

# Evolution and origins of SARS-CoV-2 and related coronaviruses

Introduction to Evolution and Scientific Inquiry

Spring 2020, Dr. Spielman

# Zoonosis

- Virus that normally infects one animal species infects a NEW/DIFFERENT species
  - Sometimes from a new mutation
  - Sometimes from an existing mutation
  - Sometimes no mutation at all – it just can infect multiple species

Image from April 2019

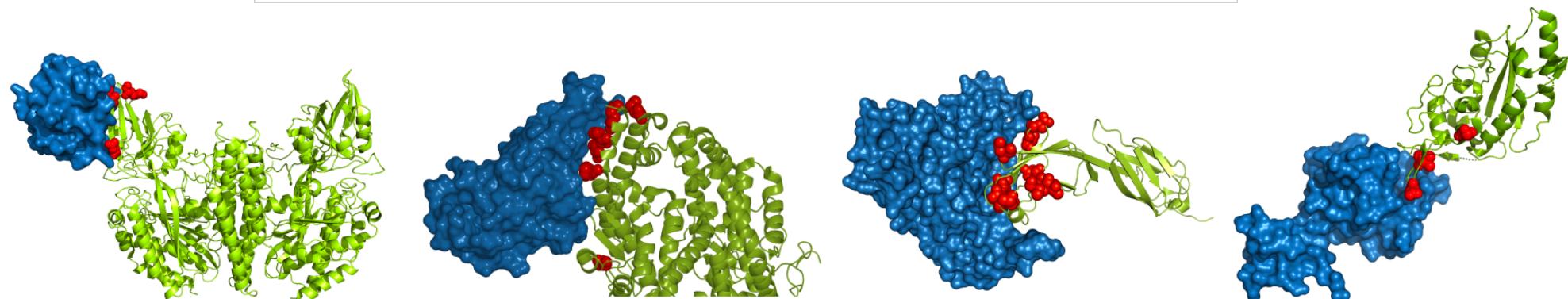
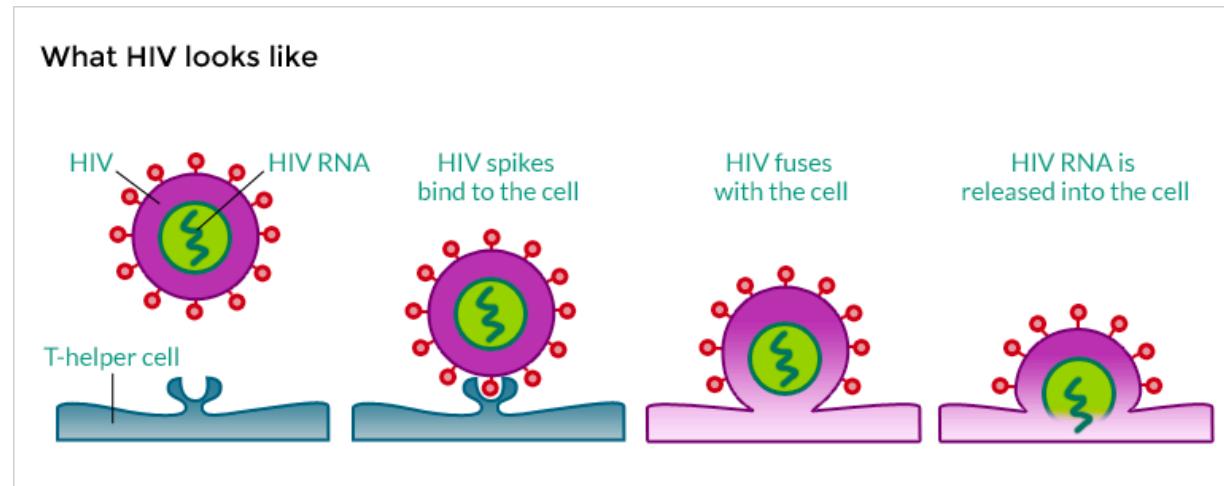


[www.cdc.gov/onehealth](http://www.cdc.gov/onehealth)

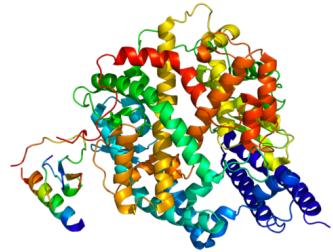
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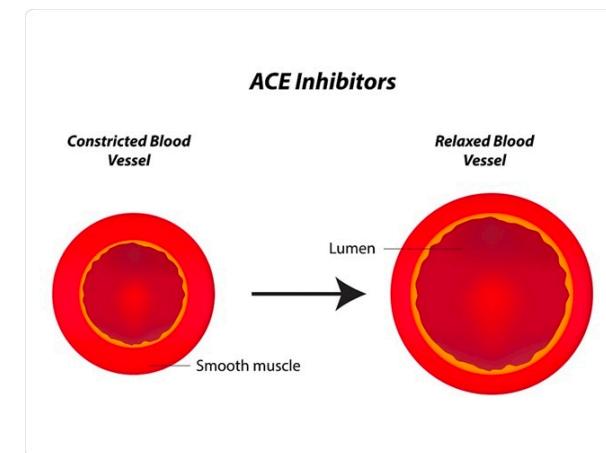
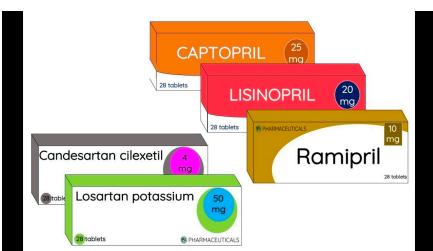
# Viruses bind host receptors or other cell-surface proteins



# ACE2: Angiotension-converting enzyme 2



- ACE constricts blood flow
- ACE inhibitors relax veins to improve blood flow.  
Used to treat...
  - Heart disease
  - Angiotension
  - Diabetes
  - Migraines
  - Chronic kidney diseases



nature  
medicine

BRIEF COMMUNICATION

<https://doi.org/10.1038/s41591-020-0868-6>

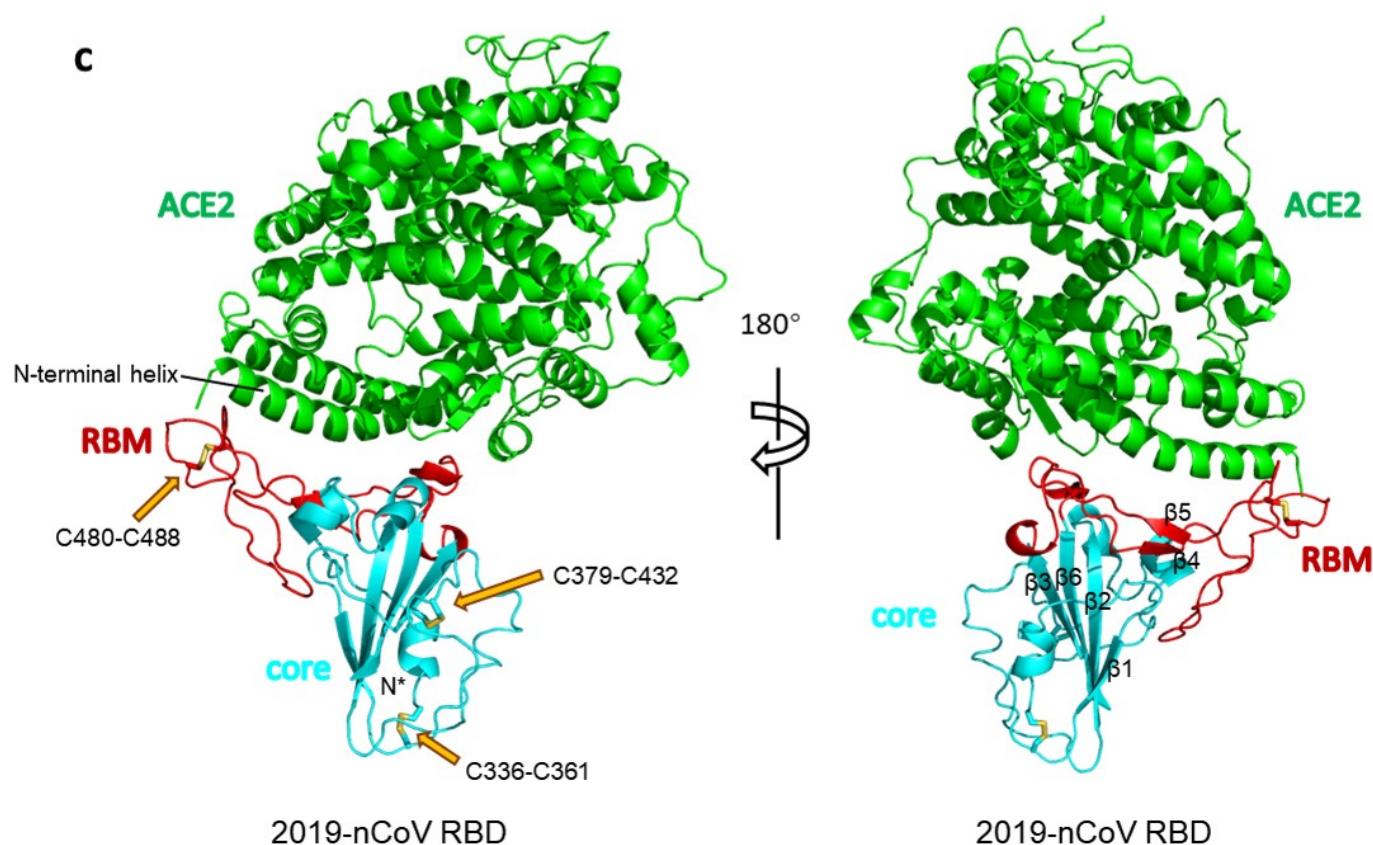
Check for updates

**SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes**

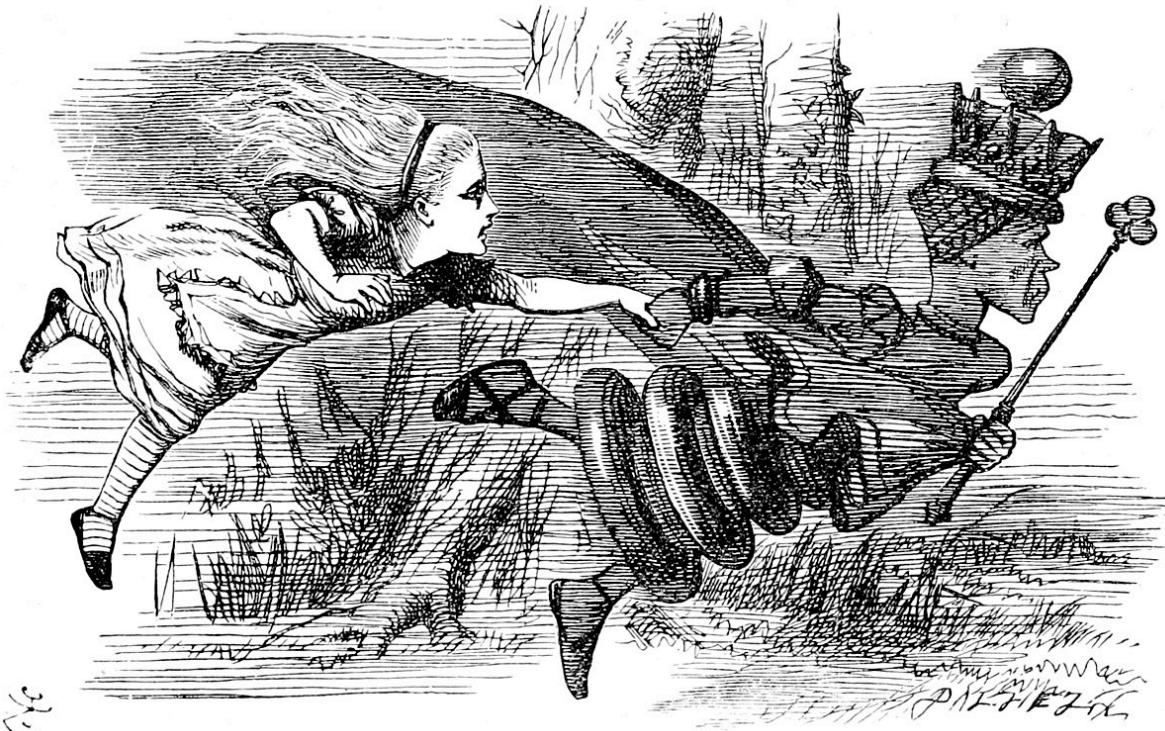
Waradon Sungnak<sup>1</sup>✉, Ni Huang<sup>1</sup>, Christophe Bécaïn<sup>1</sup>✉, Marijn Berg<sup>3,4</sup>, Rachel Queen<sup>5</sup>, Monika Litvinukova<sup>1,6</sup>, Carlos Talavera-López<sup>1</sup>, Henrike Maatz<sup>6</sup>, Daniel Reichart<sup>7</sup>, Fotios Sampaziotis<sup>1</sup><sup>8,9,10</sup>, Kaylee B. Worlock<sup>11</sup>, Masahiro Yoshida<sup>1</sup><sup>11</sup>, Josephine L. Barnes<sup>11</sup> and HCA Lung Biological Network<sup>1</sup>✉

<https://www.nature.com/articles/s41591-020-0868-6>

# Structure of ACE2 bound to SARS-CoV-2

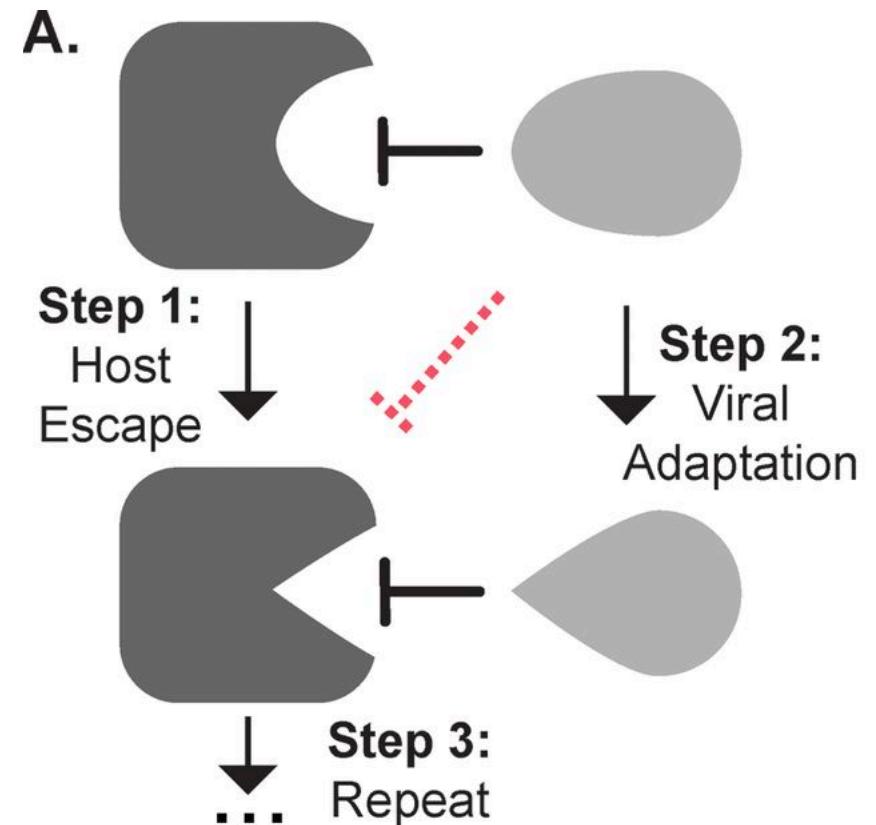


# Recall “Red Queen Hypothesis” (Evolutionary Arms Race)



“Now, here, you see, it takes all the running you can do, to keep in the same place.” -Lewis Carroll

[https://en.wikipedia.org/wiki/Red\\_Queen\\_hypothesis](https://en.wikipedia.org/wiki/Red_Queen_hypothesis)



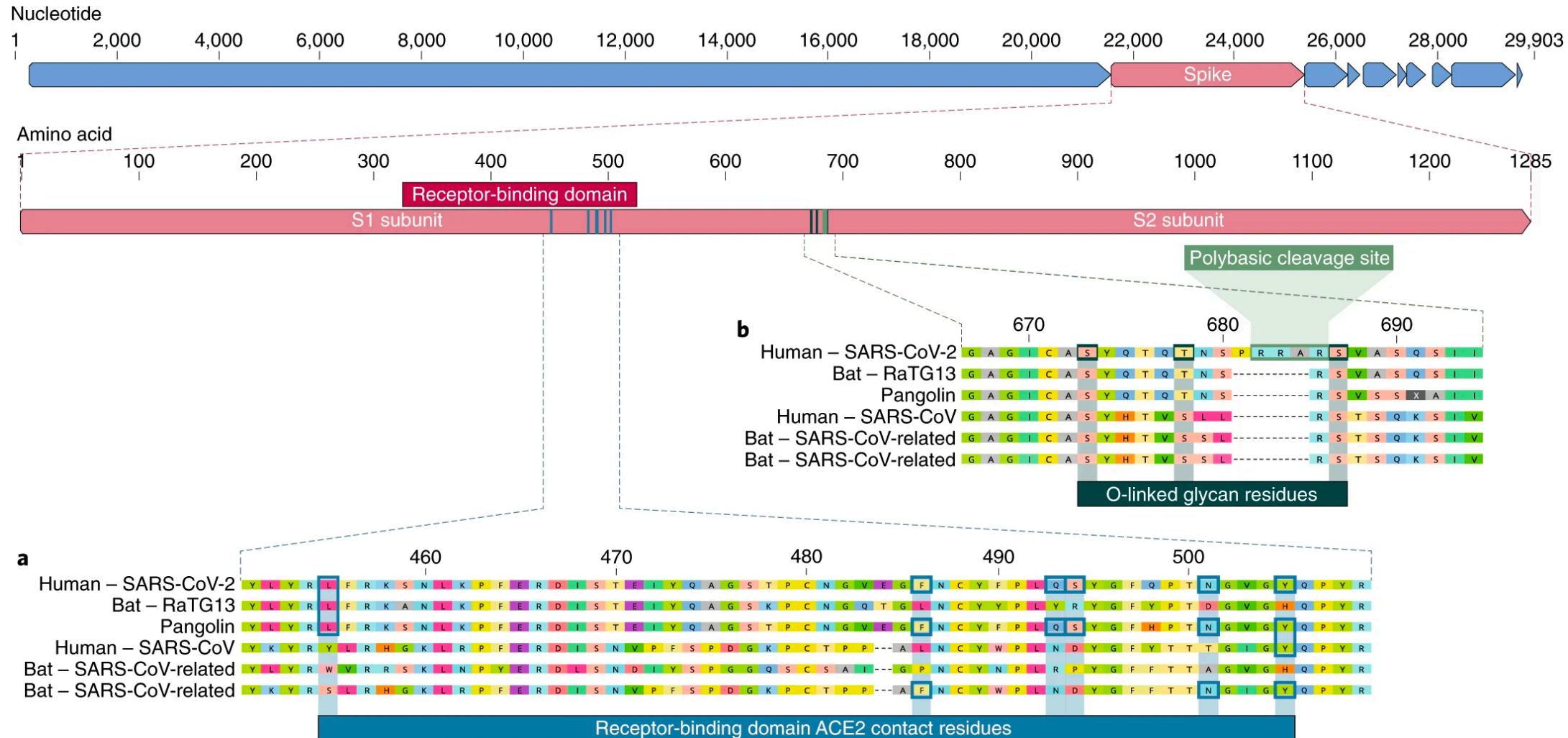
<https://jvi.asm.org/content/90/7/3280>

**correspondence** Check for updates

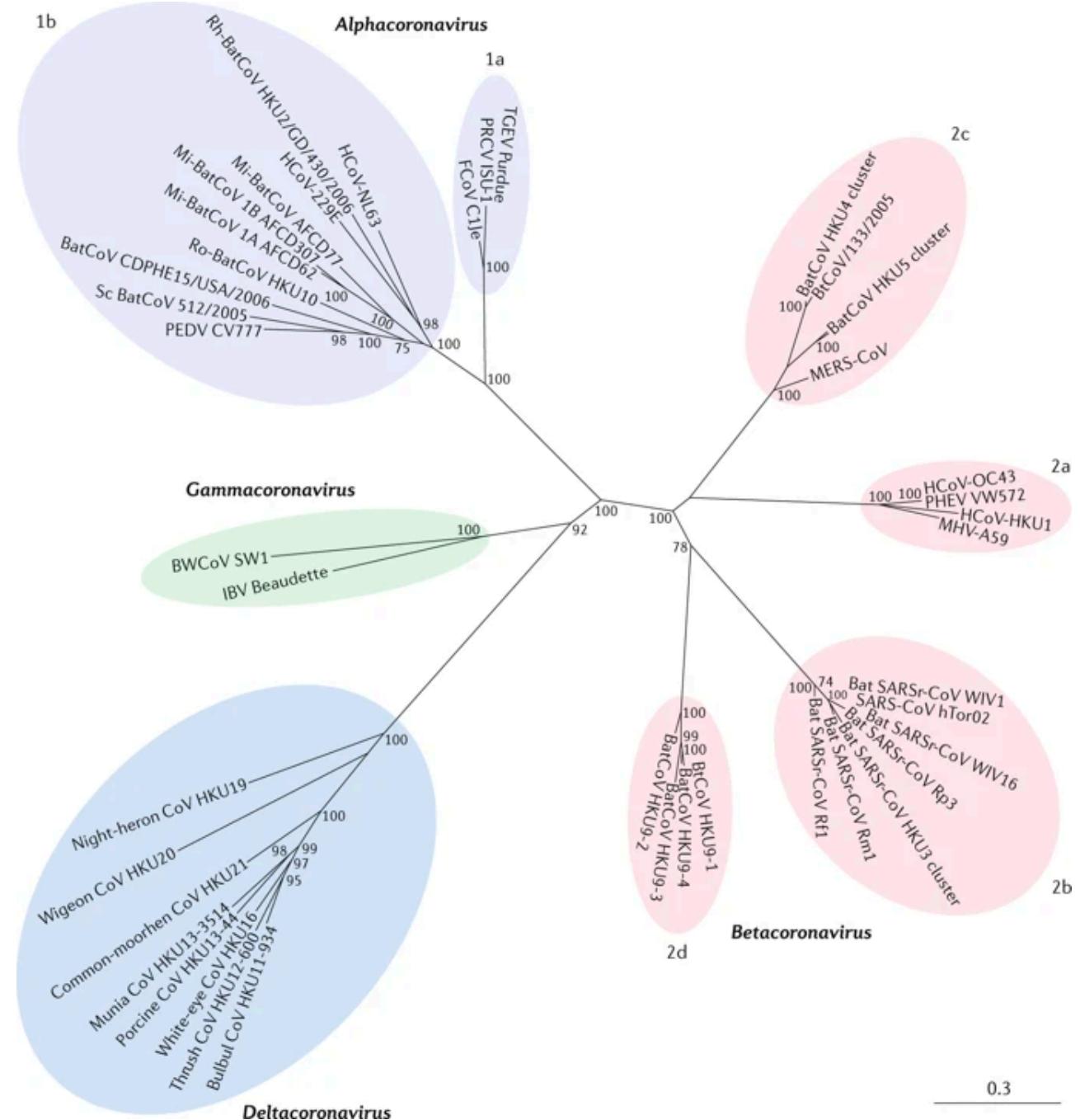
# The proximal origin of SARS-CoV-2

Kristian G. Andersen<sup>1,2</sup>✉, Andrew Rambaut<sup>1,3</sup>, W. Ian Lipkin<sup>4</sup>, Edward C. Holmes<sup>1,5</sup> and Robert F. Garry<sup>6,7</sup>  
<sup>1</sup>Department of Immunology and Microbiology, The Scripps Research Institute, La Jolla, CA, USA.  
<sup>2</sup>Scripps Research Translational Institute, La Jolla, CA, USA. <sup>3</sup>Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, UK. <sup>4</sup>Center for Infection and Immunity, Mailman School of Public Health of Columbia University, New York, NY, USA. <sup>5</sup>Marie Bashir Institute for Infectious Diseases and Biosecurity, School of Life and Environmental Sciences and School of Medical Sciences, The University of Sydney, Sydney, Australia. <sup>6</sup>Tulane University, School of Medicine, Department of Microbiology and Immunology, New Orleans, LA, USA. <sup>7</sup>Zalgen Labs, Germantown, MD, USA.  
✉e-mail: andersen@scripps.edu

<https://www.nature.com/articles/s41591-020-0820-9>



# “Full” (not at all full) diversity of coronaviruses



Research from 2018

<https://doi.org/10.1038/s41579-018-0118-9>

# Other human coronaviruses are also from zoonosis

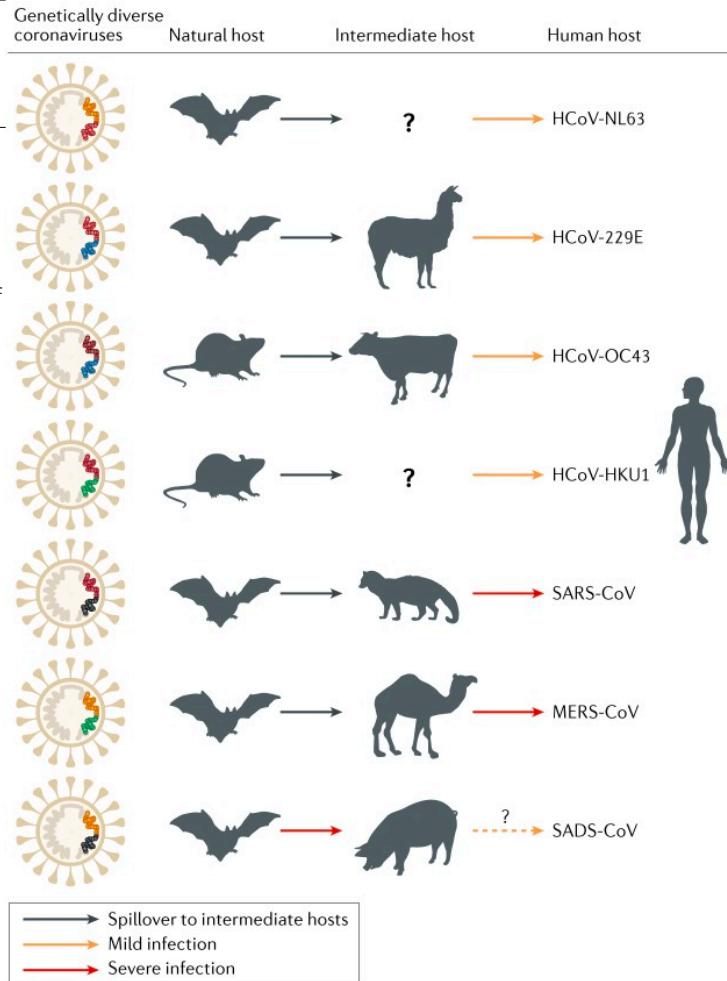
## Origin and evolution of pathogenic coronaviruses

Jie Cui<sup>1</sup>, Fang Li<sup>2</sup> and Zheng-Li Shi<sup>1\*</sup>

Abstract | Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are two highly transmissible and pathogenic viruses that emerged in humans at the beginning of the 21st century. Both viruses likely originated in bats, and genetically diverse coronaviruses that are related to SARS-CoV and MERS-CoV were discovered in bats worldwide. In this Review, we summarize the current knowledge on the origin and evolution of these two pathogenic coronaviruses and discuss their receptor usage; we also highlight the diversity and potential of spillover of bat-borne coronaviruses, as evidenced by the recent spillover of swine acute diarrhoea syndrome coronavirus (SADS-CoV) to pigs.

Research from 2018

<https://doi.org/10.1038/s41579-018-0118-9>



Early 2020 information

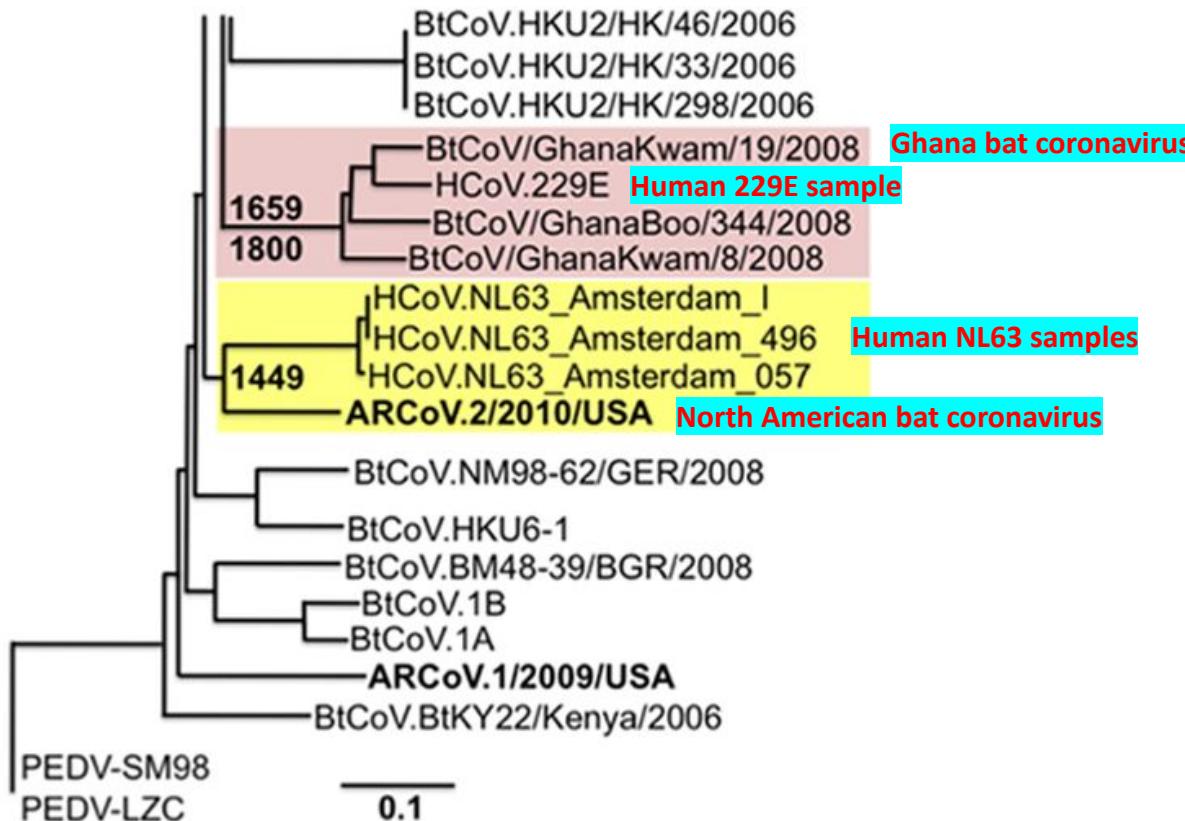
Table 1.

Classification and source of Coronaviruses affecting humans until the emergence of the 2019-nCoV.

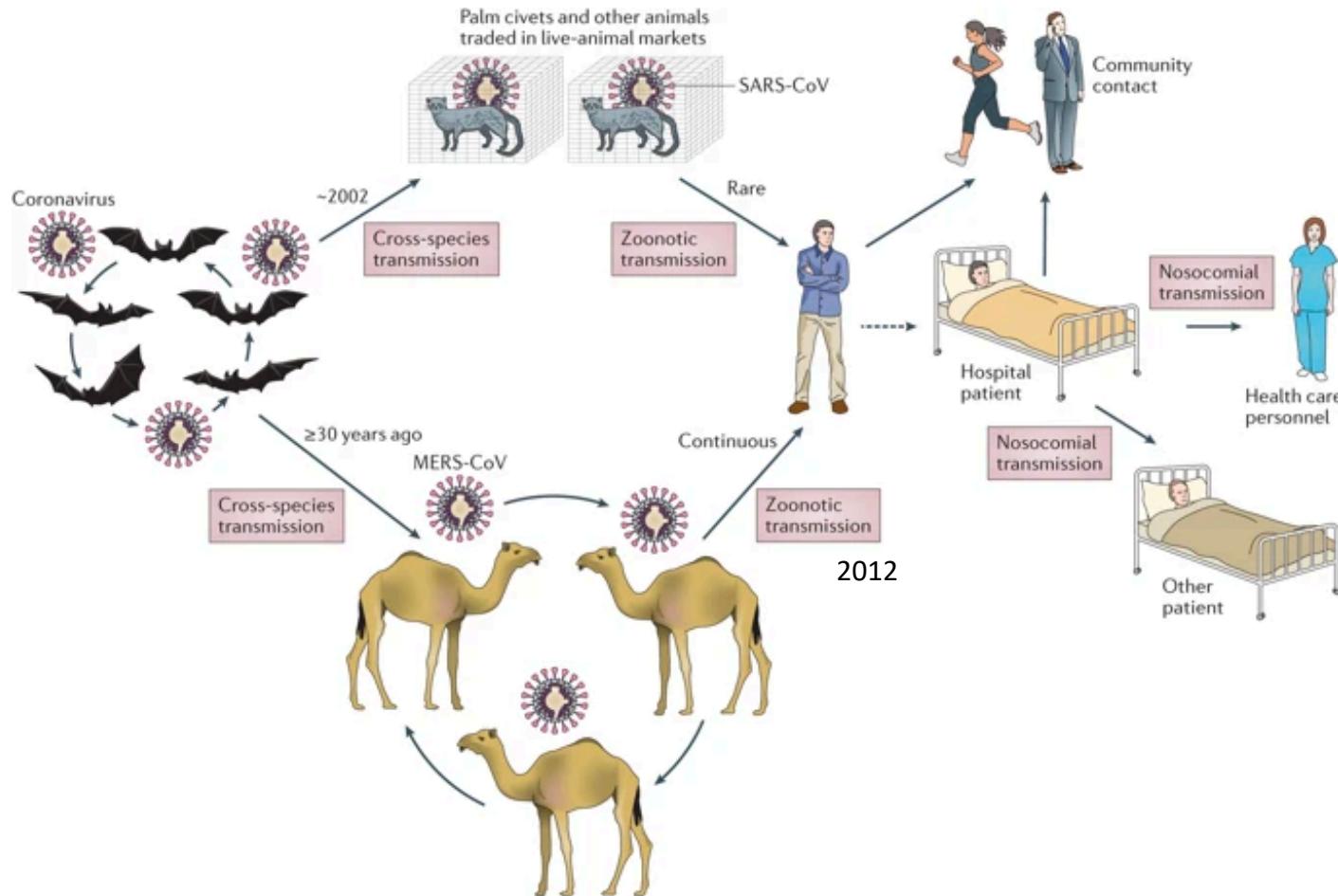
Genus	Virus	Natural host	Intermediate host	Disease	Receptor
Alphacoronavirus	HCoV-NL63	Bats	Unknown	Mild respiratory tract infections	Angiotensin converting enzyme 2
	HCoV-229E	Bats	Camelids	Mild respiratory tract infections	Human aminopeptidase N
Betacoronavirus	HCoV-OC43	Rodents	Bovine	Mild respiratory tract infections	9-O-acetylsialic acids
	HCoV-HKU1	Rodents	Unknown	Mild respiratory tract infections and pneumonia	9-O-acetylsialic acids
	SARS-CoV	Bats	Masked palm civettes	Severe acute respiratory syndrome	Angiotensin converting enzyme 2
	MERS-CoV	Bats	Camelids	Severe acute respiratory syndrome	Dipeptidyl peptidase-4
	2019-nCoV	Bats	Unknown	Severe acute respiratory syndrome	Angiotensin converting enzyme 2

<https://doi.org/10.1093/femspd/ftaa006>

# Other human coronaviruses are also from zoonosis



# SARS-CoV-2 emergence “shouldn’t” surprise us



Nature Reviews | Microbiology

# SARS-CoV-2 emergence “shouldn’t” surprise us

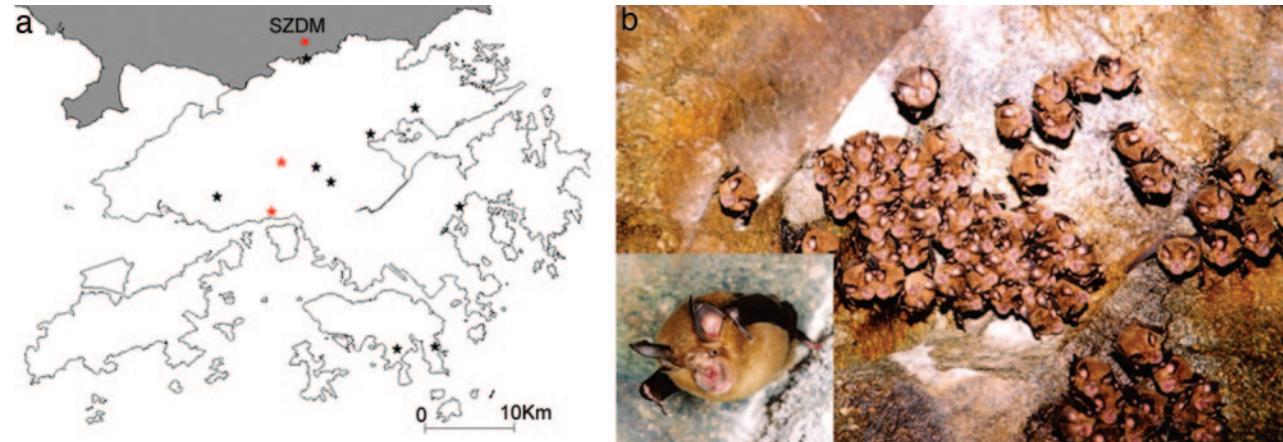
## Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats

Susanna K. P. Lau<sup>\*†‡§</sup>, Patrick C. Y. Woo<sup>\*†‡§</sup>, Kenneth S. M. Li\*, Yi Huang\*, Hoi-Wah Tsoi\*, Beatrice H. L. Wong\*, Samson S. Y. Wong<sup>\*†‡</sup>, Suet-Yi Leung<sup>¶</sup>, Kwok-Hung Chan\*, and Kwok-Yung Yuen<sup>\*†‡§||</sup>

<sup>\*</sup>Department of Microbiology, <sup>†</sup>Research Centre of Infection and Immunology, <sup>‡</sup>State Key Laboratory of Emerging Infectious Diseases, and

<sup>¶</sup>Department of Pathology, University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong Special Administrative Region, China

Research from 2005



# SARS-CoV-2 emergence “shouldn’t” surprise us



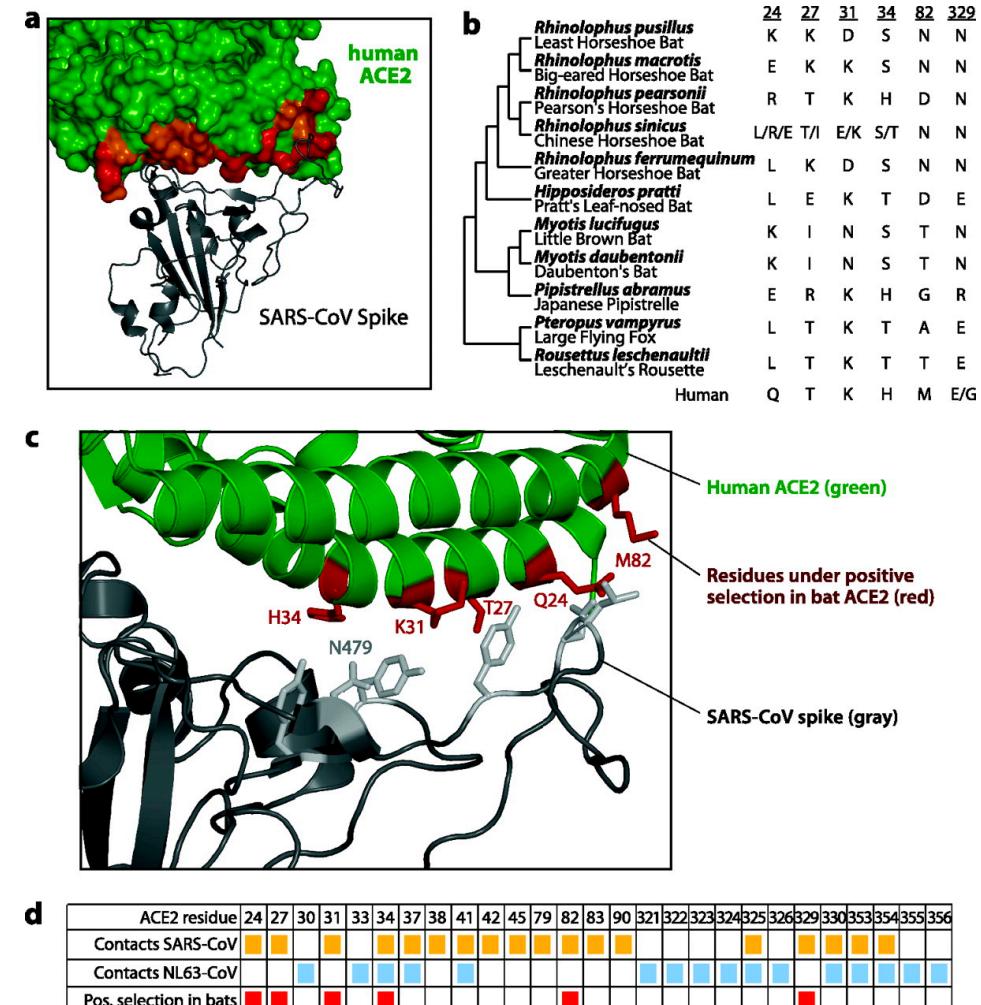
## Evidence for ACE2-Utilizing Coronaviruses (CoVs) Related to Severe Acute Respiratory Syndrome CoV in Bats

Ann Demogines,<sup>a</sup> Michael Farzan,<sup>b</sup> and Sara L. Sawyer<sup>a</sup>

Department of Molecular Genetics and Microbiology, Institute for Cellular and Molecular Biology, University of Texas at Austin, Austin, Texas, USA;<sup>a</sup> and Department of Microbiology and Immunobiology, Harvard Medical School, New England Primate Research Center, Southborough, Massachusetts, USA<sup>b</sup>

In 2002, severe acute respiratory syndrome (SARS)-coronavirus (CoV) appeared as a novel human virus with high similarity to bat coronaviruses. However, while SARS-CoV uses the human angiotensin-converting enzyme 2 (ACE2) receptor for cellular entry, no coronavirus isolated from bats appears to use ACE2. Here we show that signatures of recurrent positive selection in the bat ACE2 gene map almost perfectly to known SARS-CoV interaction surfaces. Our data indicate that ACE2 utilization preceded the emergence of SARS-CoV-like viruses from bats.

Research from 2012



# SARS-CoV-2 emergence “shouldn’t” surprise us

LETTER

Research from 2013

doi:10.1038/nature12711

## Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor

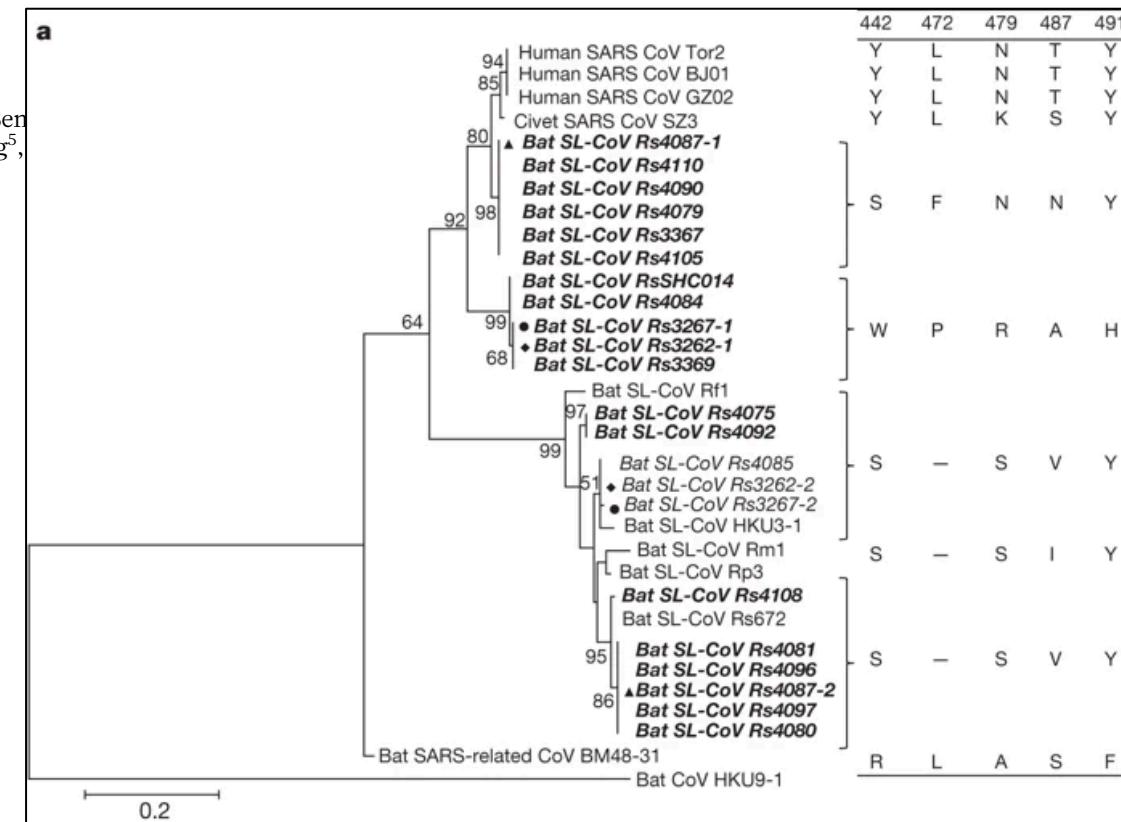
Xing-Yi Ge<sup>1\*</sup>, Jia-Lu Li<sup>1\*</sup>, Xing-Lou Yang<sup>1\*</sup>, Aleksei A. Chmura<sup>2</sup>, Guangjian Zhu<sup>2</sup>, Jonathan H. Epstein<sup>2</sup>, Jonna K. Mazet<sup>3</sup>, Ben Wei Zhang<sup>1</sup>, Cheng Peng<sup>1</sup>, Yu-Ji Zhang<sup>1</sup>, Chu-Ming Luo<sup>1</sup>, Bing Tan<sup>1</sup>, Ning Wang<sup>1</sup>, Yan Zhu<sup>1</sup>, Gary Crameri<sup>4</sup>, Shu-Yi Zhang<sup>5</sup>, Lin-Fa Wang<sup>4,6</sup>, Peter Daszak<sup>2</sup> & Zheng-Li Shi<sup>1</sup>

### Editorial Summary

#### A SARS-like virus in bats

Peter Daszak and colleagues identify two novel coronaviruses from Chinese horseshoe bats that are closely related to severe acute respiratory syndrome coronavirus (SARS-CoV), the cause of a pandemic during 2002 and 2003.

They also isolate a live virus from these bats that has high sequence identity to SARS-CoV and that can infect human cells using ACE2, the same receptor that is used by SARS-CoV. The results provide the strongest evidence to date that horseshoe bats are natural reservoirs of SARS-CoV.



# SARS-CoV-2 emergence “shouldn’t” surprise us

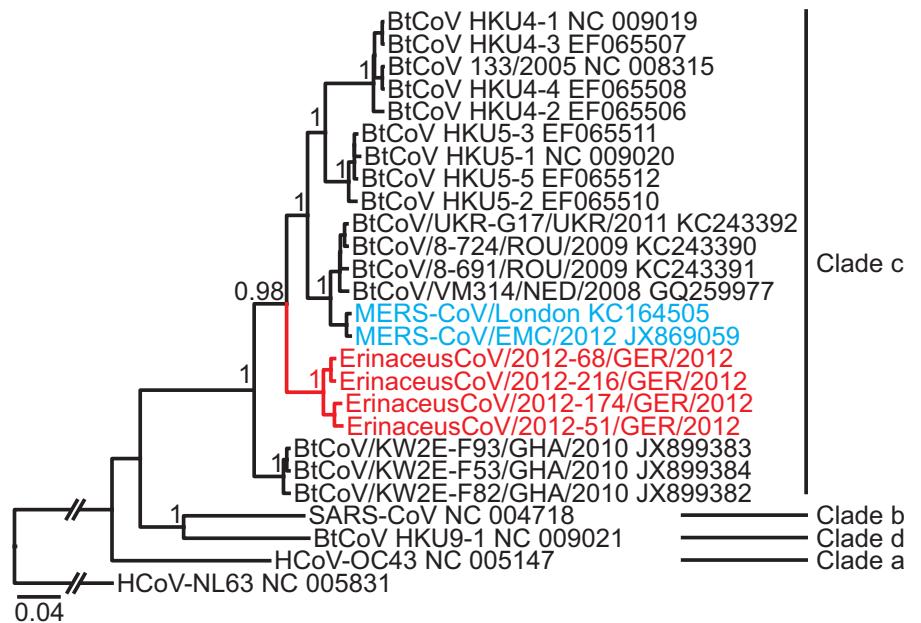


## Characterization of a Novel Betacoronavirus Related to Middle East Respiratory Syndrome Coronavirus in European Hedgehogs

Victor Max Corman,<sup>a</sup> René Kallies,<sup>a</sup> Heike Philippss,<sup>b</sup> Gertraude Göpner,<sup>b</sup> Marcel Alexander Müller,<sup>a</sup> Isabella Eckerle,<sup>a</sup> Sebastian Brünink,<sup>a</sup> Christian Drosten,<sup>a</sup> Jan Felix Drexler<sup>a</sup>

Institute of Virology, University of Bonn Medical Centre, Bonn, Germany<sup>a</sup>; Igel-Schutz-Initiative e.V., Laatzen, Germany<sup>b</sup>

Research from 2014



**FIG 1** Betacoronavirus phylogeny, including the novel viruses from European hedgehogs. Bayesian phylogeny of an 816-nucleotide RdRp gene sequence fragment corresponding to positions 14822 to 15637 in MERS-CoV strain EMC/2012 (GenBank accession no. [JX869059](#)). The novel *Erinaceus* viruses are shown in red, and MERS-CoVs in blue.

# SARS-CoV-2 emergence “shouldn’t” surprise us

LETTERS

Research from 2015

A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence

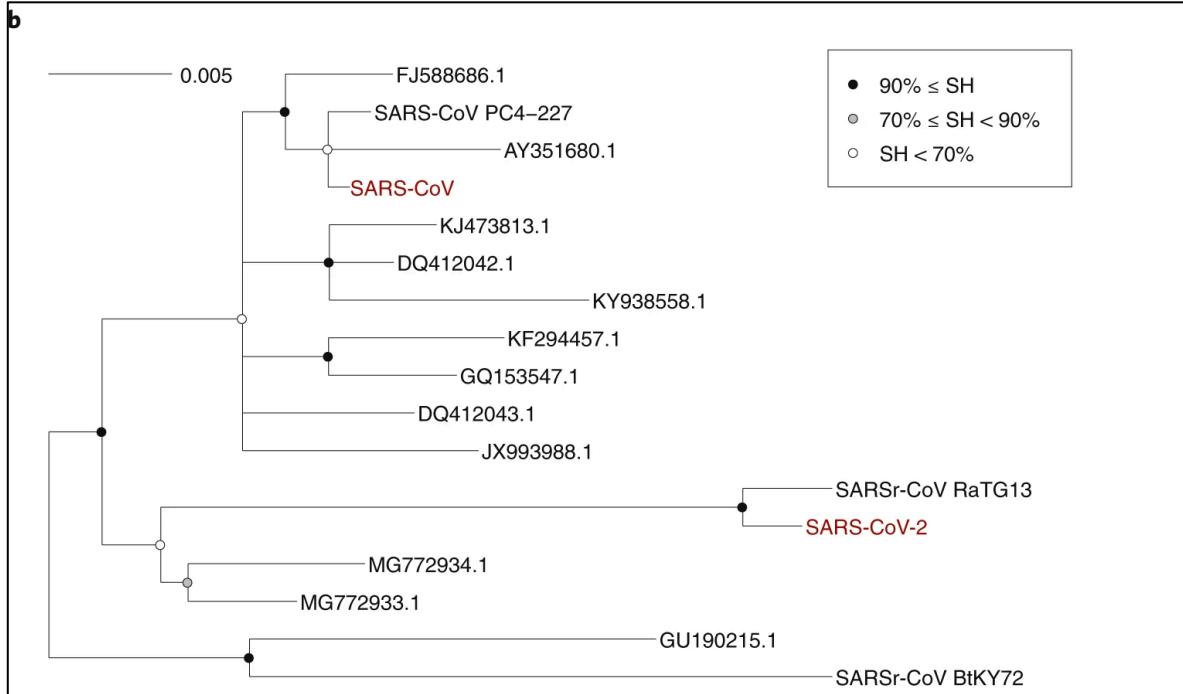
Vineet D Menachery<sup>1</sup>, Boyd L Yount Jr<sup>1</sup>, Kari Debbink<sup>1,2</sup>, Sudhakar Agnihothram<sup>3</sup>, Lisa E Gralinski<sup>1</sup>, Jessica A Plante<sup>1</sup>, Rachel L Graham<sup>1</sup>, Trevor Scobey<sup>1</sup>, Xing-Yi Ge<sup>4</sup>, Eric F Donaldson<sup>1</sup>, Scott H Randell<sup>5,6</sup>, Antonio Lanzavecchia<sup>7</sup>, Wayne A Marasco<sup>8,9</sup>, Zhengli-Li Shi<sup>4</sup> & Ralph S Baric<sup>1,2</sup>

“The results indicate that group 2b viruses encoding the SHC014 spike in a wild-type backbone can efficiently use multiple orthologs of the SARS receptor human angiotensin converting enzyme II (ACE2), replicate efficiently in primary human airway cells and achieve *in vitro* titers equivalent to epidemic strains of SARS-CoV.”

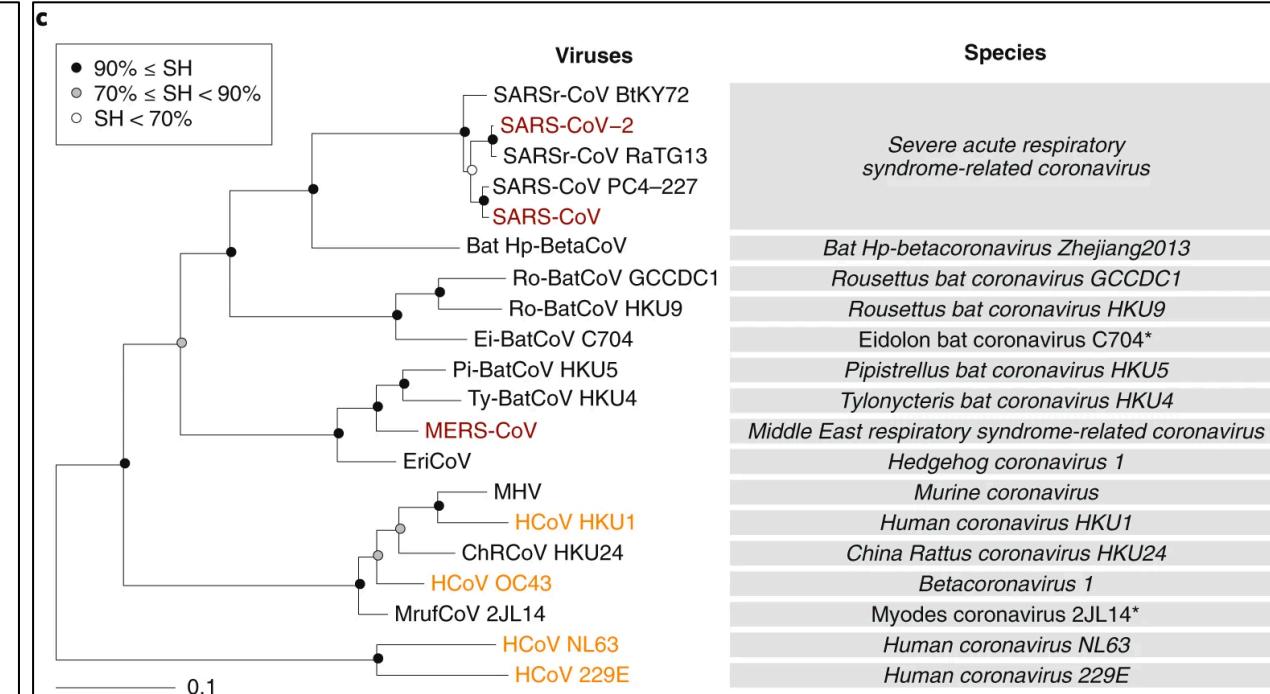
**Translation: Bat coronaviruses are “out there” that can, by chance, ALREADY infect humans. They just haven’t done so \*yet\*.**

# Phylogenetics identifies origins of SARS-CoV2

SARS-CoV and SARS-CoV2 with other bat SARS-like viruses



Betacoronaviruses and alphacoronavirus outgroup



CONSENSUS STATEMENT

<https://doi.org/10.1038/s41564-020-0695-z>

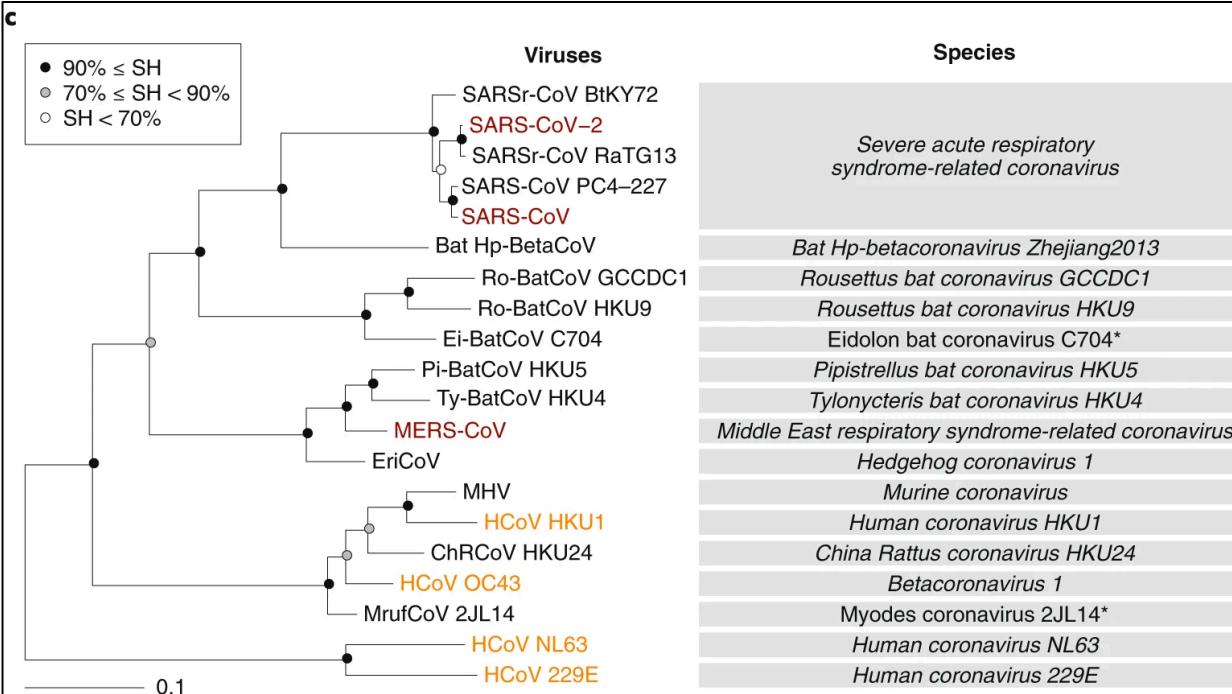
nature  
microbiology

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OPEN

The species *Severe acute respiratory syndrome-related coronavirus*: classifying 2019-nCoV and naming it SARS-CoV-2

# Studying PRECISE origins requires LOTS of sampling



*Rhinolophus affinis*

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**bioRxiv**  
THE PREPRINT SERVER FOR BIOLOGY

bioRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary and should not be regarded as conclusive, guide clinical practice/health-related behavior, or be reported in news media.

New Results

**Synonymous mutations and the molecular evolution of SARS-CoV-2 origins**

Rasmus Nielsen, Hongru Wang, Lenore Pipes

doi: <https://doi.org/10.1101/2020.04.20.052019>

This article is a preprint and has not been certified by peer review [what does this mean?].

**Abstract** Info/History Metrics Preview PDF

Most recent common ancestor:

RaTG13 - SARS-CoV-2: ~57 years

- ~96% sequence identity overall
- ~93% identity in Spike gene

bioRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary reports that have not undergone peer review. They should not be regarded as conclusive, guide clinical practice/health-related behavior, or be reported in news media as verified information.

## New Results

**A novel bat coronavirus reveals natural insertions at the S1/S2 cleavage site of the Spike protein and a possible recombinant origin of HCoV-19**

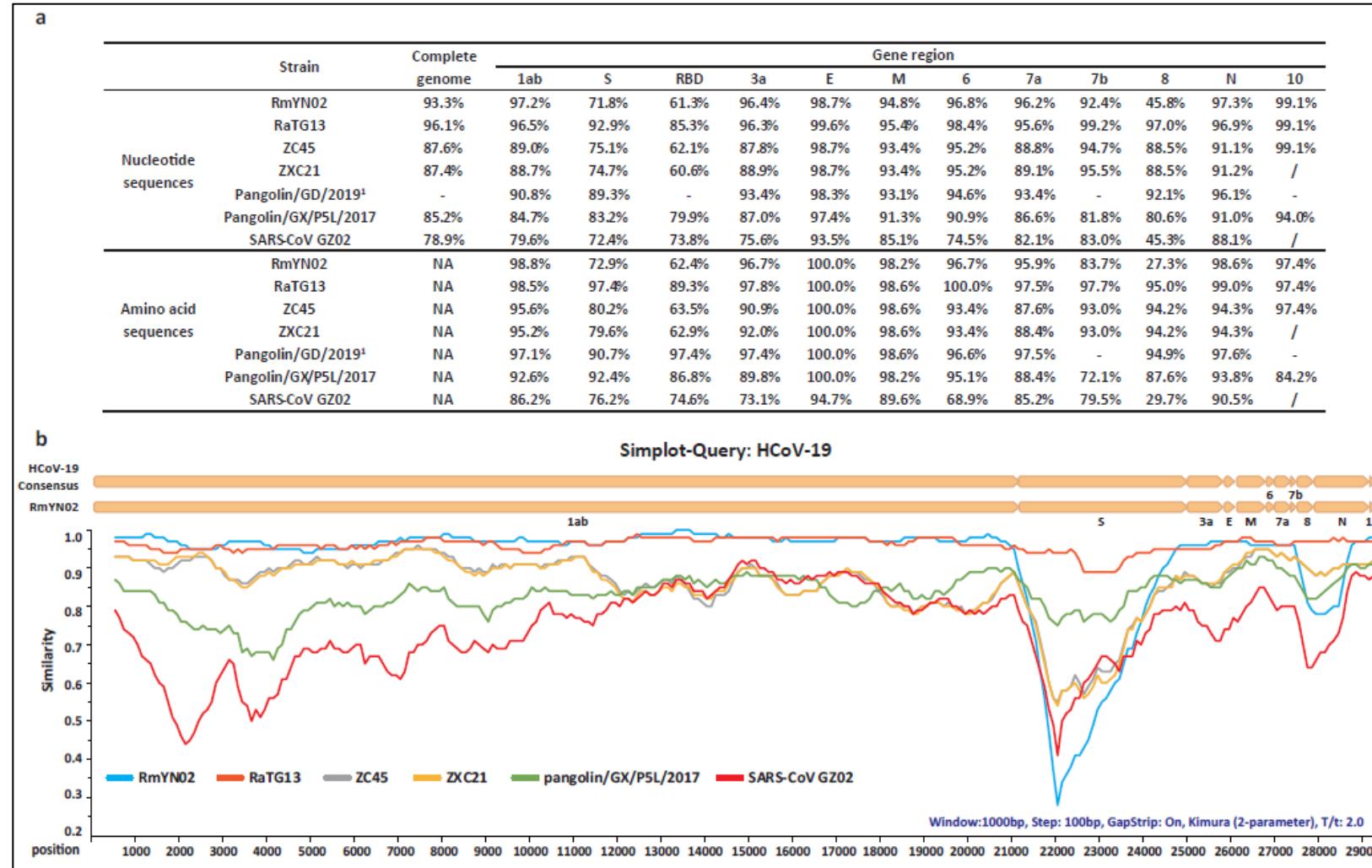
Hong Zhou, Xing Chen, Tao Hu, Juan Li, Hao Song, Yanran Liu, Peihan Wang, Di Liu, Jing Yang, Edward C. Holmes, Alice C. Hughes, Yuhai Bi, Weifeng Shi

doi: <https://doi.org/10.1101/2020.03.02.974139>

This article is a preprint and has not been certified by peer review [what does this mean?].

“Between May and October 2019, we collected a total of 302 samples from 227 bats from Mengla County, Yunnan Province in southern China. These bats belonged to 20 different species....

The samples comprised multiple tissues, including patagium ( $n=219$ ), lung ( $n=2$ ) and liver ( $n=3$ ), and feces ( $n=78$ ).”



Study on last slide estimates 37 year divergence since RmYN02.

# Lots of recombination in the sarbecoviruses

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New Results

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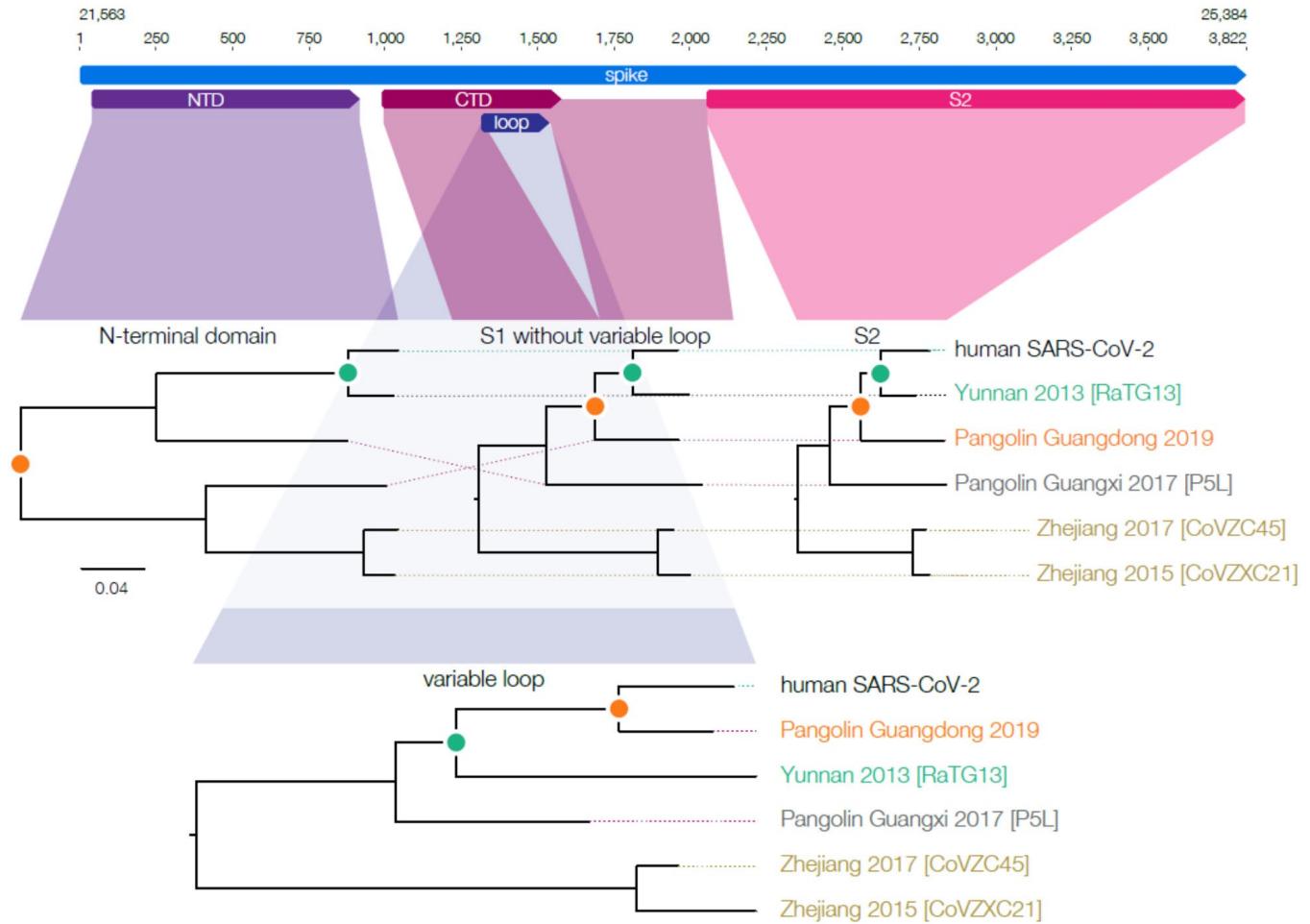
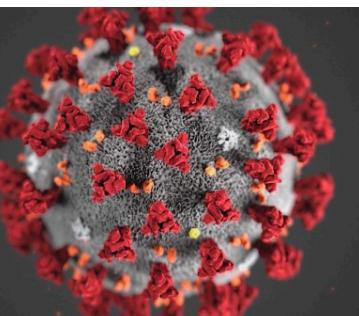
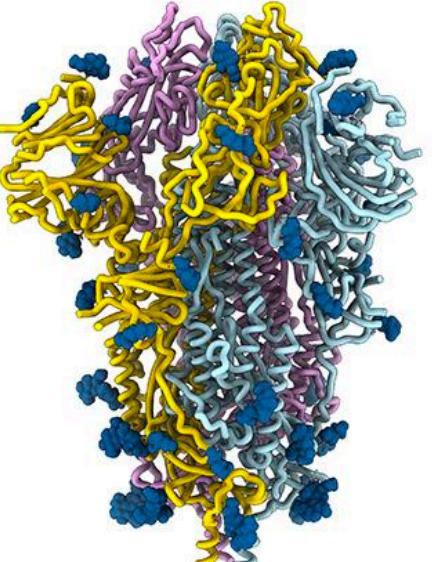
**Evolutionary origins of the SARS-CoV-2 sarbecovirus lineage responsible for the COVID-19 pandemic**

Maciej F Boni, Philippe Lemey, Xiaowei Jiang, Tommy Tsan-Yuk Lam, Blair Perry, Todd Castoe, Andrew Rambaut, David L Robertson

doi: <https://doi.org/10.1101/2020.03.30.015008>

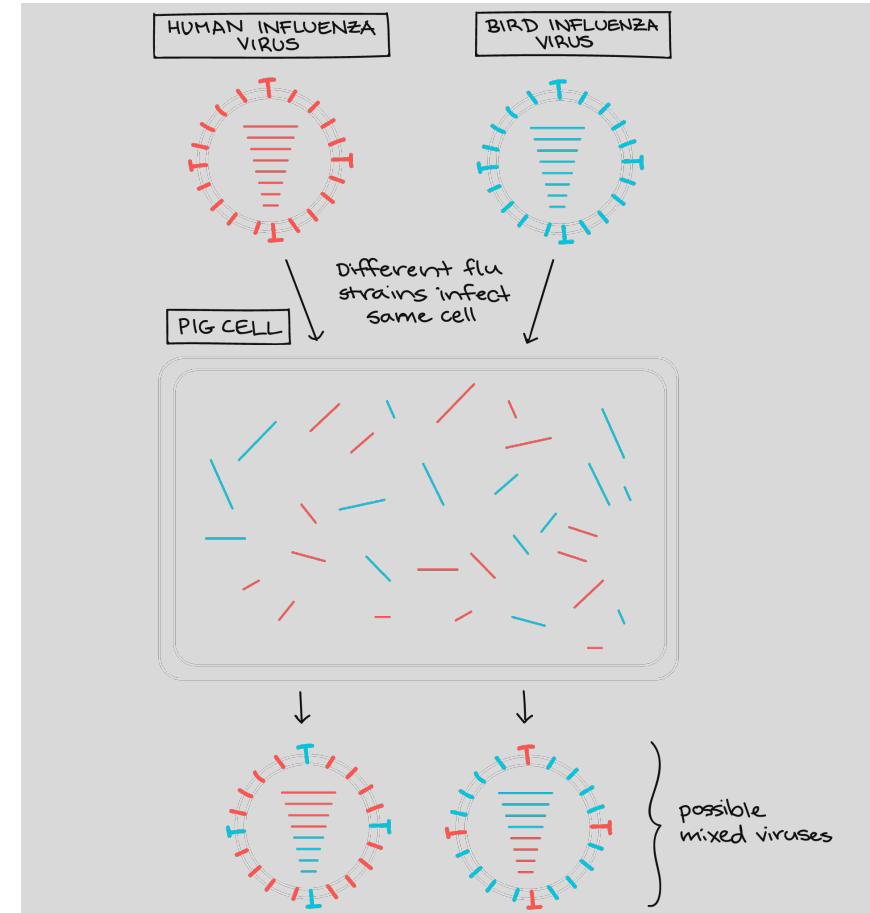
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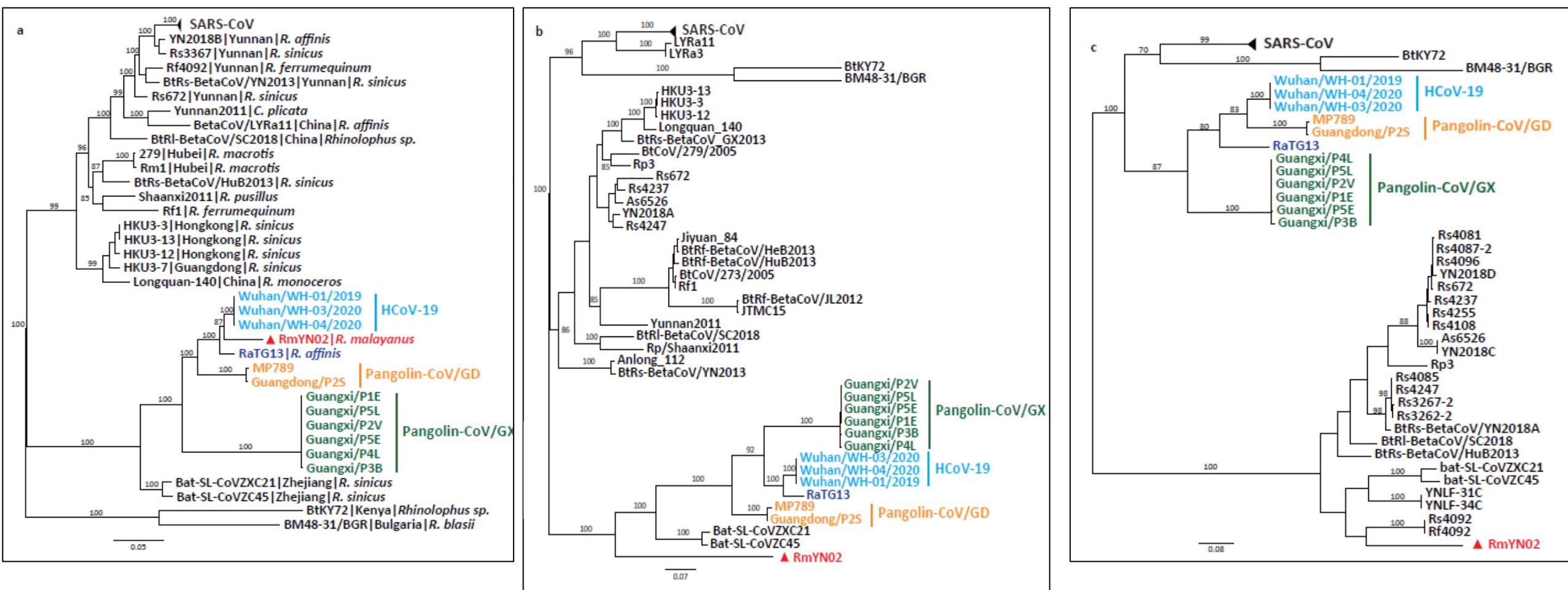
**Abstract** Full Text Info/History Metrics [Preview PDF](#)



# Virus recombination (influenza-specific image)

- Leads to DIFFERENT phylogenies across regions of the genome





a) Phylogenetic tree of the full-length virus genome. (b) the S gene. (c) the RBD.

New mutations are not leading to new strains.  
New mutations are not leading to new strains.



# Phylogeographic analysis of the current outbreak



bioRxiv is receiving many new papers on coronavirus SARS-CoV-2. A reminder: these are preliminary reports that have not been peer-reviewed, practice/health-related behavior, or be reported in news media as established information.

New Results

[Comment on this paper](#)

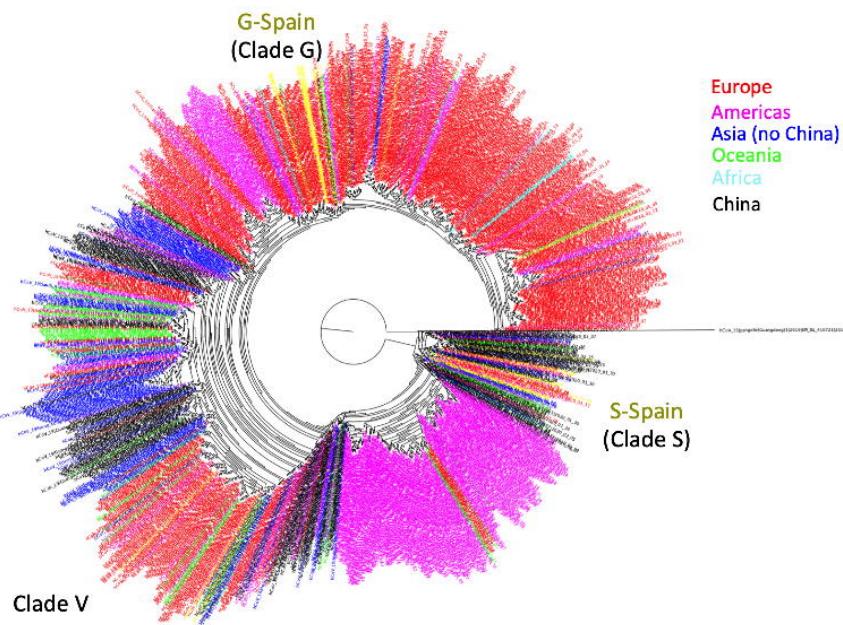
## Phylodynamics of SARS-CoV-2 transmission in Spain

Francisco Díez Fuertes, María Iglesias Caballero, Sara Monzón, Pilar Jiménez, Sarai Varona, Isabel Cuesta, Ángel Zaballos, Michael M. Thomson, Mercedes Jiménez, Javier García Pérez, Francisco Pozo, Mayte Pérez Olmeda, José Alcamí, Inmaculada Casas

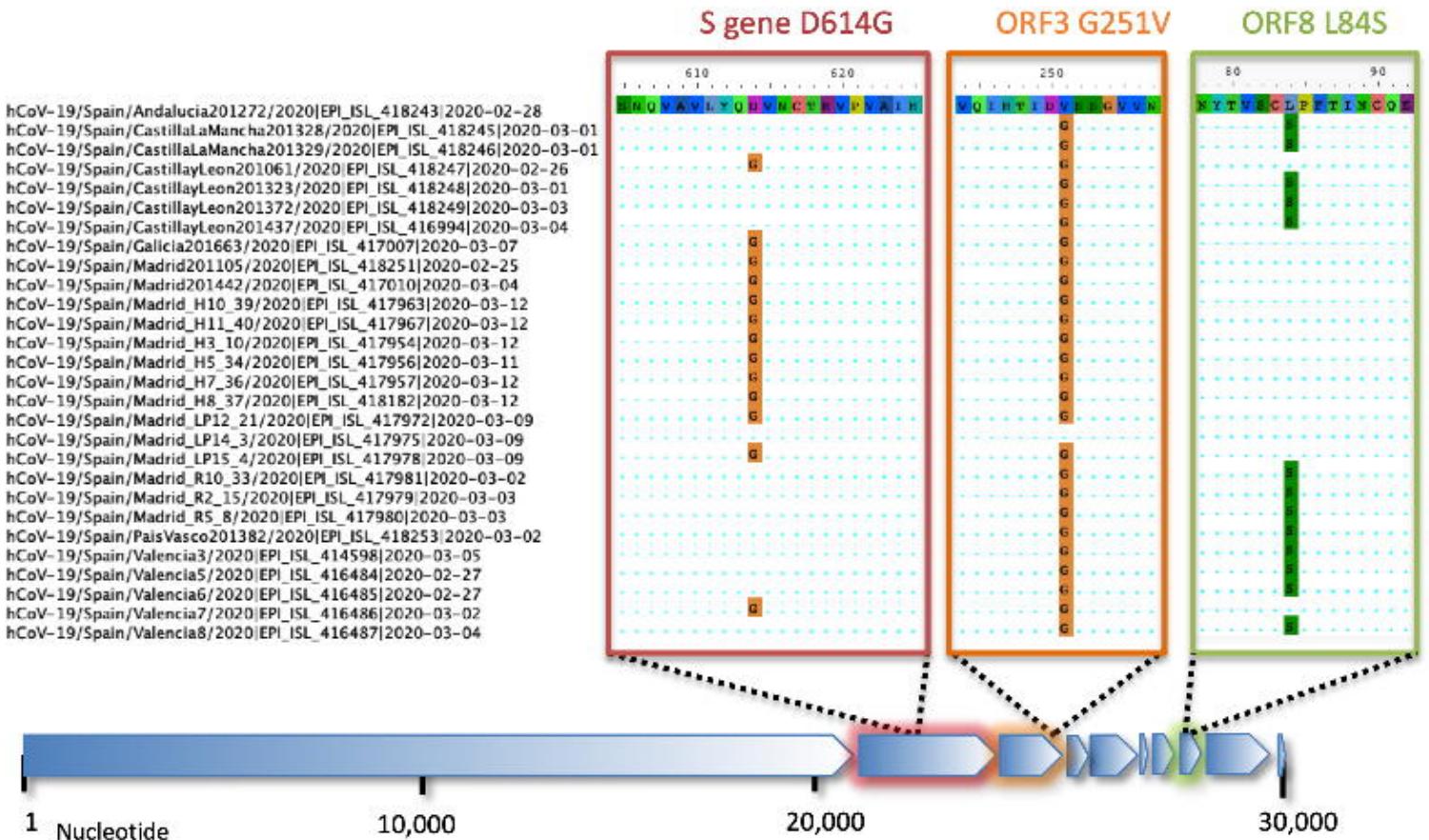
doi: <https://doi.org/10.1101/2020.04.20.050039>

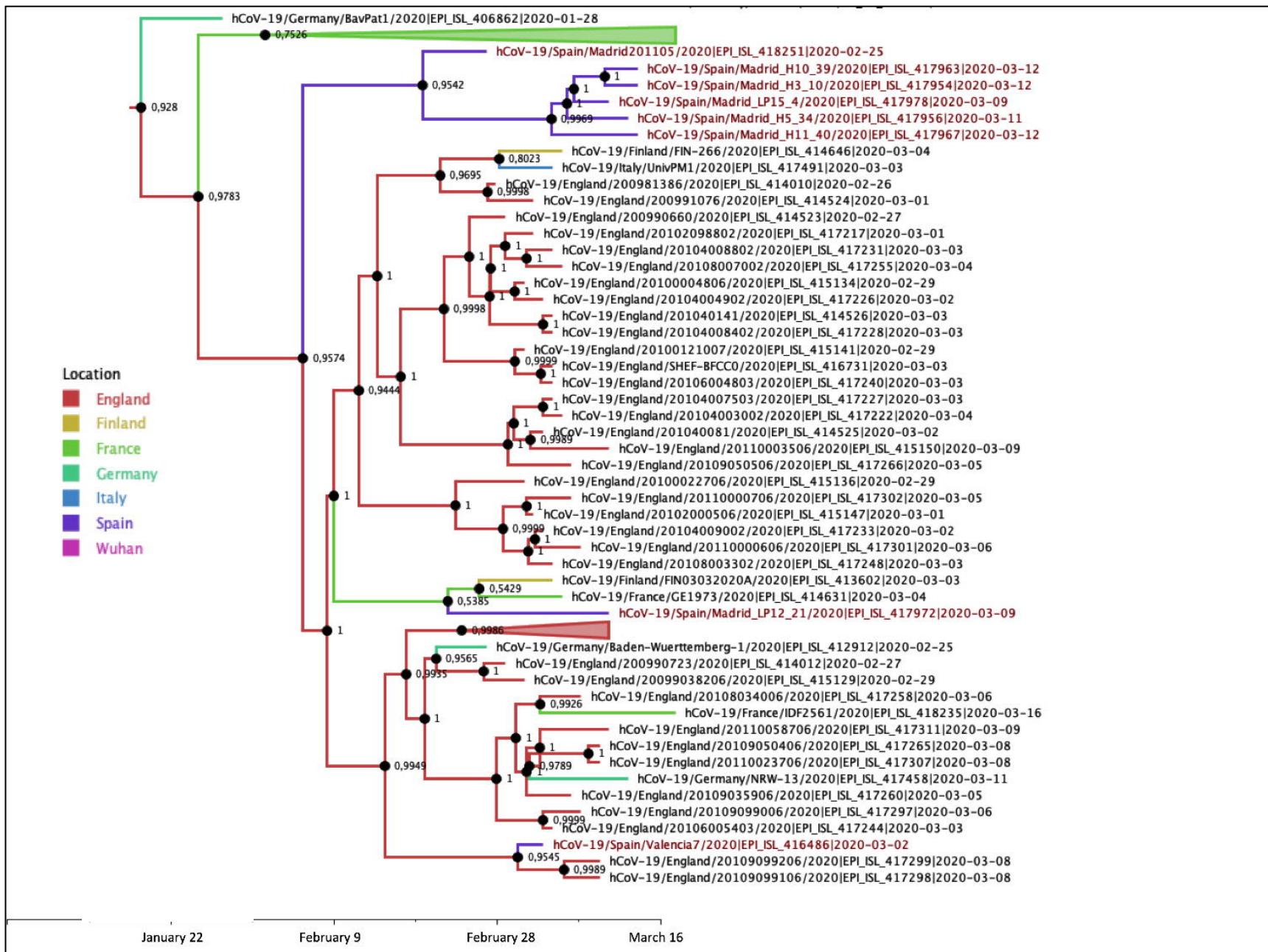
This article is a preprint and has not been certified by peer review [what does this mean?].

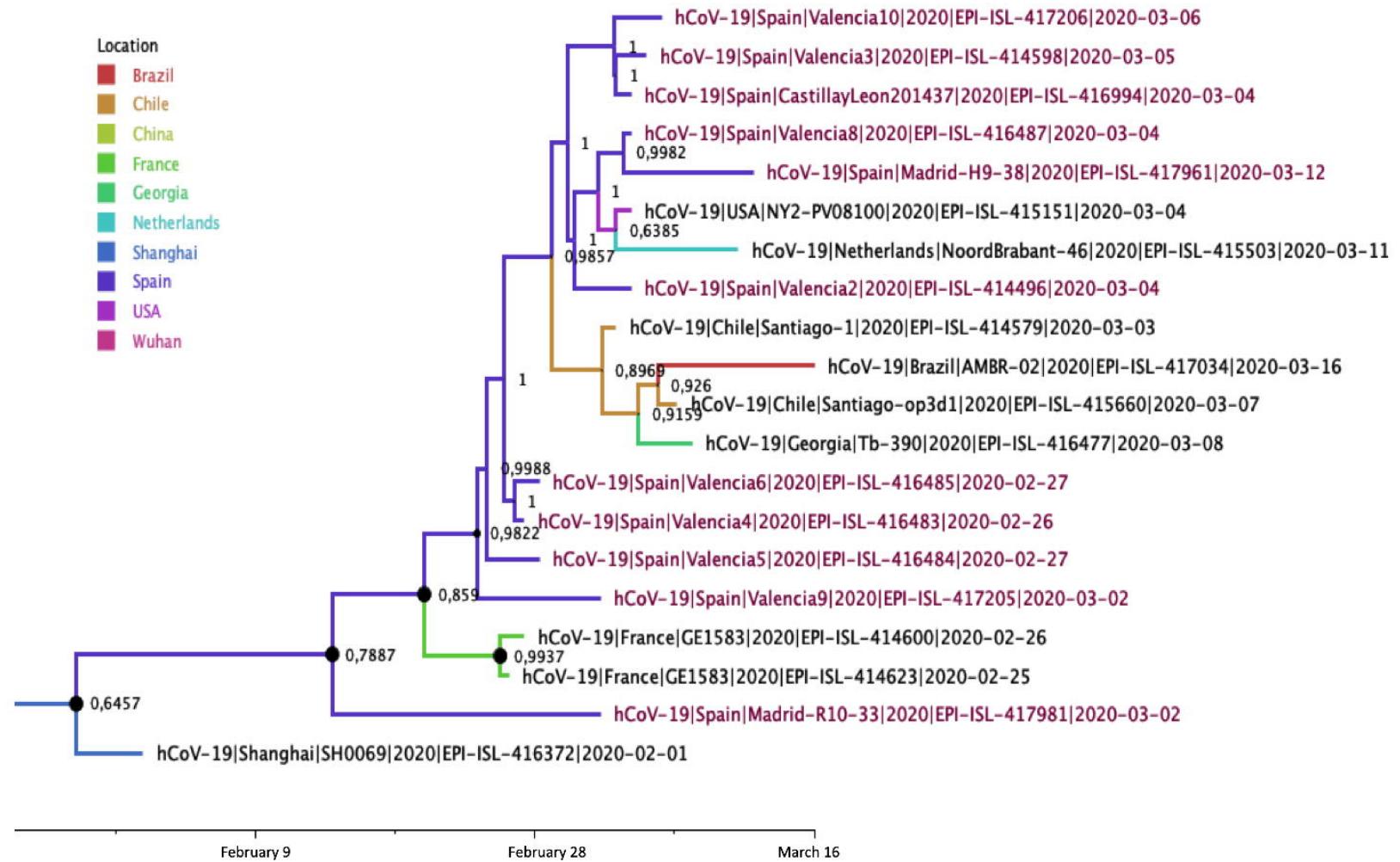
<https://www.biorxiv.org/content/10.1101/2020.04.20.050039v1>



hCoV-19/Spain/Andalucia201272/2020|EPI\_ISL\_418243|2020-02-28  
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hCoV-19/Spain/CastillaLaMancha201329/2020|EPI\_ISL\_418246|2020-03-01  
hCoV-19/Spain/CastillaLeon201061/2020|EPI\_ISL\_418247|2020-02-26  
hCoV-19/Spain/CastillaLeon201323/2020|EPI\_ISL\_418248|2020-03-01  
hCoV-19/Spain/CastillaLeon201372/2020|EPI\_ISL\_418249|2020-03-03  
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hCoV-19/Spain/Valencia8/2020|EPI\_ISL\_416487|2020-03-04







# Follow me now to nextstrain.org !

- <https://twitter.com/nextstrain/status/1253051831426723841?s=12>

Recommended follows on twitter (a **very** limited and kind of **biased** set...)

- Me! @stephspiel
- NextStrain @nextstrain
  - Trevor Bedford @trvrb
  - Richard Neher @richardneher
  - Emma Hodcroft @firefoxx66
- Jesse Bloom @bloomlab
- Sam Scarpino @svscarpino
- Lauren Meyers' Lab @meyerslab
- Akiko Iwasaki @VirusesImmunity
- Andy Rambaut\* @arambaut
- Eddie Holmes @edwardholmes
- Oliver Pybus @EvolveDotZoo
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- Carl Zimmer @carlzimmer
- Ed Yong @edyong209
- We rate dogs @dog\_rates wait how'd this get here what's happening