

**HIV DRP Seminar Series**

**From SARS, MERS, to COVID-19,  
understanding of the interspecies transmission of  
bat coronaviruses**

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**27 April, 2020**



# Our work



- **Distribution, genetic evolution, and dynamics of bat/rodent viruses in China**
- **Pathogenesis studies of novel bat viruses**
- **Innate immune response of bat to virus infection**

# Bat virus discovered by our group

Astrovirus

Adenovirus: **6 isolates**

Adno-associated virus

Circovirus

Coronavirus: **3 isolates**

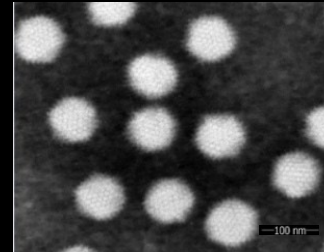
Filovirus

Hantavirus

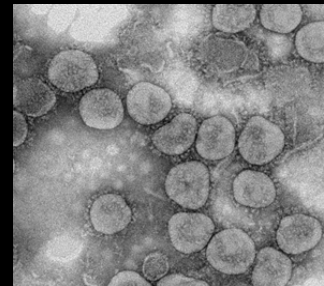
Hepadnavirus

Reovirus: **8 isolates**

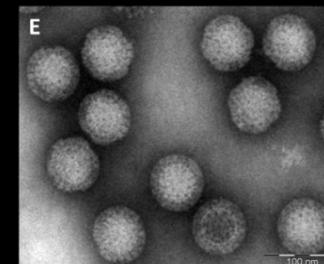
Paramyxovirus



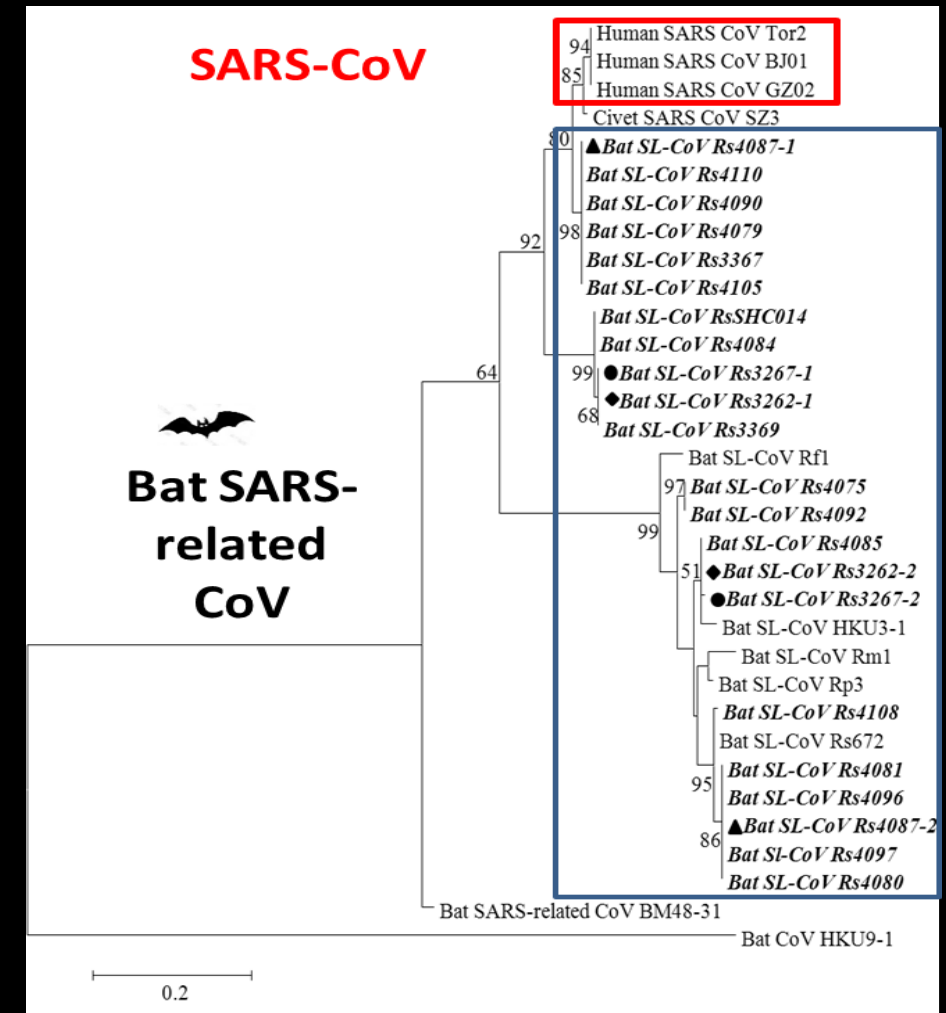
Adenovirus



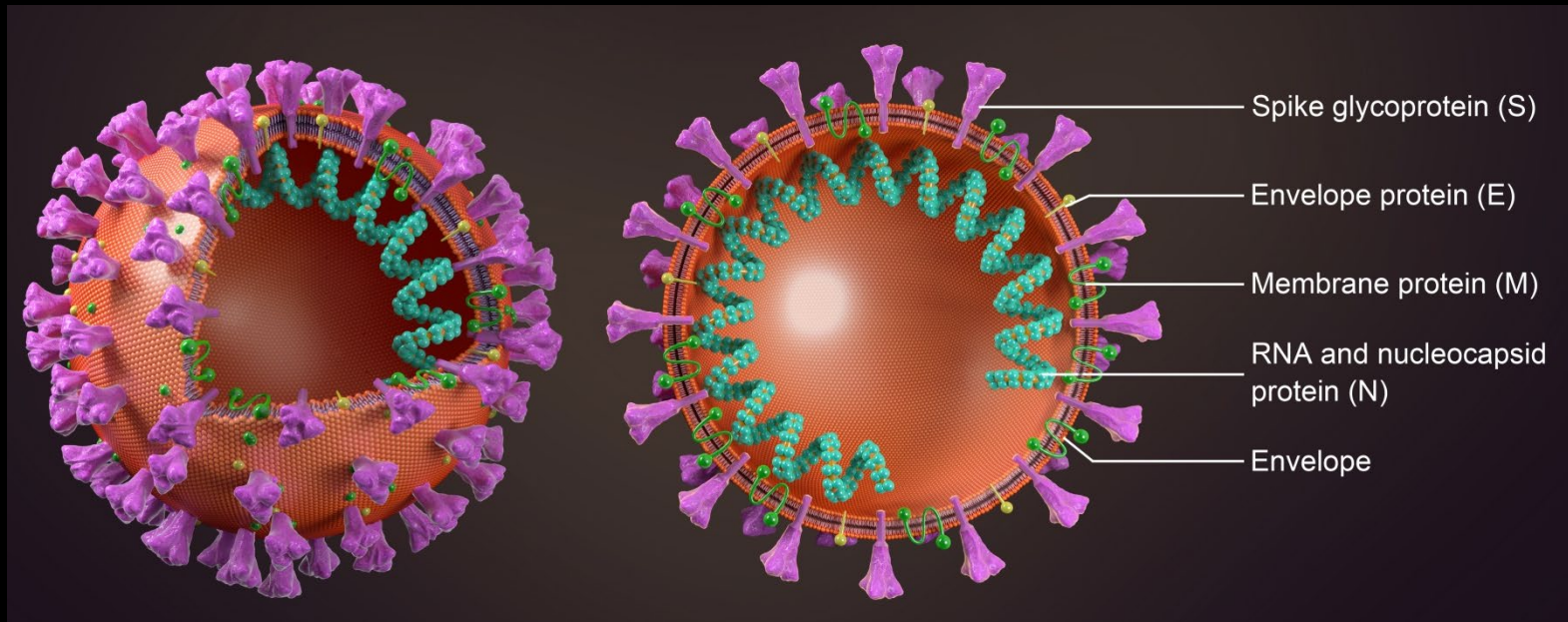
Coronavirus



Reovirus



# Coronavirus

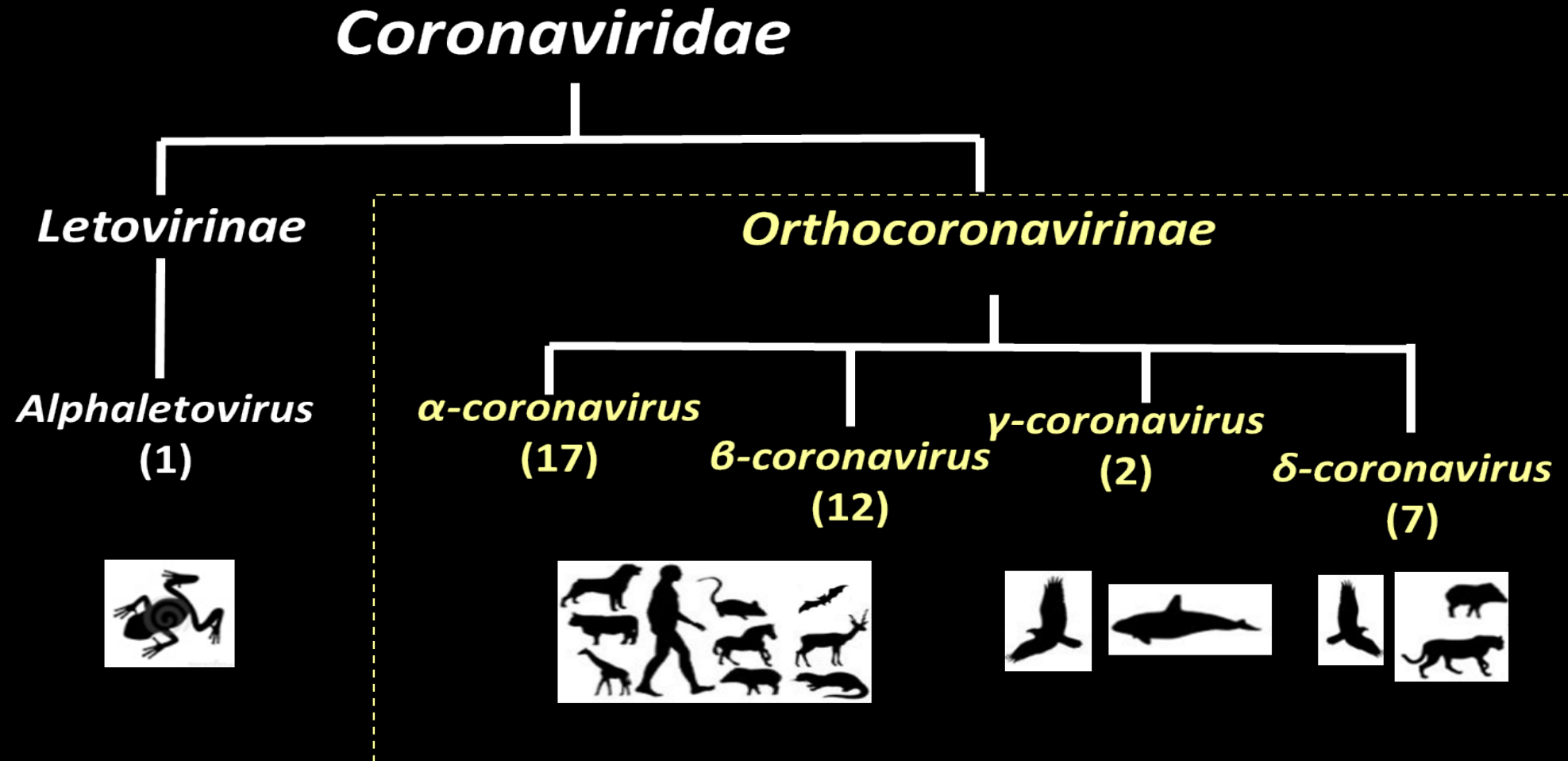


**120-140 nm**

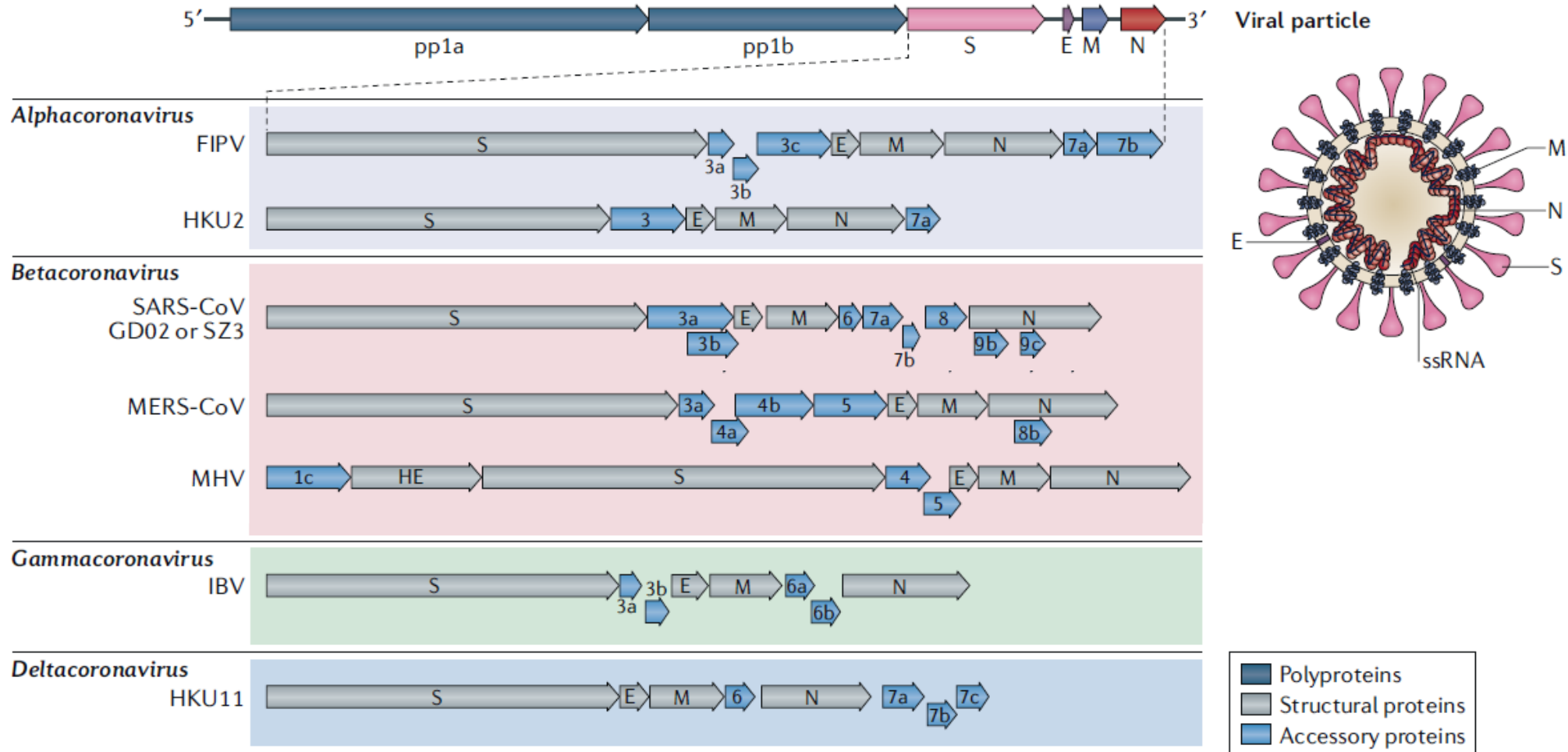
**Enveloped, single-strand, positive-sense RNA (27-32 kb)**



# Coronavirus taxonomy

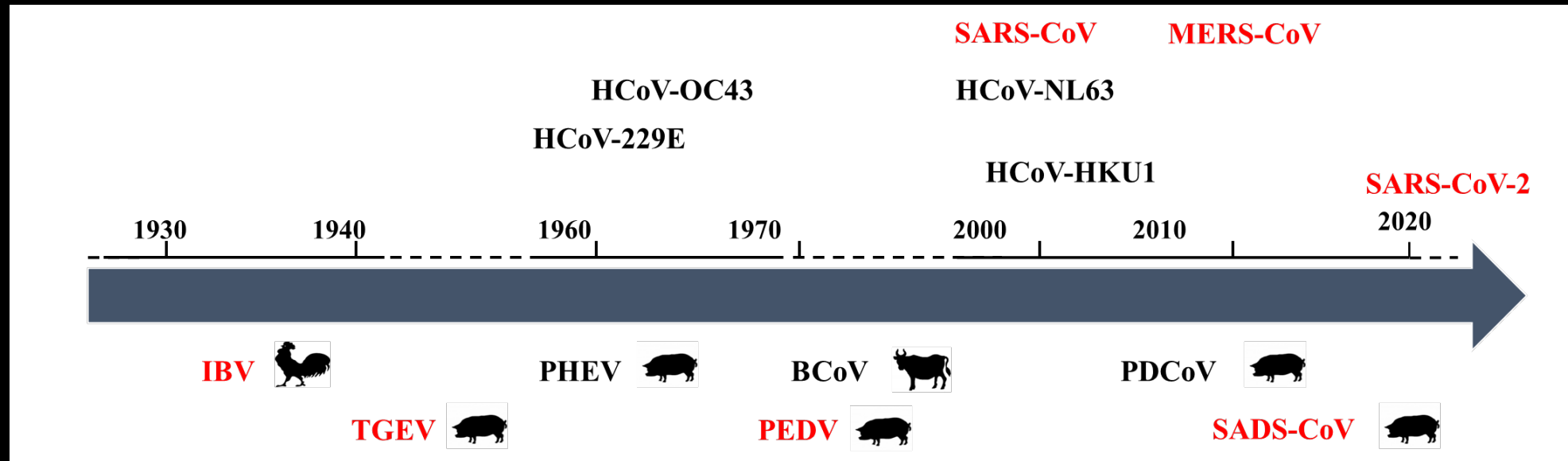


# Coronavirus genome structure



# Emerging coronavirus diseases

## Coronavirus associated with human diseases



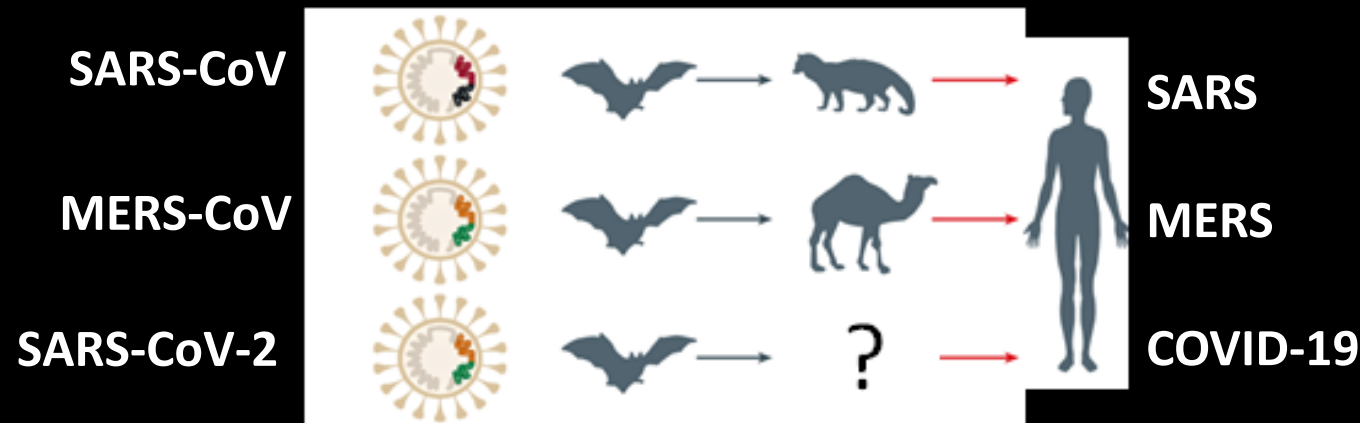
## Coronavirus associated with animal diseases

# SARS, MERS and COVID-19

**SARS/SARS-CoV:** 2002.12-2003.7, 29 countries,  
8096 cases with 774 deaths, ~10% mortality

**MERS/MERS-CoV:** 2012-2019.11, Middle East countries, 27 countries,  
2494 cases, 858 deaths, 34.4% mortality

**COVID-19/SARS-CoV-2:** > 146 million cases and >3 million deaths

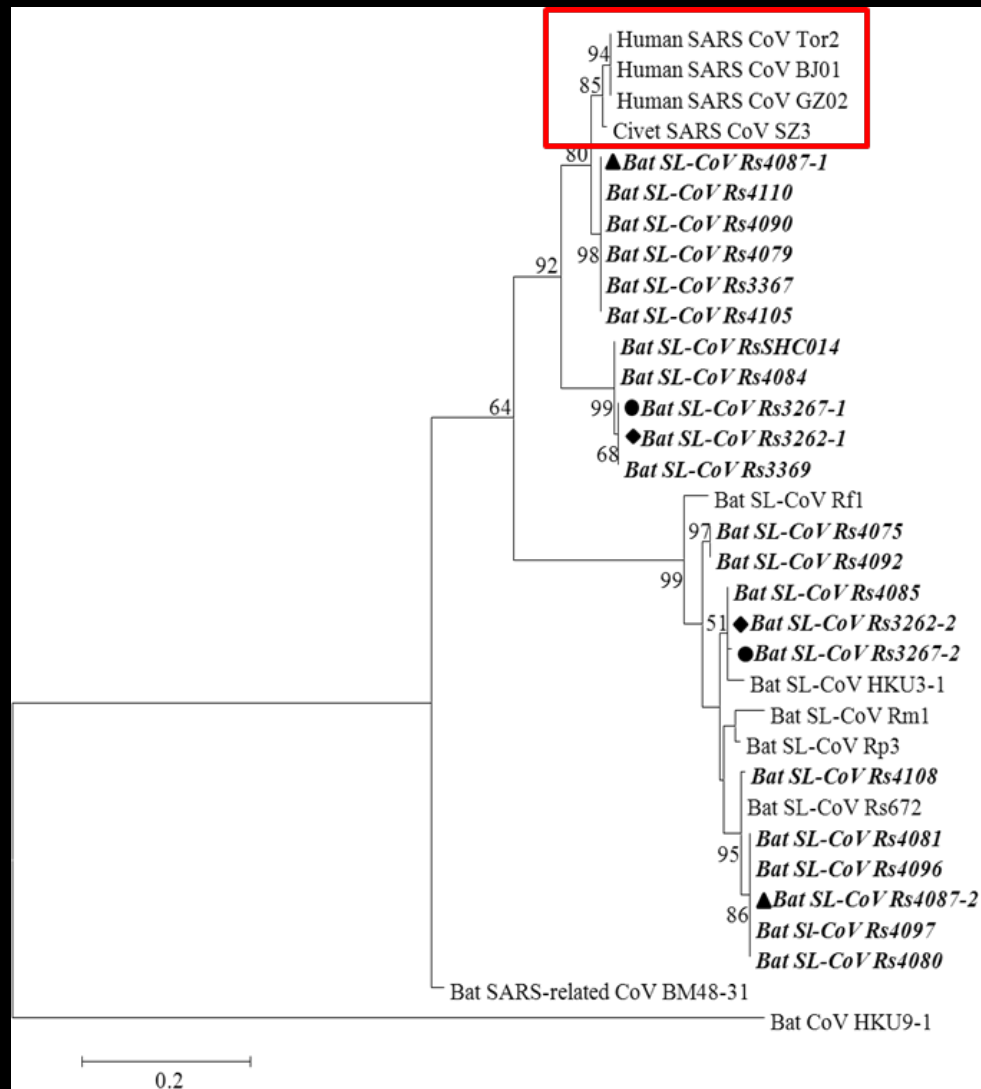


# Animal origin of SARS-CoV



Guan *et al.*, Science, 2003

# SARS-CoV closest ancestors found in bats

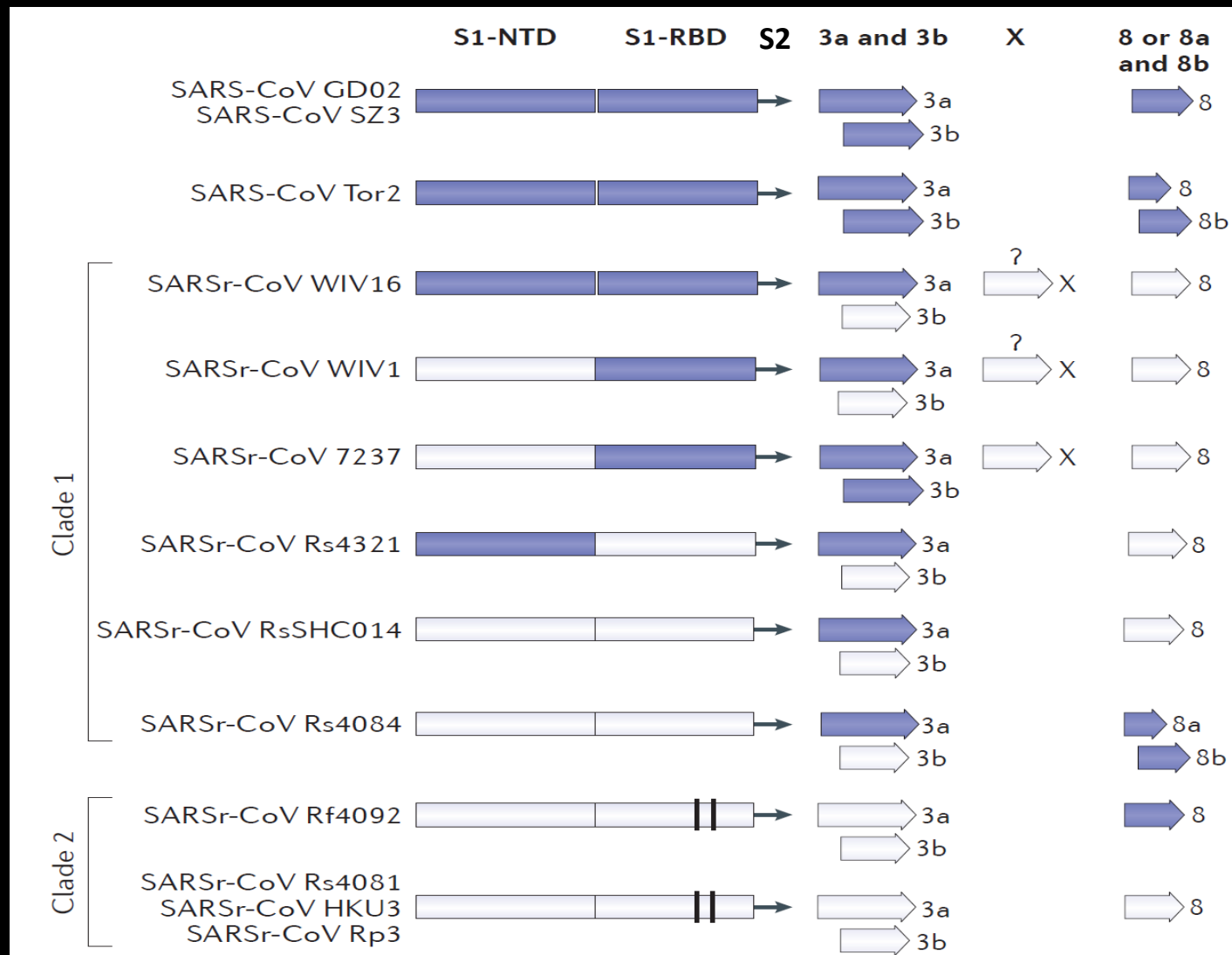


SARS-CoV

SARS-CoV ancestors  
(genome sequence identities >95%)

Bat SARSr-coV

# Major variations in bat SARS-related CoV

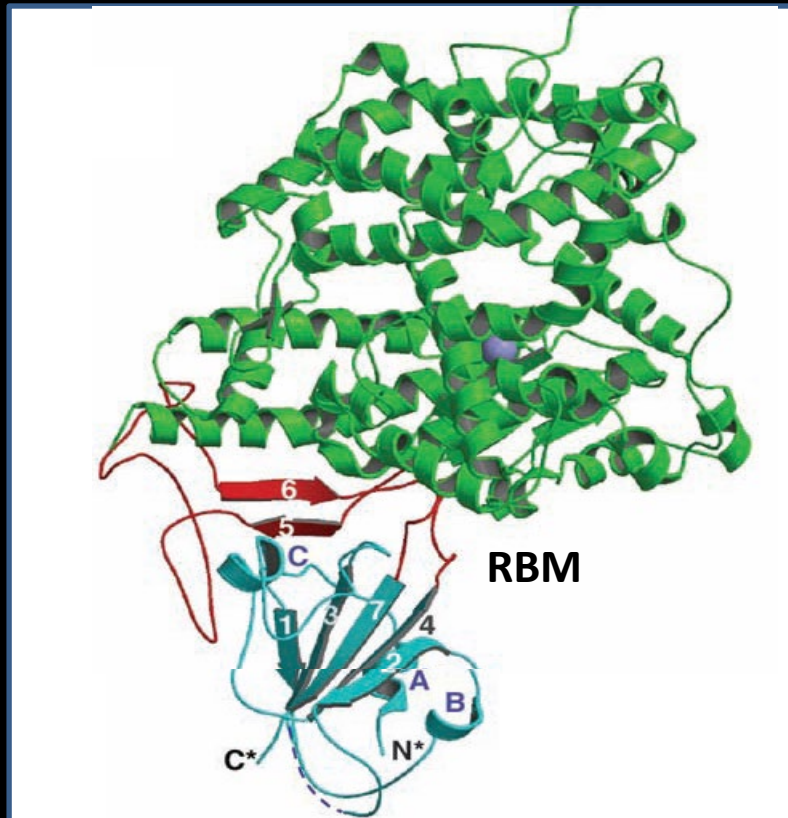


Hu et al., *PLoS Pathogens*, 2017; Cui et al., *Nat Rev Microbiol*, 2019



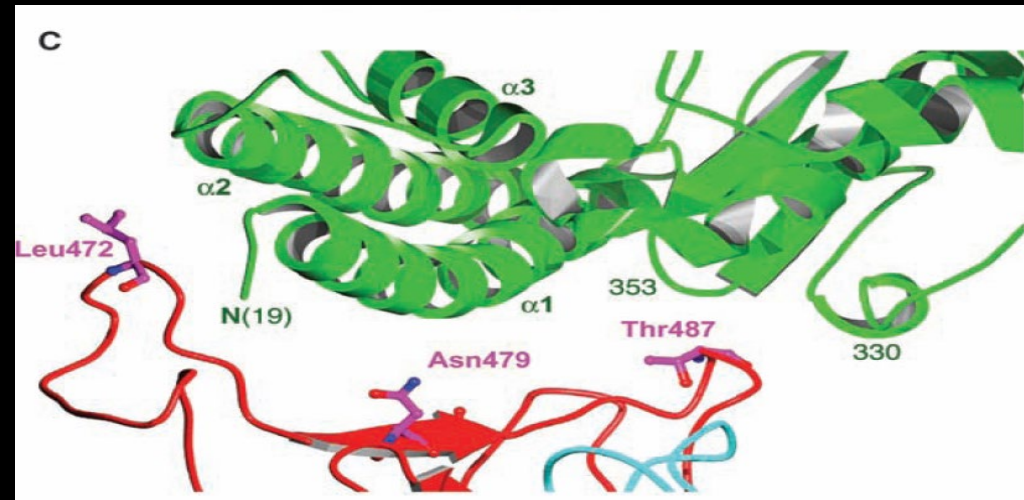
# Angiotensin converting enzyme 2 (ACE2) is a receptor for SARS-CoV

ACE2



Receptor binding domain, RBD

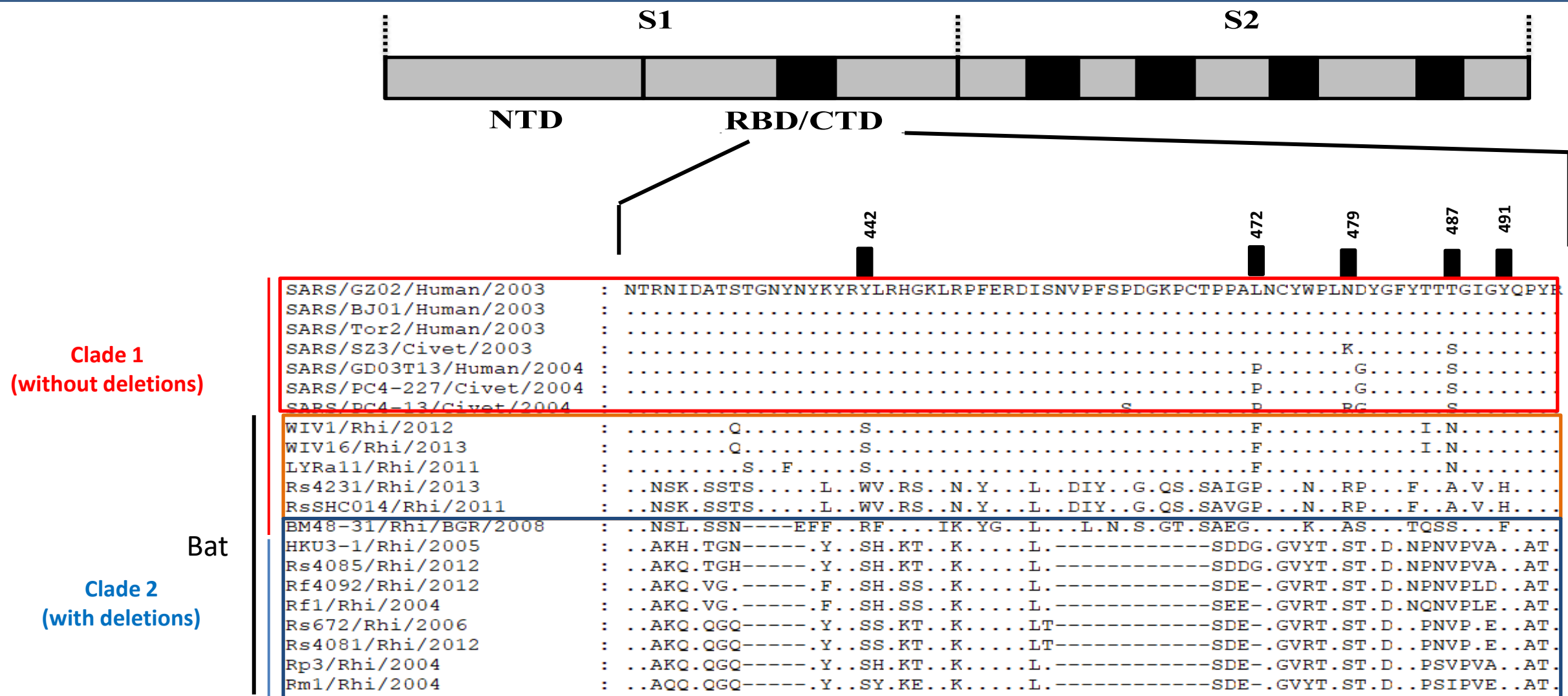
ACE2



Receptor binding motif, RBM

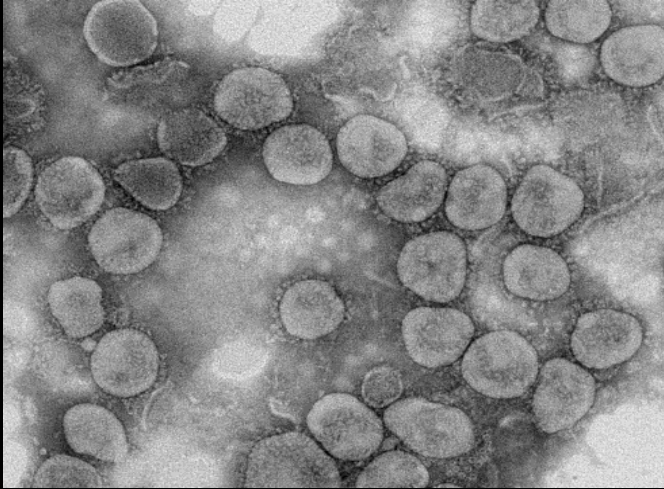
Li *et al.*, *Nature*, 2003;  
Li *et al.*, *Sciences*, 2005

# Variations in receptor binding motif of bat SARS-related CoVs

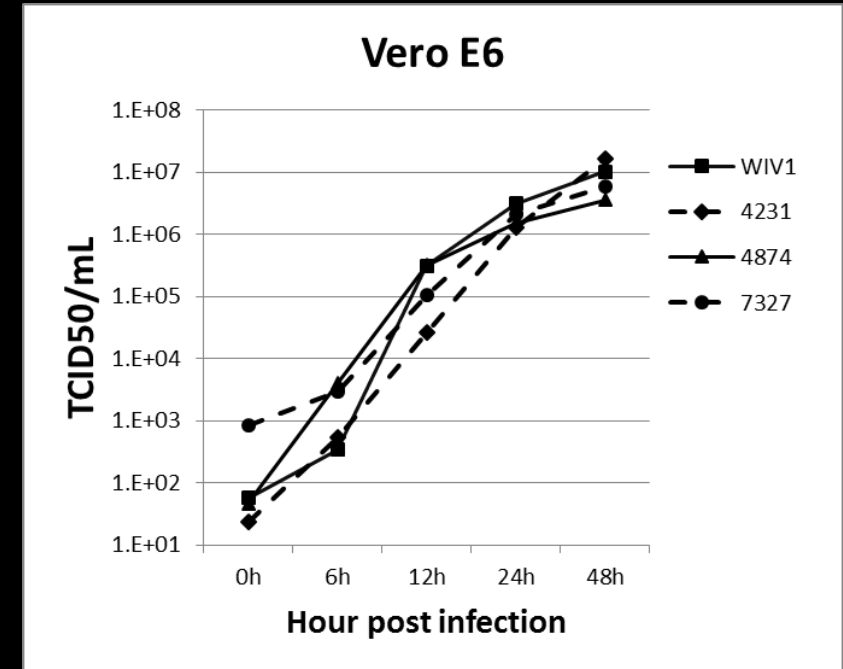
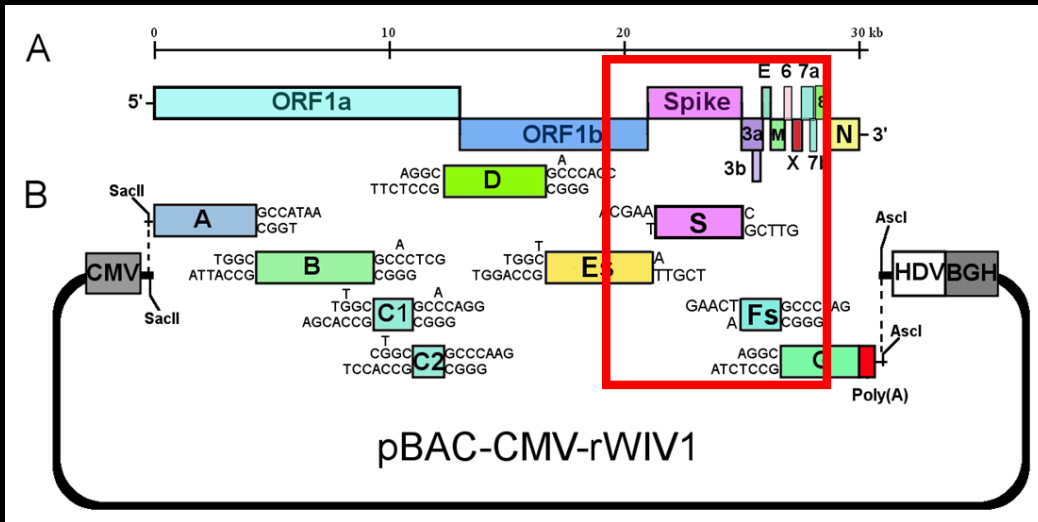
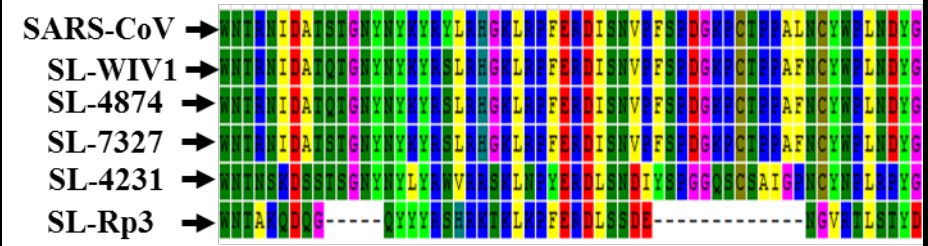


# Bat SARS-related CoV clade 1 utilises human ACE2 as receptor

WIV1, 16, 4874

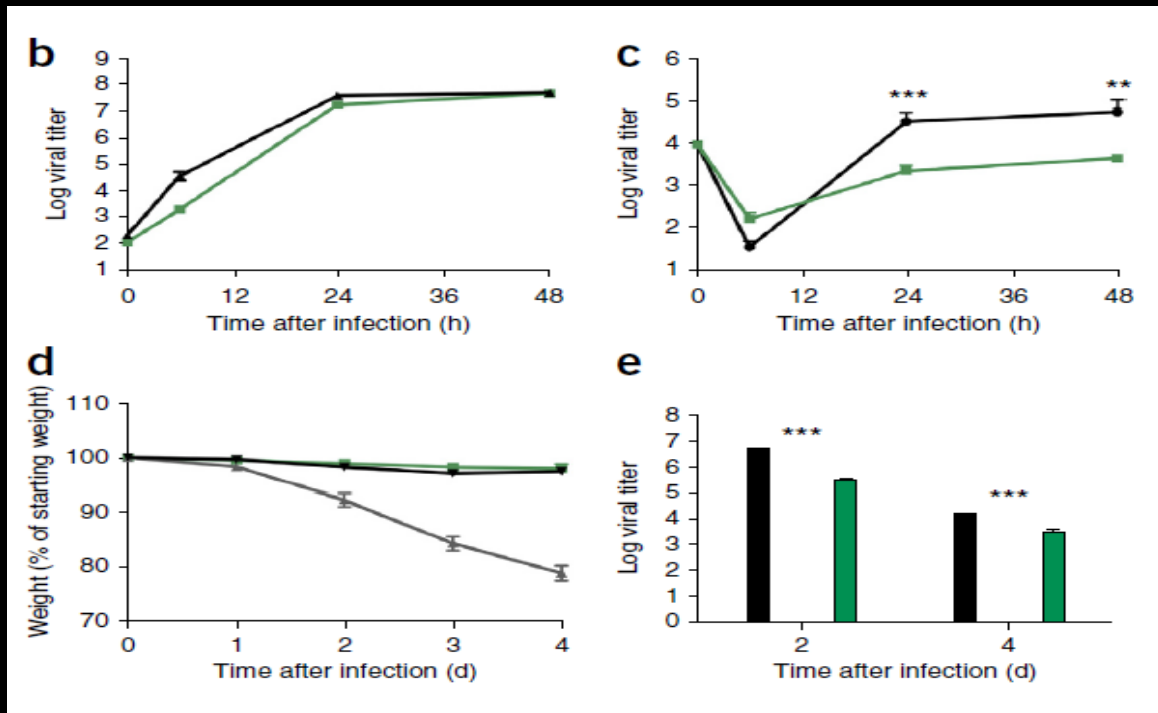


RBM



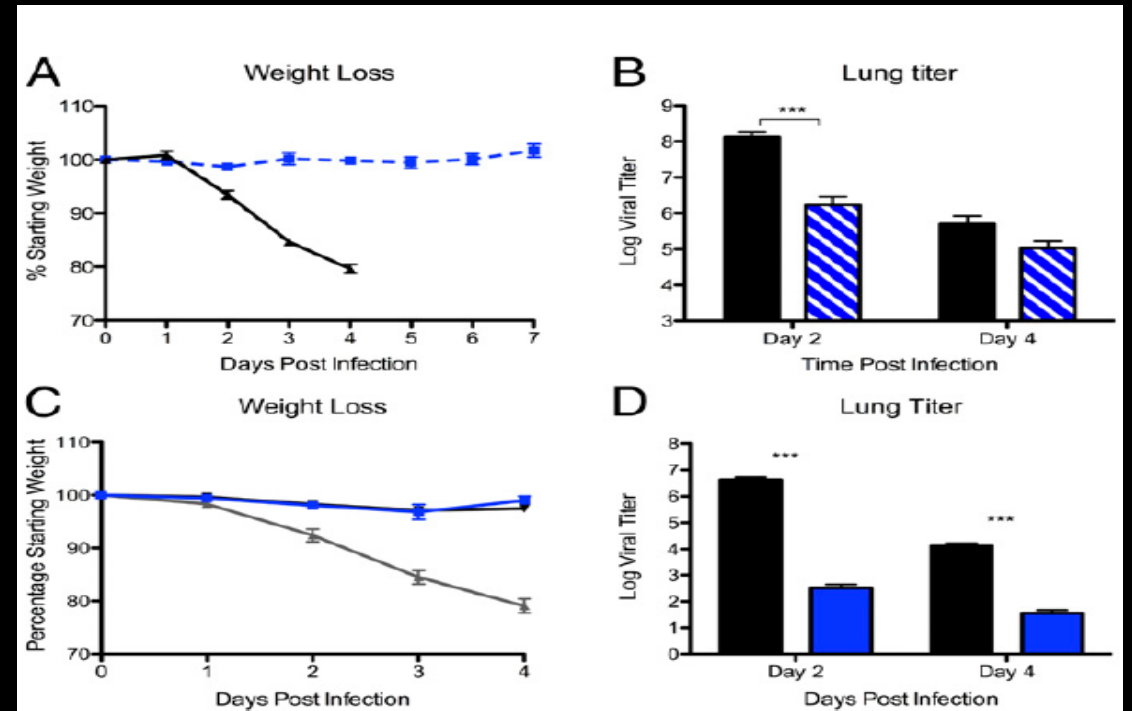
Ge et al., Nature, 2013; Yang et al., JVI, 2016; Zeng et al., JVI, 2016; Hu et al. PLOS Pathogens, 2017

# Pathogenesis of bat SARS-related-CoVs in human ACE2 transgenic mice



SARS-CoV and SHC014

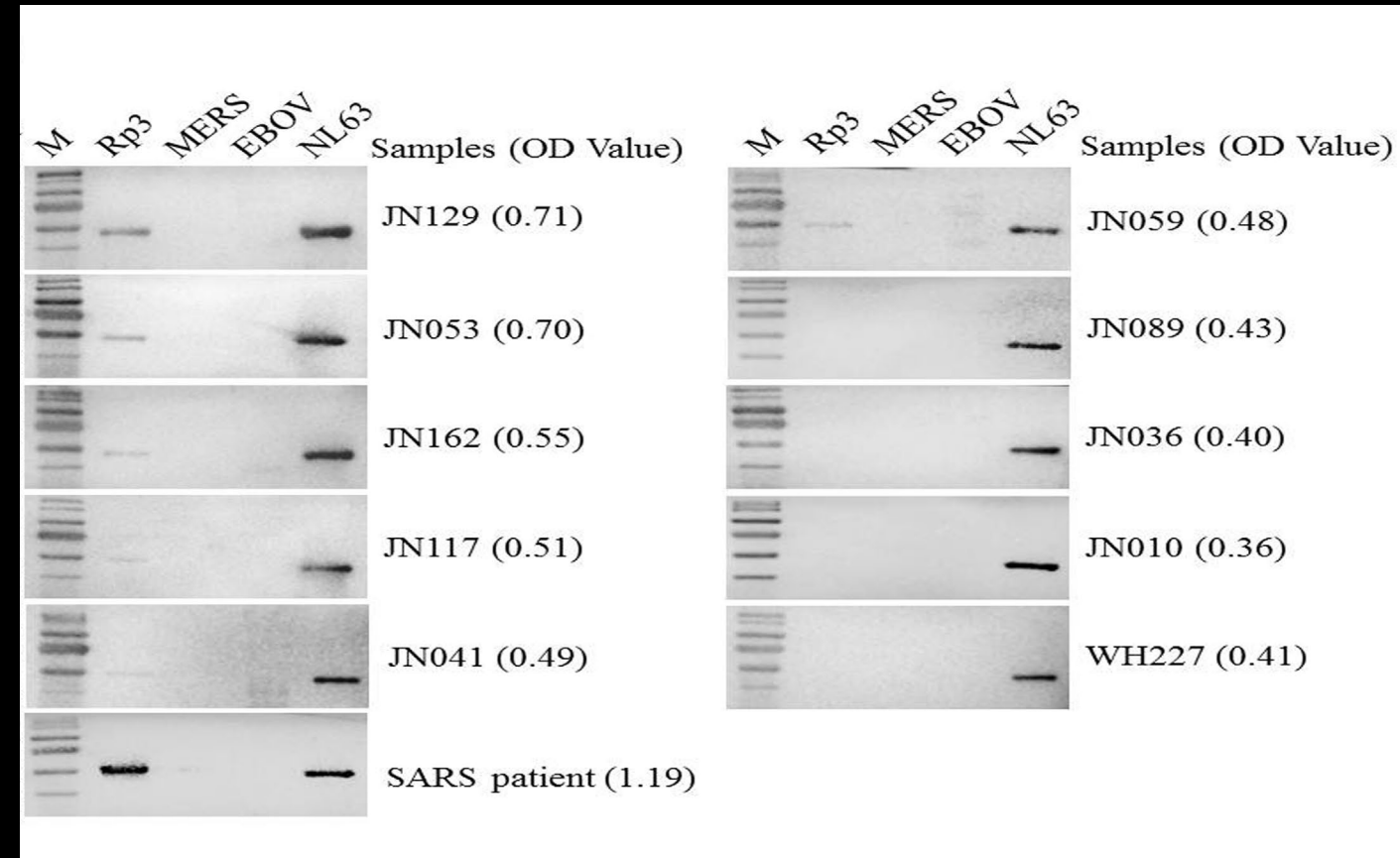
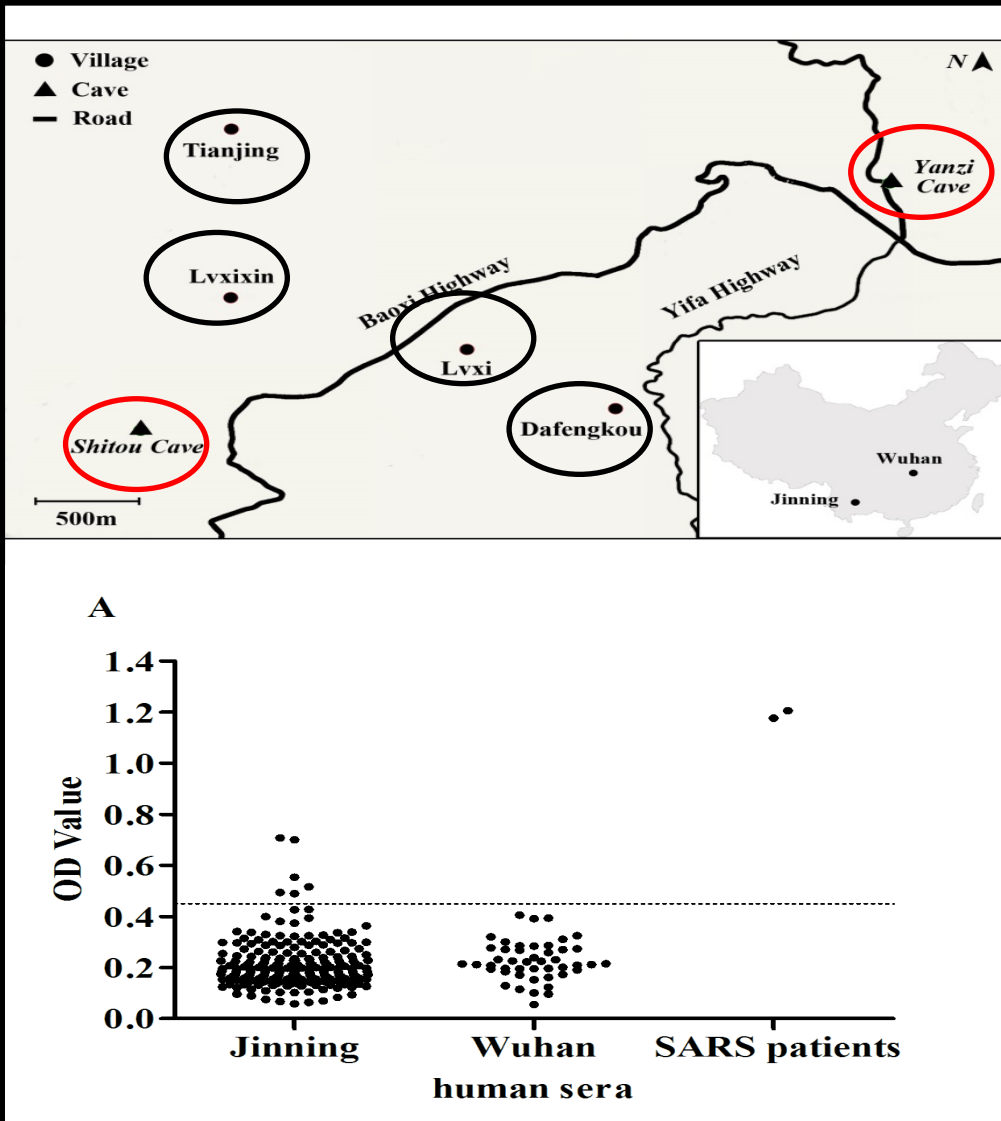
Menachery *et al.*, *Nat Med*, 2015



SARS-CoV and WIV1

Menachery *et al.*, *PNAS*, 2016

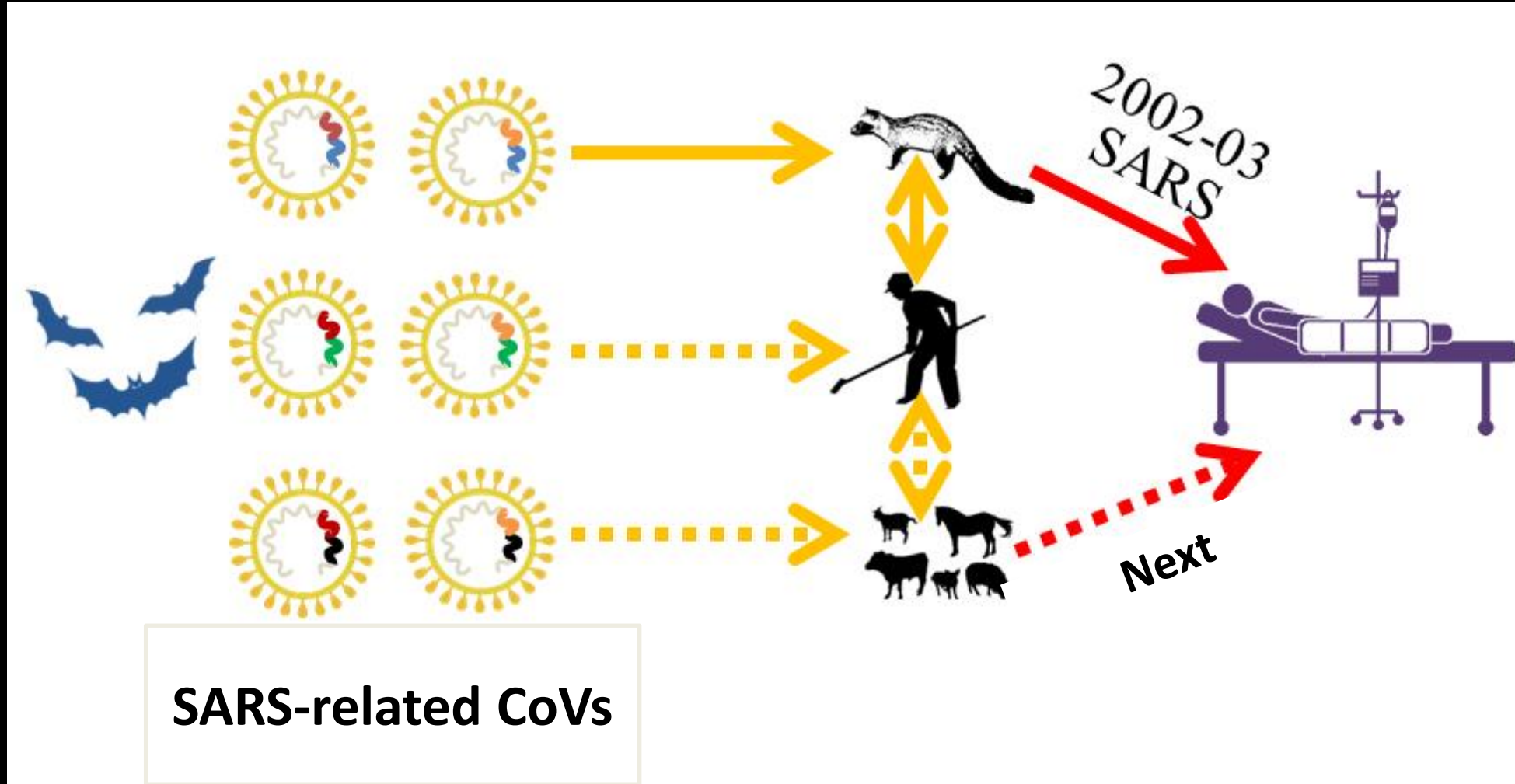
# Serological evidence of bat SARS-related CoV infection in human



Wang et al. Virol Sin, 2018



# Bat SARS-related CoV have potential risk of spillover

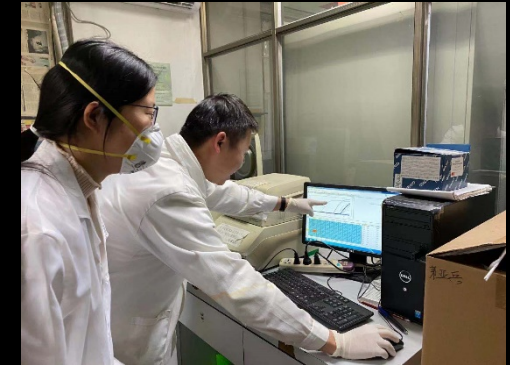
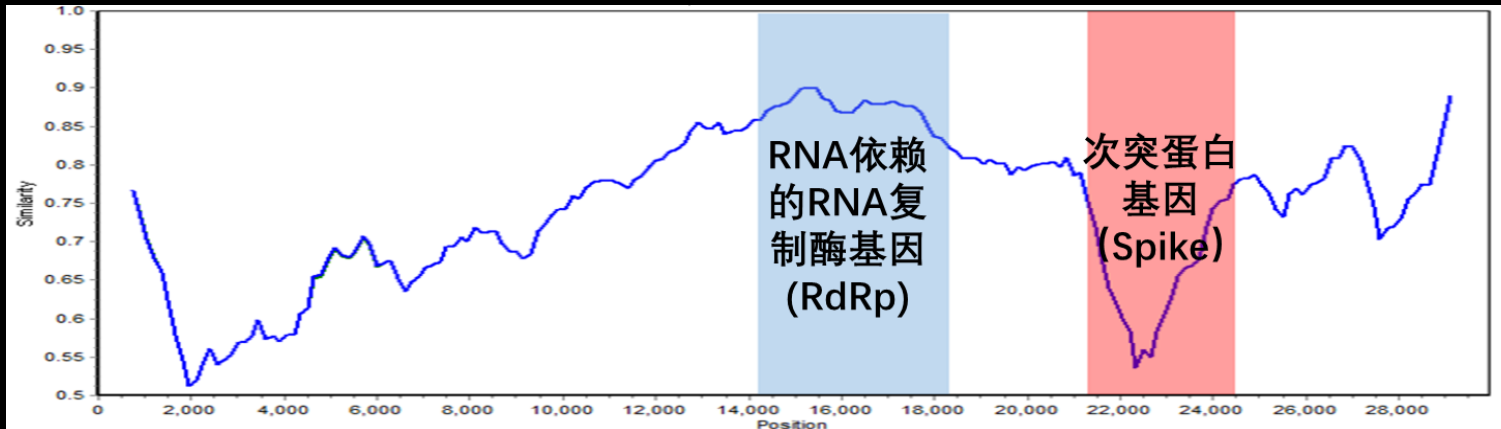


# Pathogen identification of COVID-19

Dec. 30, 2019-Jan. 02 2020



Dr. Dingyu Zhang



Pan-PCR targeting the RdRp of alpha and beta-CoV: **4/7 positive**

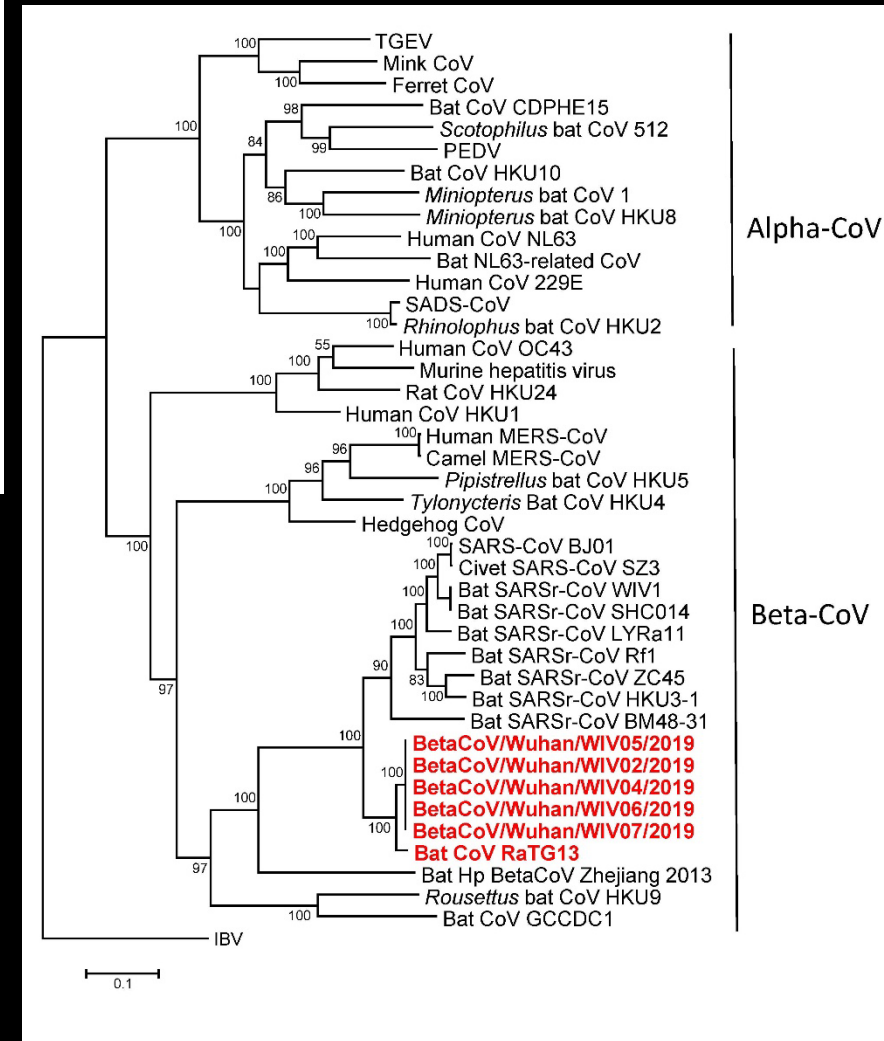
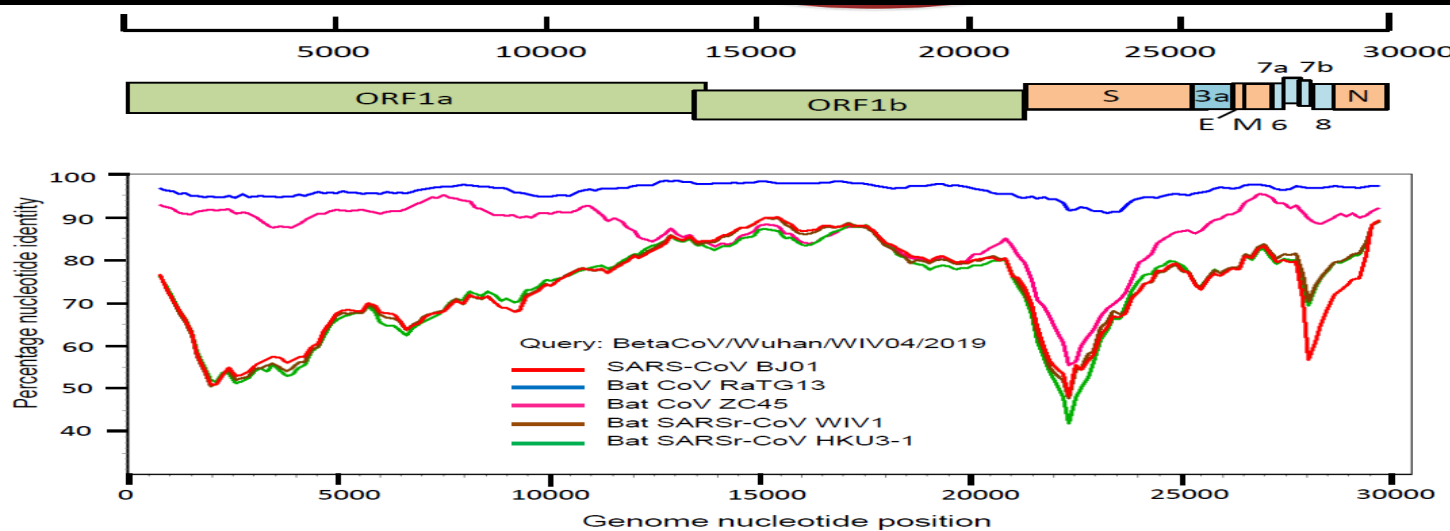
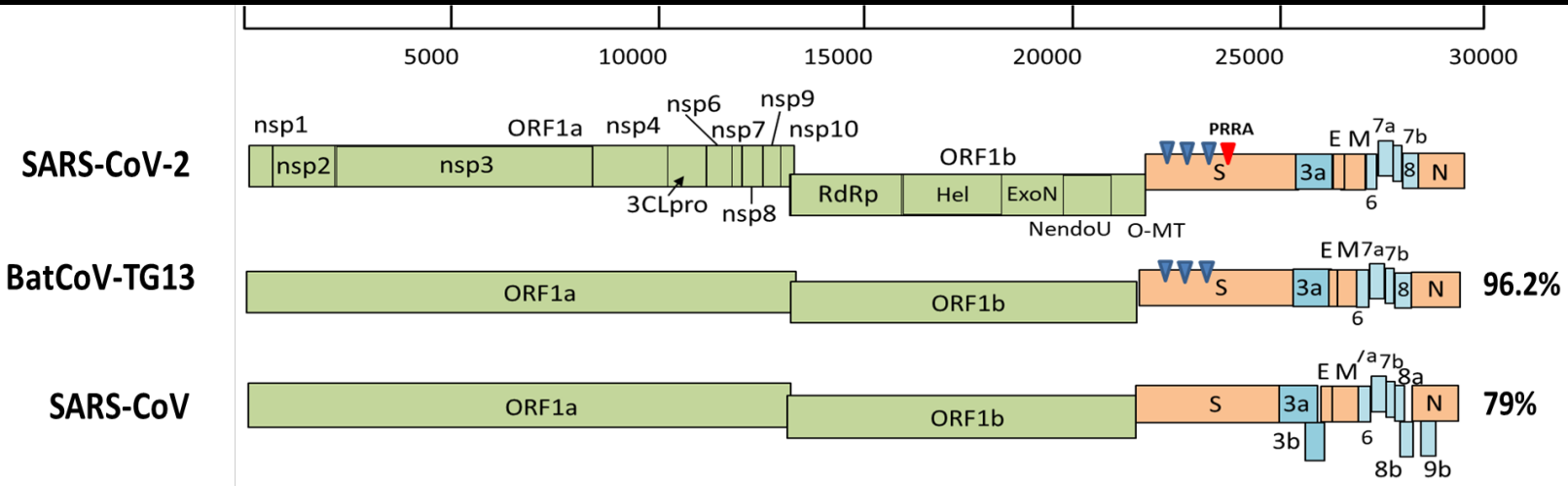
Pan-qPCR targeting the RdRp of SARS-related CoV: **5/7 positive**

qPCR targeting the spike gene of the novel coronavirus: **7/7 positive**

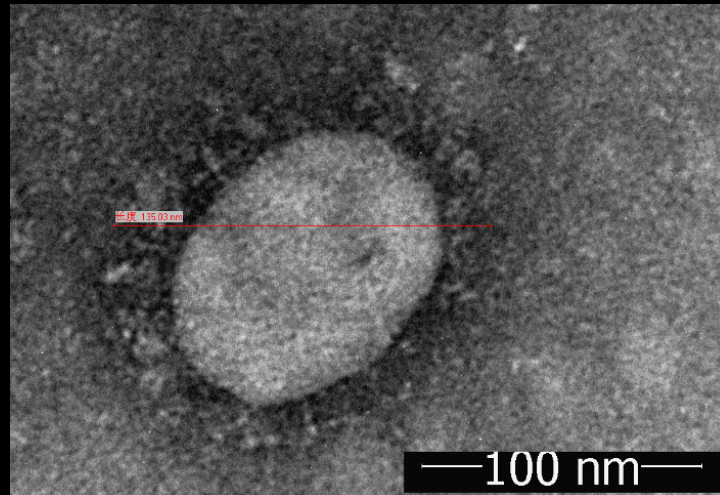
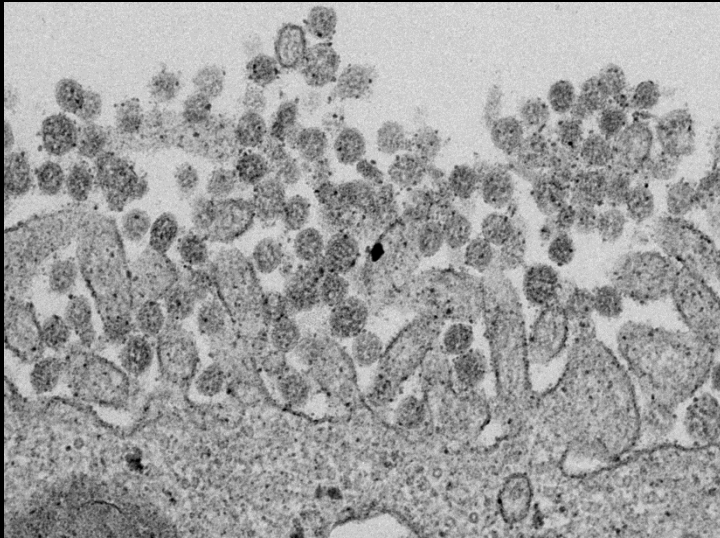
*Zhou et al., Nature, 2020*



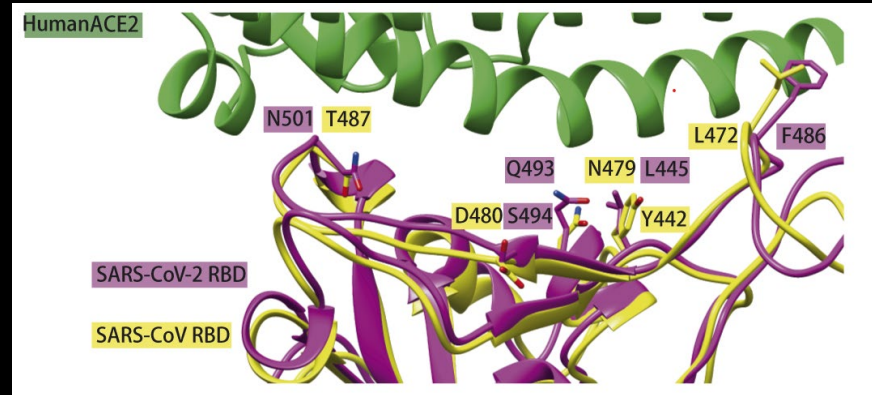
# Genome identification of SARS-CoV-2



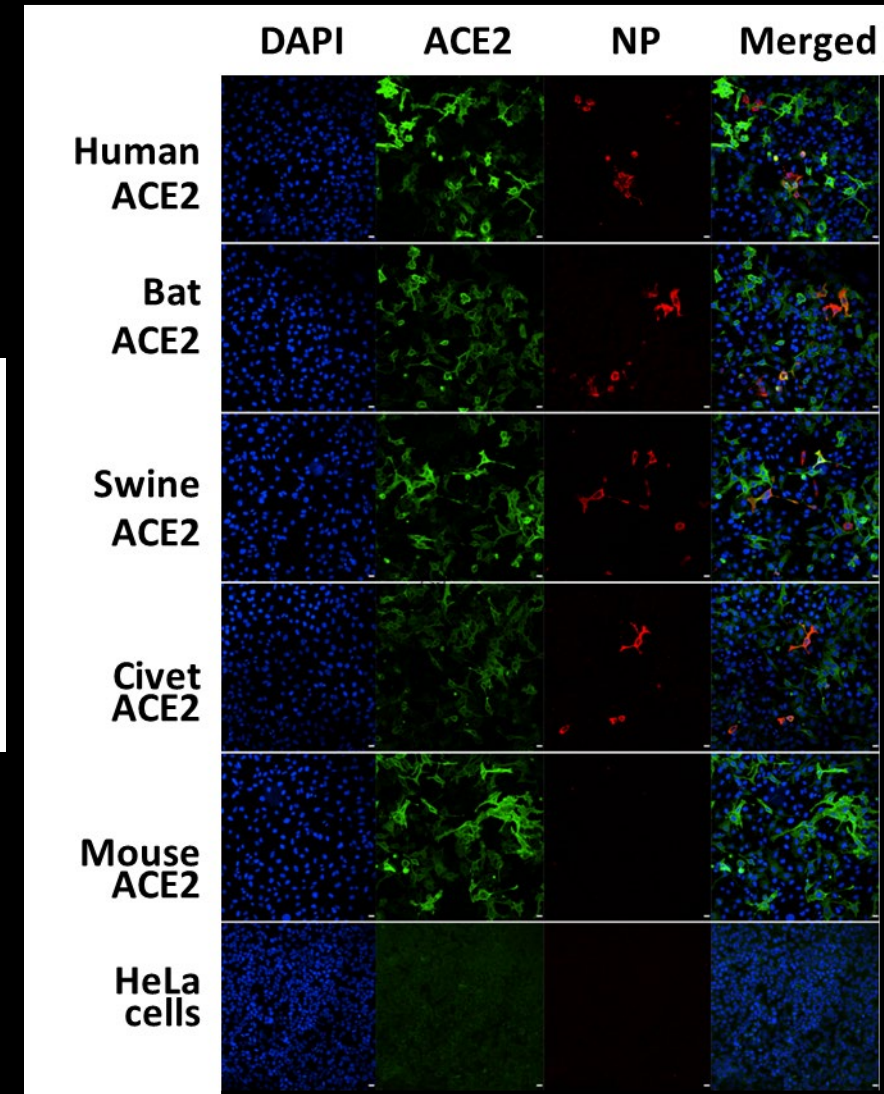
# ACE2 is a functional receptor of SARS-CoV-2



Human ACE2

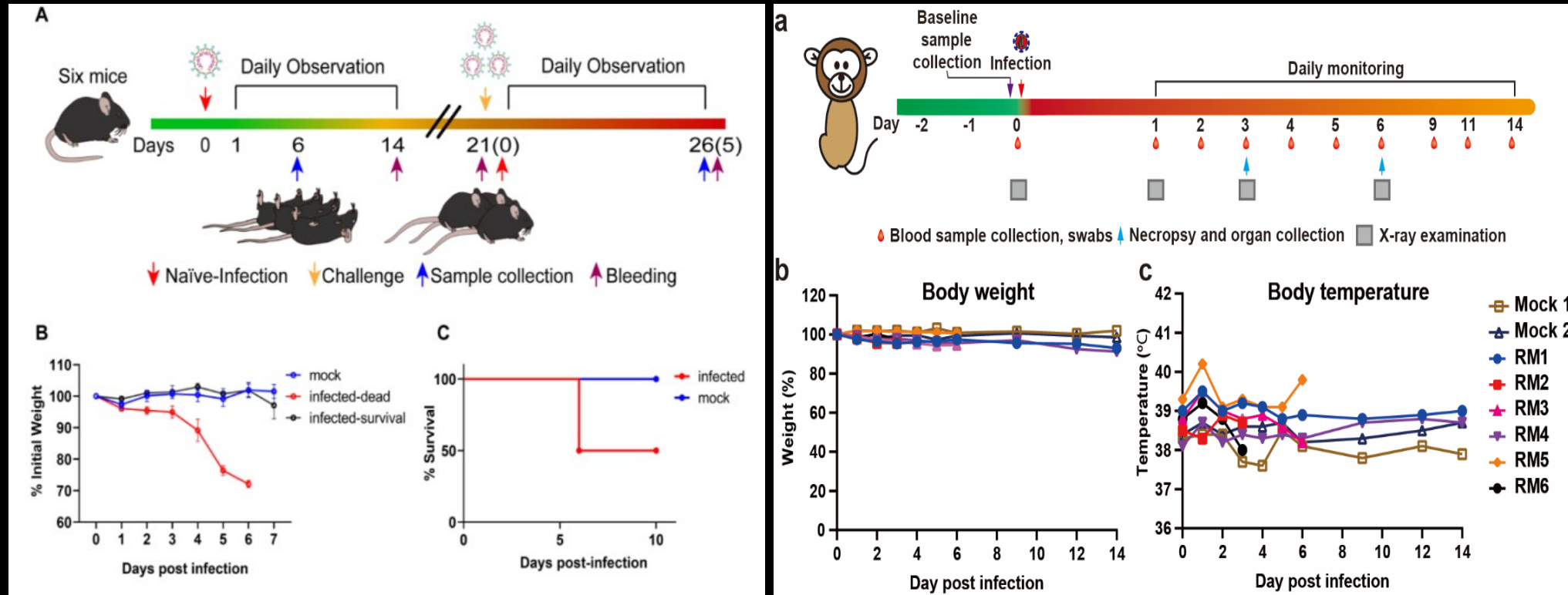


Receptor binding motif



SARS-CoV-2 utilises ACE2 from human, civet, bats and pig to enter cells

# SARS-CoV-2 induces pneumonia in human ACE2 mice and *Rhesus macaques*



Support the evaluation of vaccines, monoclonal antibodies and antiviral drugs

Jiang *et al.*, *Cell*, 2020; Shan *et al.*, *Cell Research*, 2020



# SARS-CoV-2, a newly emerged coronavirus

- No history of human infection before the December, 2019
- No matched viral sequences were reported before the COVID-19 outbreak
- Majority of the early COVID-19 patients had link to the market



**Are market animals the direct sources of SARS-CoV-2?**

# SARS-CoV-2 origins: animal sources?

- SARS-CoV-2 RNA was detected in the market environment
- No SARS-CoV-2 RNA was detected in the frozen food of the market
- No SAR-CoV-2 was detected in the wild animals around Wuhan farms



# SARS-CoV-2 origins: susceptible animals

**Natural infections** cat, dog, mink, tiger, lion, snow leopard

**Experimental infections:** Monkey, golden hamster, ferret, Chinese tree shrew

**Susceptible hosts by ACE2 analyses:** Rabbit, fox, civet, lynx, pig, hot badger, ferret badger, raccoon dog, rhinolophus bat, Tadarida bat, pteropus bat





# SARS-CoV-2 origins: cold chain?



Liu et al., Biosaf Health, 2020



# SARS-CoV-2 origins: evolutionary ancestors

**SARS-CoV-2**

**RaTG13**

**RshSTT182**

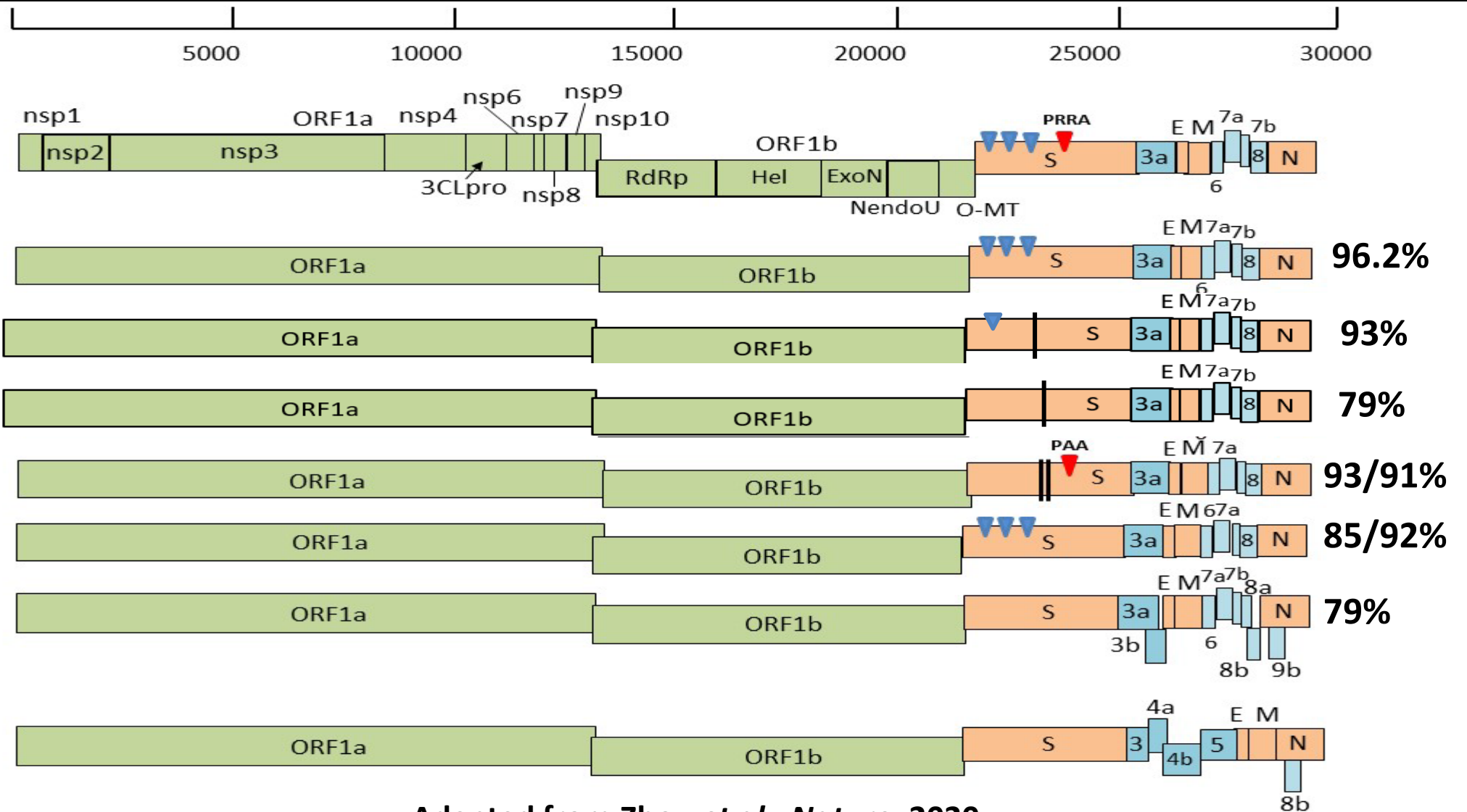
**Rc-o319**

**RmYN02/  
RacCS203**

**Pangolin CoVs**

**SARS-CoV-1 &  
related CoVs**

**MERS-CoV**



# SARS-CoV-2 related spikes have different binding affinity to human ACE2

Homolog	Relative binding	Relative cellular entry (a.u.)*
GD-Pangolin	0.13	n.d.
SARS-CoV-2	0	1.24
SARS-CoV-1	-0.48	1.00
LYRa11	-0.66	0.14
RaTG13	-2.16	n.d.
HKU3-1	<-4.41	0.02
BM48-31	<-4.41	0.02

\*measurements from Letko et al. 2020

RBD homolog	Mammalian-expressed, monomeric ACE2 ( $K_D$ , nM)	Deep mutational scan, dimeric ACE2 ( $K_{D,app}$ , nM)
SARS-CoV-2	92	0.016
WIV1	363	0.017
SARS-CoV-1	575	0.028
RaTG13	not detectable	2.675
ZXC21	not detectable	>1000
ZC45	not detectable	>1000

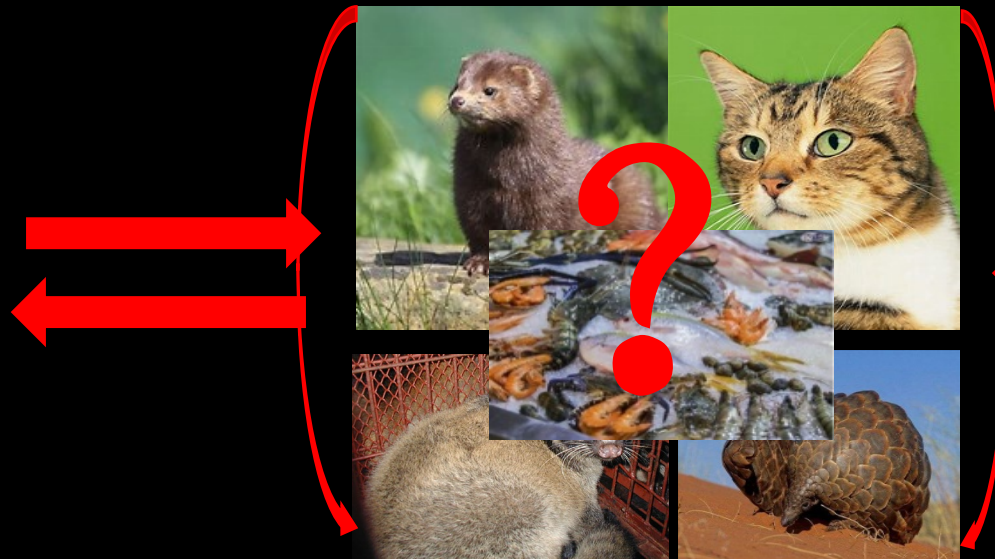
SARS-CoV-2 > Pangolin CoVs > SARS-CoV-1 > WIV1 > TG13

Daniel *et al.*, *Science*, 2020; Wall *et al.*, *Cell*, 2020; Starr *et al.*, *Cell*, 2020

# Probable origins of SARS-CoV-2

Susceptible host

Natural host

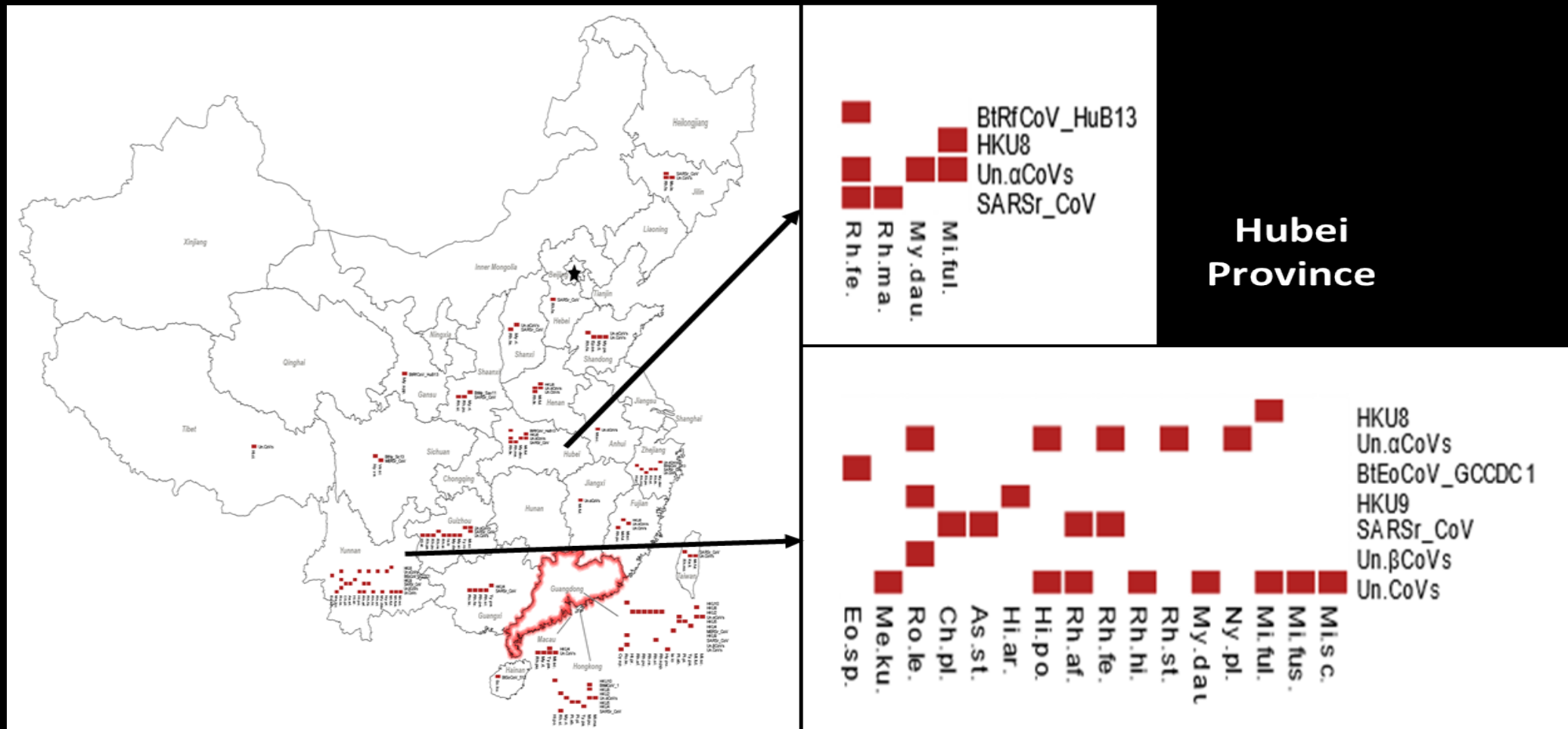


Zhou et al., *Nature*, 2020



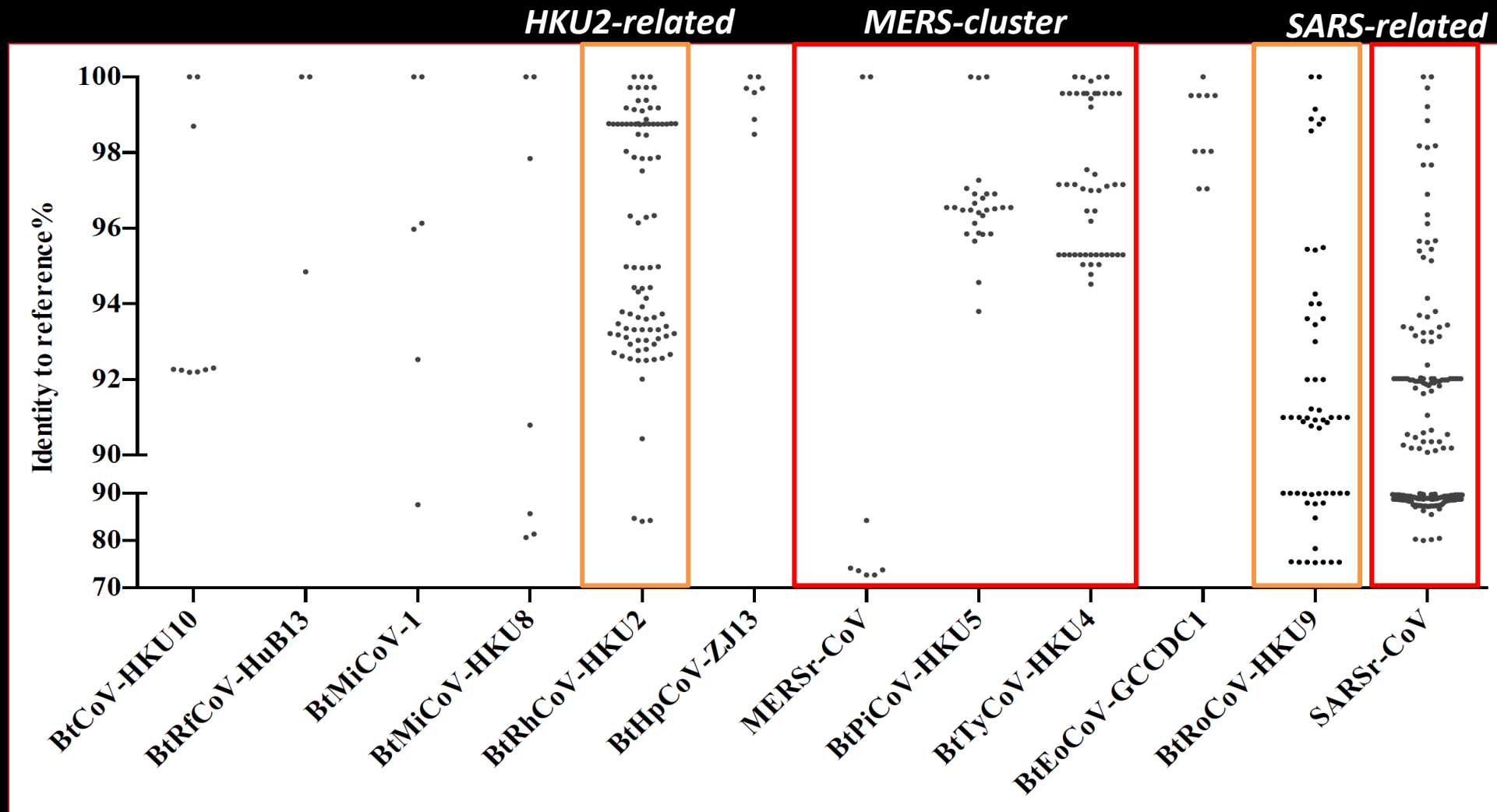
Lam et al., *Nature*, 2020  
Xiao et al., *Nature*, 2020

# Distribution of bat coronaviruses in China

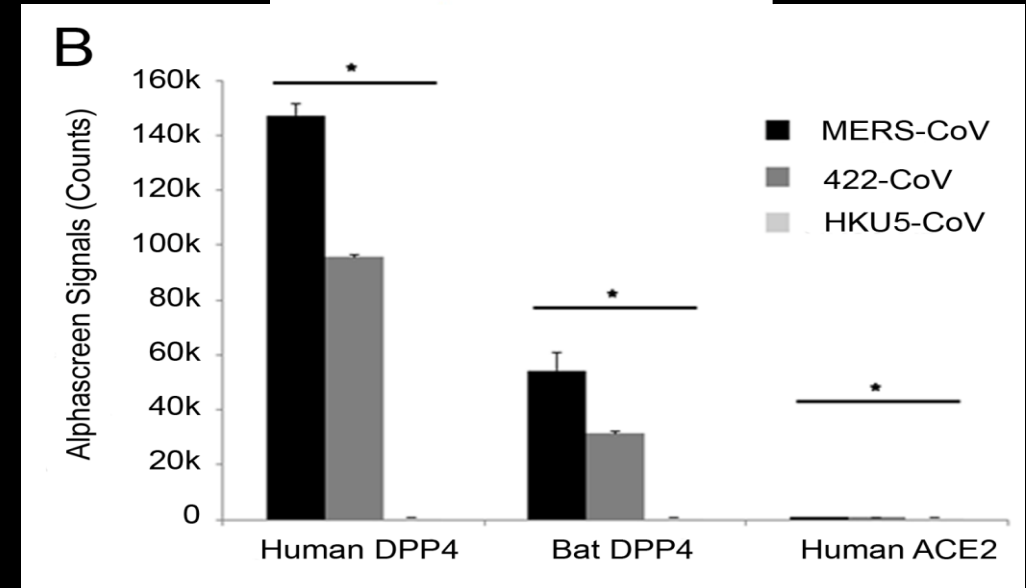
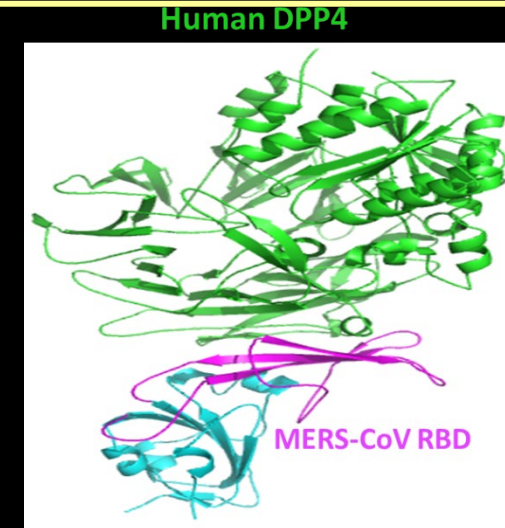
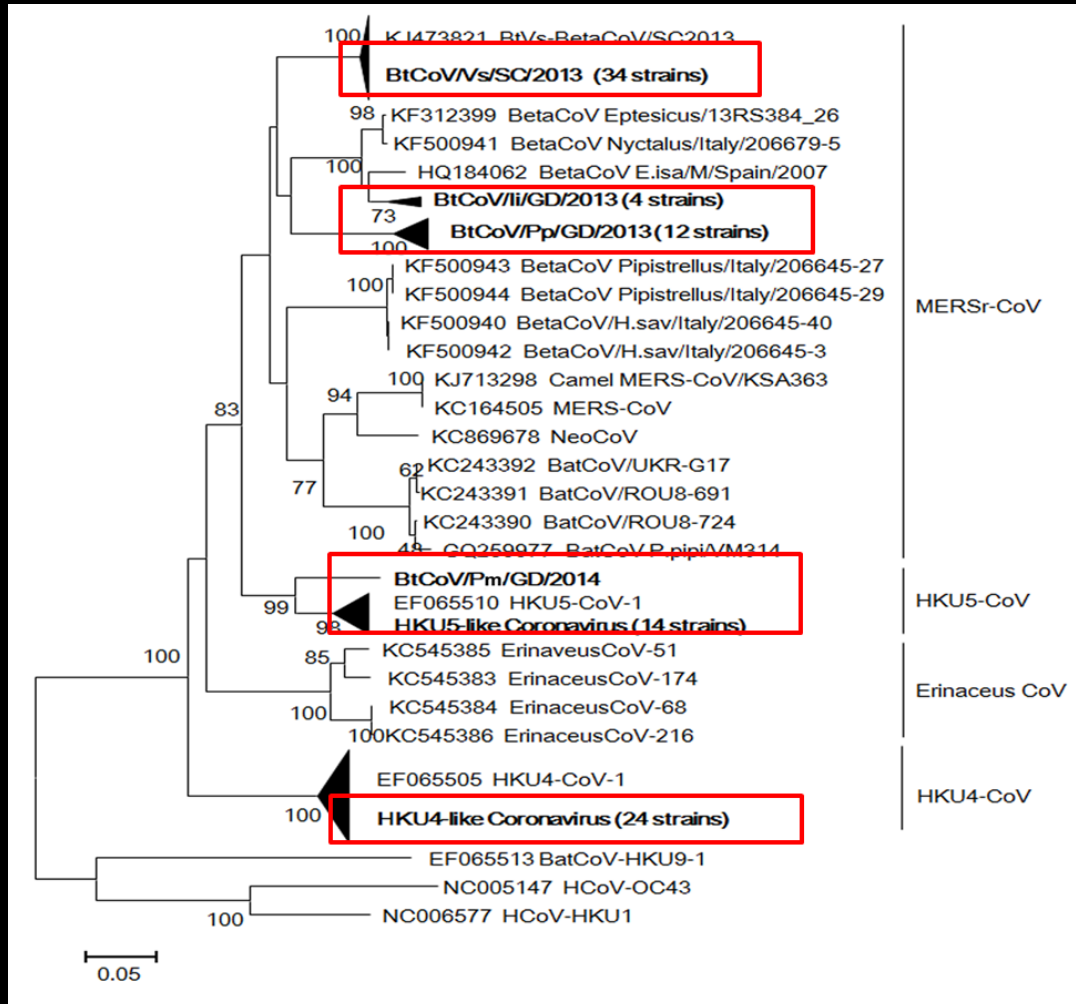


Higher diversity of bats and coronaviruses in South and southwest China

# Diversity of bat coronaviruses in China

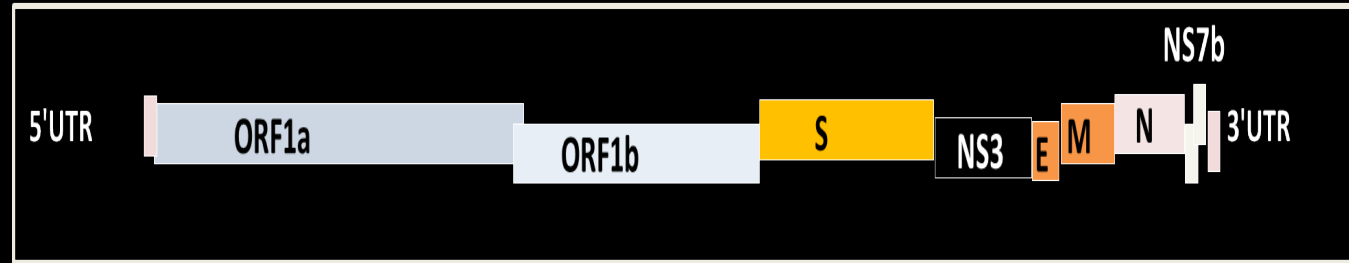
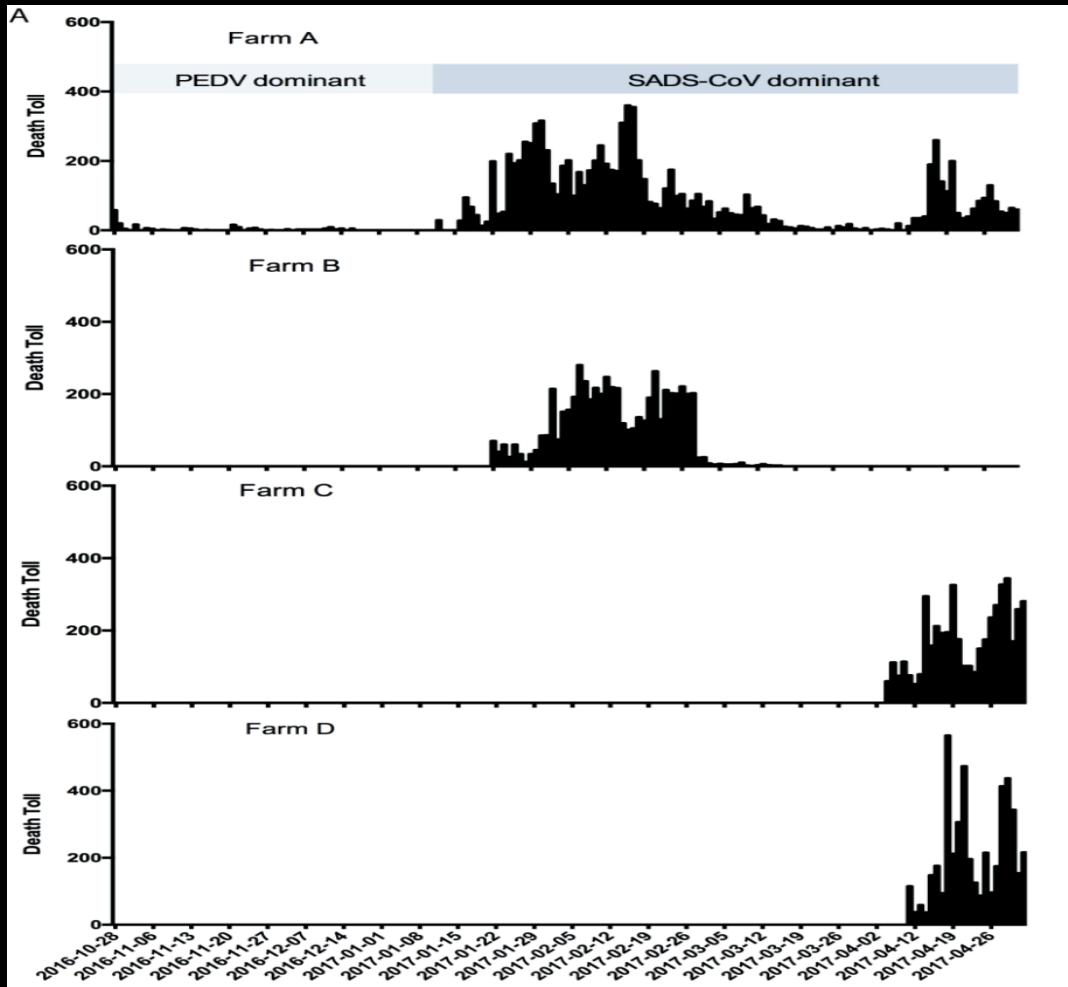


# MERS-CoV-cluster viruses use human DPP4 as receptor





# Bat coronavirus causes swine acute diarrhea syndrome (SADS)

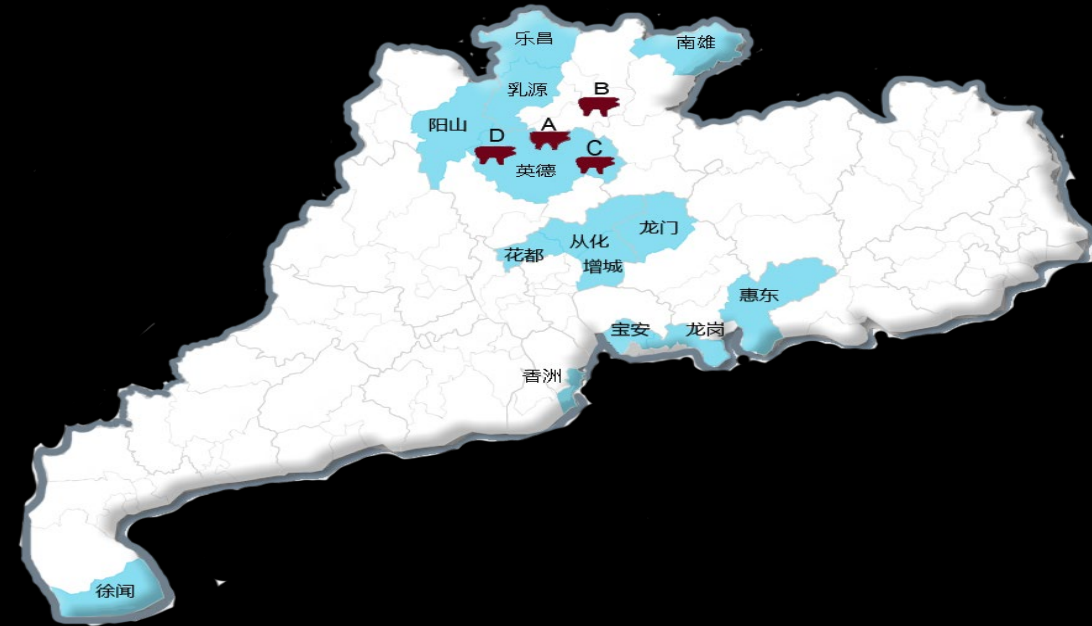
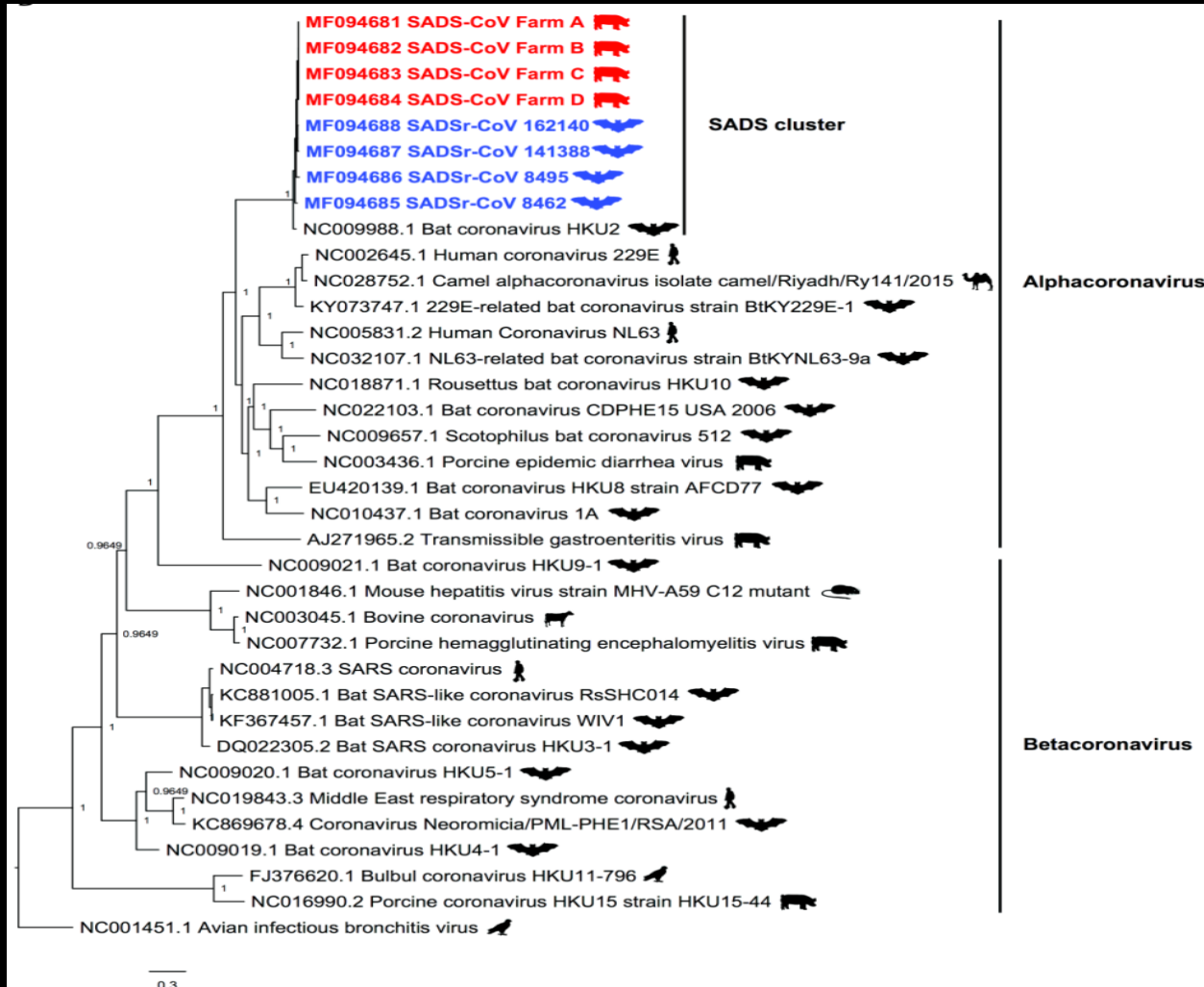


**Homologous to bat coronavirus HKU2:**

- Genome sequence: 95%
- Spike protein sequence: 86%

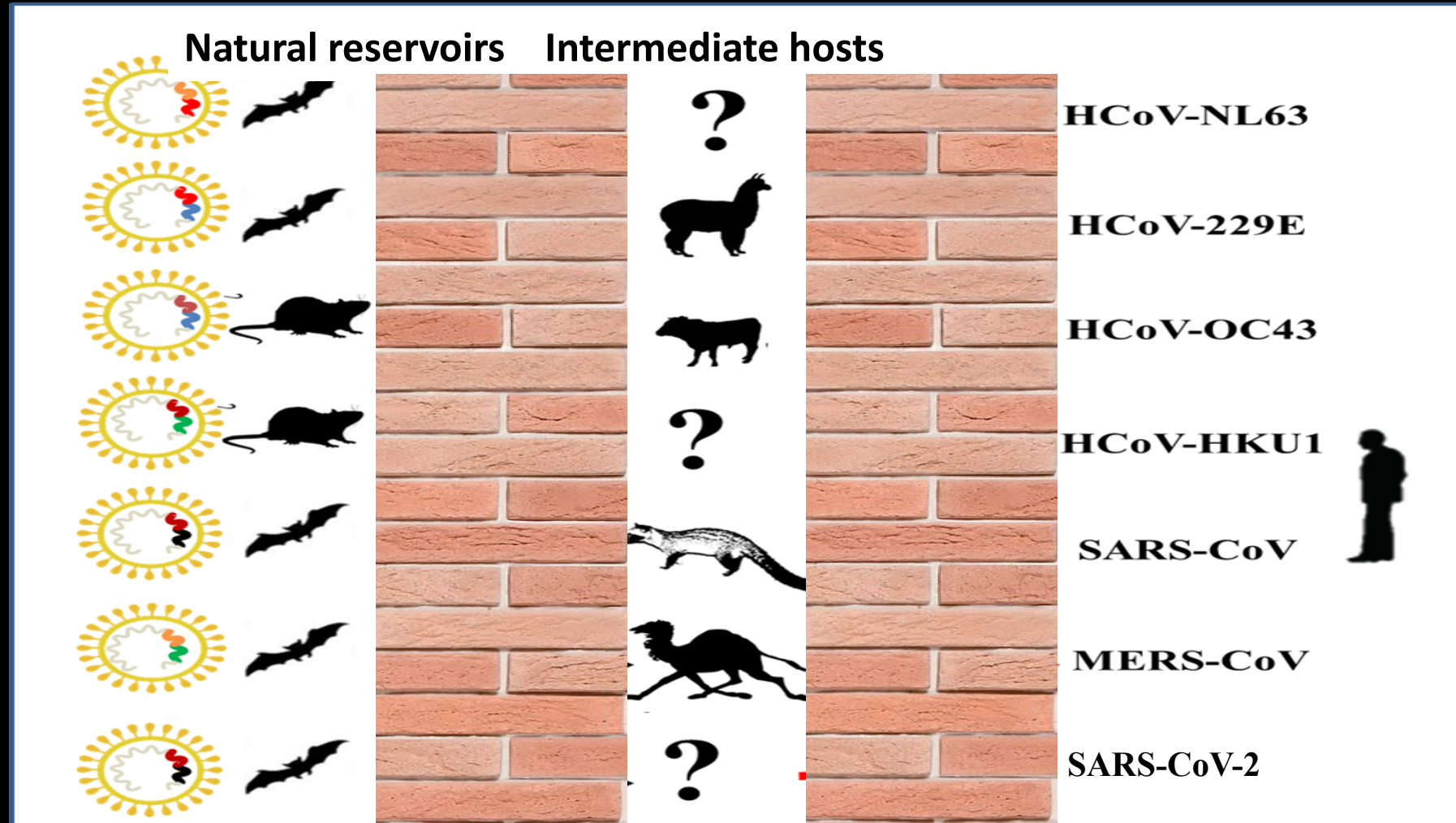


# Bat origin of SADS-CoV



- From 591mbat samples, 9.8% are positive
- Genome seuqneces: 96-98%
- Spike protein sequences: 87-98%

# Animal origins of human coronaviruses



# Surveillance is the best strategy for preventing the zoonosis

Early detection, early warning, early intervention



“Find the virus before they find us”

# Summary

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**Bat are natural reservoirs of coronaviruses, including SARS-CoV-1/-2, MERS-CoV and SADS-CoV**

**Bat coronaviruses are highly diverse and have potential to interspecies transmission to domestic animals and humans**

**Long-term and extensive surveillance should be conducted in the future to prevent the potential zoonosis caused by coronaviruses**

**Thank you!**