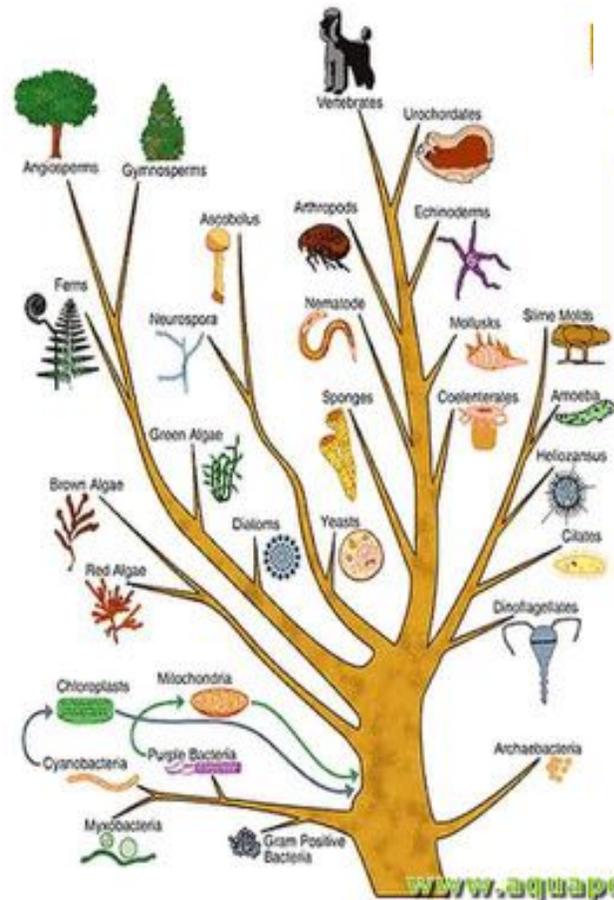
Séquence publiée le 23 Janvier 2020

ADN -> **ARN** -> PROTEINE



Comprendre l'histoire évolutive des organismes et des microorganismes

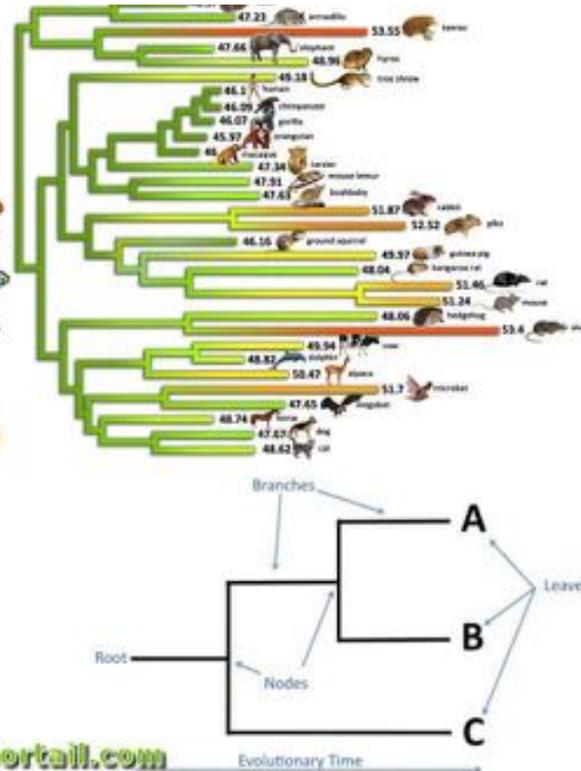
Analyses Morphologiques



Analyses Moleculaires

a.

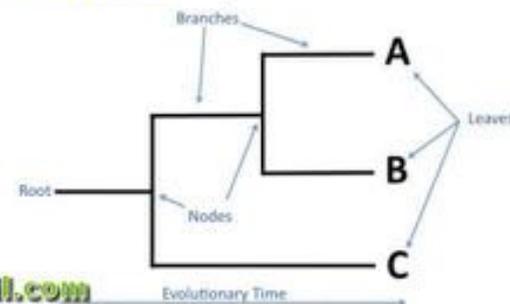
A	-- LP-TRR-PY-----DSATAP-GYMAVGDAAAHV-N
B	-- LP-TRR-PY-----DSATAP-GFMAVGDAAGHV-N
C	-- LP-TRR-PY-----DSAVHP-GYMAIGDAAGHV-N
D	-- LP-TRR-PY-----DSAVHP-GYVAIGDAAGHV-N



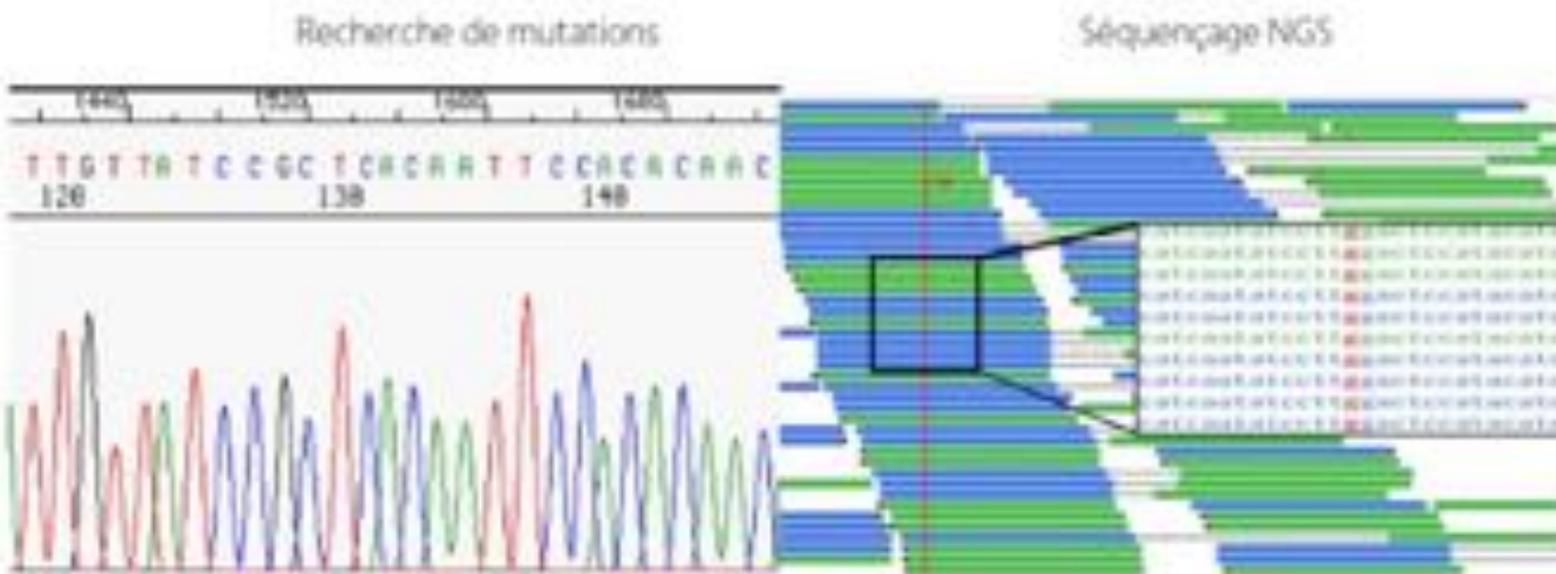
Modèles d'évolution



Arbre "phylogénétiques"



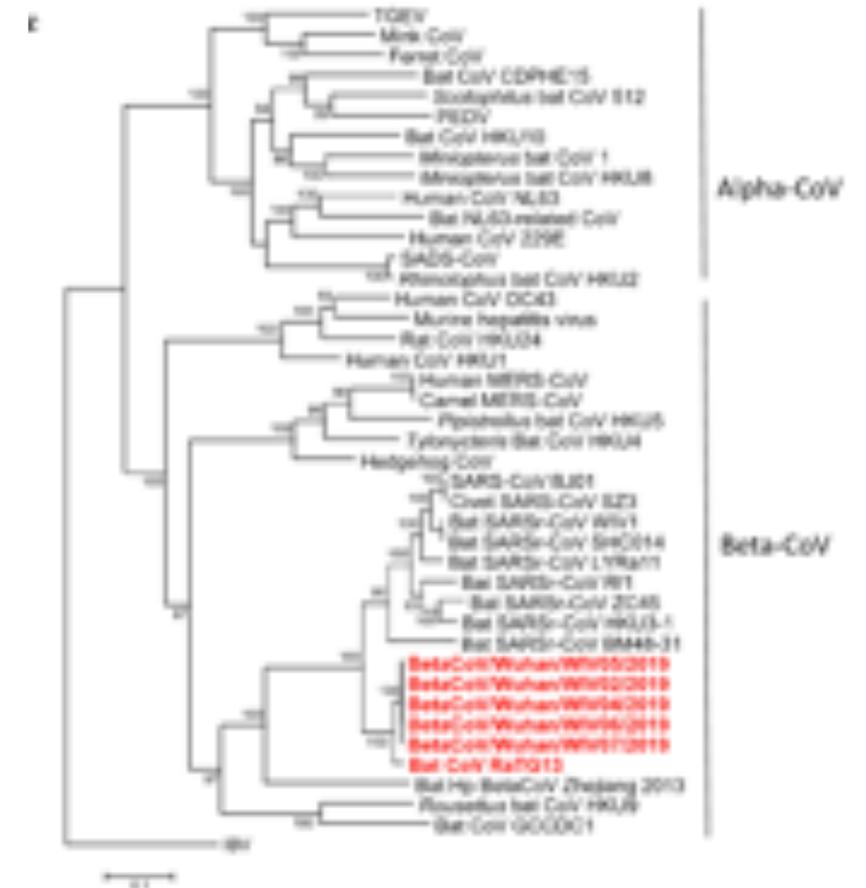
Phylogénétique : déterminer le niveau de parenté avec des (virus) existants



Horloge “moléculaires” permettent d’estimer le temps depuis l’émergence

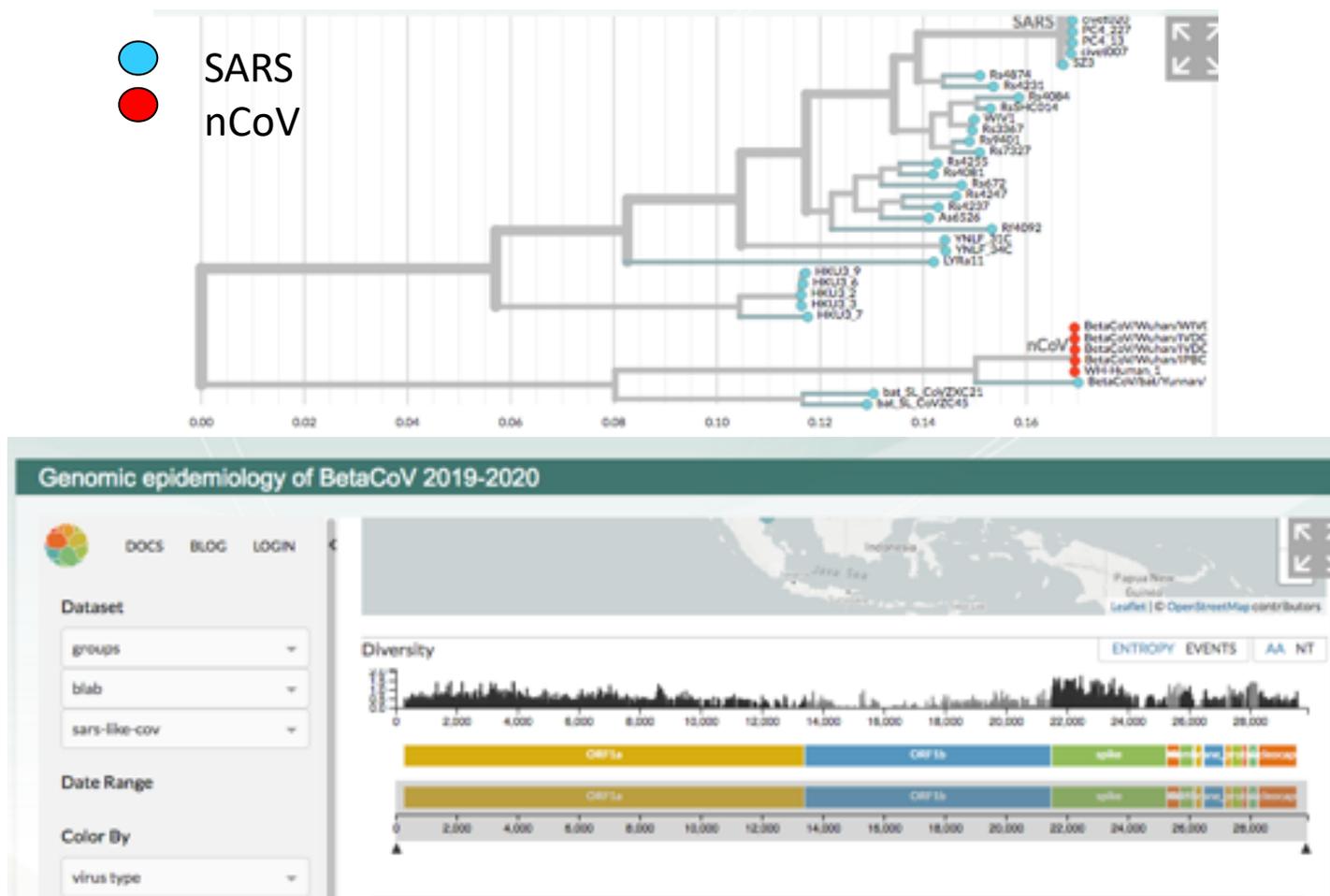
Ex: 2019 nCoV a une origine “chauve souris”

Ce virus circule chez l’Homme depuis très peu de temps



Les outils: Gisaid.org

partage des données au niveau Mondial pour suivre l'évolution du virus et les routes de migration

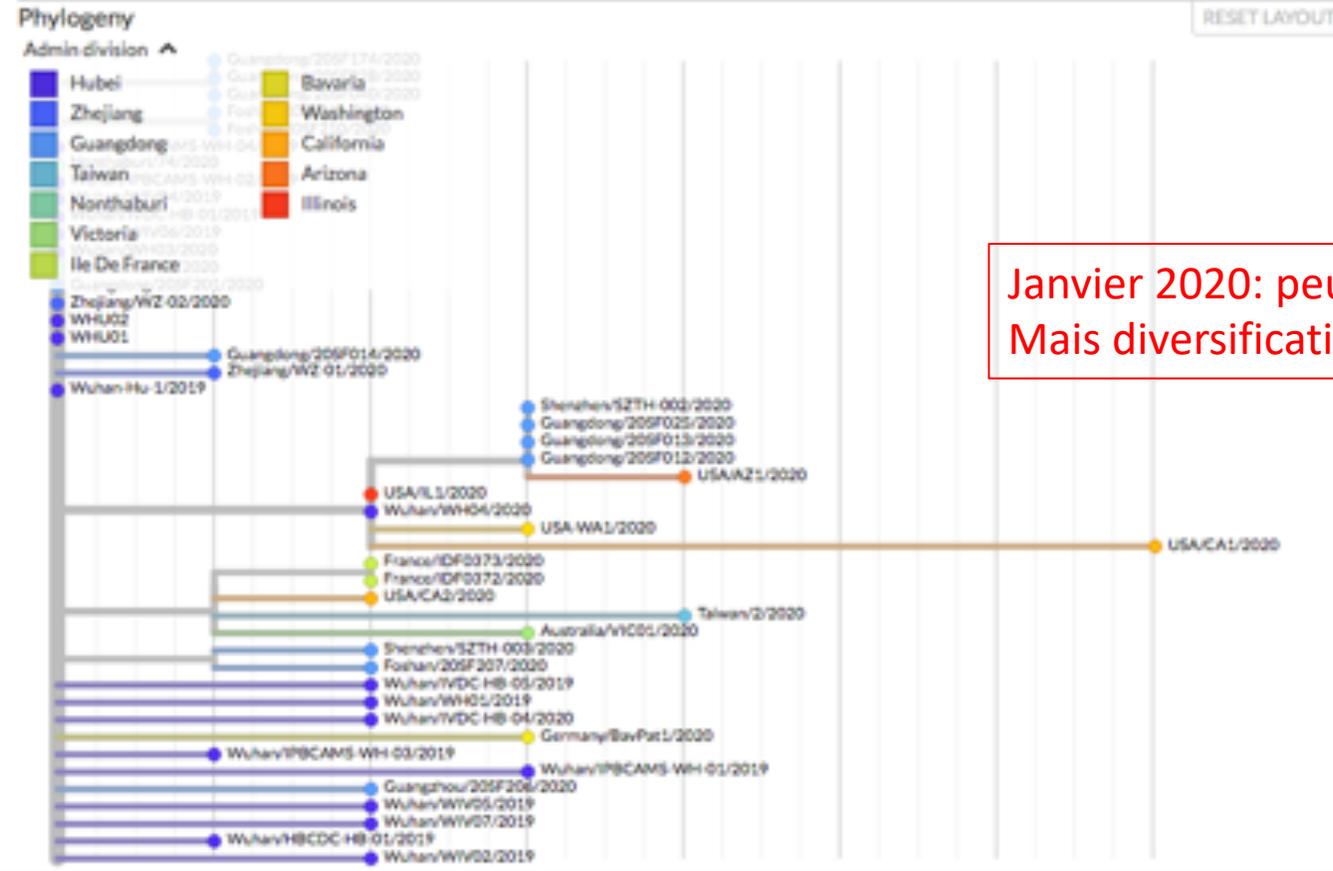


Genomic epidemiology of novel coronavirus (nCoV)

Built with github.com/nextstrain/ncov using data from [GISAI](https://gisaid.org/)D.

Showing 47 of 47 genomes sampled between Dec 2019 and Jan 2020.

Hadfield *et al.*, *Bioinformatics* 2018



<https://nextstrain.org/ncov>

Genomic epidemiology of novel coronavirus (nCoV)

Built with github.com/nextstrain/ncov using data from [GISAID](https://gisaid.org).

Showing 47 of 47 genomes sampled between Dec 2019 and Jan 2020.

<https://nextstrain.org/ncov>

Phylogeny

RESET LAYOUT

Admin division

- Hubei
- Zhejiang
- Guangdong
- Taiwan
- Nonthaburi
- Victoria
- Ile De France
- Bavaria
- Washington
- California
- Arizona
- Illinois



Genomic epidemiology of novel coronavirus (nCoV)

Built with github.com/nextstrain/ncov using data from [GISAID](https://gisaid.org).

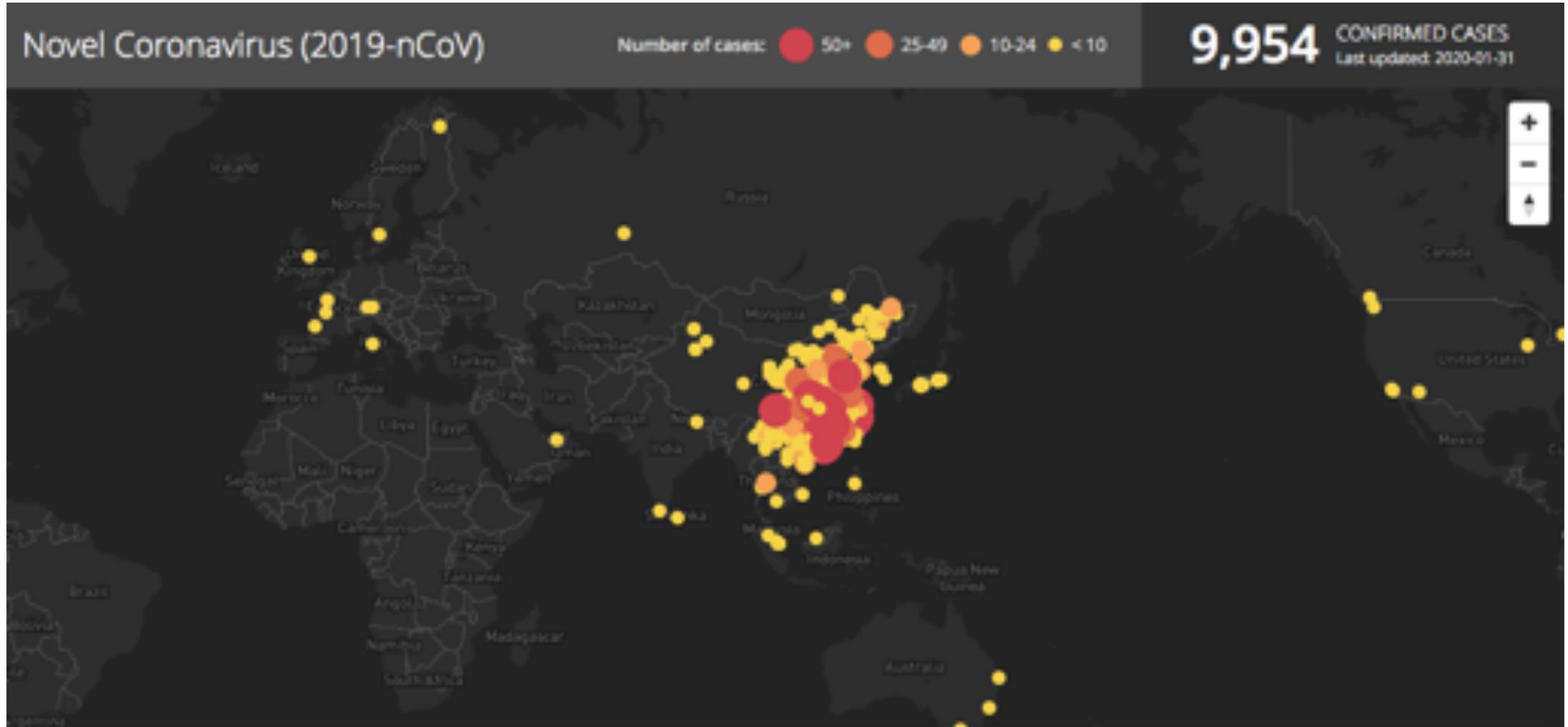
Showing 47 of 47 genomes sampled between Dec 2019 and Jan 2020.

<https://nextstrain.org/ncov>



COVID-19 : de l'épidémie à la pandémie

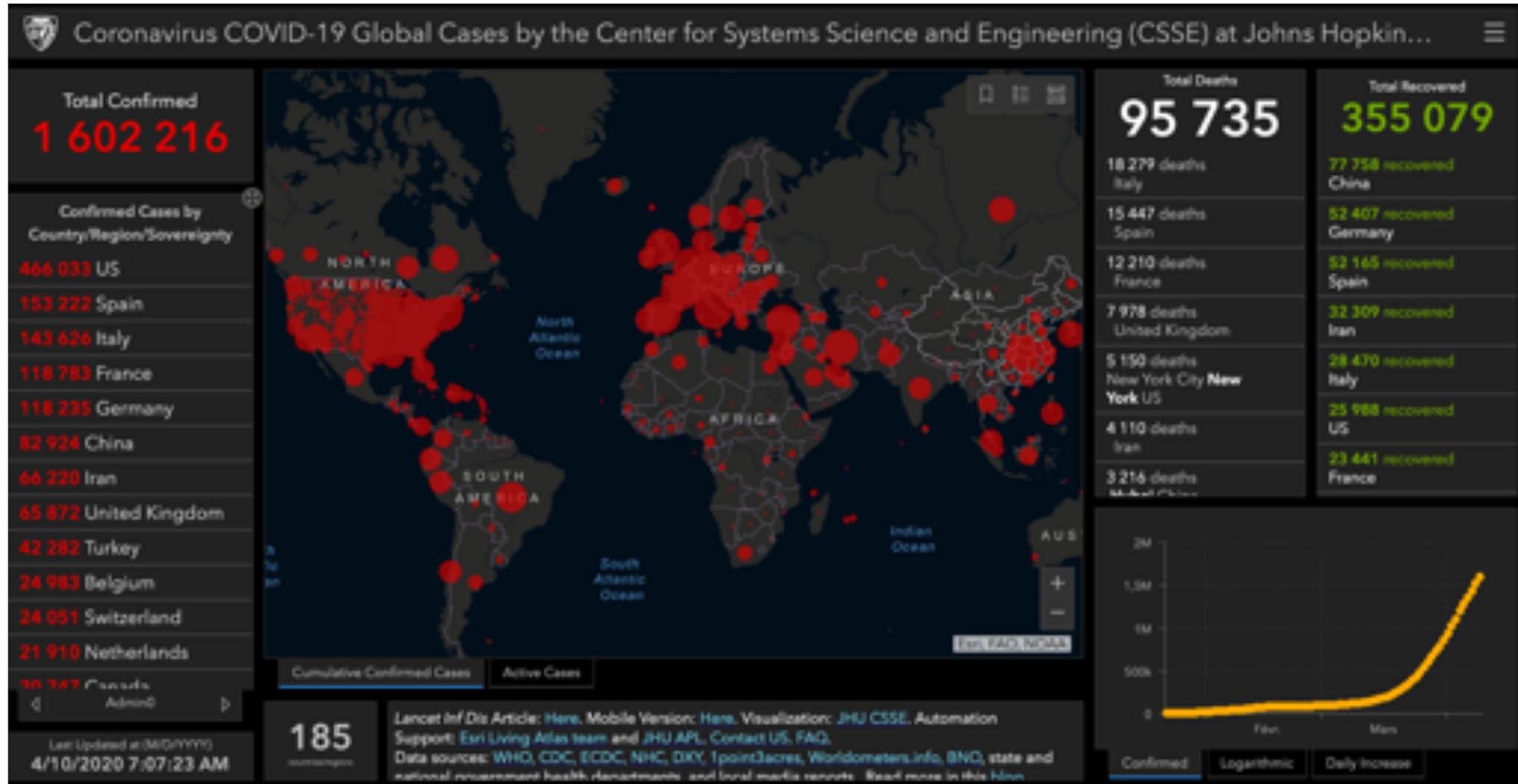
31 Janvier 2020



<https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6>

COVID-19 : de l'épidémie à la pandémie

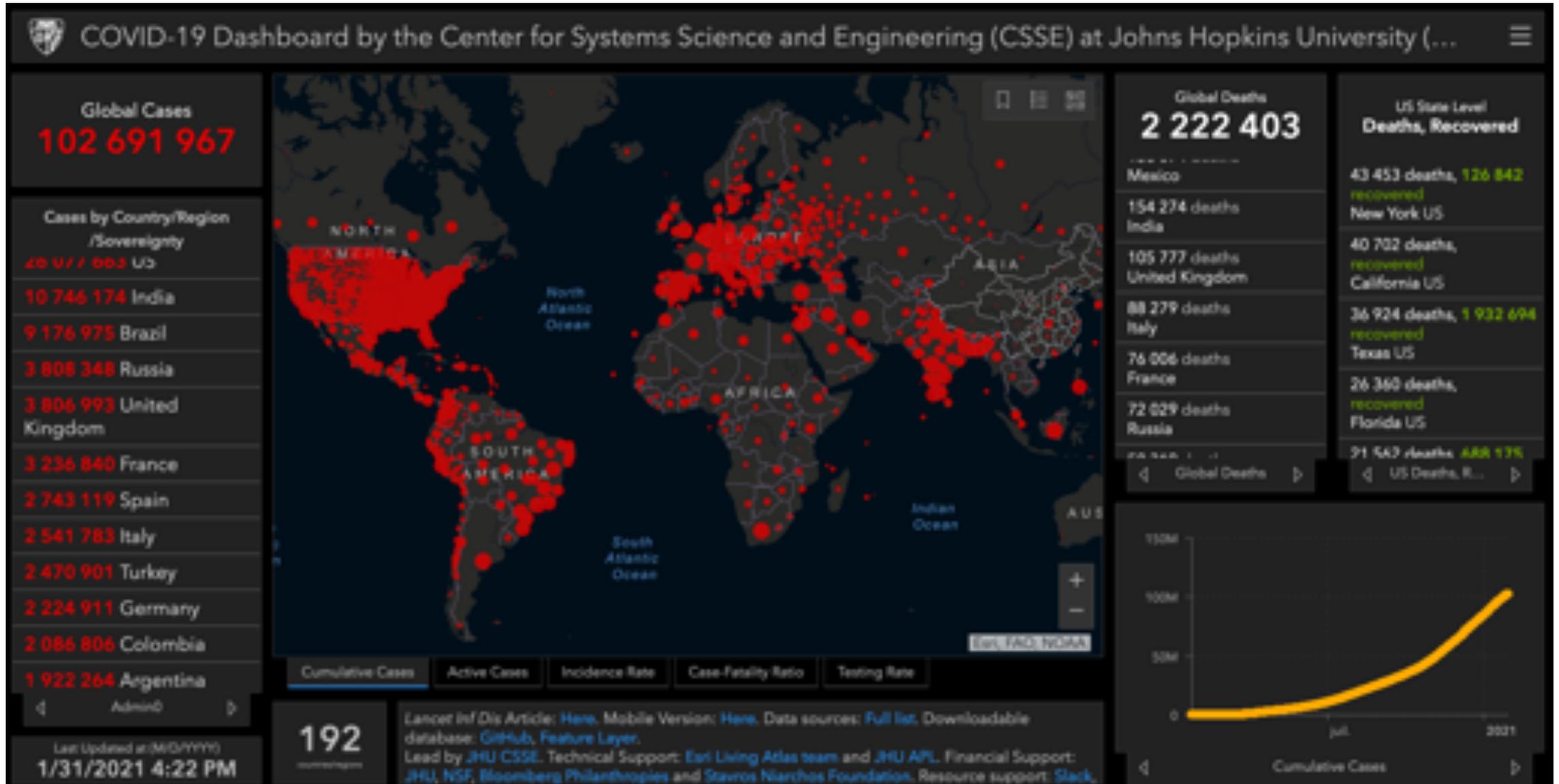
10 Avril 2020



<https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6>

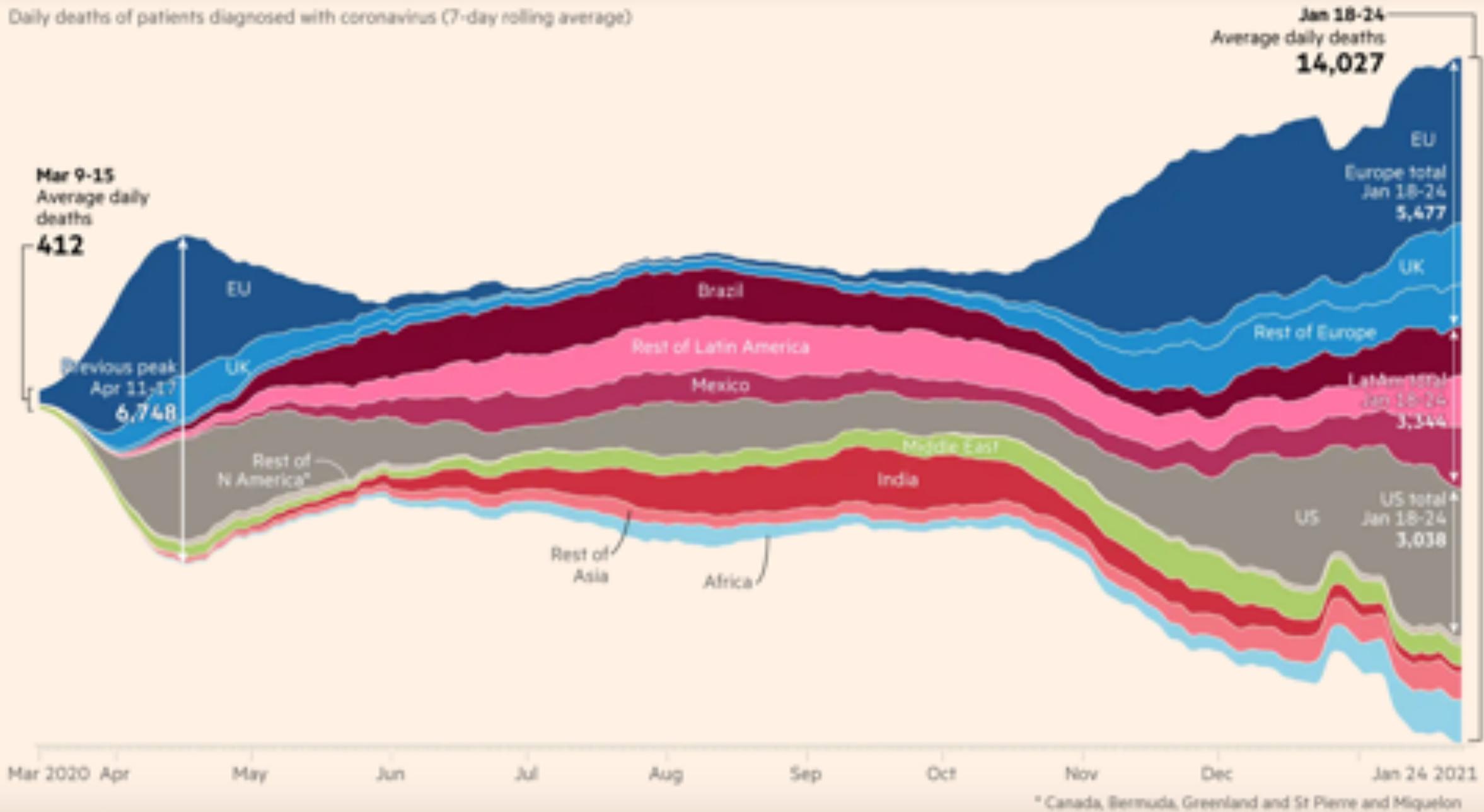
COVID-19 : de l'épidémie à la pandémie

31 Janvier 2021



Taux de mortalité = 2,1%

Daily deaths of patients diagnosed with coronavirus (7-day rolling average)



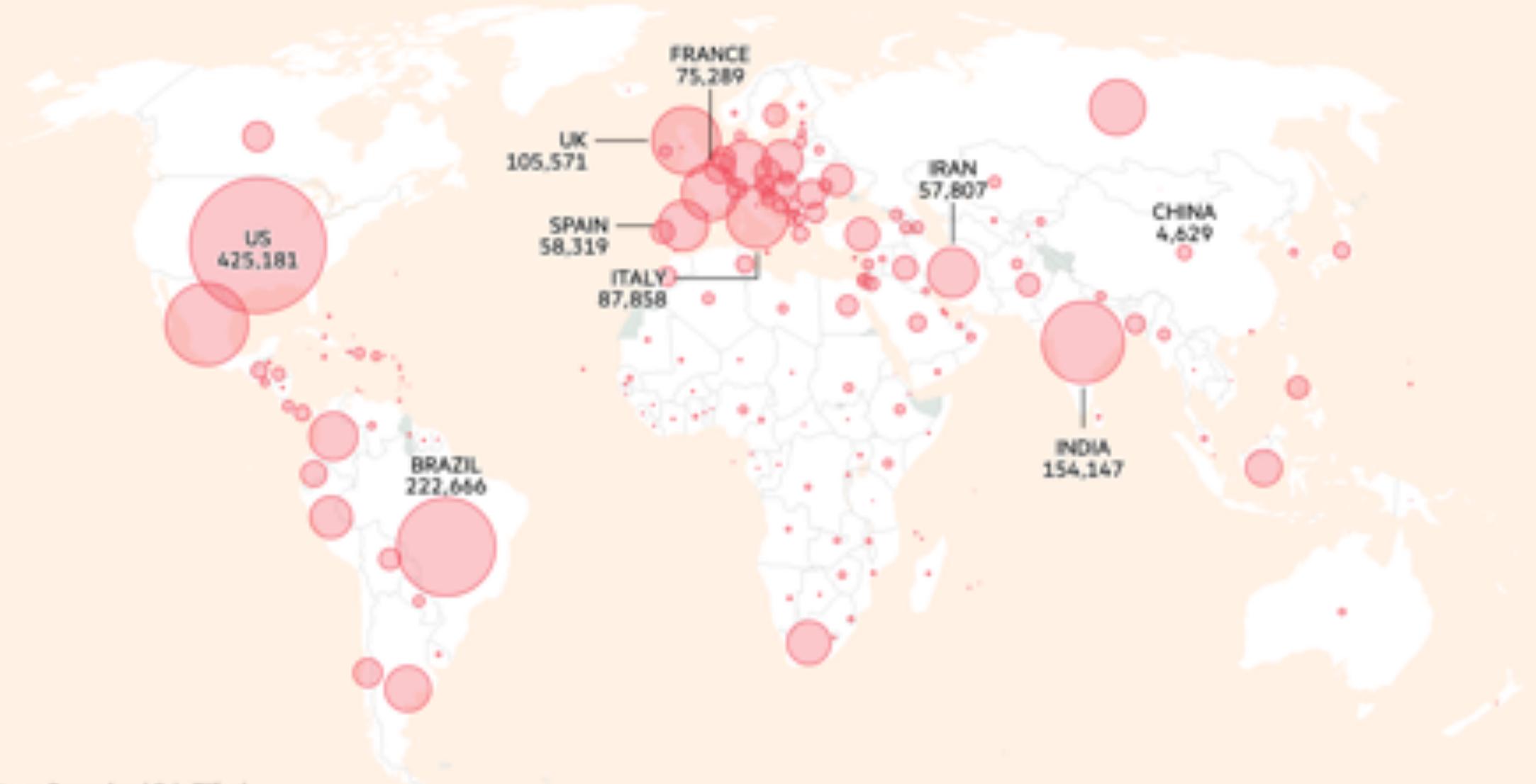
* Canada, Bermuda, Greenland and St Pierre and Miquelon

Mapping the coronavirus outbreak

As of 6.15pm January 30 GMT

Confirmed cases
101.7m

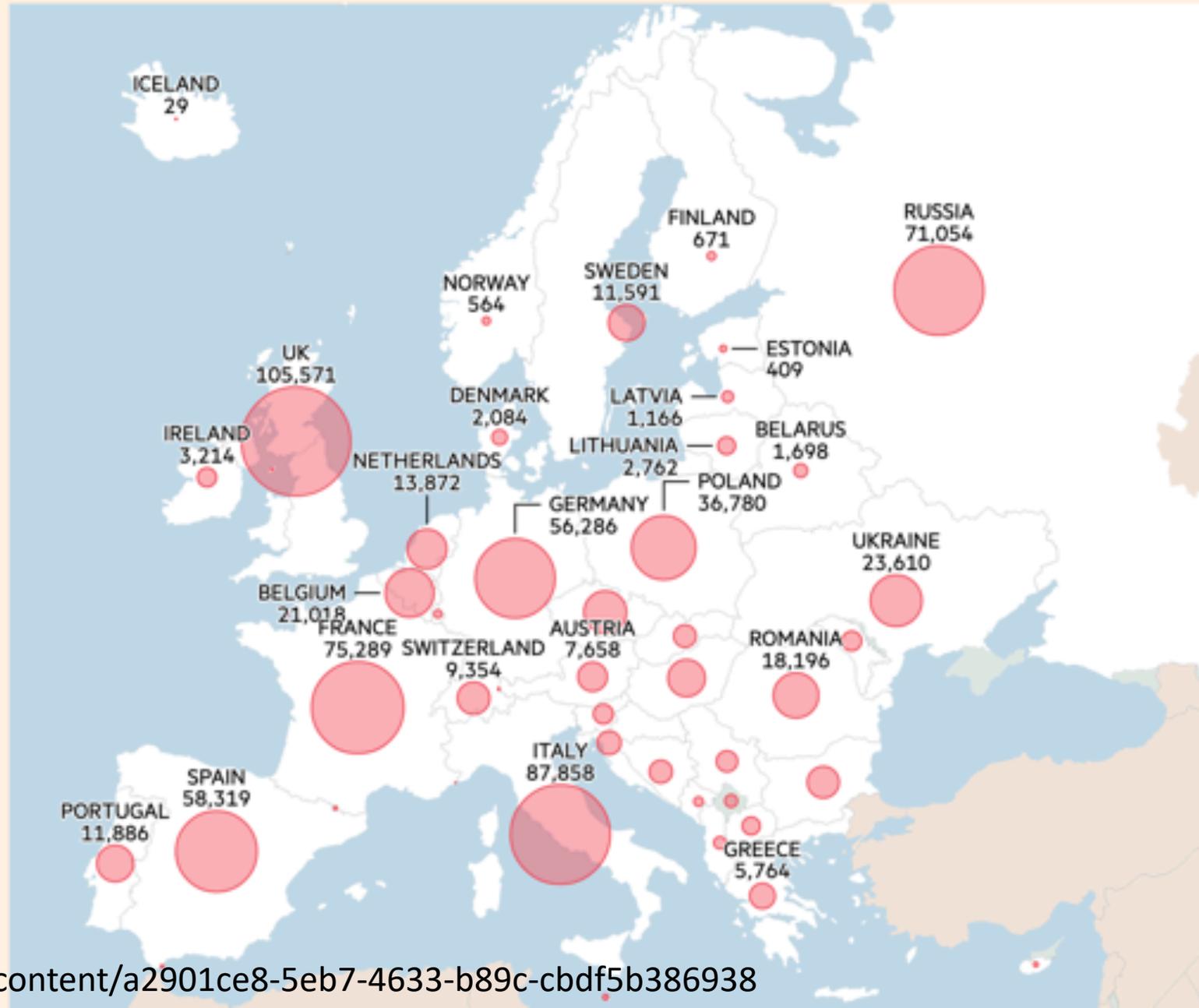
Deaths
2.2m



Graphic: Steven Bernard and Cain Tifford

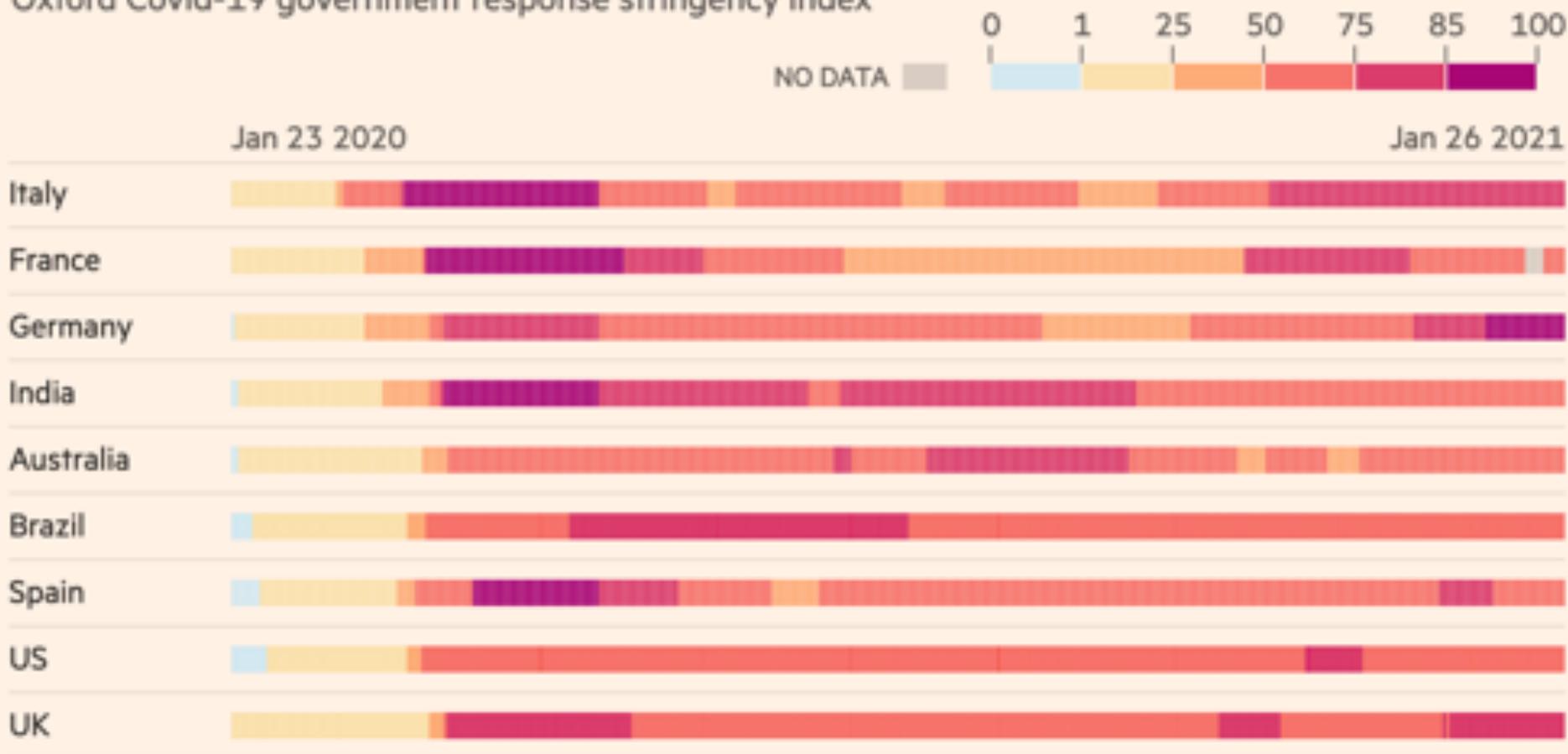
Coronavirus situation in Europe

Total deaths as of 6.15pm January 30 GMT



Global responses to the pandemic

Oxford Covid-19 government response stringency index

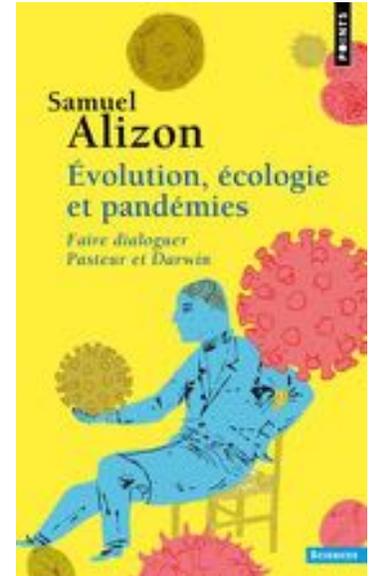
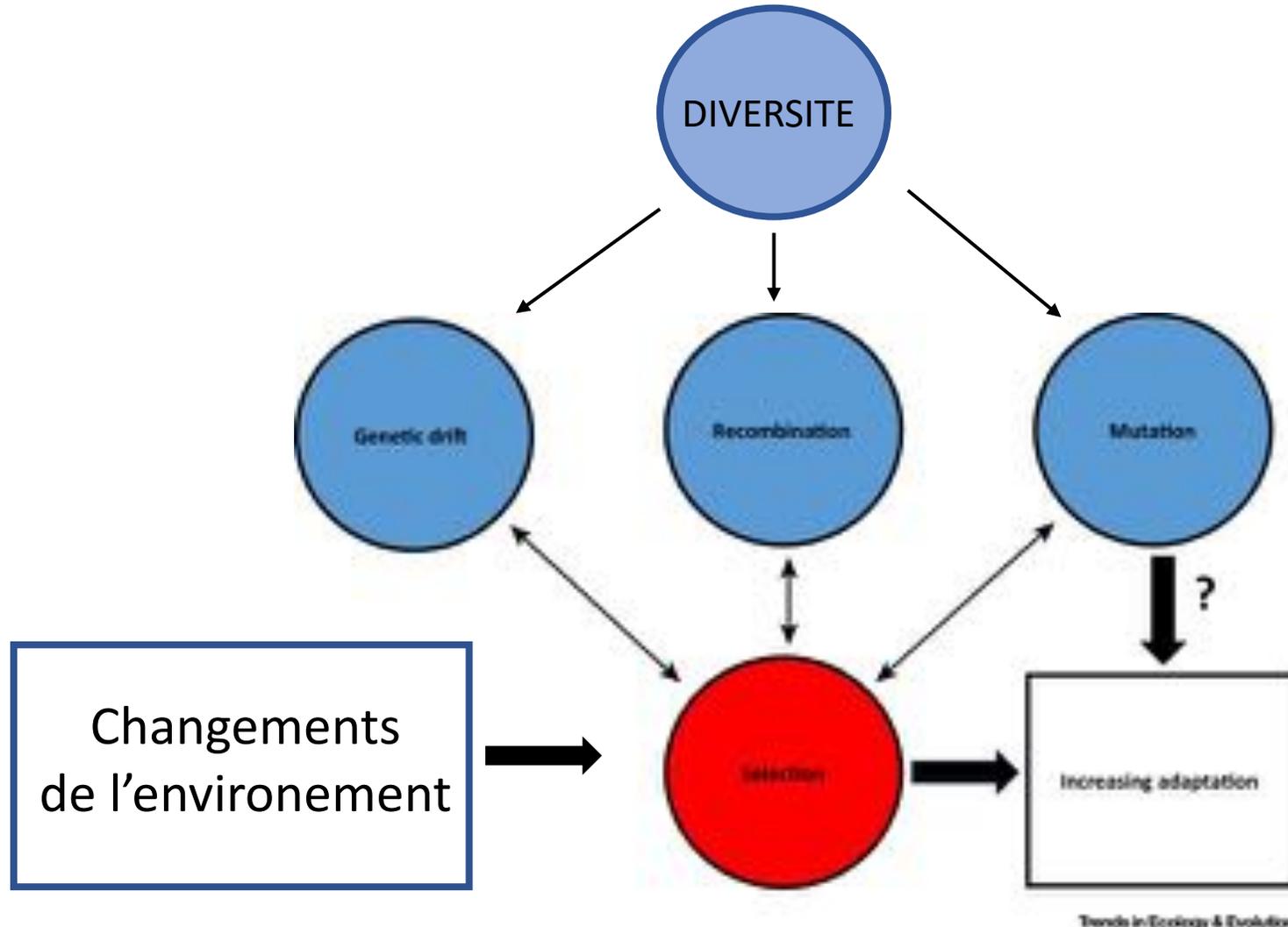
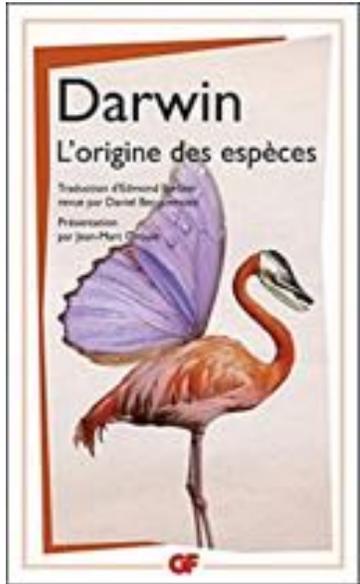


Graphic: Max Harlow, Caroline Nevitt and Aleksandra Wisniewska

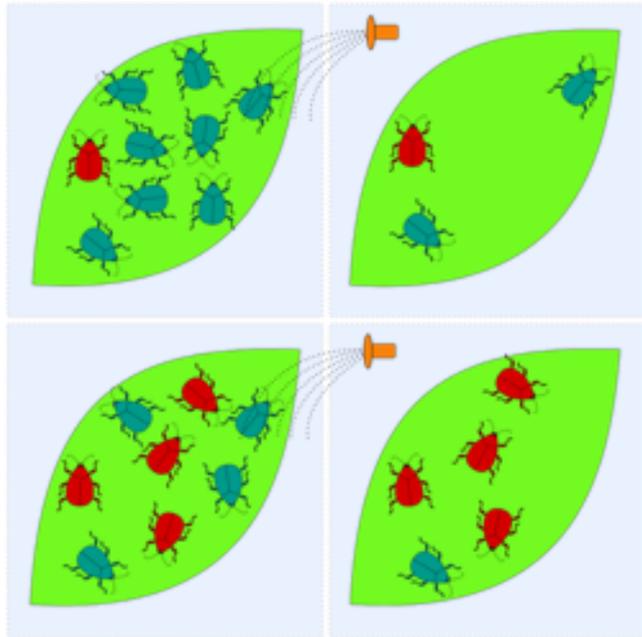
Source: Blavatnik School of Government, University of Oxford

© FT

Evolution des (micro)organismes



Exemple de la resistance aux antibiotiques, aux insecticides



Avant le DDT

1935 – Before DDT Spraying



1955 – During DDT Spraying



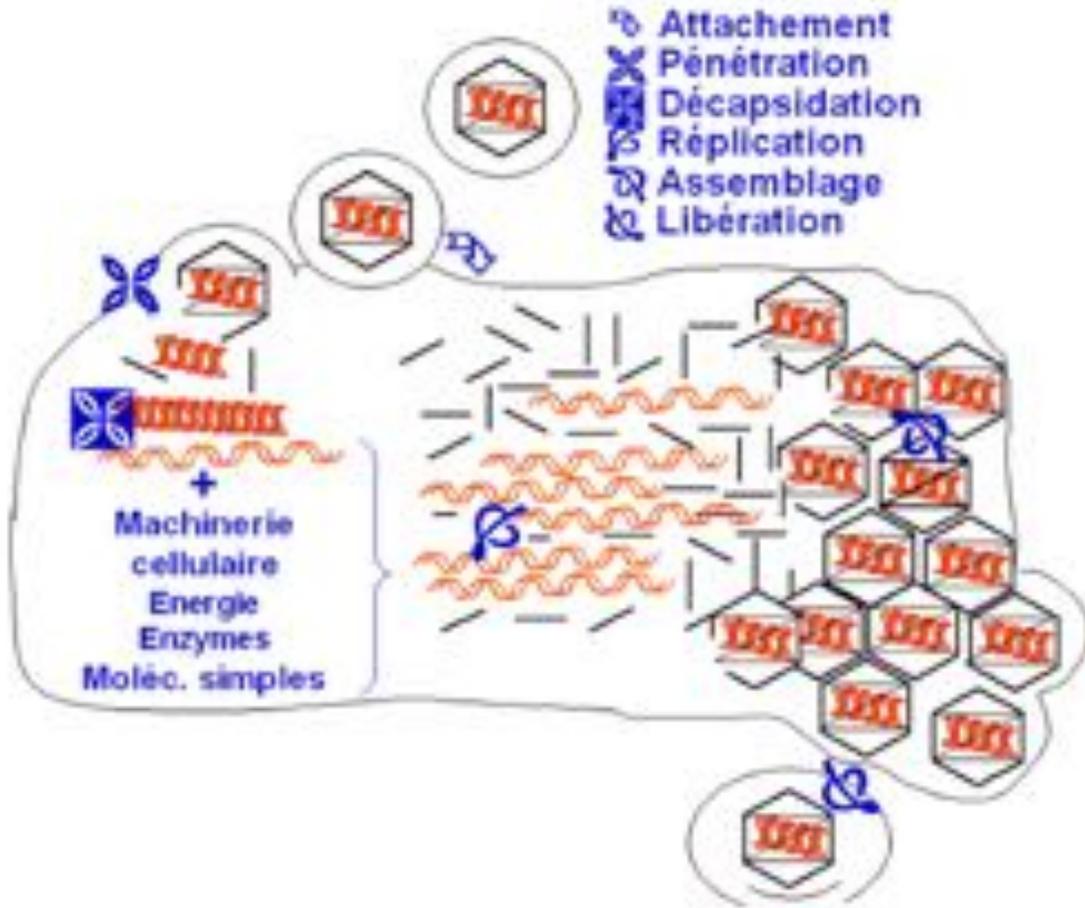
Après le DDT

1995 – After DDT Spraying



■ Distribution of mosquito (Please note: presence of vector does not automatically indicate presence of disease)

Evolution virale

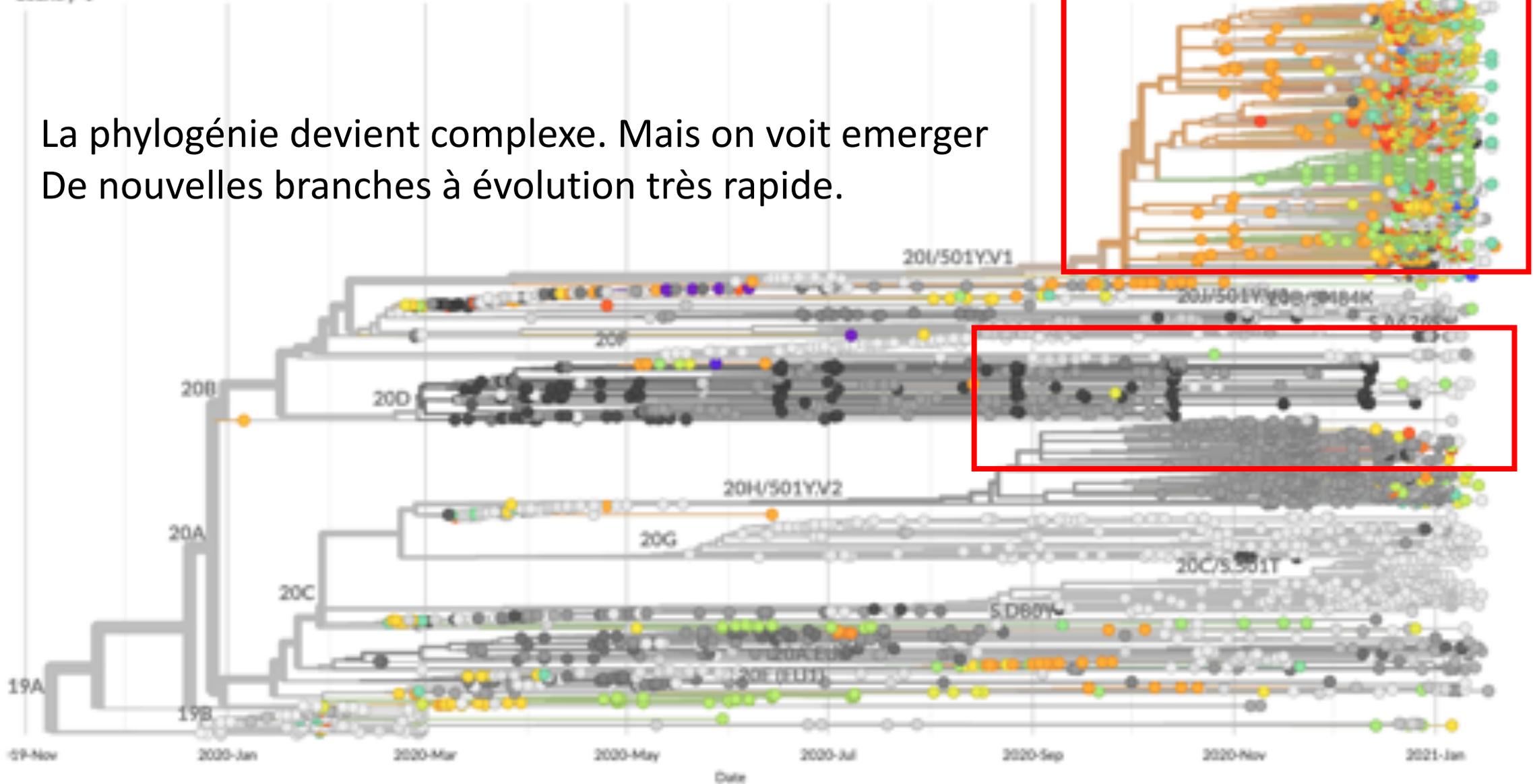


- **Reproduction rapide et efficace :**
1 virus -> des milliers / centaines de milliers
- **Tres grande diversité génétique**
intra-hôte et inter-hôte (mutations etc)
- **Très grande capacité d'adaptation**
-> sélection intra- et inter-hôte sur un grand nombre de génotypes possibles

Showing 4968 of 4968 genomes sampled between Dec 2019 and Jan 2021.

Phylogeny

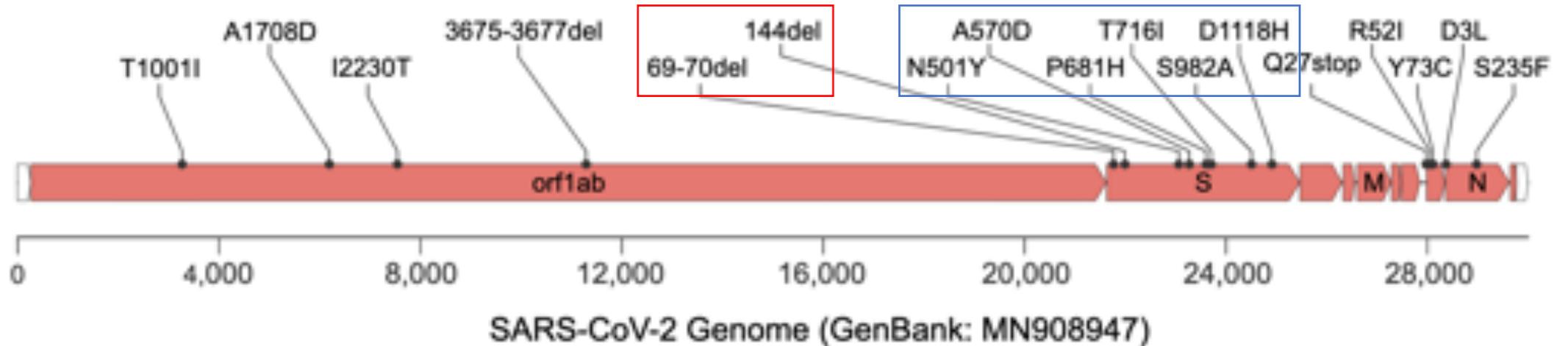
Country ▾



La phylogénie devient complexe. Mais on voit émerger
De nouvelles branches à évolution très rapide.

Les changements dans le genome: les “variants of concern” (VOC)

B 1.1.17: VOC-V1 UK



17 mutations (non-silencieuses) dans le VOC-V1 (8 dans Spike)

Grubaugh et al., 2021

<https://www.cell.com/action/showPdf?pii=S0092-8674%2821%2900087-8>

Variant: S:N501

UK, Afrique du Sud, Brésil

20A.EU1

20A.EU2

S:N501

S:E484

S:H69-

S:N439K

S:Y453F

S:S98F

S:L452R

S:D80Y

Propose changes to this section

Dedicated S:N501 Nextstrain build

Mutation Information

- **S:N501** has appeared multiple times independently: each can be associated with different accompanying mutations
- Amino-acid changes are **S:N501Y** (nucleotide mutation **A 23863 T**), **S:N501T** (nucleotide mutation **A 23864 C**), and **S:N501S** (nucleotide mutation **A 23864 G**)

S:N501

This mutation is in the receptor binding domain (RDB), important to ACE2 binding and antibody recognition.

- May be associated with adaptation to rodents and mustelids: **S:N501T** in ferrets ([Richard et al., Nature Comm.](#)) and mink ([Welkers et al., Virus Evolution](#)); **S:N501Y** in mice ([Gu et al. Science](#)).
 - Some have speculated on the risk of a possible persistent reservoir in wild rodents/mustelids
- May increase ACE2 binding ([Bloom Lab ACE2 binding website](#)) - in particular it is predicted to do this by increasing the time spent in the 'open' conformation ([Teruel et al., bioRxiv](#))
- **S:N501Y** was found in longitudinally-collected samples from an immunocompromised patient ([Choi et al., NEJM](#))
- In one study, sera from previously infected patients neutralised viruses with **S:501M** and **S:501Y** equally ([Xie et al., bioRxiv](#))

The specific mutation **S:N501Y** is found in 3 variants reported at the end of 2020/beginning of 2021, in:

- the UK (20U/501Y.V1)
- South Africa (20H/501Y.V2)
- Brazil (20J/501Y.V3)



Variant: S:E484

Afrique du Sud/Brésil

20A.EU1
20A.EU2
S:N501
S:E484
S:H69-
S:N439K
S:Y453F
S:S98F
S:L452R
S:D80Y

Propose changes to this section

Dedicated S:E484 Nextstrain build

Mutation Information

S:E484 has appeared multiple times independently around the world: each can be associated with different accompanying mutations

S:E484

This mutation is in the receptor binding domain (RBD), important to ACE2 binding and antibody recognition.

- Mutations at **S:E484** may significantly reduce convalescent serum neutralization ([\(Liu Greaney et al., medRxiv\)](#))
- There has been a case of reinfection associated with **S:E484K**: a woman previously infected with a non-**S:E484K** variant of SARS-CoV-2 was later reinfected with a virus carrying the **S:E484K** mutation ([\(Liu Nonaka et al., PrePrints\)](#))
- In one study co-incubating SARS-CoV-2 with convalescent plasma, neutralization was completely escaped at day 73 due to an **S:E484K** mutation ([\(Liu Andreato et al., bioRxiv\)](#))
- In another study co-incubating pseudotyped virus with SARS-CoV-2 spike proteins and monoclonal antibodies, neutralization both by monoclonal antibodies and to convalescent sera was significantly reduced in viruses with S:E484 mutations ([\(Liu Liu et al., bioRxiv\)](#))

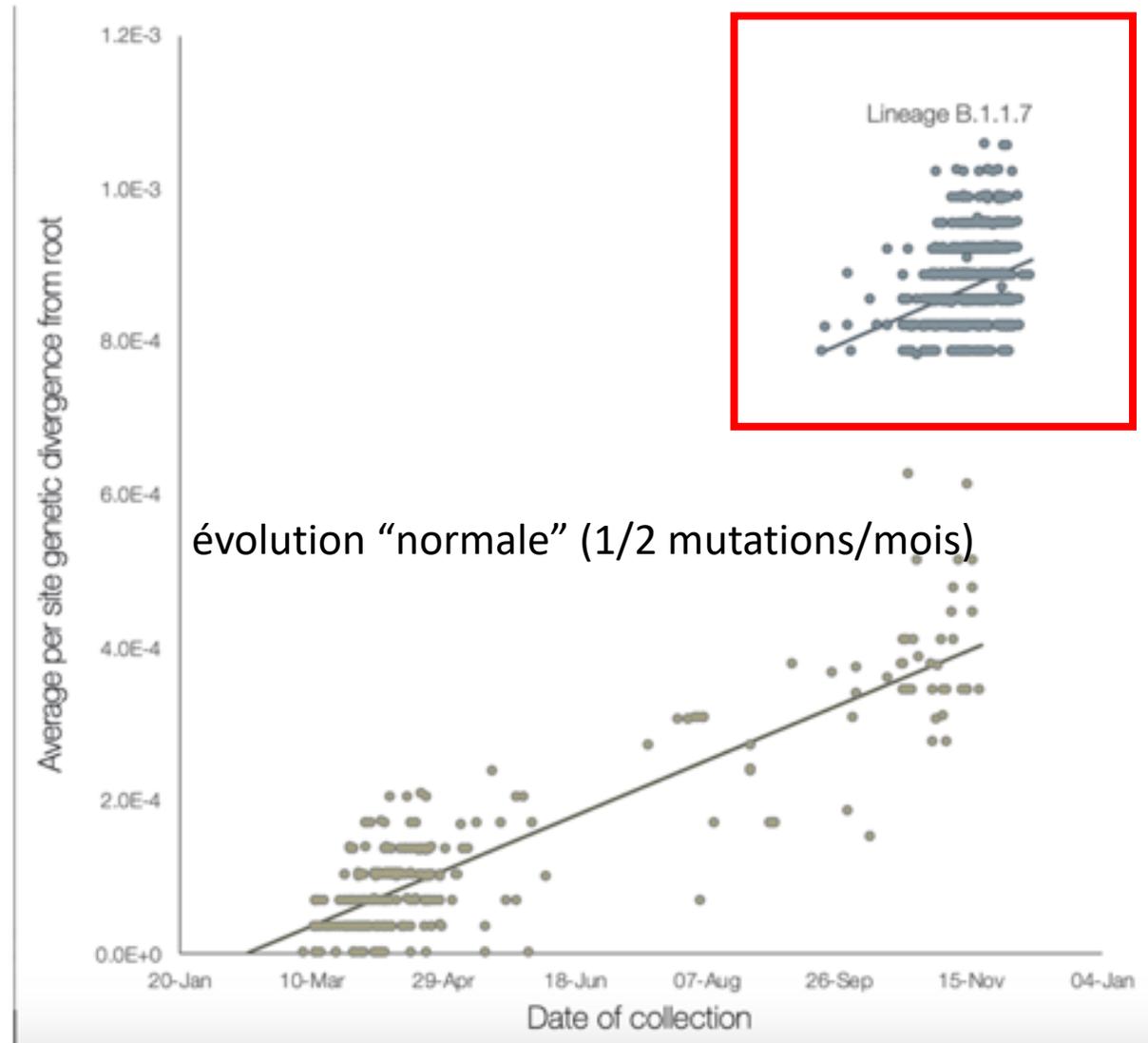
The specific mutation **S:E484K** is found in 3 variants reported at the end of 2020/beginning of 2021, in:

- South Africa (20H/501Y.V2)
- Brazil (20J/501Y.V3)
- Brazil (20B/S.484K)

Pourquoi certains variants inquietent?

Une vitesse d'évolution très rapide

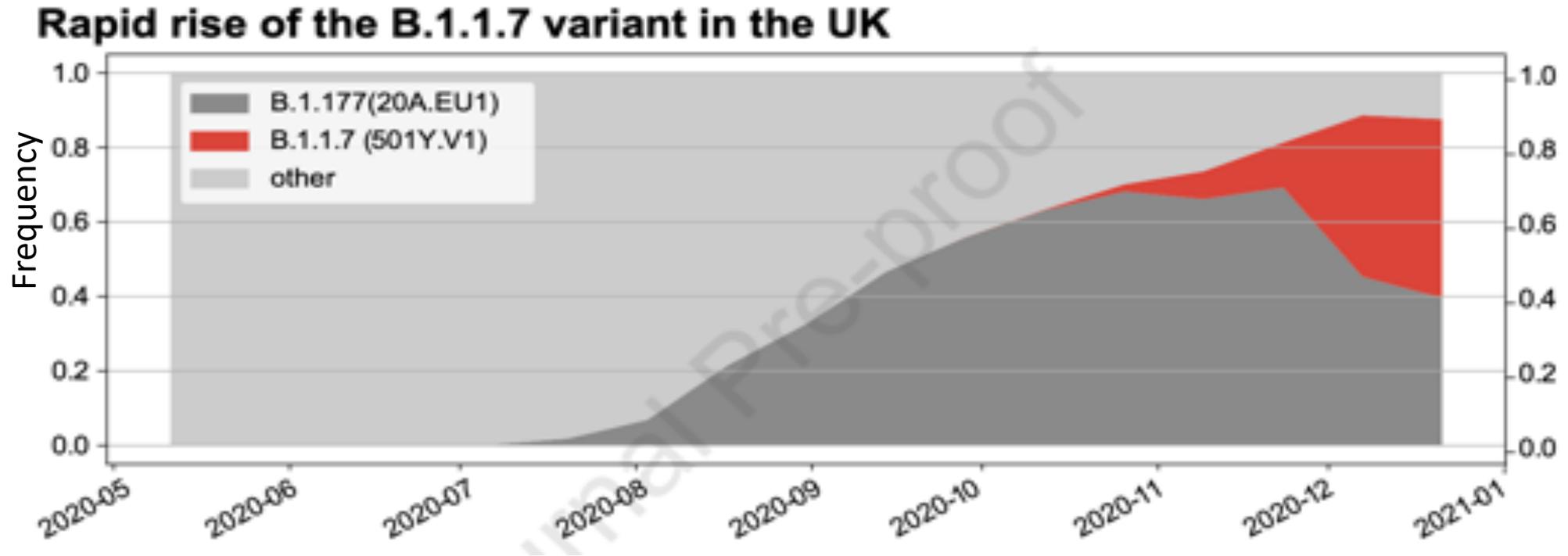
VOC-V1 UK



Nombreuses mutations et
Vitesse d'évolution rapide

Une augmentation en fréquence très rapide

VOC-V1 UK



VOC-V1 a une plus grande transmissibilité (>50%) -> "élimination" du virus historique par compétition
Mutations-> Sélection (transmissibilité)

Une diffusion dans le monde très rapide

VOC-V1 UK

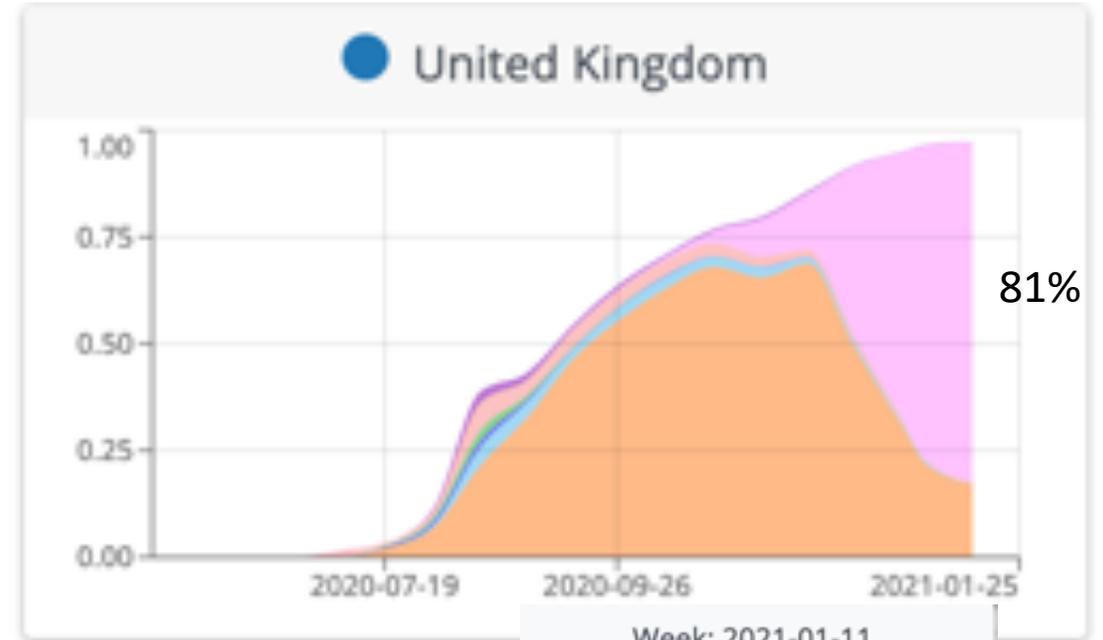
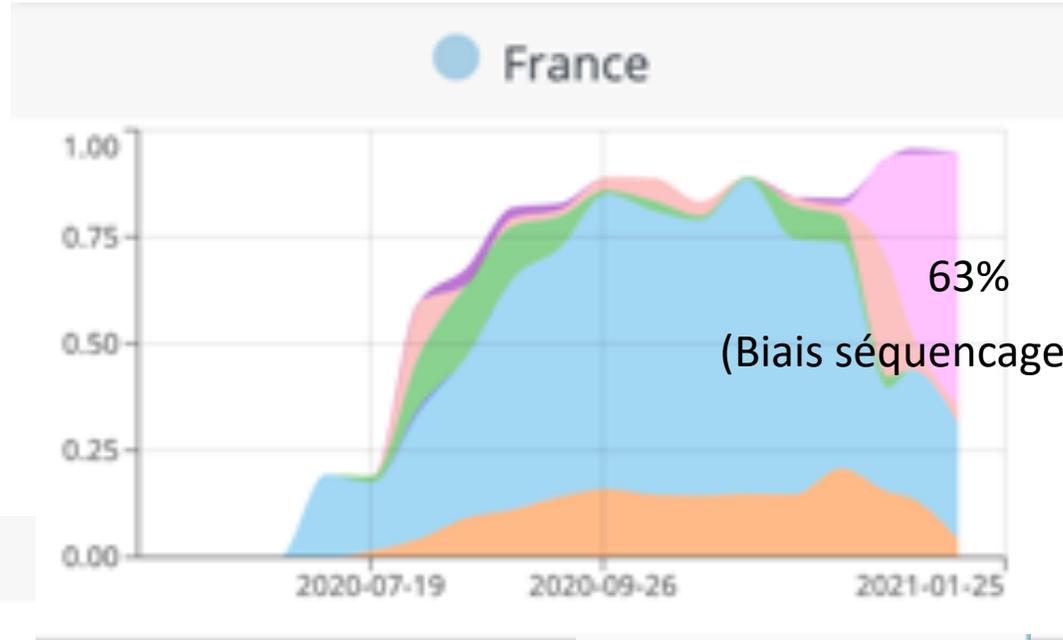


Grubaugh et al., 2021

<https://www.cell.com/action/showPdf?pii=S0092-8674%2821%2900087-8>



Epidemiology moléculaire



▼ Variants

- 20A.EU1
- 20A.EU2
- S:A626S
- S:D80Y
- S:L452R
- S:N439K
- S:N501
- S:S98F
- S:V1122L
- S:Y453F

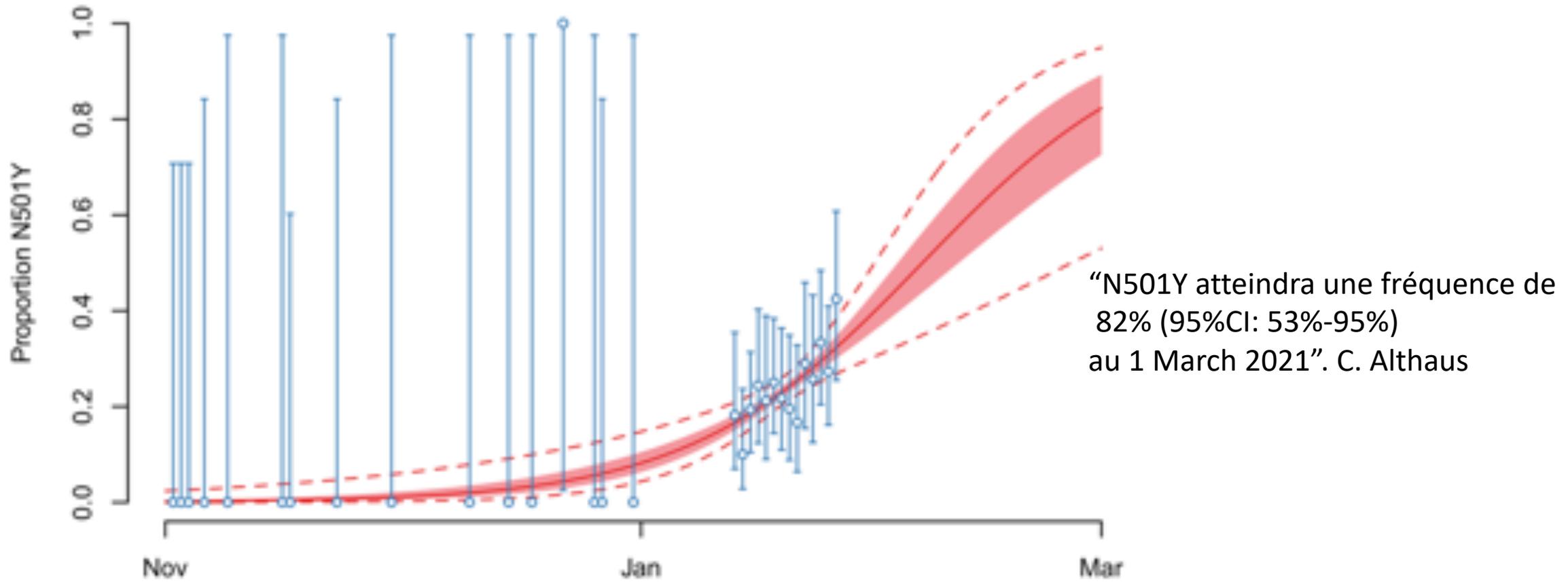
Week: 2021-01-11

Variant	Num seq
S:N501	57
20A.EU2	26
S:N439K	4
20A.EU1	4
S:Y453F	-
S:V1122L	-
S:S98F	-
S:L452R	-
S:D80Y	-
S:A626S	-

Week: 2021-01-11

Variant	Num seq
S:N501	6907
20A.EU1	1485
S:N439K	38
20A.EU2	10
S:S98F	4
S:L452R	1
S:A626S	1
S:Y453F	-
S:V1122L	-
S:D80Y	-

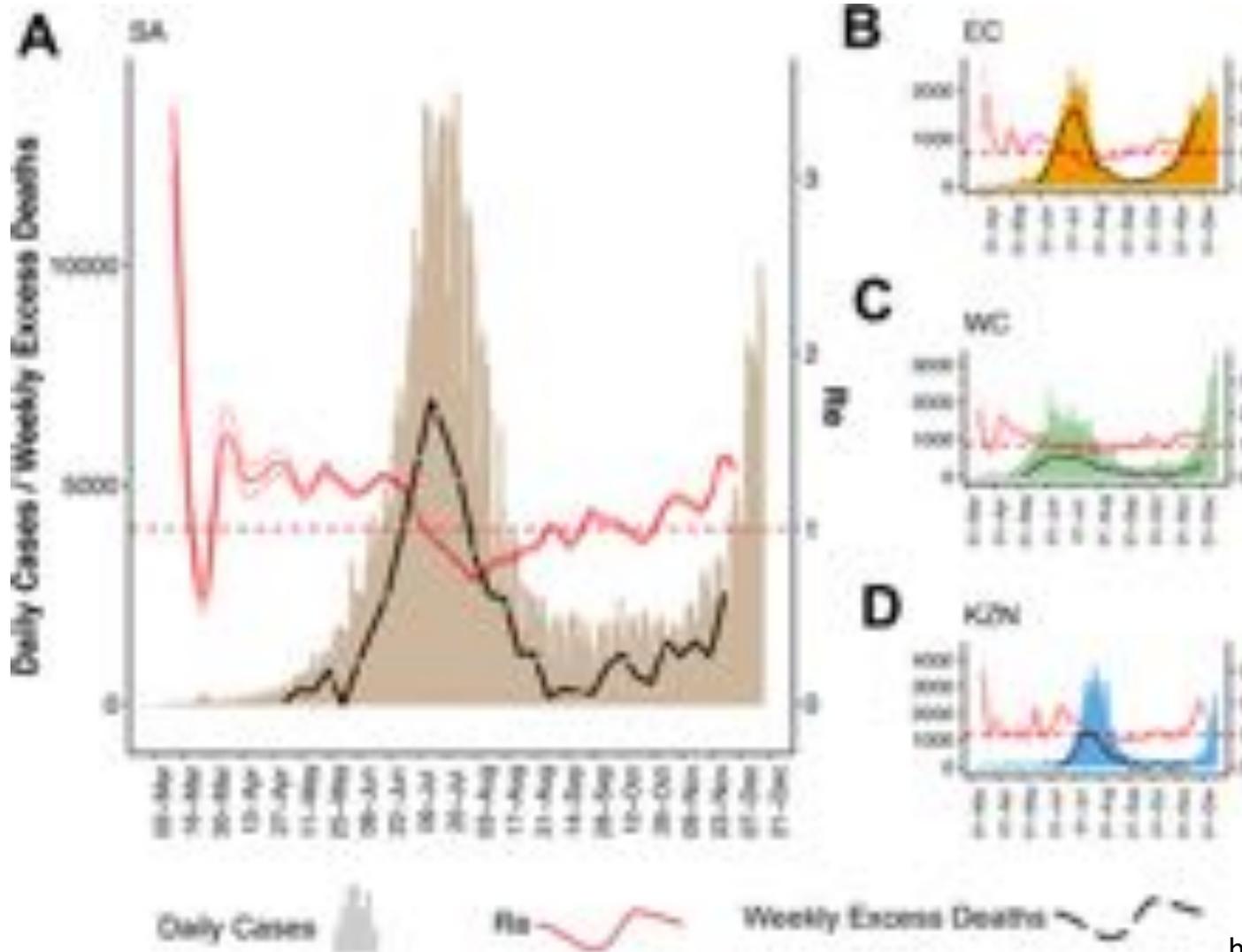
N501Y in Geneva, Switzerland



Les variants circulants dans le Monde



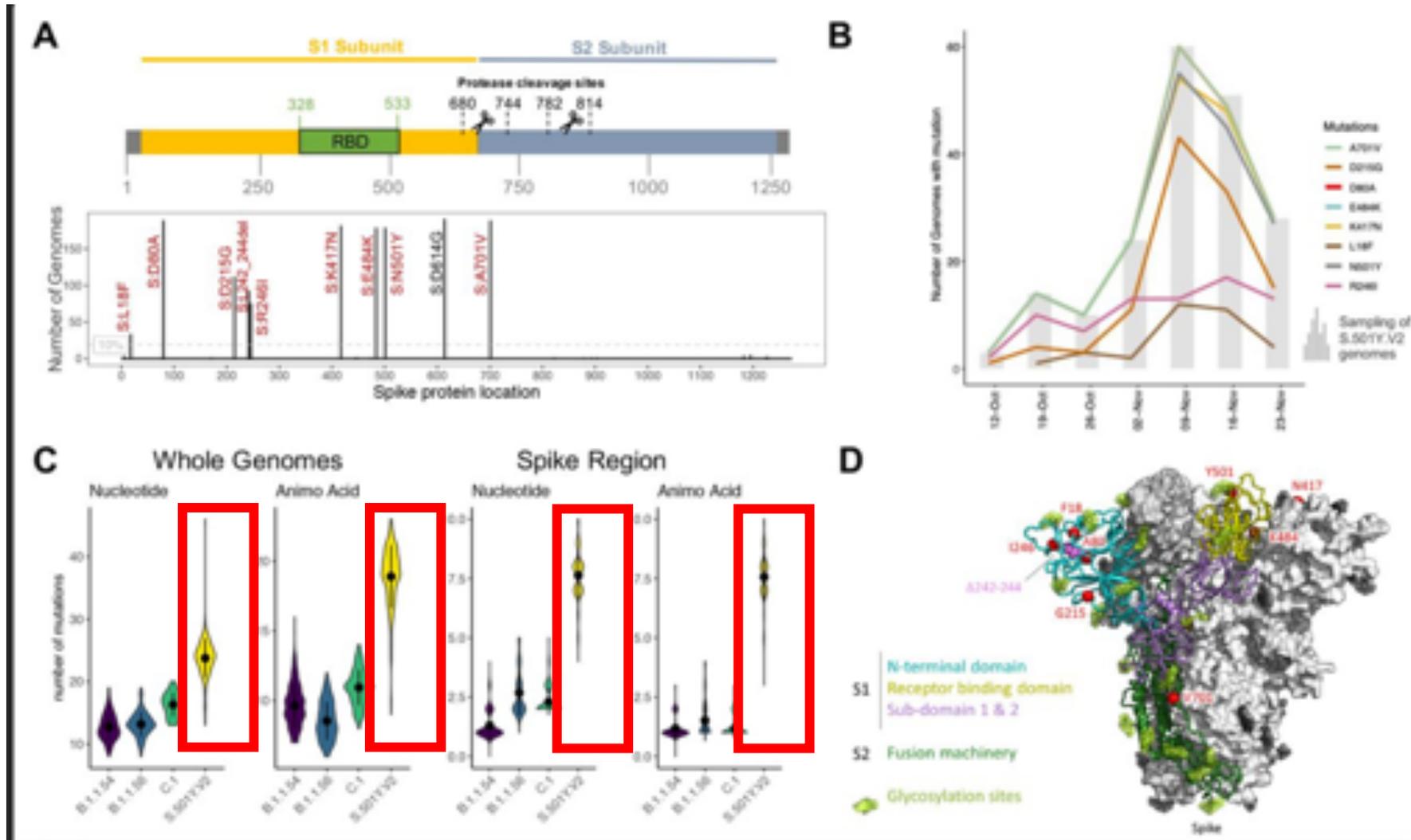
Le variants Sud Africain



- Nombreuses re-infections
- Selection de mutations “adaptatives”
- Augmentation de la transmissibilité?
- Echappement à l’immunité?

Tegally et al., 2021

Le variants Sud Africain



Variant Sud Africain en Europe?

South African variant of Covid found in eight areas of England

Door-to-door testing launched as cases found in Hertfordshire, Surrey, Kent, Walsall, Sefton and three London boroughs

- [Coronavirus - latest updates](#)
- [See all our coronavirus coverage](#)

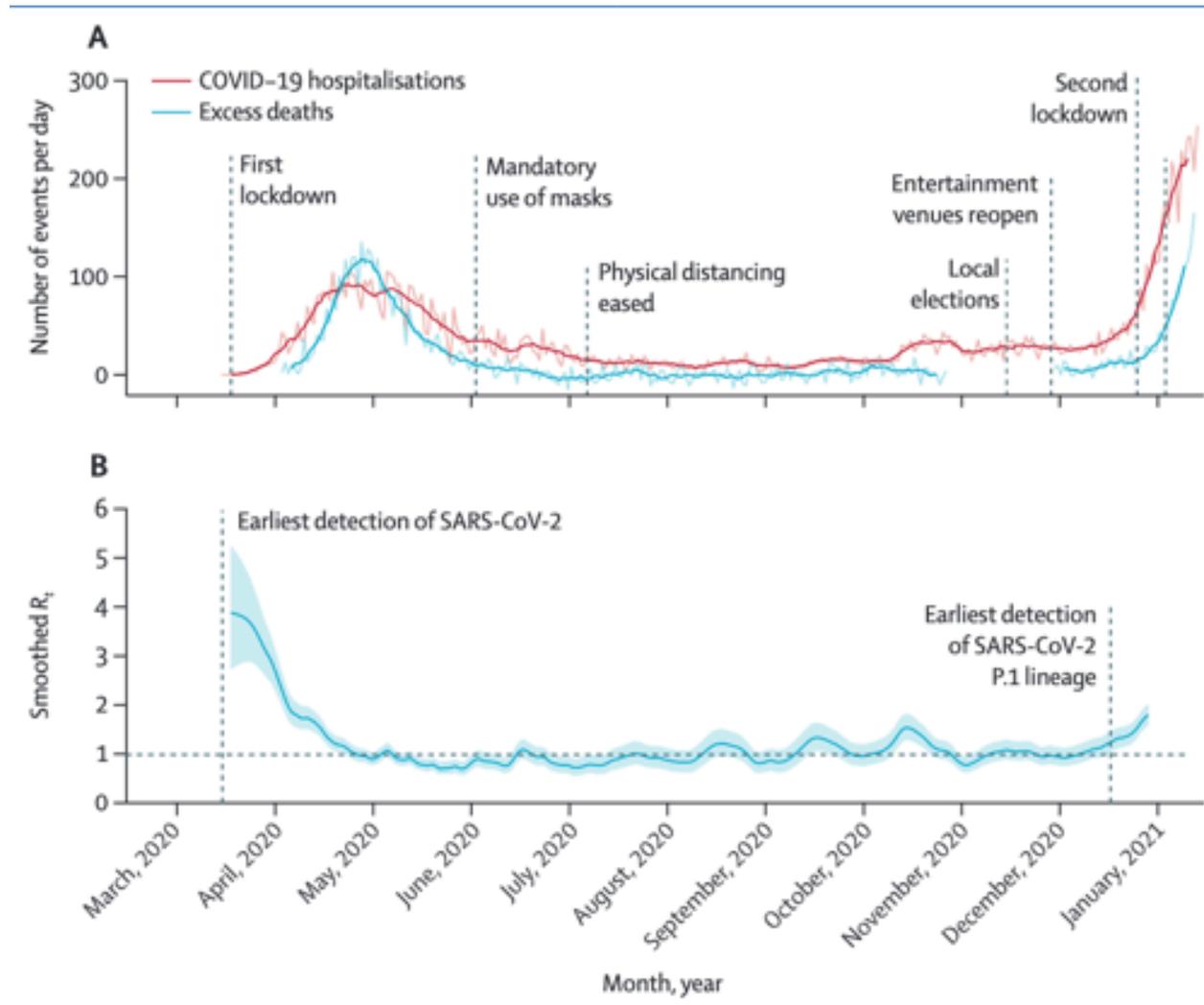


▲ Covid signage in London. All adults in affected postcodes will be urged to get a PCR swab test and public health officials will start doing door-to-door this week. Photo: Ian - Anthony Harwood/Rev/Quitterturk

The South African variant of coronavirus has been discovered in eight areas of England

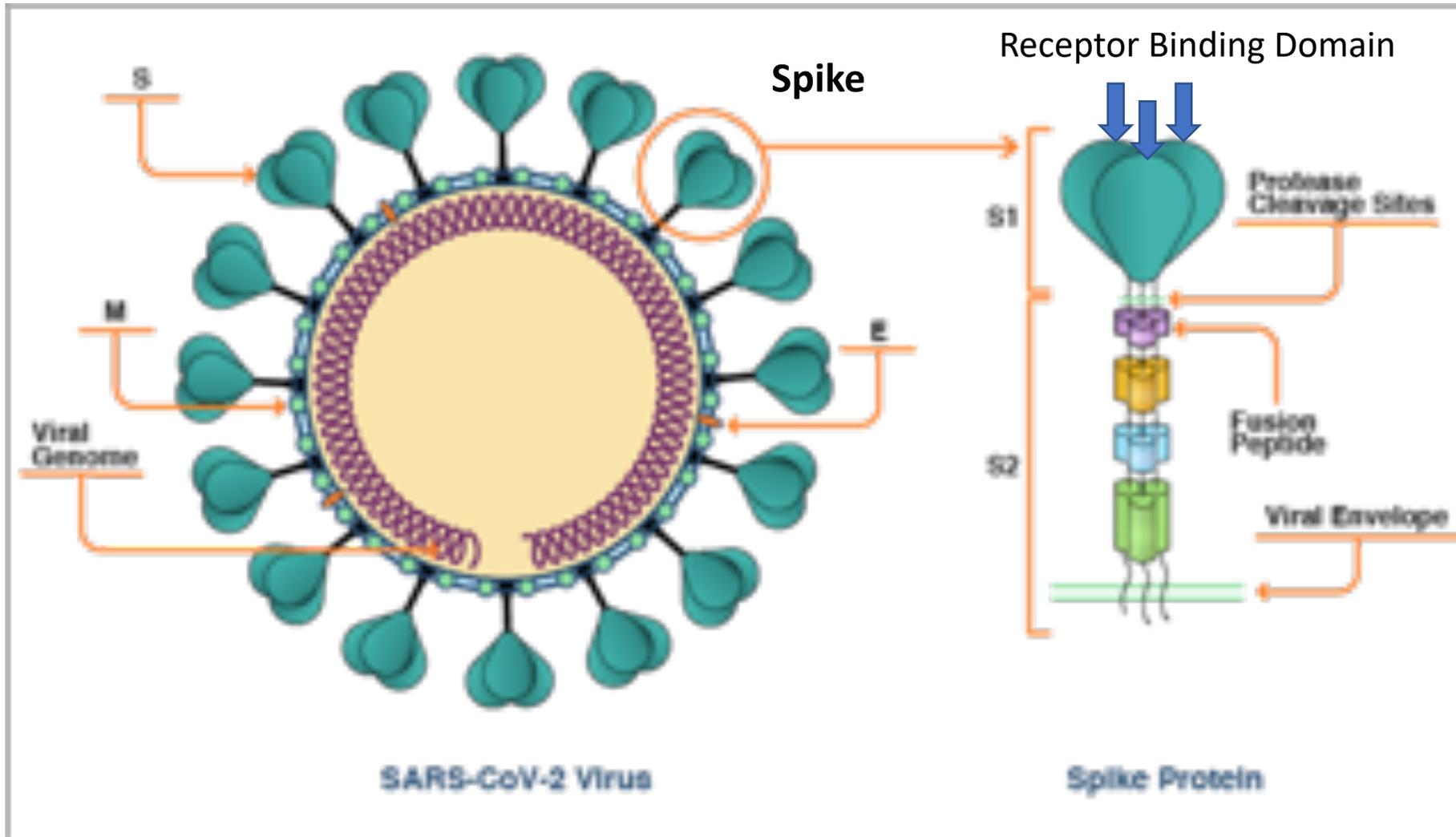


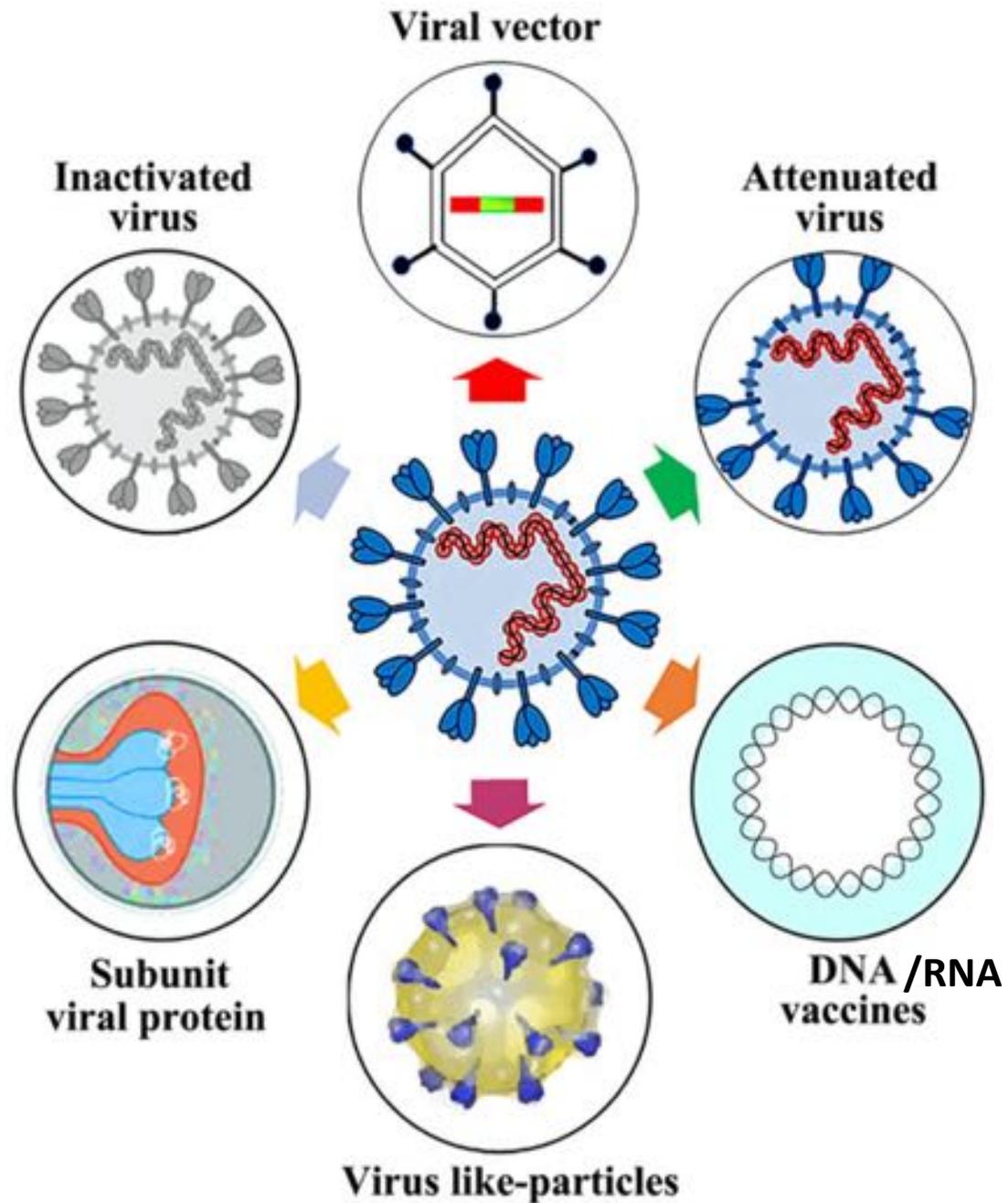
Les VOC V3 (Brésil): situation inquiétante à Manaus



- Immunité collective importante (>50%)
- Selection de mutations “adaptatives”
- Transmissibilité?
- Echappement à l’immunité?
- Efficacité de la vaccination?

Stratégies Vaccinales

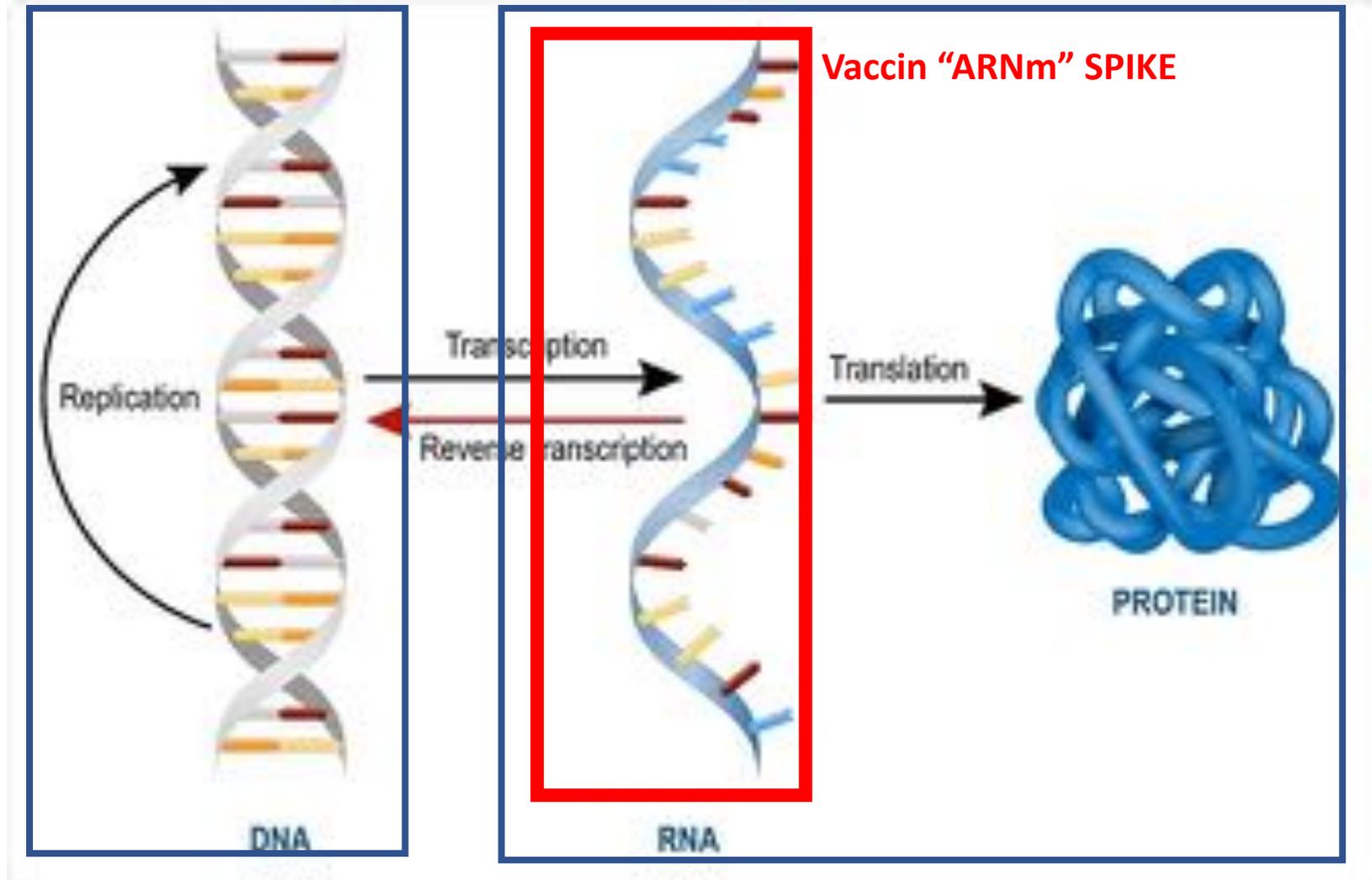




- Virus inactivés
- Virus atténués
- Vecteur viraux
- Pseudo particules virales
- Sous-unités protéiques
- Vaccins ADN/ARN

Chaque vaccin a des avantages/inconvénients (Immunité, effets secondaires, coût etc)

Le vaccin ARN -> nos cellules “fabriquent”
la proteine Spike à partir de l'ARNm



Merci de votre attention!