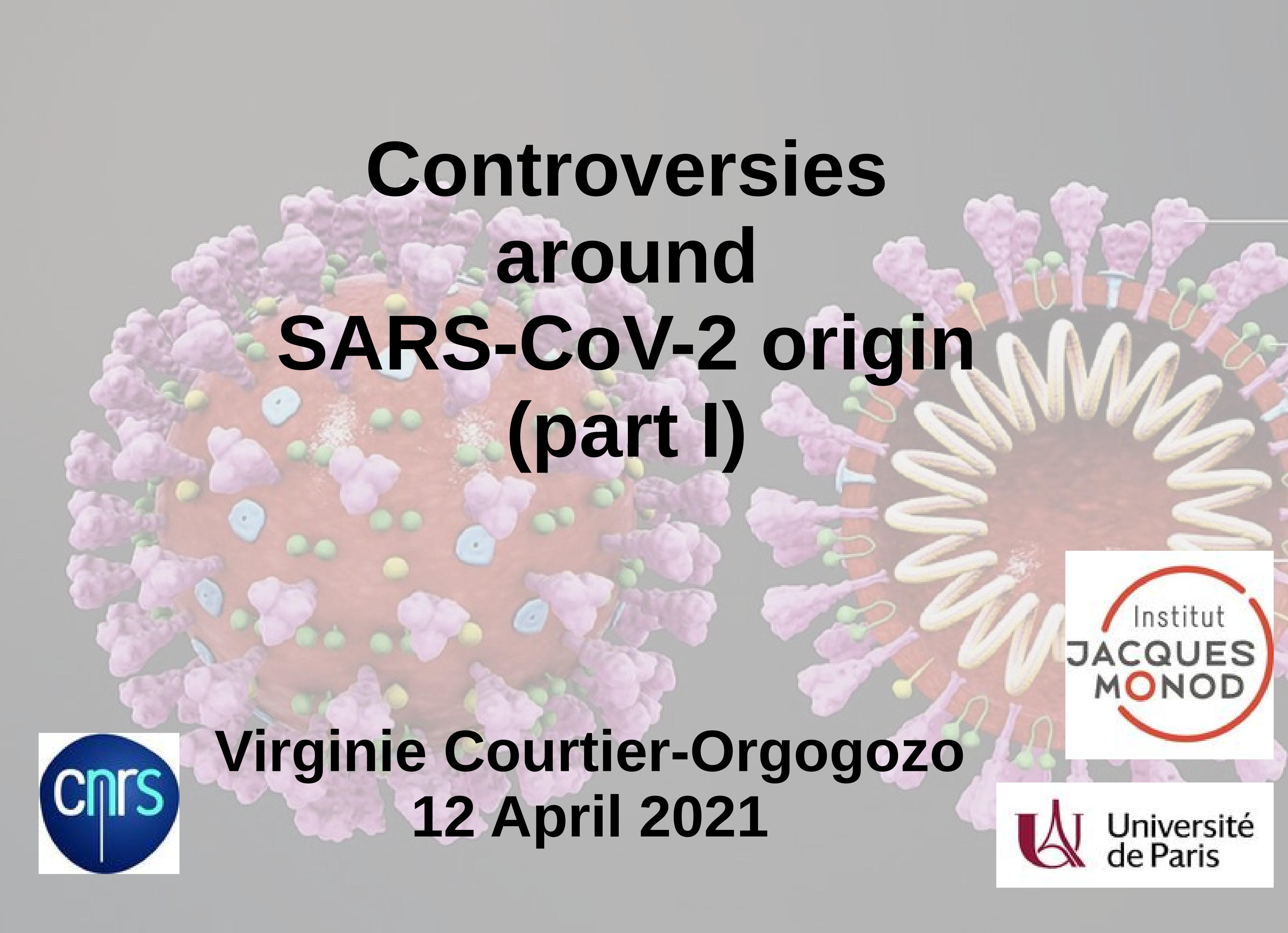


Controversies around SARS-CoV-2 origin

(part I)

Virginie Courtier-Orgogozo
12 April 2021

Thanks

Etienne Decroly (a few slides)

François Graner, José Halloy, Fabien Colombo, Florence Débarre, Guillaume Achaz, Jacques van Helden

Scientists attending our recurrent workshop

Monali Rahalkar, @TheSeeker268, @franciscodeasis, @gdemaneuf, @BillyBostickson

China-WHO joint report

30 March 2021

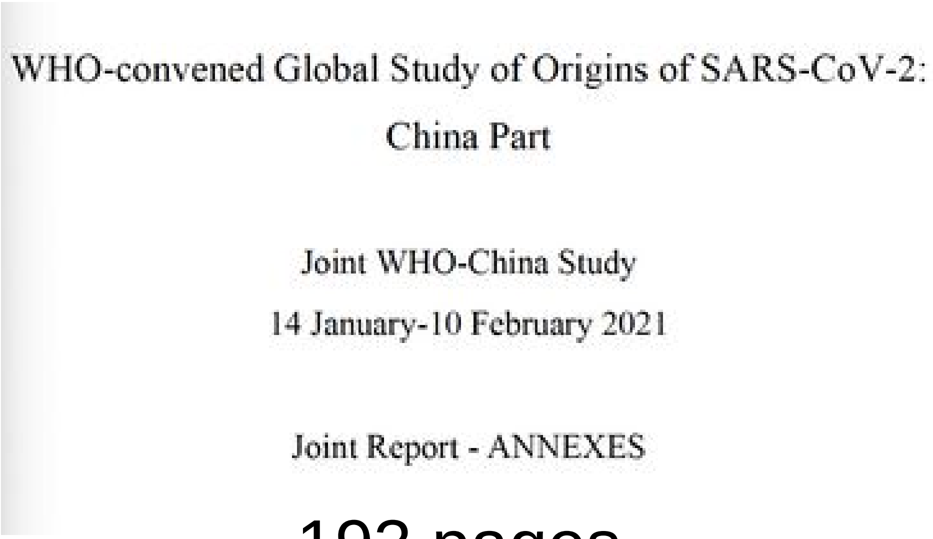
“The joint team’s assessment of likelihood of each possible pathway was as follows:
- direct zoonotic spillover is considered to be a **possible-to-likely** pathway;
- introduction through an intermediate host is considered to be a **likely to very likely** pathway;
- introduction through cold/ food chain products is considered a **possible** pathway;
- introduction through a laboratory incident was considered to be an **extremely unlikely** pathway.”

WHO-convened Global Study of Origins of SARS-CoV-2:
China Part

Joint WHO-China Study
14 January-10 February 2021

Joint Report

123 pages



WHO-convened Global Study of Origins of SARS-CoV-2:

China Part

Joint WHO-China Study

14 January-10 February 2021

Joint Report - ANNEXES

193 pages

https://www.who.int/news/item/30-03-2021-who-calls-for-further-studies-data-on-origin-of-sars-cov-2-virus-reiterates-that-all-hypotheses-remain-open

https://www.washingtonpost.com/context/who-report-on-covid-19/adfecdd0-a81d-4f87-903a-83902544ee81/

https://www.who.int/docs/default-source/coronaviruse/who-convened-global-study-of-origins-of-sars-cov-2-china-part-annexes.pdf

WHO Director-General
Dr Tedros Adhanom Ghebreyesus

"As far as WHO is concerned, **all hypotheses remain on the table.** This report is a very important beginning, but it is not the end. We have not yet found the source of the virus, and we must continue to follow the science and leave no stone unturned as we do."

30 March 2021

https://www.who.int/news/item/30-03-2021-who-calls-for-further-studies-data-on-origin-of-sars-cov-2-virus-reiterates-that-all-hypotheses-remain-open

What we know

The various hypotheses

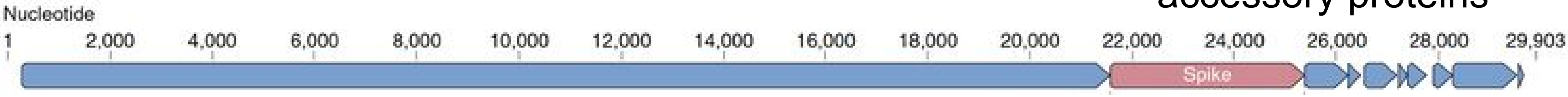
Lack of transparency

Controversies

RNA virus

30kb

Structural and
accessory proteins



ORF1ab: 16 proteins involved in genome transcription and replication

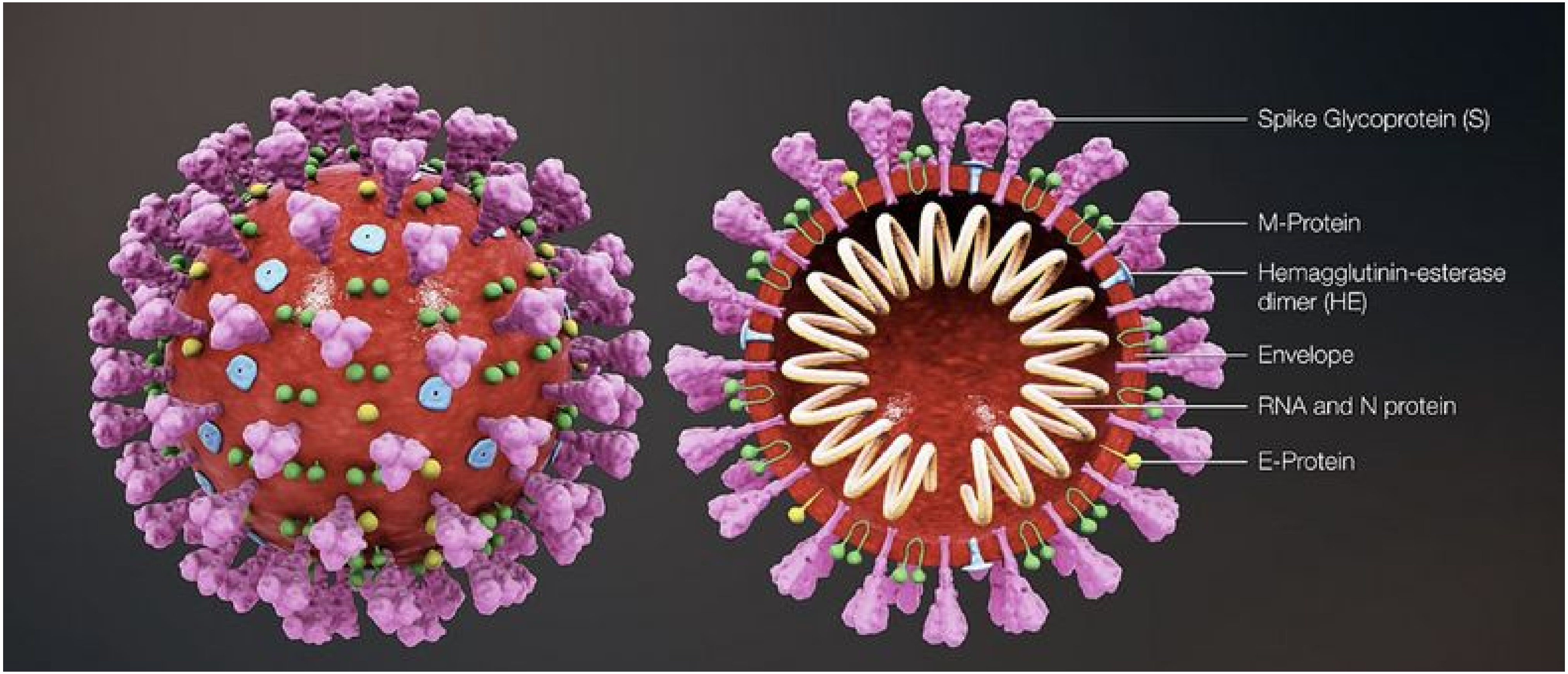
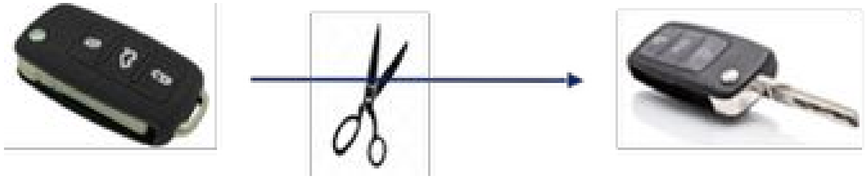
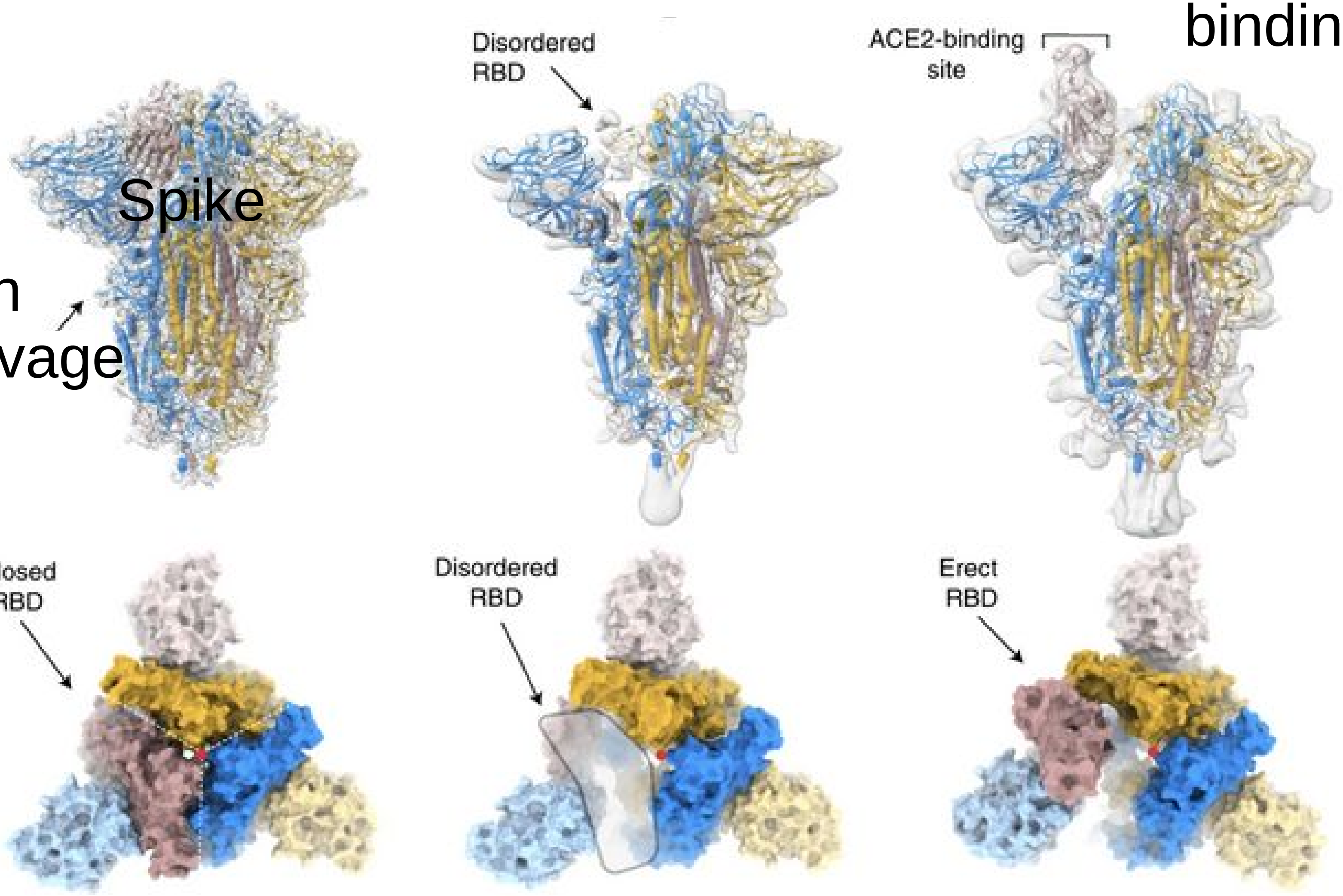


Image: https://commons.wikimedia.org/wiki/File:3D_medical_animation_coronavirus_structure.jpg

“Priming” changes Spike



RBD: receptor-binding domain



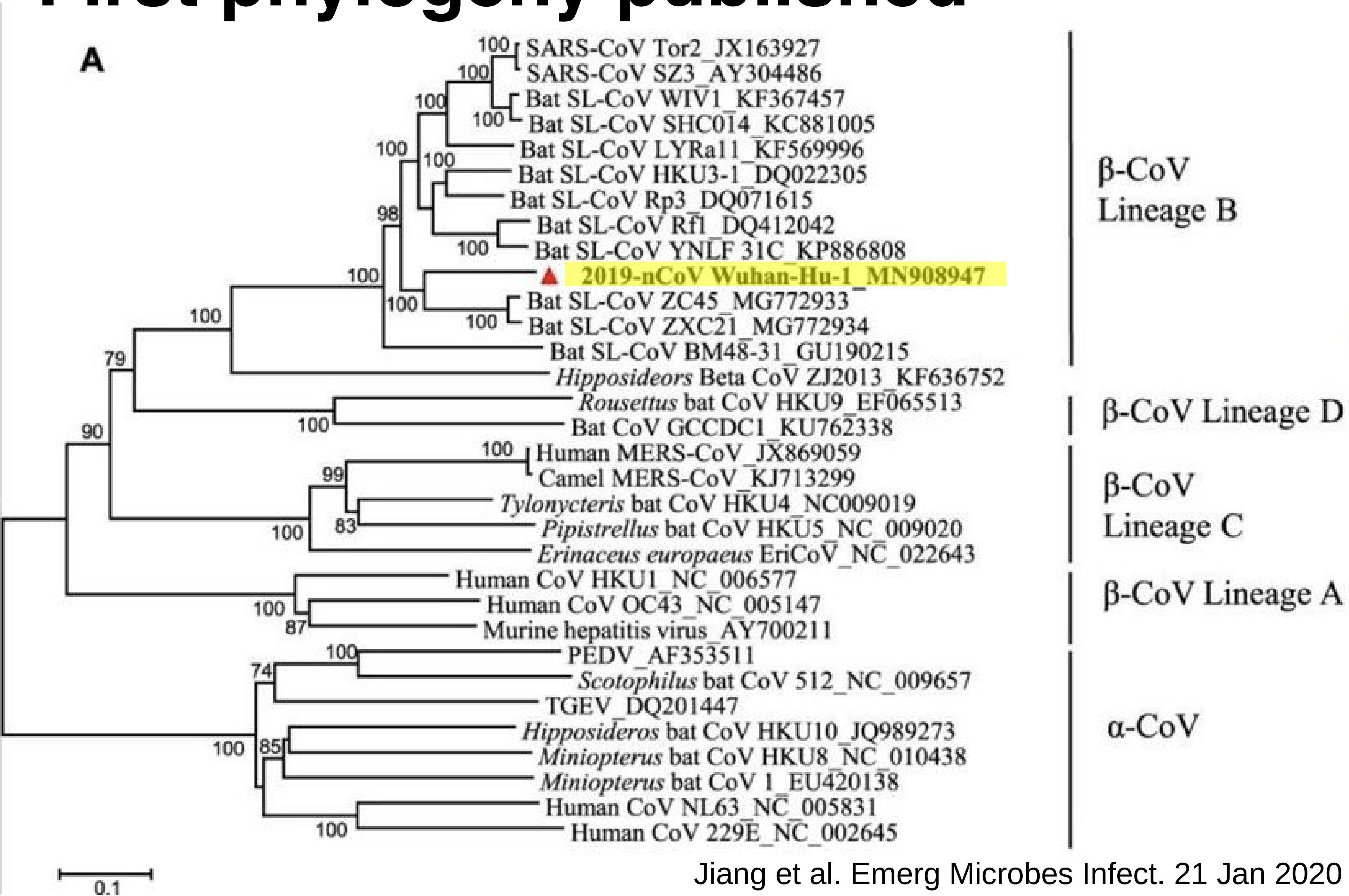
Spike

Furin cleavage site

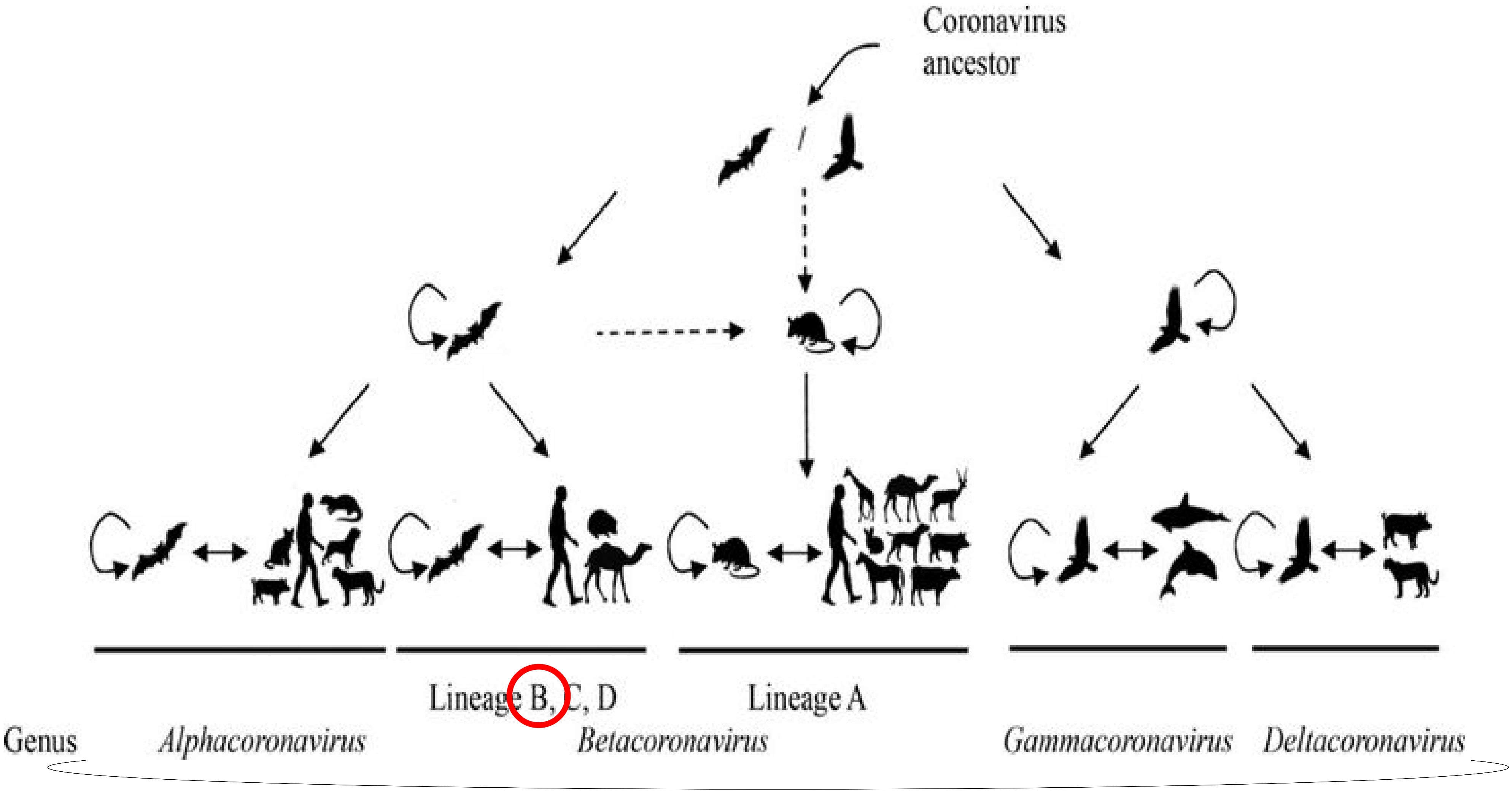
https://www.nature.com/articles/s41594-020-0468-7

Wrobel et al. 2020

First phylogeny published



Jiang et al. Emerg Microbes Infect. 21 Jan 2020
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7033706/

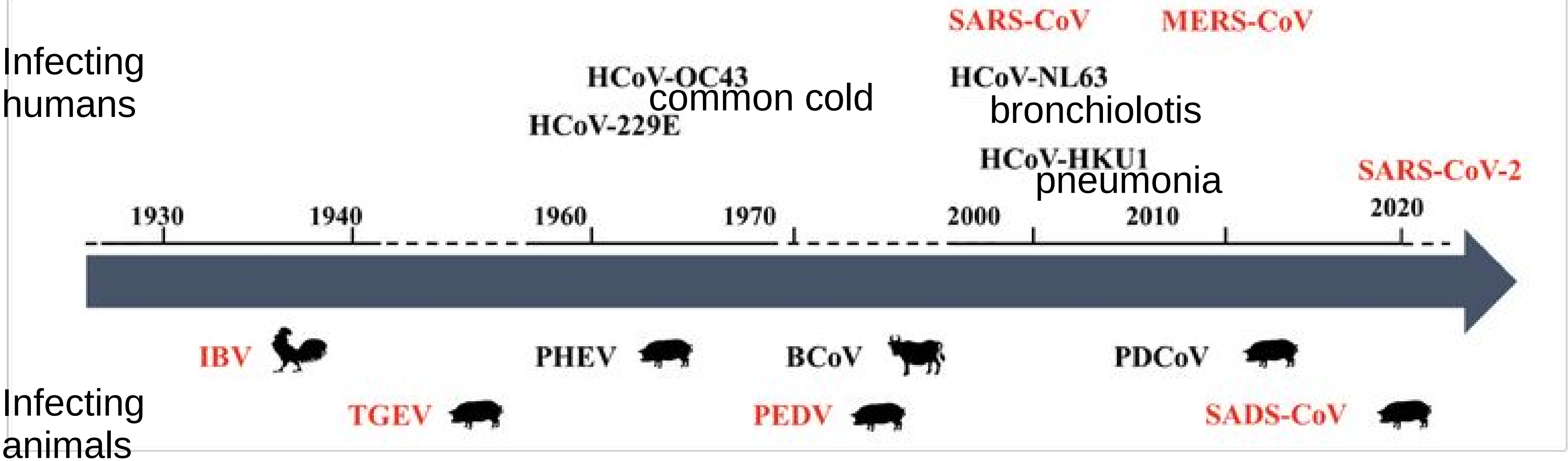


Orthocoronavirinae

SARS-CoV-2

Etienne Decroly

Emergence of coronavirus outbreaks



Severe respiratory disease

Infecting
humans

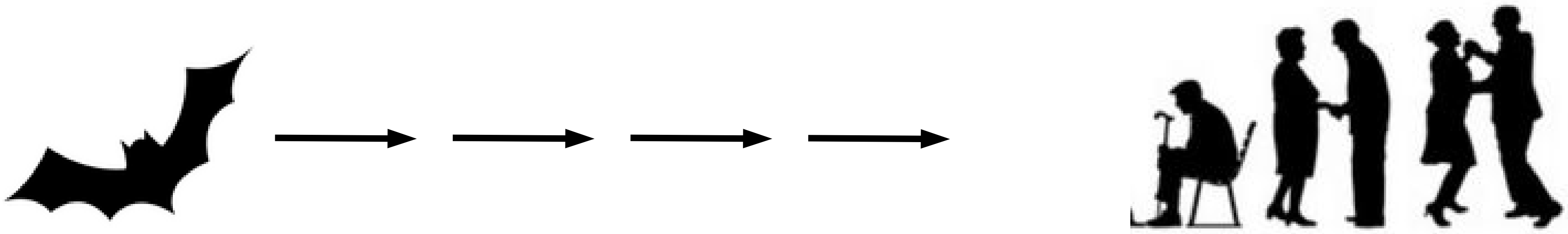
common cold

bronchiolotis

pneumonia

Infecting
animals

Adapted from Zheng-Li Shi

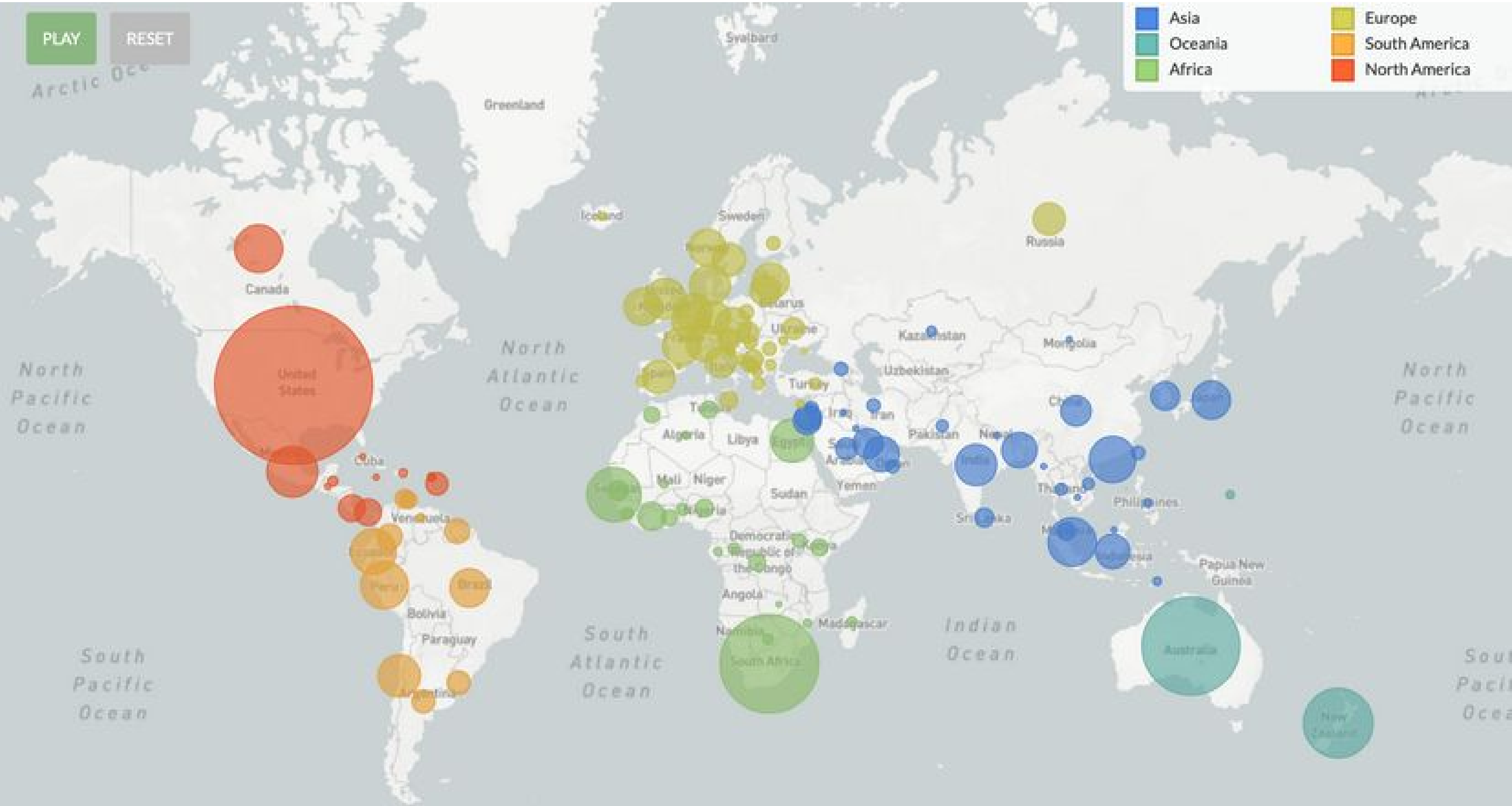


Bats

Outbreak in Wuhan

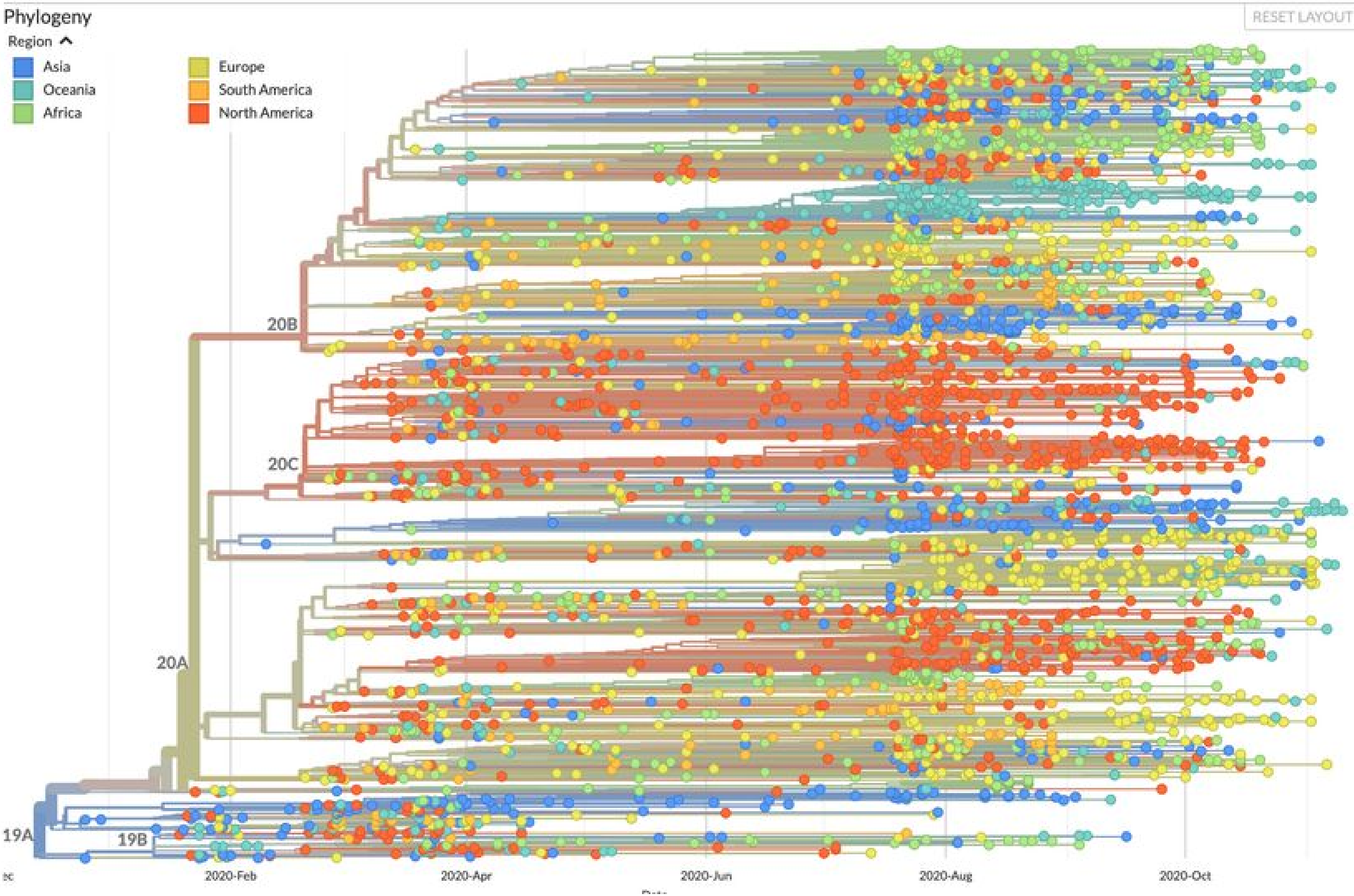
December 2019

SARS-CoV-2 sequences at nextstrain.org



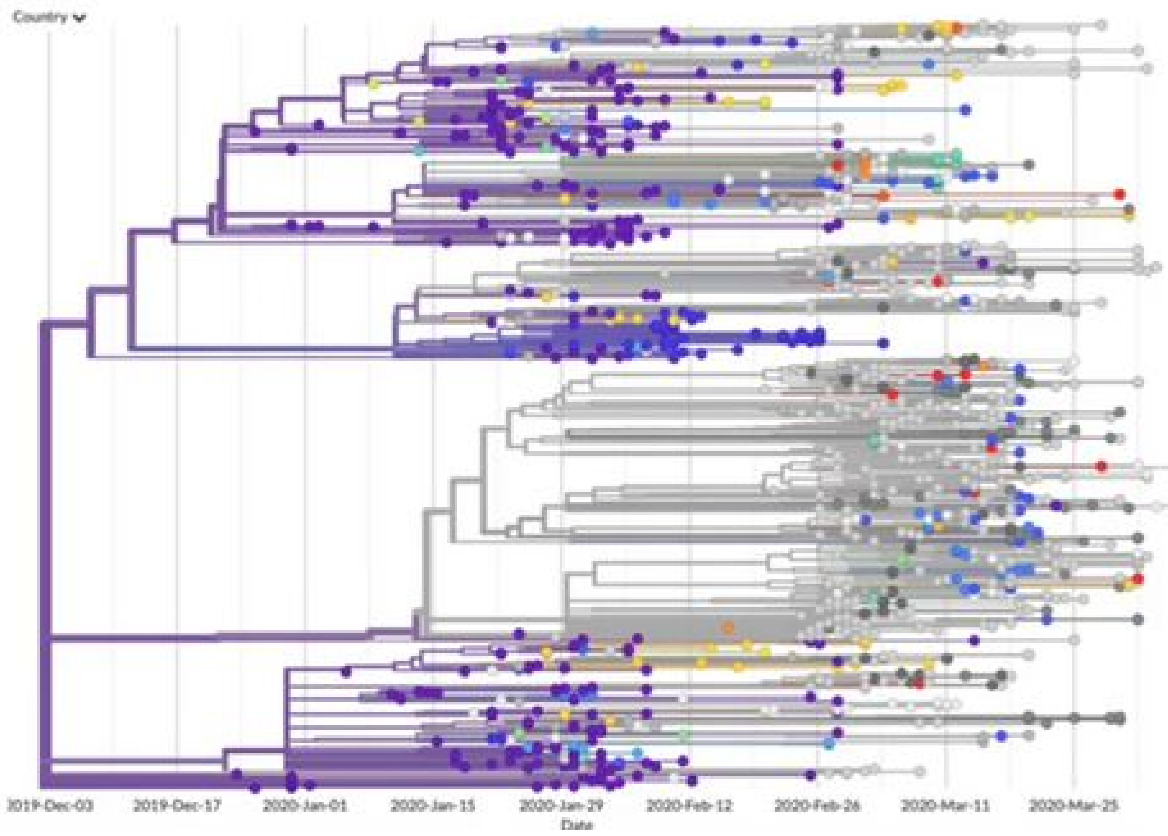
https://nextstrain.org/

Showing 3335 of 3335 genomes sampled between Dec 2019 and Nov 2020.



Early spread within Asia

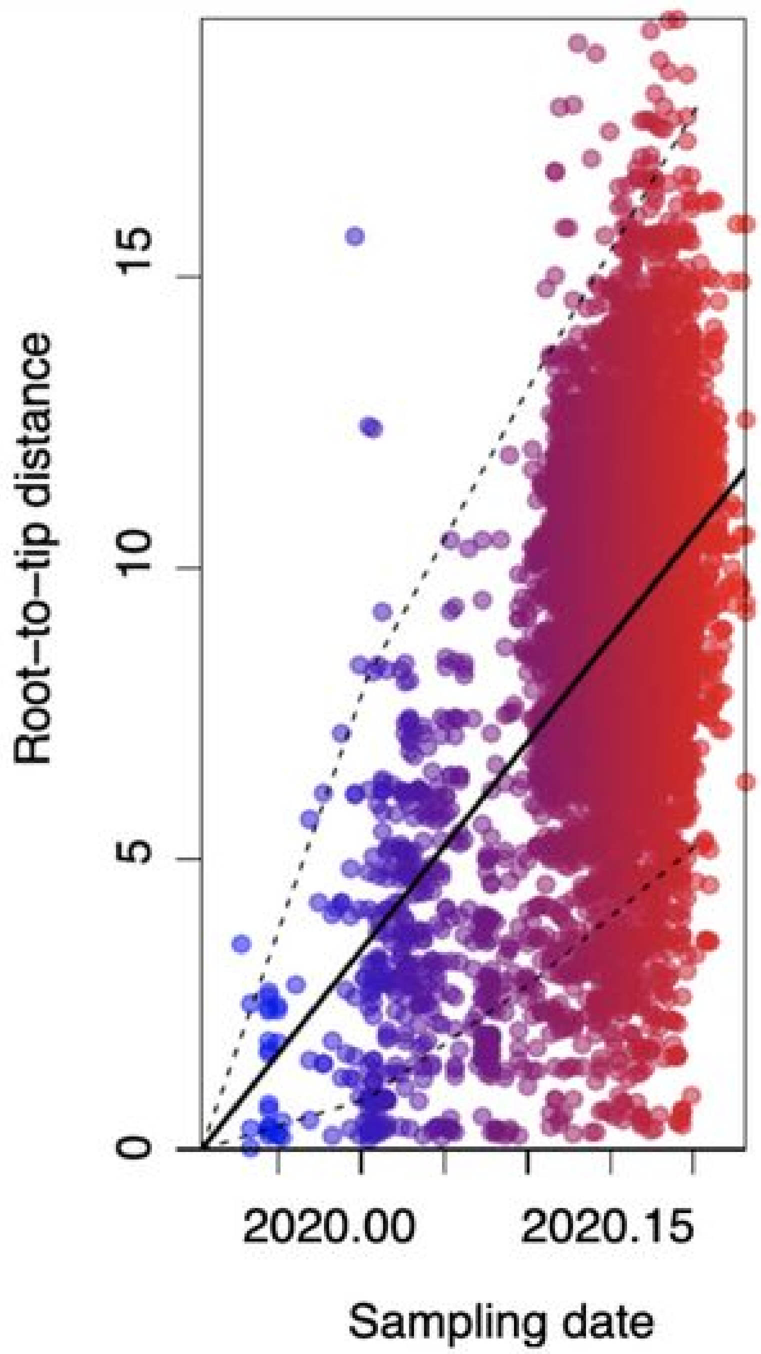
- The common ancestor of circulating viruses appears to have emerged in Wuhan, China, in late Nov or early Dec 2019.
- Accordingly, the majority of sampled and inferred ancestral cases were located in Asia during this early period.
- This is consistent with circulation largely within China and some exported cases to other countries in Asia for the first month of the outbreak.



https://nextstrain.org/

Increase in genetic diversity over time

on average 2 mutations
per month



Van Dorp et al. 2020

Did it start in Wuhan?

- all the initial Asian genome sequences are extremely close and seem to arise from the same ancestor
- all the subsequent cases in Europe and North American branch off from the Asian genomes

So very likely in China, in Wuhan or nearby.

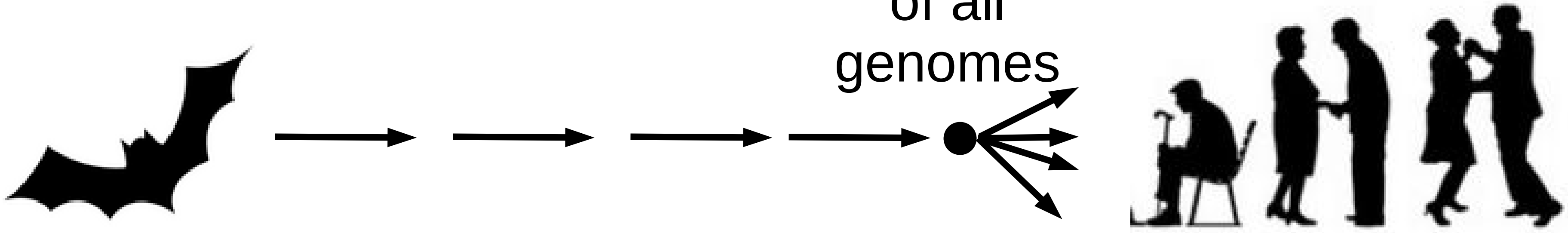
When?

SARS-CoV-2 accumulates on average 2 mutations per month so we can infer that the ancestor of all initial Asian genome sequences dated from Nov-early Dec.

However

Human patient 0 may have occurred earlier and in another place: maybe several previous clusters died off, and only one unfortunately took off in Wuhan.

Conclusion: the pandemic seeded in Wuhan.



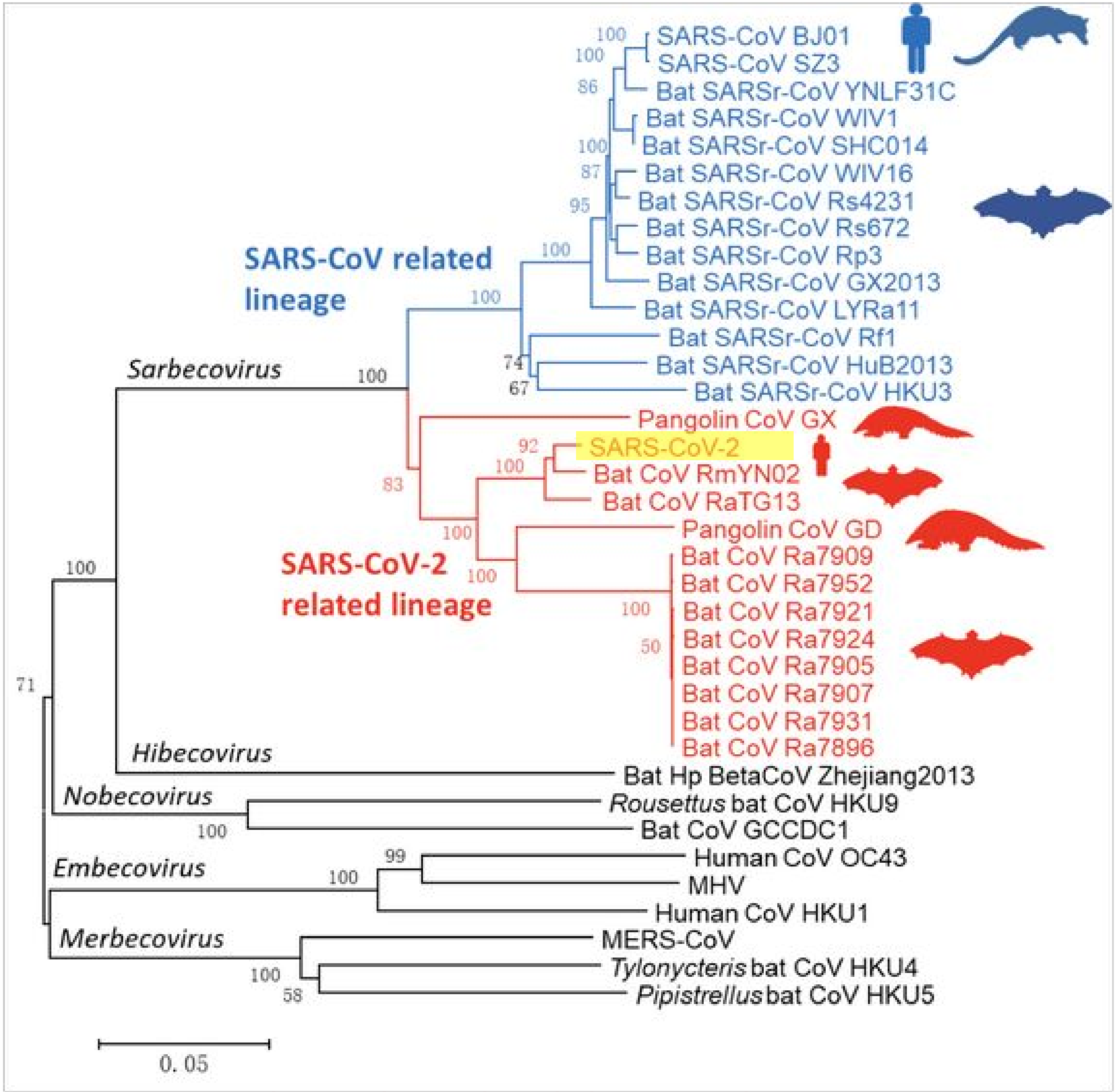
Bats

Mother
of all
genomes

Outbreak in Wuhan

Oct-Nov
2019

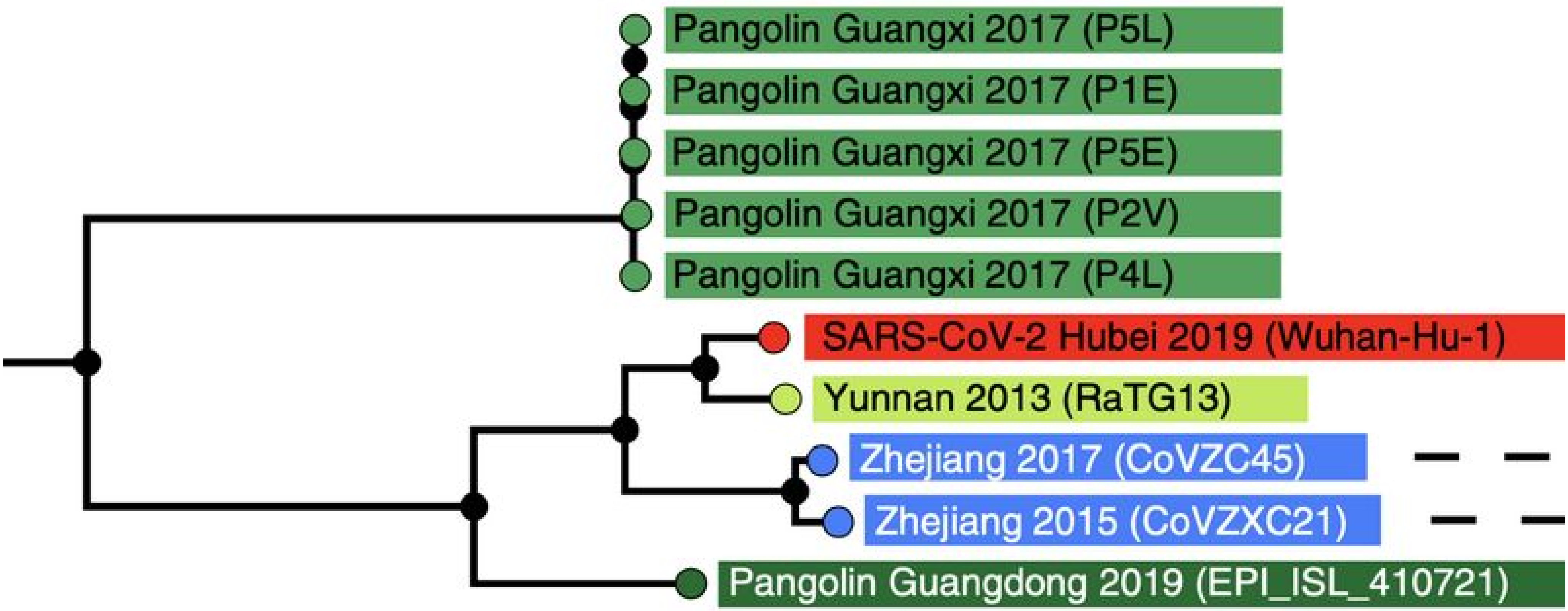
December 2019



sequences released after the outbreak (or not yet)

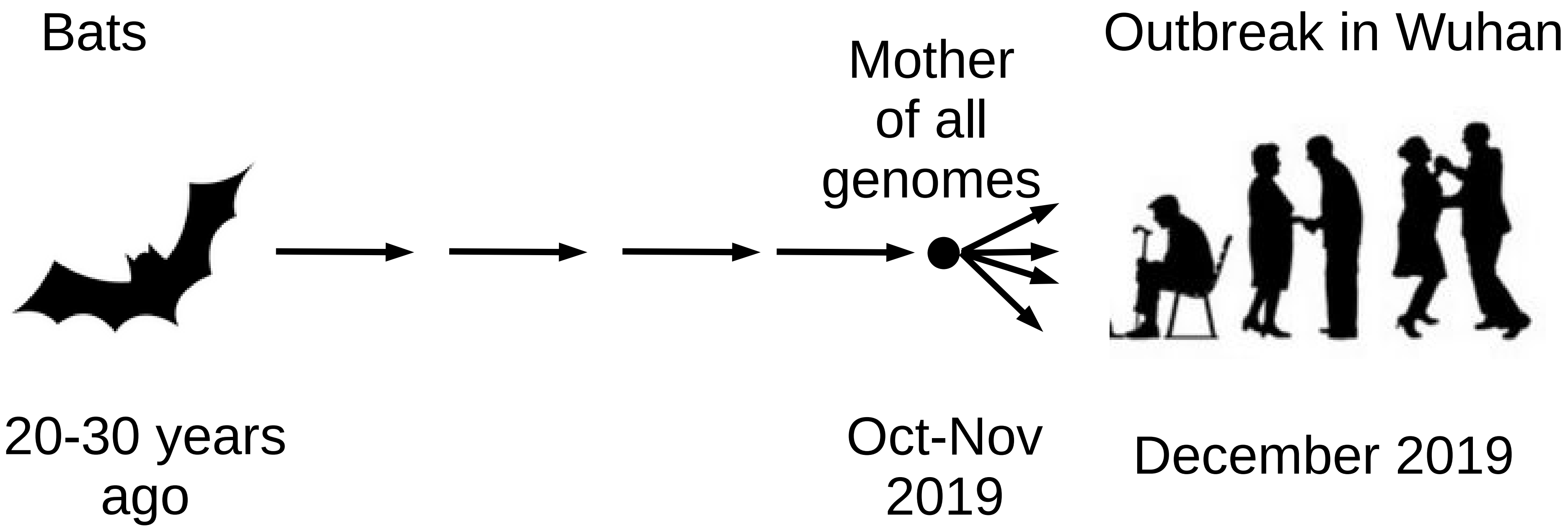
Adapted from Zheng-Li Shi

Closest full genome is RaTG13



Between SARS-CoV-2 and RaTG13:
about 1100 mutations across the whole genome
40 years (20+20)

Nature Microbiology July 2020



Bats

Mother
of all
genomes

Outbreak in Wuhan

20-30 years
ago

Oct-Nov
2019

December 2019

Possible scenarios

Fully natural origin (zoonosis, emerging infectious disease)

Contamination of a tourist/worker visiting a bat cave

Contamination of a scientist doing field work in bat cave

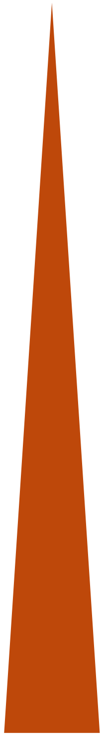
Natural sample collected and stored in a lab, then accident

Virus modified unintentionally in a lab, then accident

Virus modified for gain-of-function research, then accident

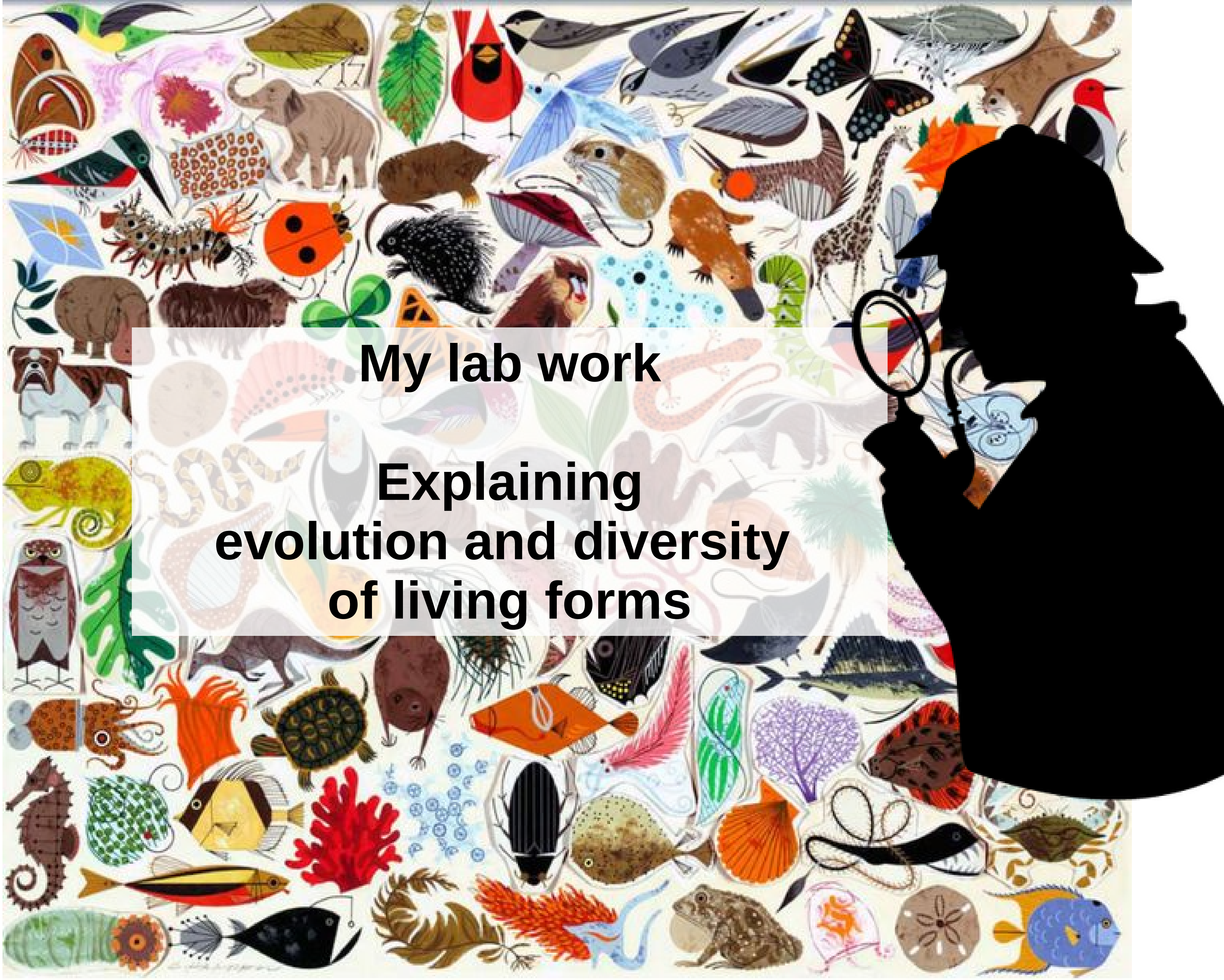
Virus modified for vaccine development, then accident

Virus released purposely



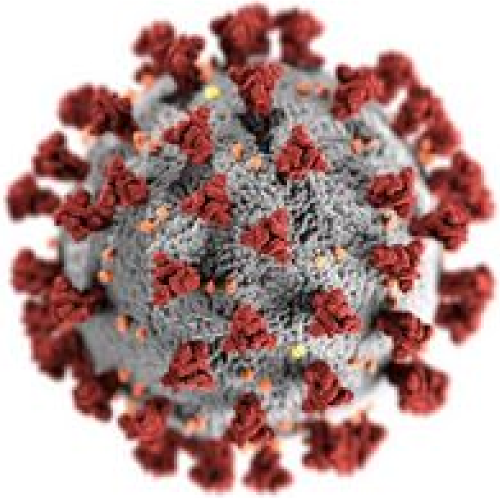
Human
Involvement

Who?
When?
Where?



My lab work

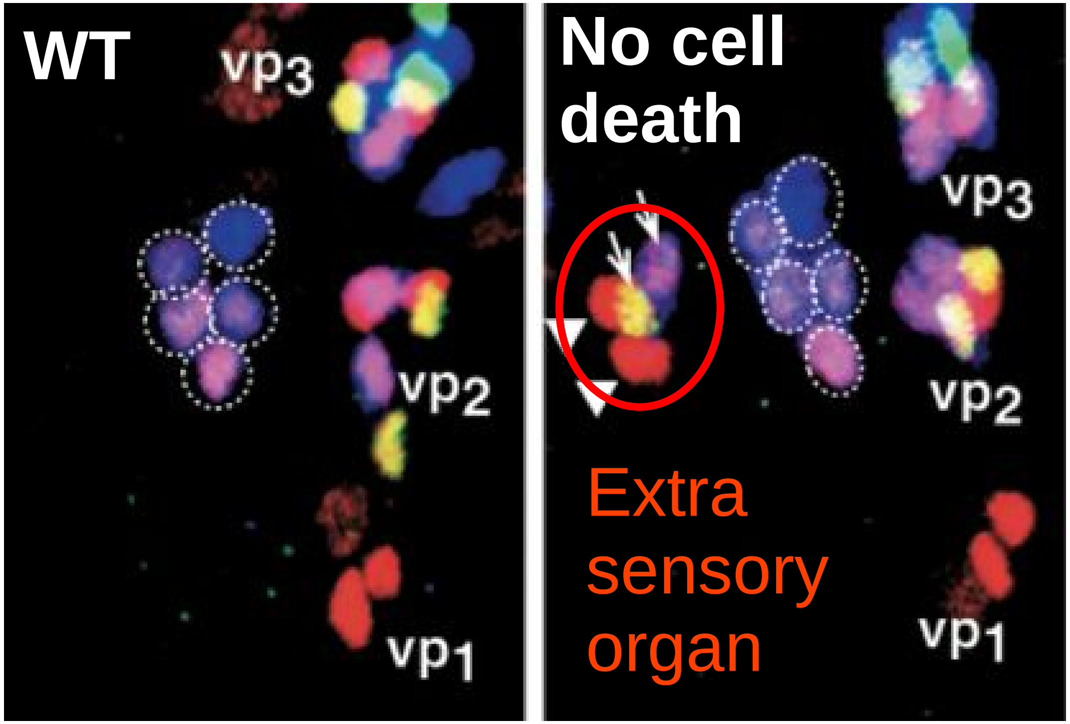
Explaining evolution and diversity of living forms

Drosophila	**Coronavirus**
	
180 Mb 1-5 million years	30 kb 20-30 years
From Ecology to Genomics	From Ecology to Genomics
No human involved	Humans possibly involved
No politics, Slow	Politics, Fast moving field

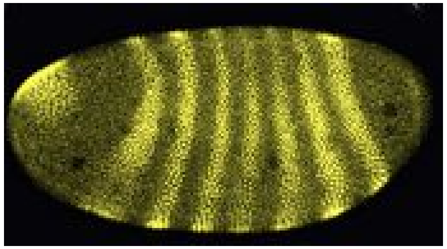
Evolution does not follow Occam’s razor/parcimony

My PhD: a sensory organ is produced and then destroyed during *Drosophila melanogaster* development

Orgogozo et al. Dev 2003



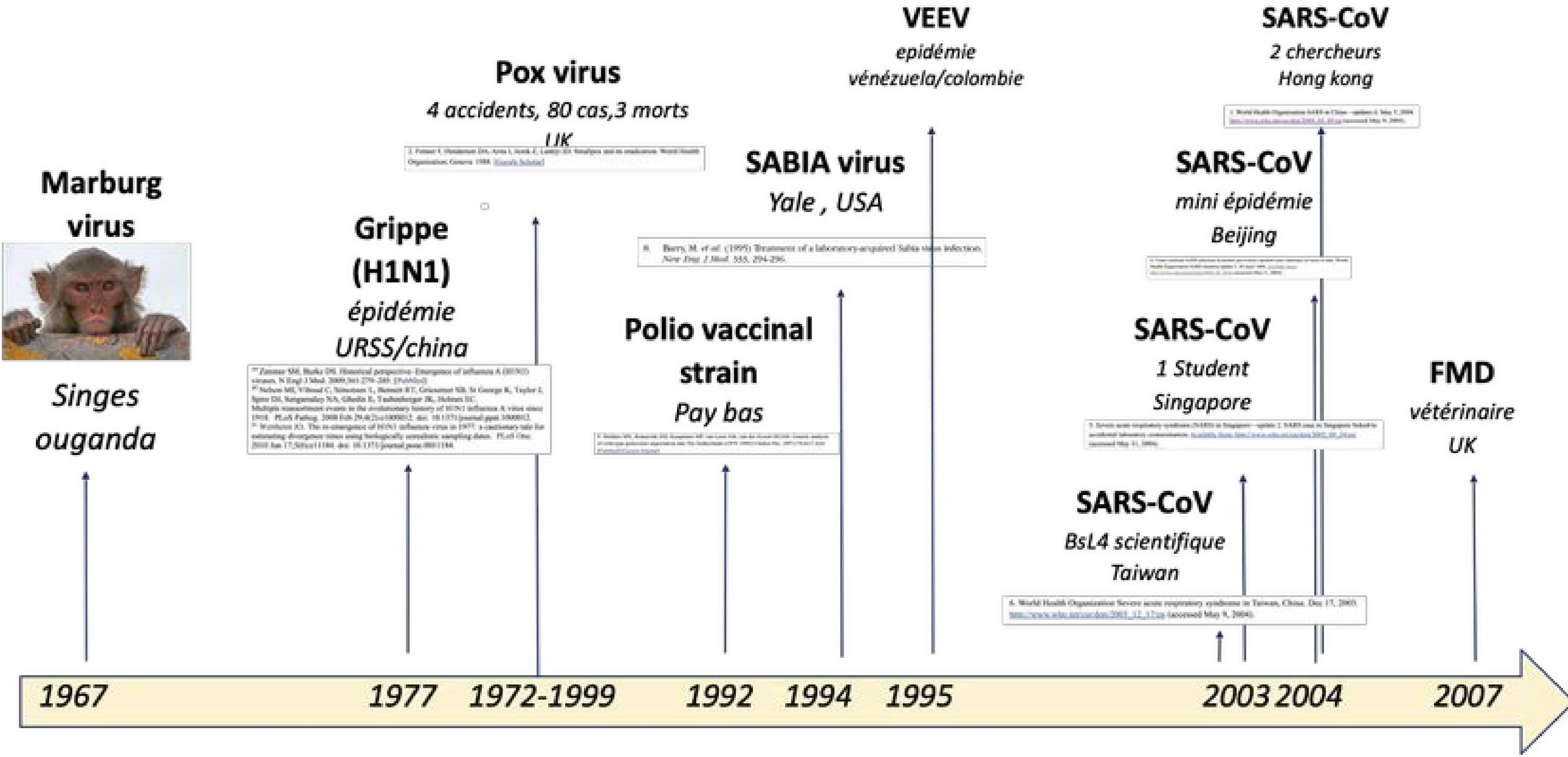
Extra sensory organ



S. Paddock

Zoonosis	**Lab incident**
Virus backbone previously unknown	Started in Wuhan where are several coronavirus labs
Impossible to construct such a virus	Coronavirus research done in Wuhan

A few lab accidents



Marburg virus
Singes ouganda
1967

Grippe (H1N1)
épidémie URSS/china
1977

Pox virus
4 accidents, 80 cas,3 morts UK
1972-1999

Polio vaccinal strain
Pay bas
1992

SABIA virus
Yale , USA
1994

VEEV
epidémie vénézuela/colombie
1995

SARS-CoV
BsL4 scientifique Taiwan

SARS-CoV
1 Student Singapore
2003

SARS-CoV
mini épidémie Beijing

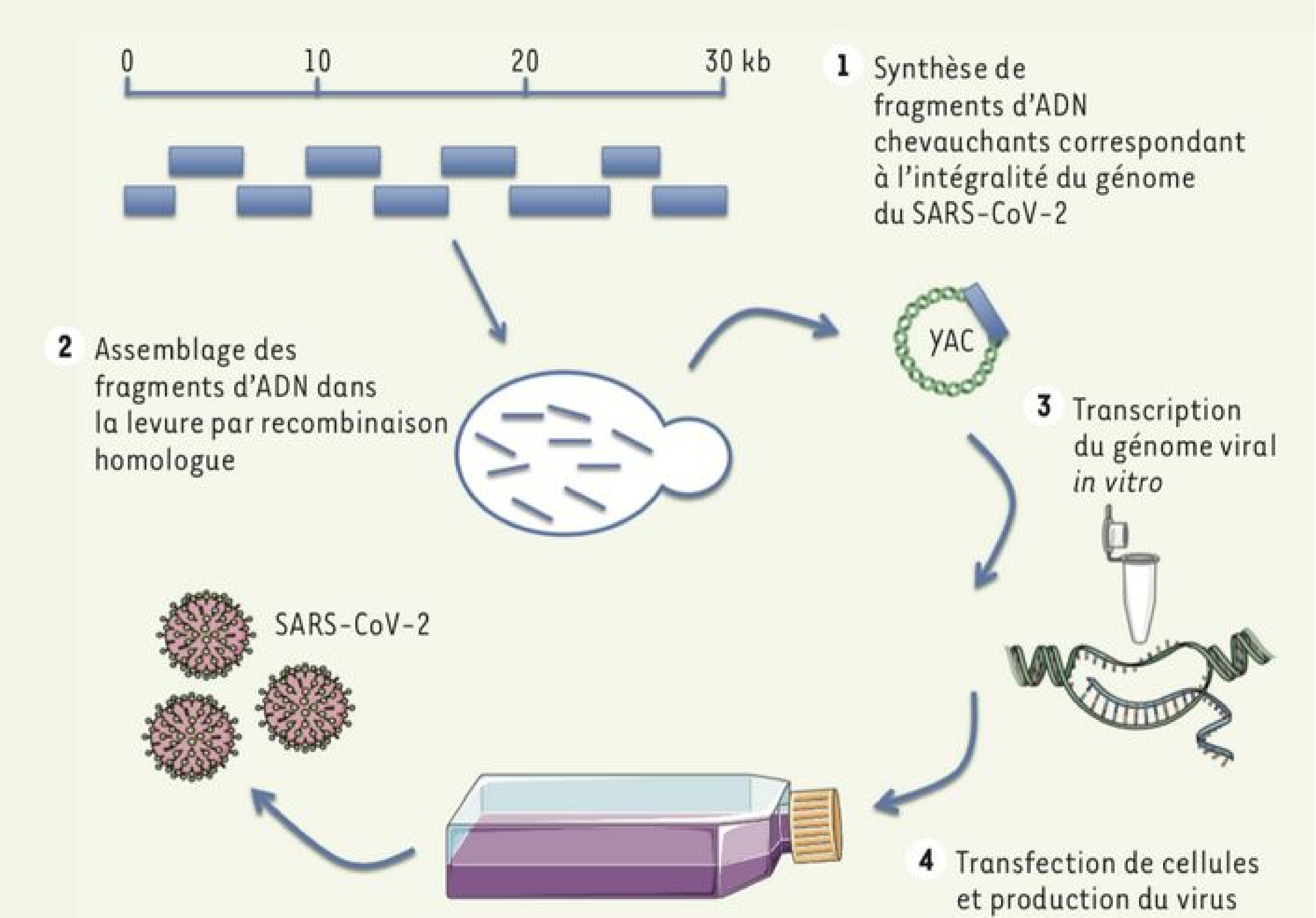
SARS-CoV
2 chercheurs Hong kong
2004

FMD
vétérinaire UK
2007

Heymann, D.L., Aylward, R.B. & Wolff, C. 2004. Dangerous pathogens in the laboratory: from smallpox to today's SARS setbacks and tomorrow's polio-free world. The Lancet 363: 1566–1568.

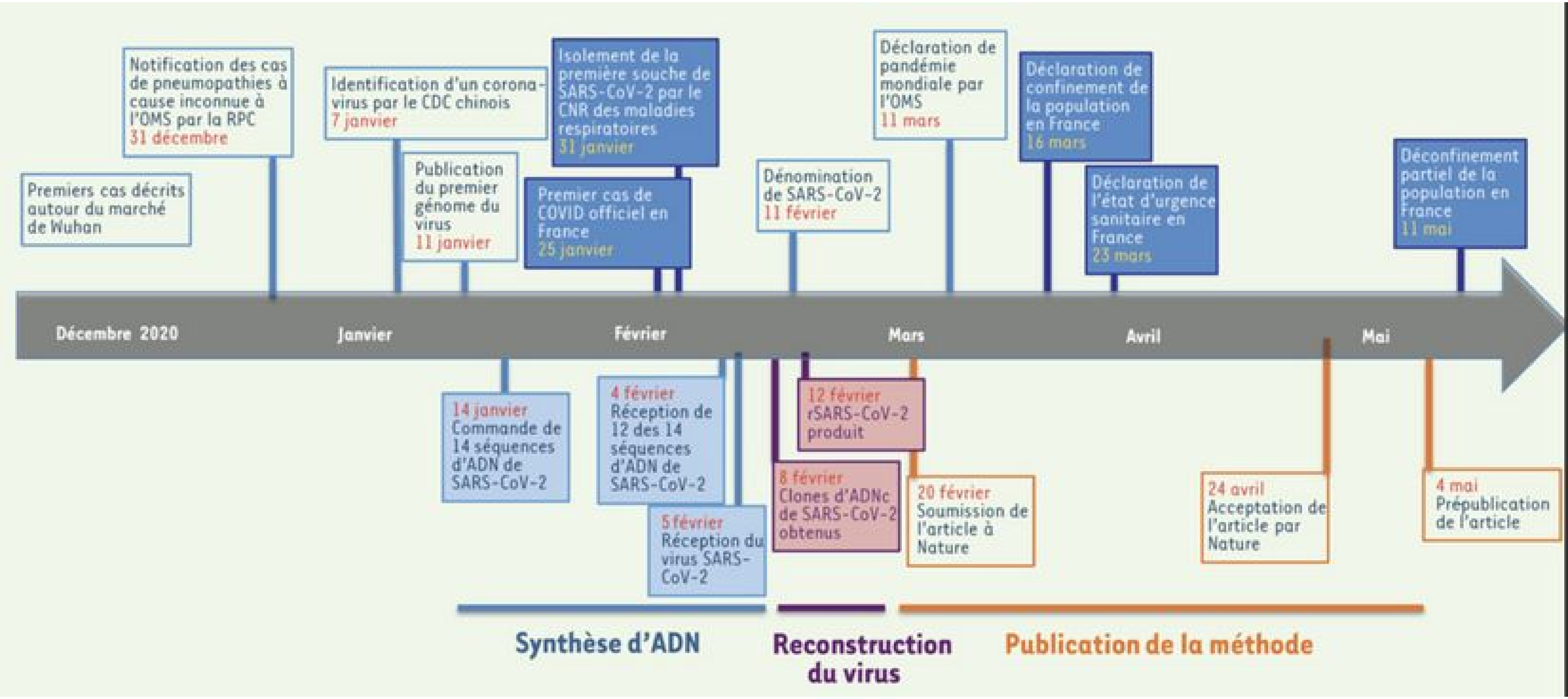
Etienne Decroly

Reconstruction of SARS-CoV-2



Iseni & Tournier, 2020

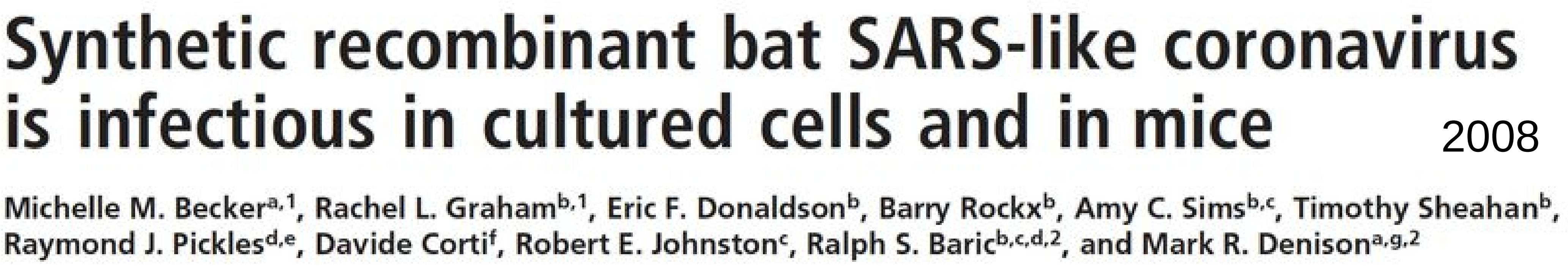
https://www.medecinesciences.org/fr/articles/medsci/full_html/2020/07/msc200189/msc200189.html



synSARS-CoV-2-GFP produced entirely from synthetic fragments (19 fragments)

https://www.medecinesciences.org/fr/articles/medsci/full_html/2020/07/msc200189/msc200189.htm

Recombining fragments in labs



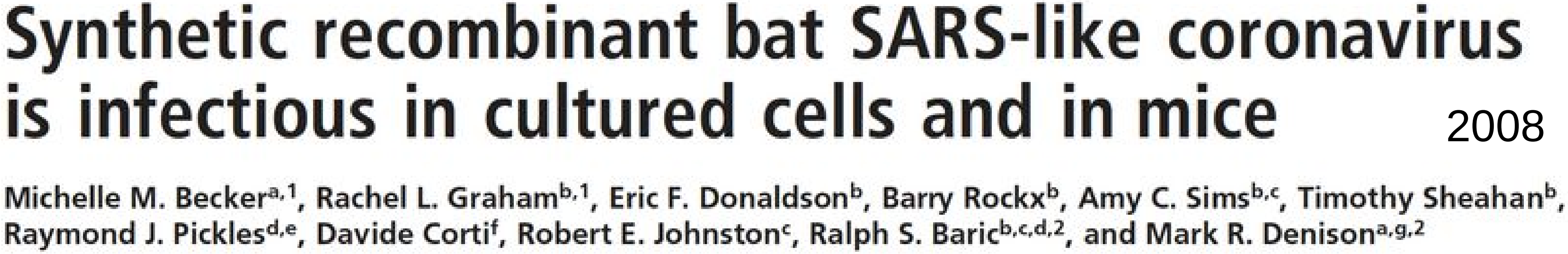
Synthetic recombinant bat SARS-like coronavirus is infectious in cultured cells and in mice

Michelle M. Becker[a,1], Rachel L. Graham[b,1], Eric F. Donaldson[b], Barry Rockx[b], Amy C. Sims[b,c], Timothy Sheahan[b], Raymond J. Pickles[d,e], Davide Corti[f], Robert E. Johnston[c], Ralph S. Baric[b,c,d,2], and Mark R. Denison[a,g,2]

2008

“we designed a consensus Bat-SCoV genome and replaced the Bat-SCoV Spike receptor-binding domain (RBD) with the SARS-CoV RBD (Bat-SRBD)”

Recombining fragments in labs



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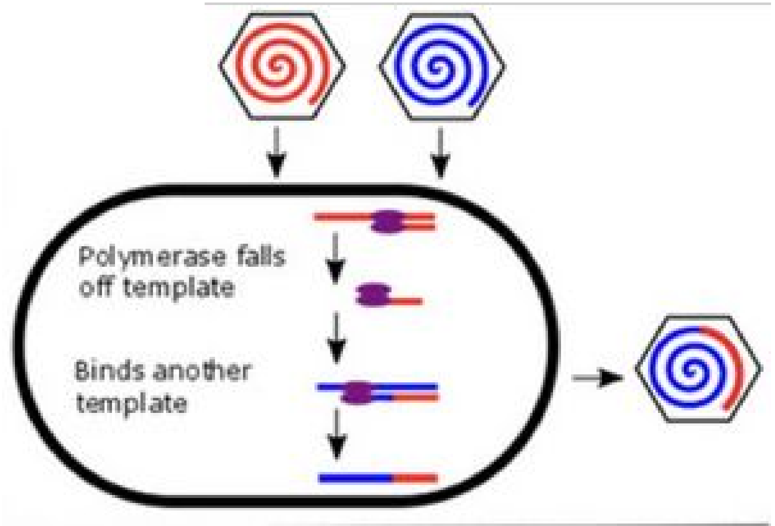
2008

“we designed a consensus Bat-SCoV genome and replaced the Bat-SCoV Spike receptor-binding domain (RBD) with the SARS-CoV RBD (Bat-SRBD)”

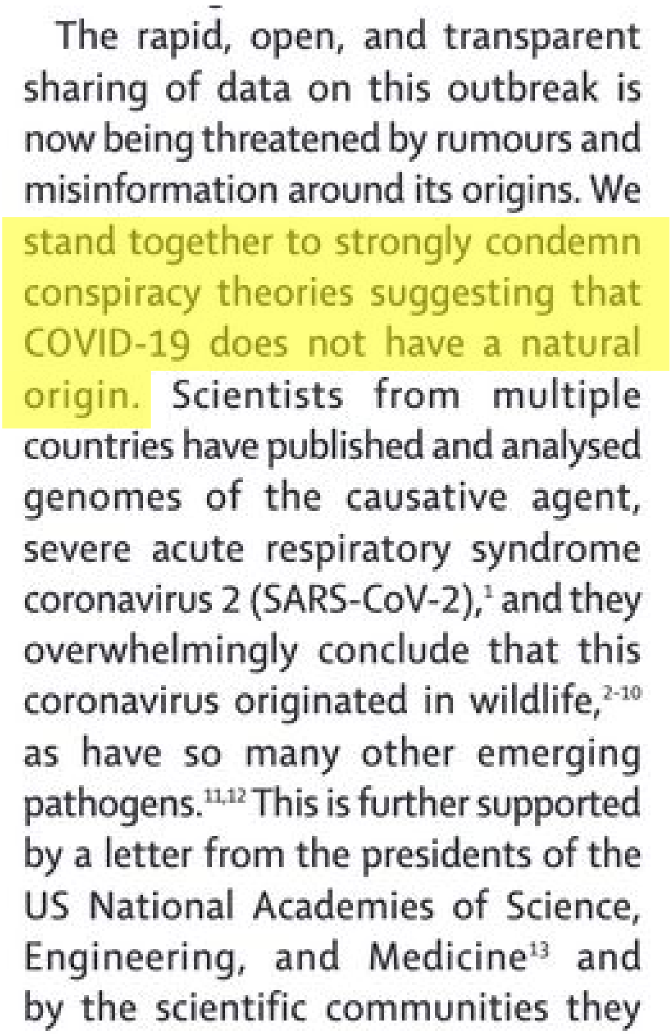
in nature

Needs co-infection



Statement in support of the scientists, public health professionals, and medical professionals of China combatting COVID-19

The Lancet
7 March 2020



The rapid, open, and transparent sharing of data on this outbreak is now being threatened by rumours and misinformation around its origins. We stand together to strongly condemn conspiracy theories suggesting that COVID-19 does not have a natural origin. Scientists from multiple countries have published and analysed genomes of the causative agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] and they overwhelmingly conclude that this coronavirus originated in wildlife,[2-10] as have so many other emerging pathogens.[11,12] This is further supported by a letter from the presidents of the US National Academies of Science, Engineering, and Medicine[13] and by the scientific communities they

We speak in one voice. To add your support for this statement, sign our letter online. LM is editor of ProMED-mail. We declare no competing interests.

Charles Calisher, Dennis Carroll, Rita Colwell, Ronald B Corley, Peter Daszak, Christian Drosten, Luis Enjuanes, Jeremy Farrar, Hume Field, Josie Golding, Alexander Gorbalenya, Bart Haagmans, James M Hughes, William B Karesh, Gerald T Keusch, Sai Kit Lam, Juan Lubroth, John S Mackenzie, Larry Madoff, Jonna Mazet, Peter Palese, Stanley Perlman, Leo Poon, Bernard Roizman, Linda Saif, Kanta Subbarao, Mike Turner

COVID19statement@gmail.com

emails retrieved by US-Right To Know association:

This letter was written by Peter Daszak and EcoHealthAlliance.
Peter Daszak intended it to
“not be identifiable as coming from any one organization or person”
but rather to be seen as “simply a letter from leading scientists”.

https://usrtk.org/biohazards-blog/ecohealth-alliance-orchestrated-key-scientists-statement-on-natural-origin-of-sars-cov-2/

EcoHealth Alliance

We speak in one voice. To add your support for this statement, sign our letter online. LM is editor of ProMED-mail. We declare no competing interests.

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COVID19statement@gmail.com

A global environmental health nonprofit organization dedicated to protecting wildlife and public health from the emergence of disease

Project “Understanding the risk of bat coronavirus emergence” (2014-2019: 3M$ including 0.5M$ given to Z-L Shi lab, renewed for 2019-2024).

Lijian Zhao 赵立坚
@zlj517

2/2 CDC was caught on the spot. When did patient zero begin in US? How many people are infected? What are the names of the hospitals? It might be US army who brought the epidemic to Wuhan. Be transparent! Make public your data! US owe us an explanation!

Voir les faits sur le COVID-19

3:37 PM · 12 mars 2020

15,2 k 16,1 k personnes tweetent à ce sujet.

Spokesman of the Chinese Ministry of Foreign Affairs

Conflits
@Conflits_FR

🇺🇸 ALERTE INFO - Donald #Trump sur l'origine du #coronavirus : "J'ai vu des preuves" que le #COVID__19 serait originaire du laboratoire de #Wuhan, mais "je ne peux pas vous en dire plus. Je n'ai pas le droit". (conférence de presse) #COVID2019 #Chine

11:35 PM · Apr 30, 2020 · Twitter Web App

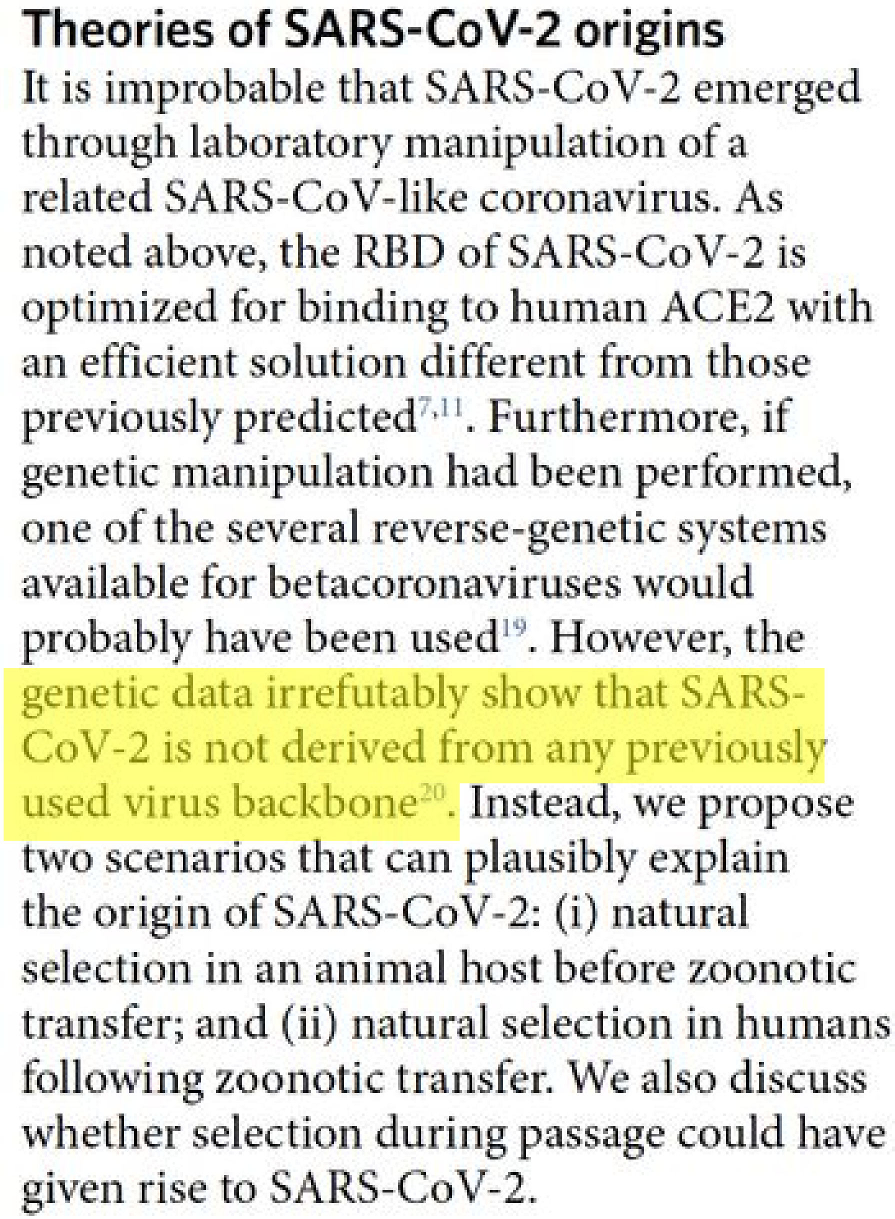

correspondence

Check for updates

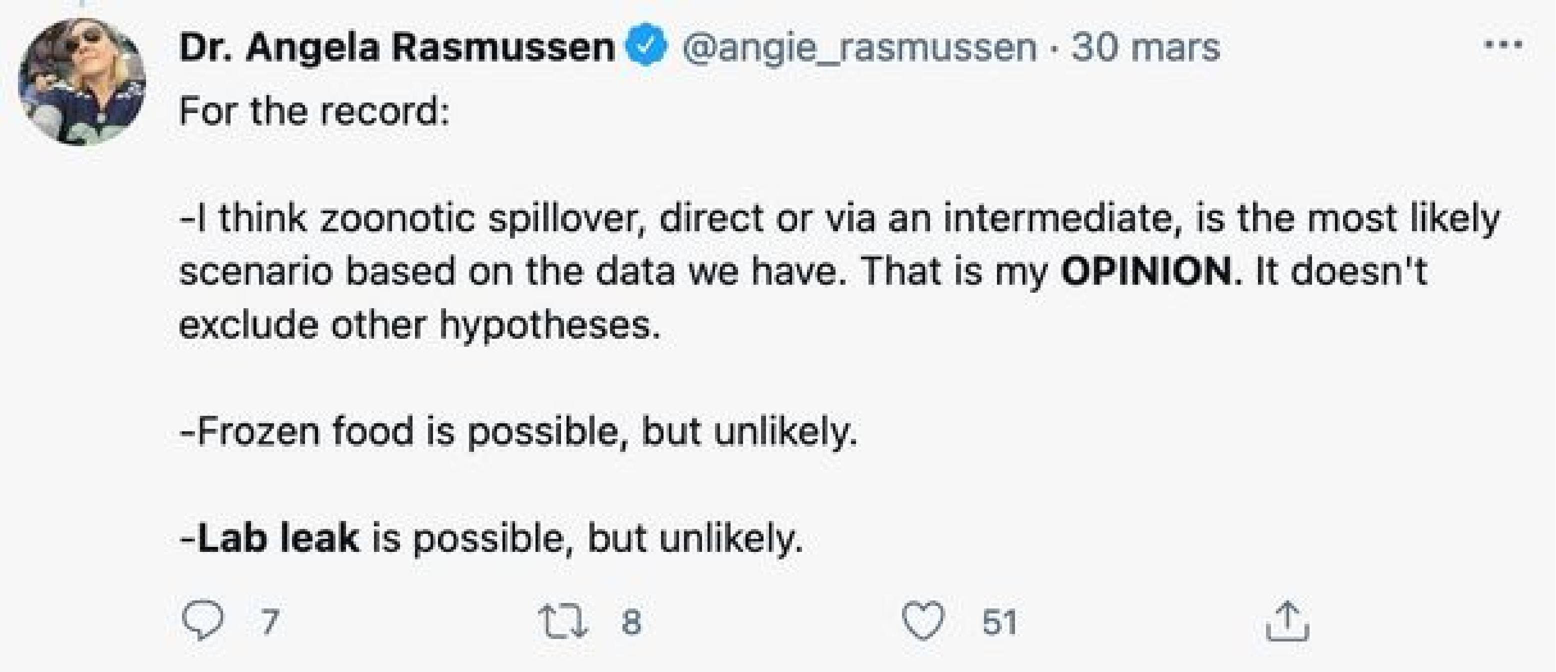
The proximal origin of SARS-CoV-2

Nature Medicine – April 2020

Kristian G. Andersen, Andrew Rambaut, W. Ian Lipkin, Edward C. Holmes and Robert F. Garry


Theories of SARS-CoV-2 origins

It is improbable that SARS-CoV-2 emerged through laboratory manipulation of a related SARS-CoV-like coronavirus. As noted above, the RBD of SARS-CoV-2 is optimized for binding to human ACE2 with an efficient solution different from those previously predicted[7,11]. Furthermore, if genetic manipulation had been performed, one of the several reverse-genetic systems available for betacoronaviruses would probably have been used[19]. However, the genetic data irrefutably show that SARS-CoV-2 is not derived from any previously used virus backbone[20]. Instead, we propose two scenarios that can plausibly explain the origin of SARS-CoV-2: (i) natural selection in an animal host before zoonotic transfer; and (ii) natural selection in humans following zoonotic transfer. We also discuss whether selection during passage could have given rise to SARS-CoV-2.



Dr. Angela Rasmussen @angie_rasmussen · 30 mars

For the record:

-I think zoonotic spillover, direct or via an intermediate, is the most likely scenario based on the data we have. That is my **OPINION**. It doesn't exclude other hypotheses.

-Frozen food is possible, but unlikely.

-**Lab leak** is possible, but unlikely.

https://twitter.com/angie_rasmussen/status/
1376920539118243841?s=20

Michael Eisen
@mbeisen

There are good political/social reasons for wanting SARS-CoV-2 to have entered humans directly from animals, and many pushing the WIV lab accident hypothesis have nefarious intent. I am nonetheless surprised at the degree of confidence people express in a natural origin.

9:15 PM · 16 janv. 2021 · Twitter Web App

175 Retweets **89** Tweets cités **801** J'aime

https://twitter.com/mbeisen/status/1350537123120570368?s=20

Different groups of people

NOT INVESTIGATING
Most experts as they are dealing with the current pandemic or have conflicts of interest

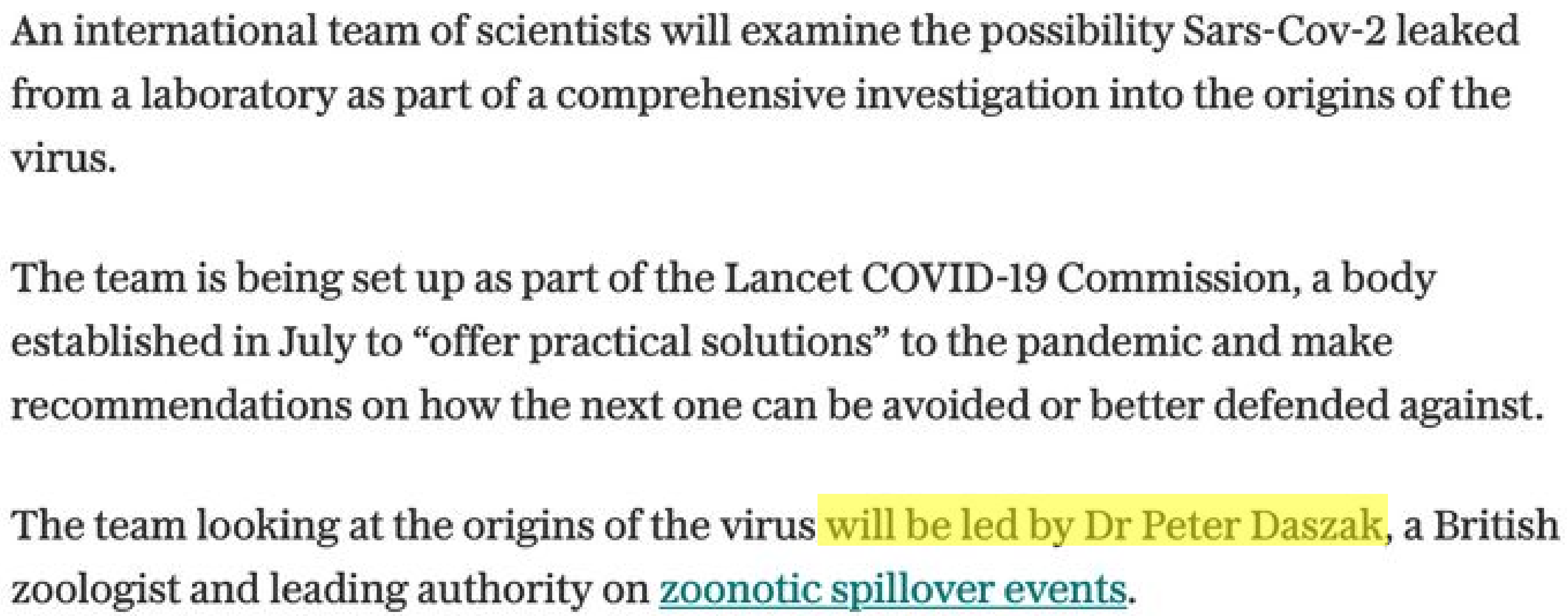
People who have already made up their minds (both sides)

INVESTIGATING
A group of active Twitter users
Biologists
@Ayjchan @MonaRahalkar @Rossana38510044 @flavinkins
Non-biologists
@BillyBostickson @TheSeeker268 @KevinMcH3
A few anonymous websites
“Nerd has power”, “Harvard to the Big House”, etc.

A few biology researchers
E. Decroly, R. Ebright, etc.

WHO commission
The Lancet commission

Lancet COVID-19 commission



An international team of scientists will examine the possibility Sars-Cov-2 leaked from a laboratory as part of a comprehensive investigation into the origins of the virus.

The team is being set up as part of the Lancet COVID-19 Commission, a body established in July to “offer practical solutions” to the pandemic and make recommendations on how the next one can be avoided or better defended against.

The team looking at the origins of the virus will be led by Dr Peter Daszak, a British zoologist and leading authority on zoonotic spillover events.

Sept 2020

https://www.telegraph.co.uk/global-health/science-and-disease/scientists-examine-possibility-covid-leaked-lab-part-investigation/

https://www.gmwatch.org/en/news/latest-news/19538-scientists-outraged-by-peter-daszak-leading-enquiry-into-possible-covid-lab-leak

What we know

The various hypotheses

Lack of transparency
Controversies

Lack of transparency and controversies

From RaTG13 to the 2012 pneumonia
The databases
The furin site
RaTG13 genome assembly
Huang Yanling
Sick researchers at WIV
The first COVID-19 patients
Event in October 2019 at WIV
Embargo on the first SARS-CoV-2 genome
The seafood market
Pangolins
EcoHealth Alliance NIH grant
Conflicts of interest
The China-WHO joint report etc.

Conclusion

SARS-CoV-2 comes from a bat coronavirus about 20 years ago.

Intermediate host?

Outbreak seeded in Wuhan late 2019.

A single mother genome of all SARS-CoV-2 viruses

Virus manipulation in labs
Controversies, lack of transparency, politics interference