



Coronavirus: What is it? Where did it come from? Where is it going?

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I respectfully acknowledge that I live and work on the unceded territory of the x^wməθkwəʔəm, Skwxwú7mesh, Stó:lō and Səlílwətaʔ/Selilwitulh Nations.

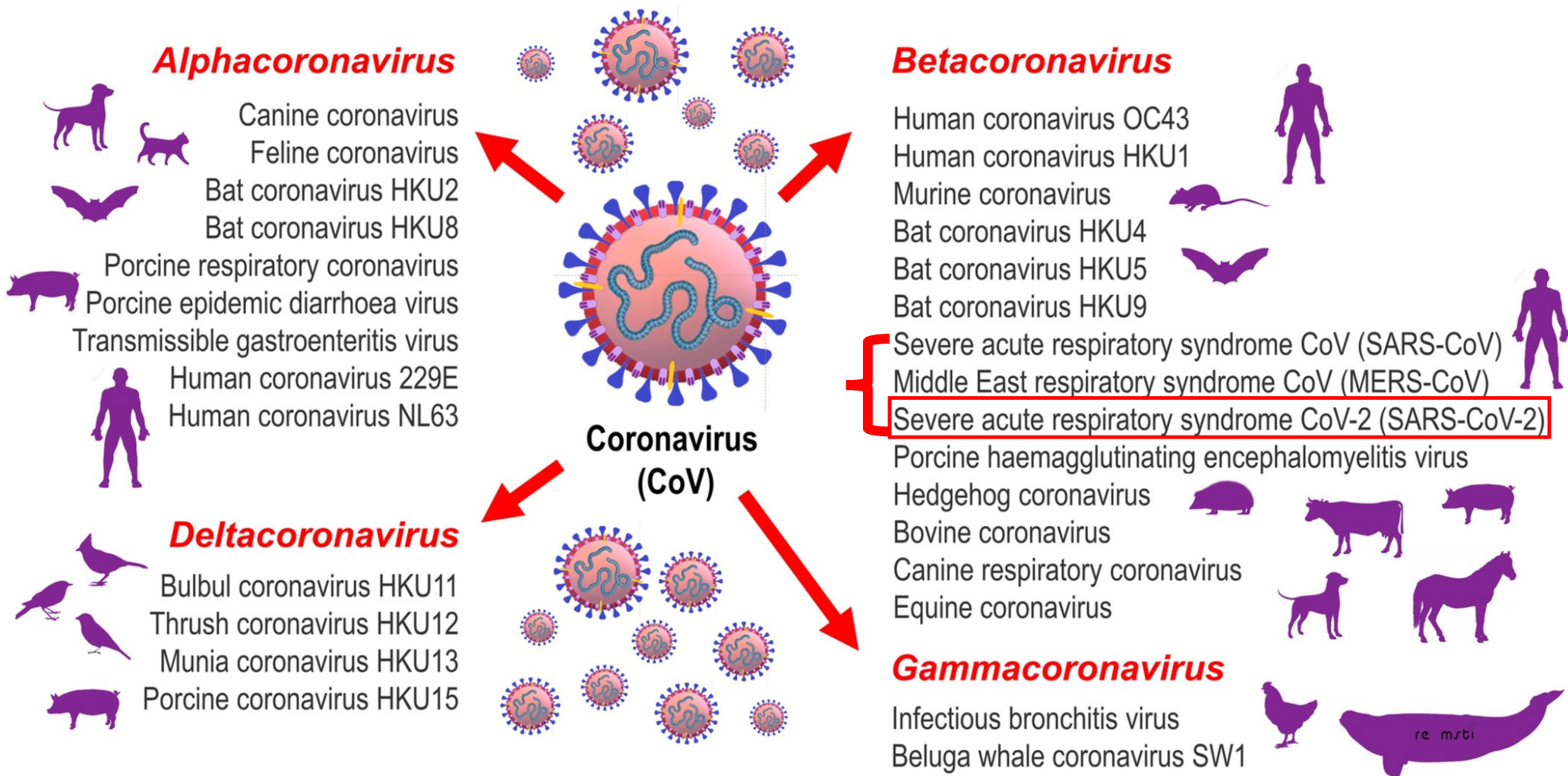
Disclosures

Have received grant/contracts paid to my institution from:

- Roche
- Hologic
- Siemens

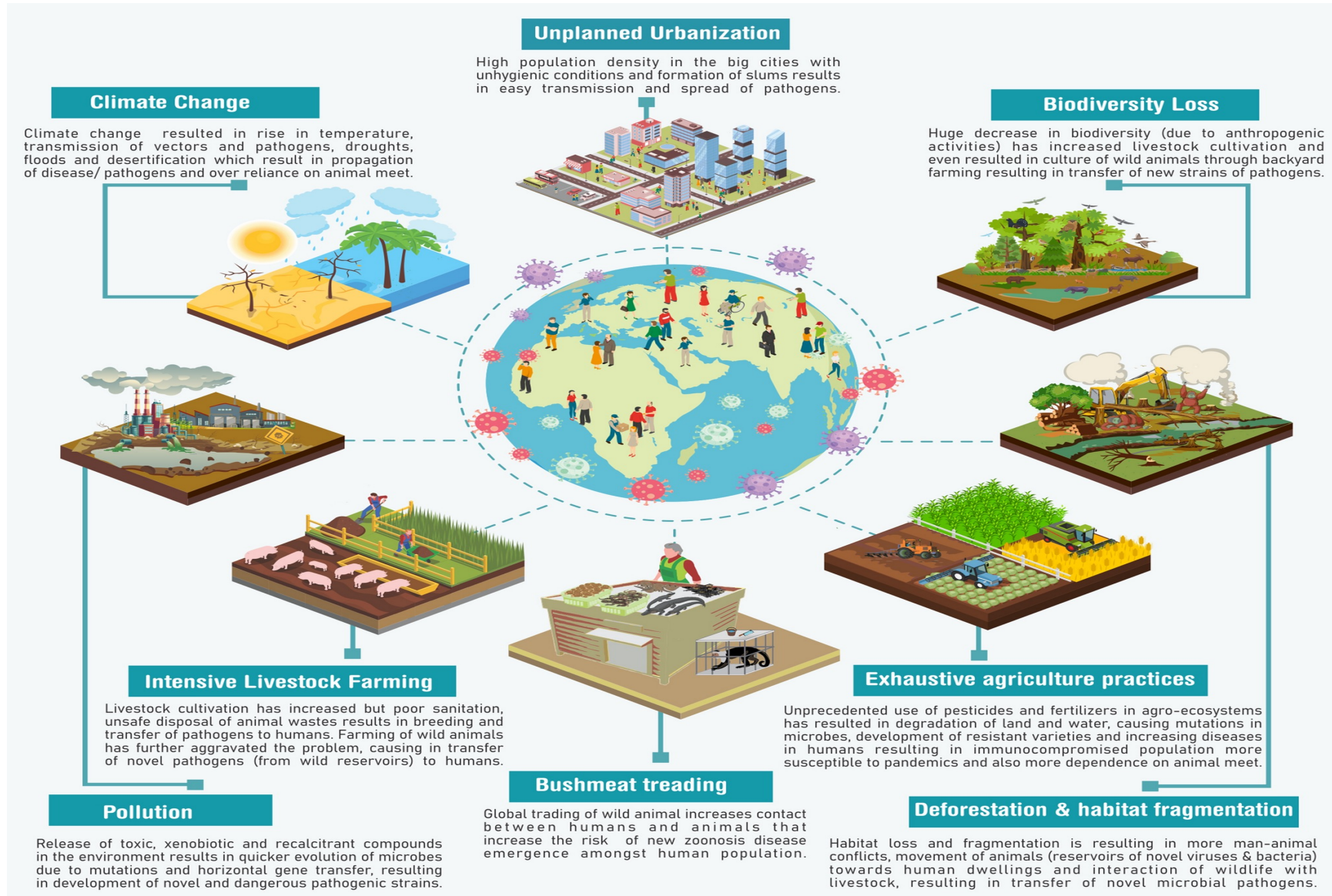
As these grants/contracts are unrelated mitigation is not required

Coronaviruses: What are they? Family of RNA viruses that infect many species



Factors that increase zoonoses include:

Mishra et al. Linkages between environmental issues and zoonotic diseases: with reference to COVID-19 pandemic. Environmental Sustainability 2021



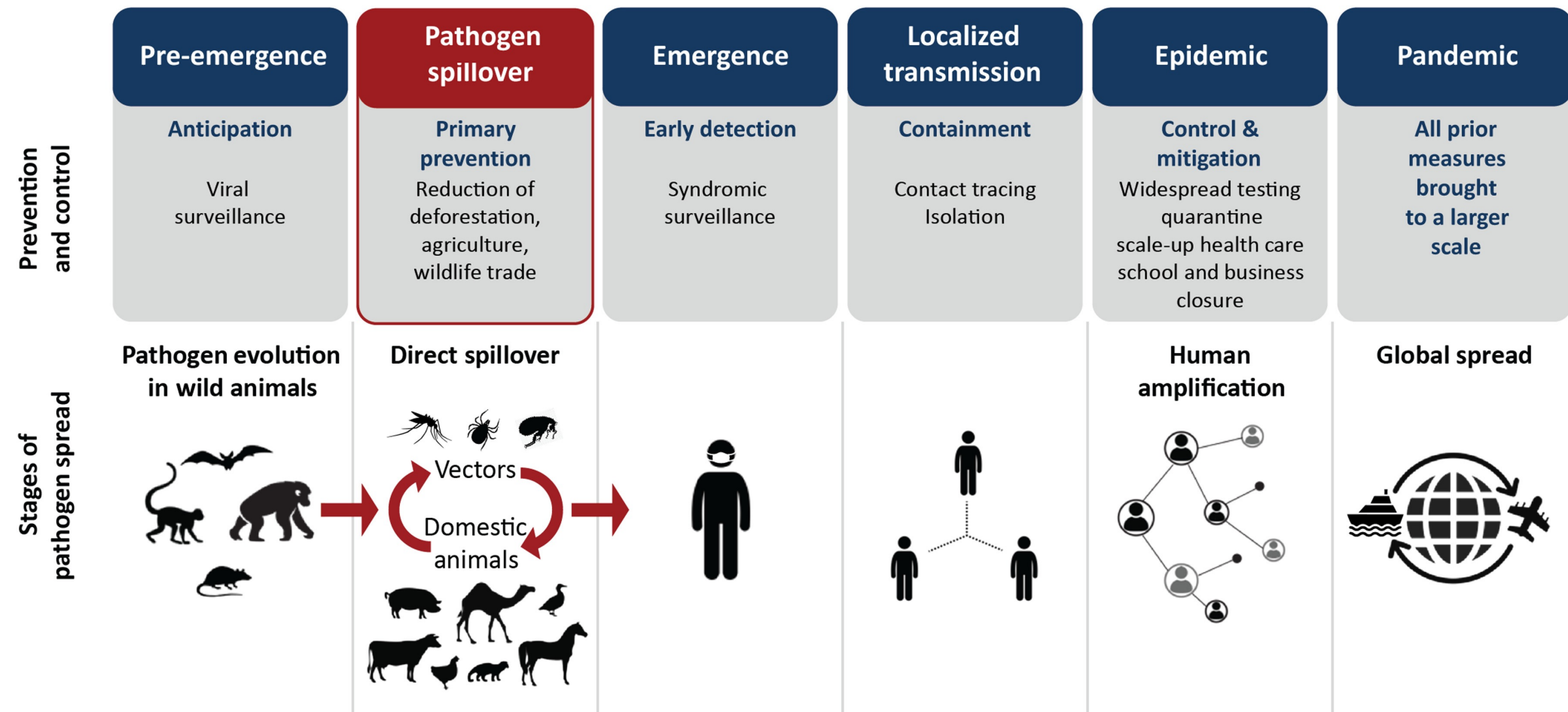
Zoonoses 101

- **Zoonotic sourced infections** → depend on the prevalence of the agent in their normal reservoir(s) → spillover rate to other species
- **Reservoir to human contact rate is important** → SARS vs MERS vs SARS-CoV-2 (humanized)
- **Transmission probability** → $R_0 < 1$ stuttering introductions vs $R_0 > 1$ sustained transmission (variants play a role)

Zoonoses 101 cont'd

- **Host immunity** → novel agent introduced into a non immune population → cross protection from prior exposure to other human coronavirus types (**HKU1**, **OC43**, NL63, & 229E)?
- **Dose** → more virus → greater transmission risk (HIV) → potential for more severe illness (Varicella) → masks
 - Children have less developed immune systems → shed more respiratory viruses, and are typically less symptomatic than adults → variant specific
- **Pathogenicity/virulence** → once humanized → person-to-person transmission → variants impact transmissibility!

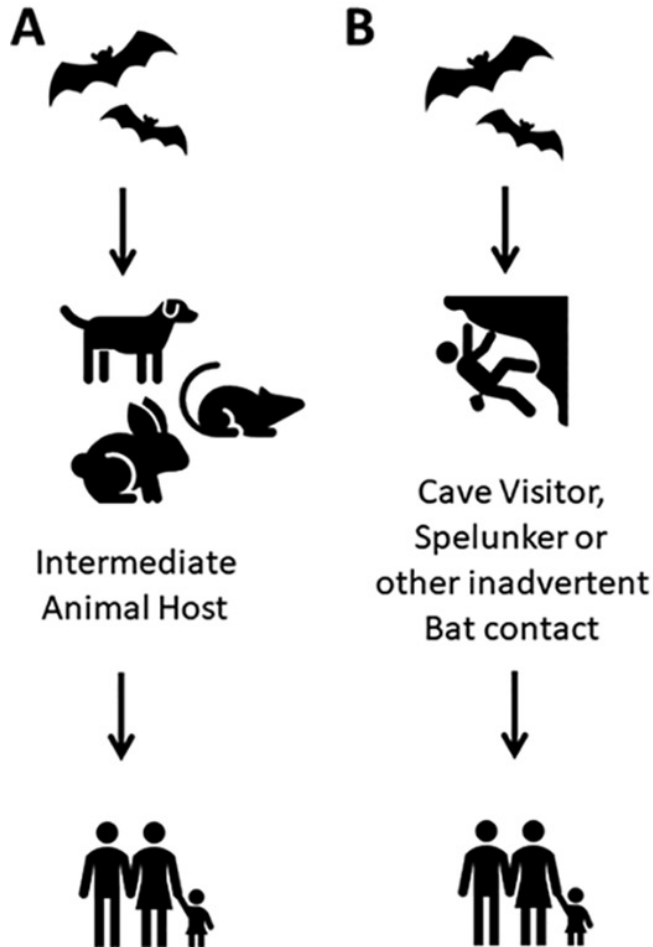
“One Health” = Interface between humans, animals and the environment



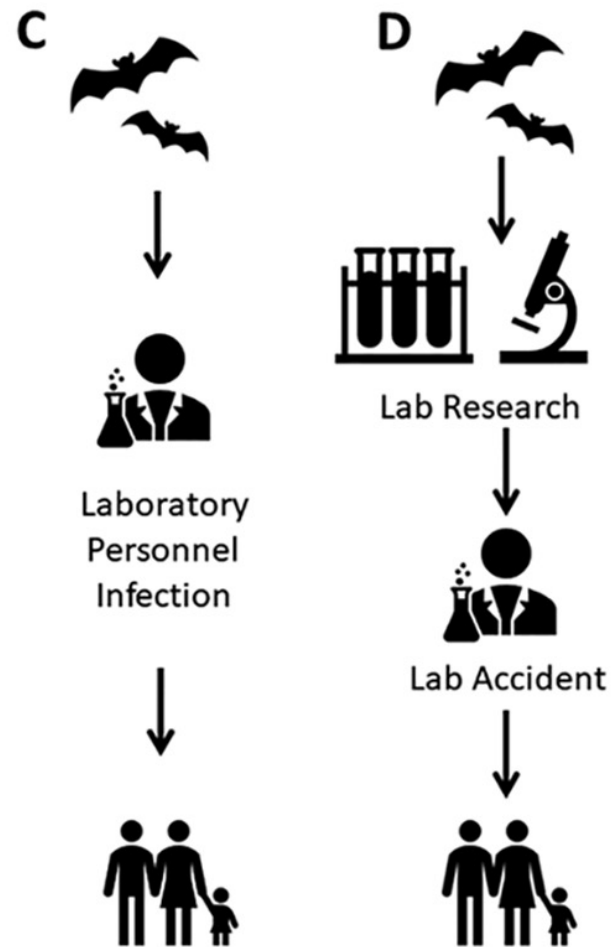
Bernstein et al. The costs and benefits of primary prevention of zoonotic pandemics, Science Advances 2022

SARS-CoV-2: Where did it come from?

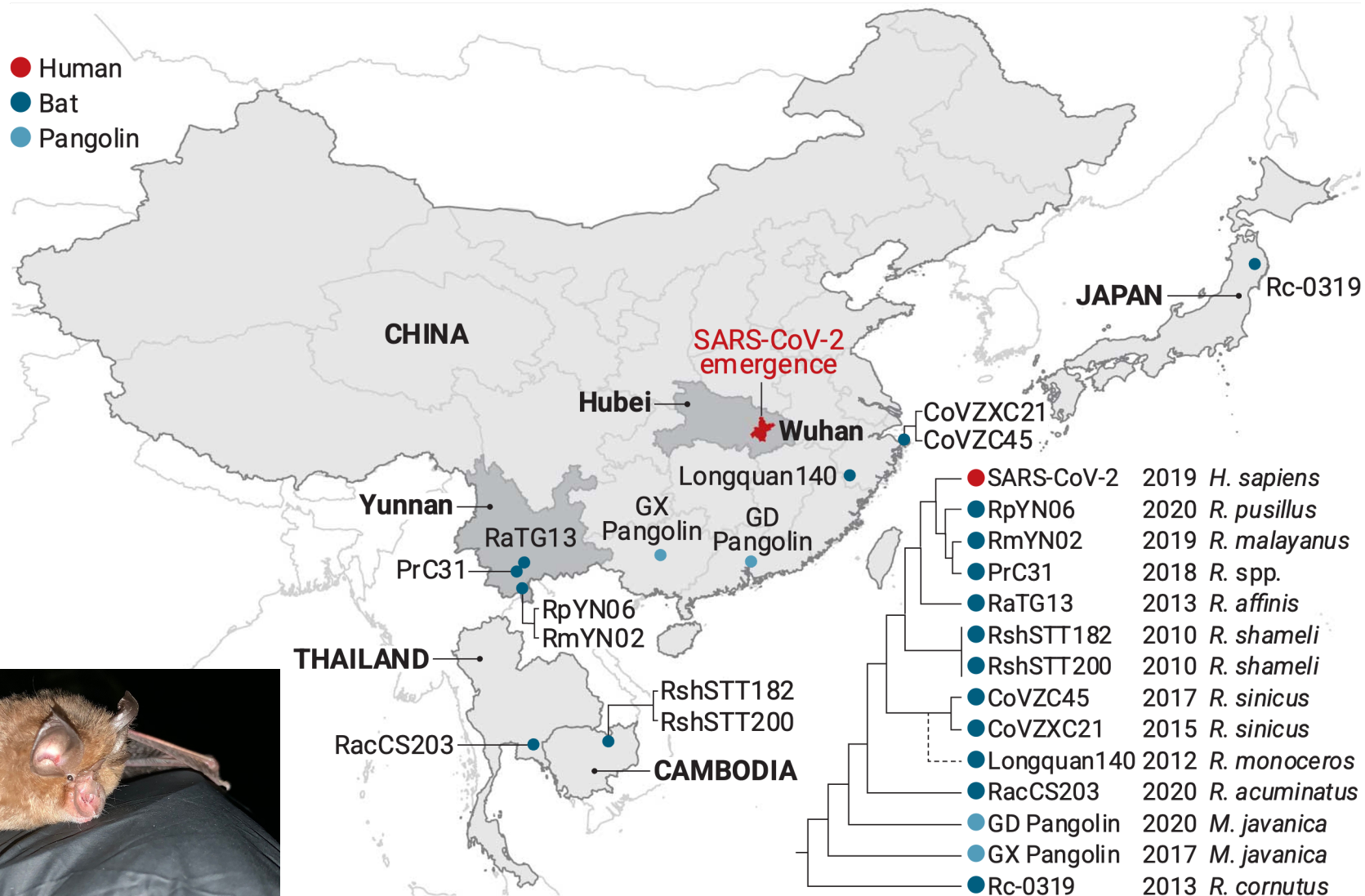
Direct Zoonosis



Laboratory-Related Origin



Casadevall et al. Can Science Help Resolve the Controversy on the Origins of the SARS-CoV-2 Pandemic? mBio 2022



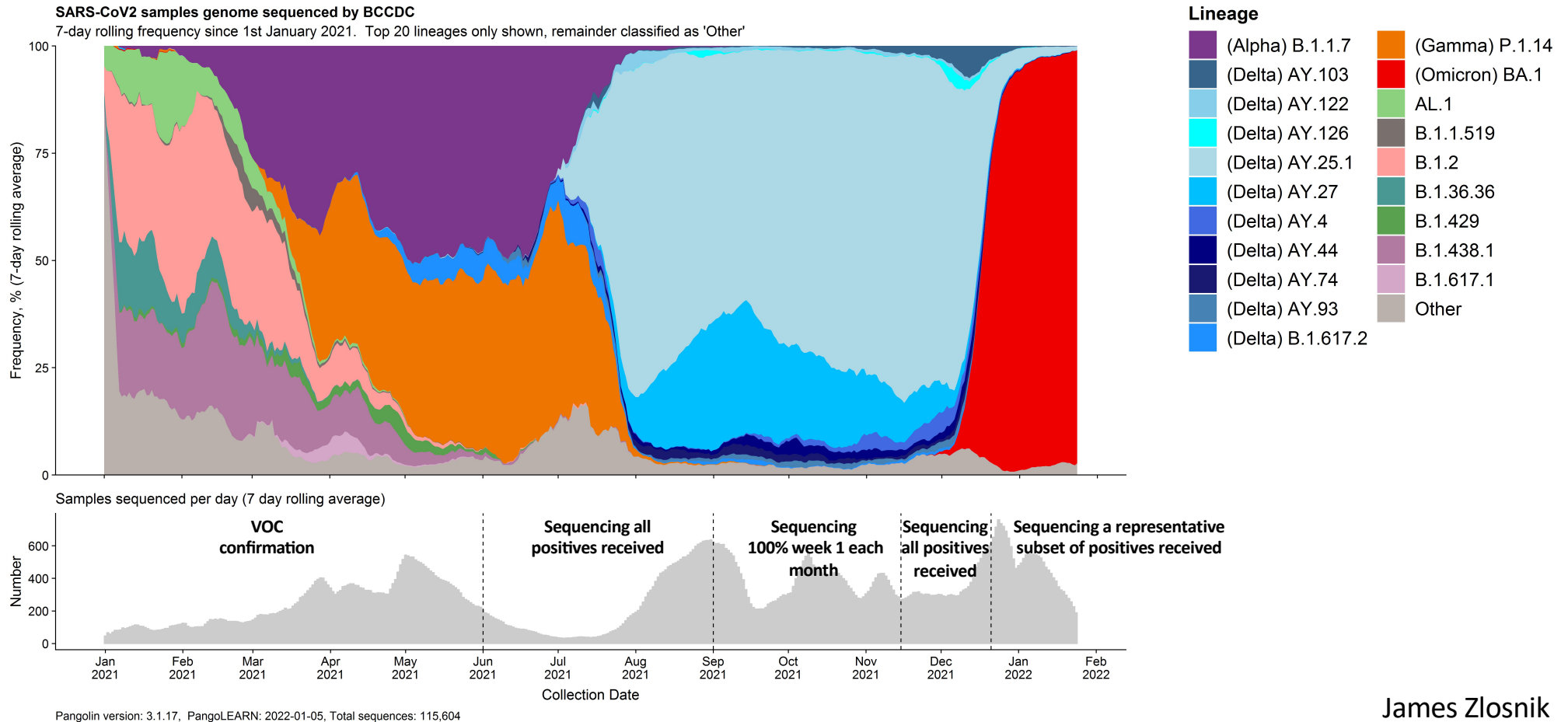
Lytras et al. The animal origin of SARS-CoV-2. Science, 2021



Genomics – Whole Genome Sequencing

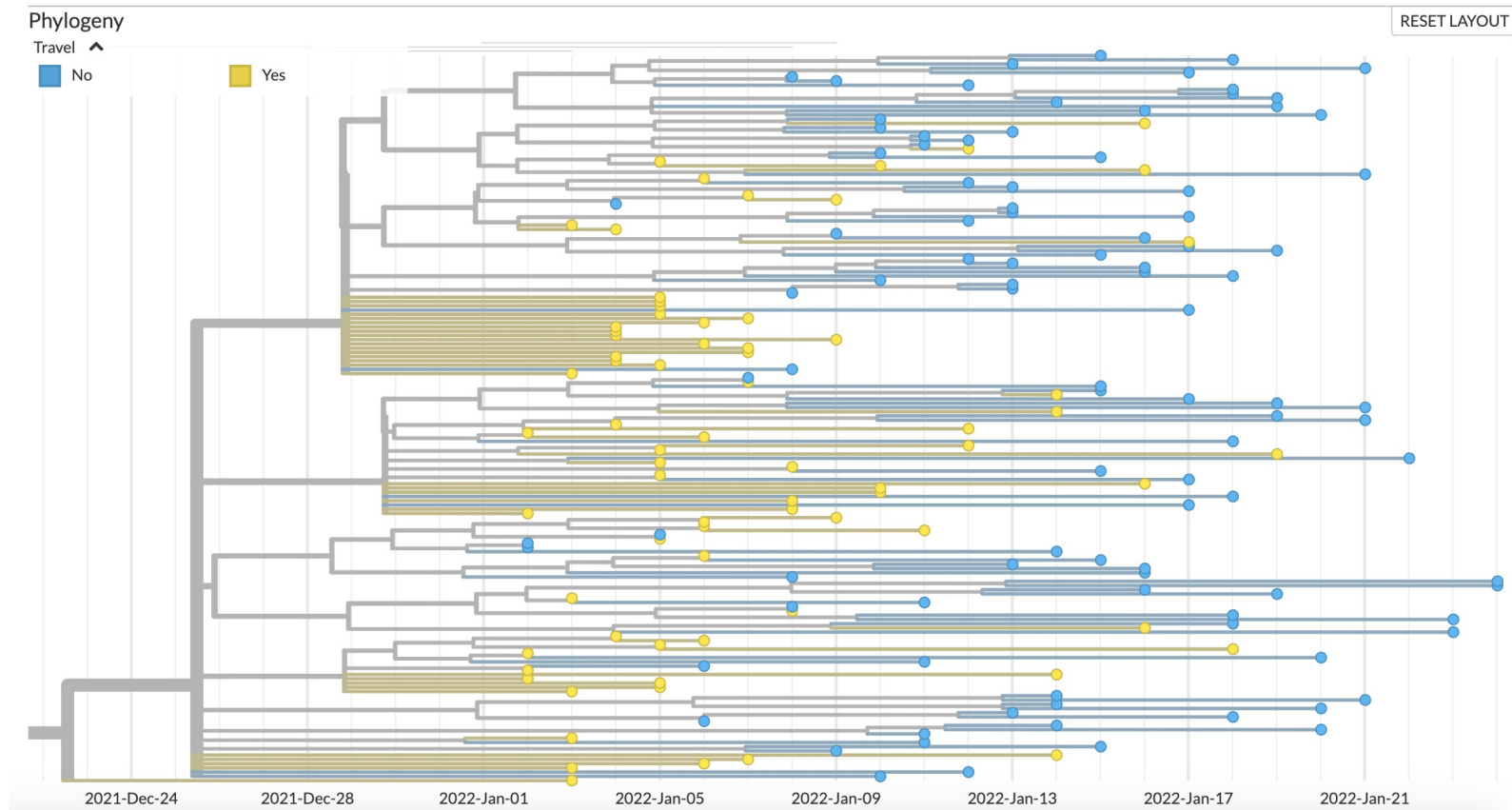
1. Enabled SARS-CoV-2 discovery
2. Sequence → creation of specific PCR tests
3. Vaccine design & therapeutic targets
4. Track spread
 - differentiate introductions of new strains from e.g., travel vs community transmission
 - determine outbreak sources: schools, LTCF, mink farms
 - monitor for variants
5. Reinfections, vaccine failures & escape mutants

SARS-CoV-2 Variants Based on WGS (n>130,000)



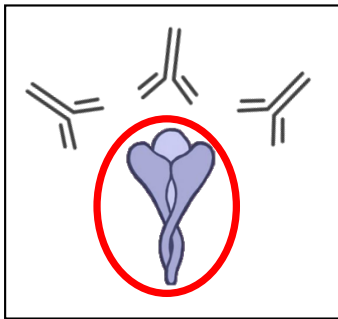
James Zlosnik

Travel vs Community Omicron BA.2 Spread

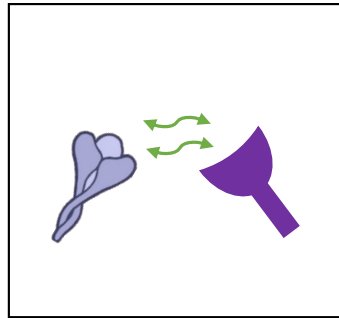


Variants can be introduced from travel or occur locally

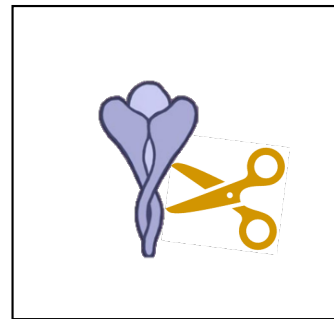
Genomics Enables Assessment of how Mutations Impact Infectivity/Transmission/Immunity



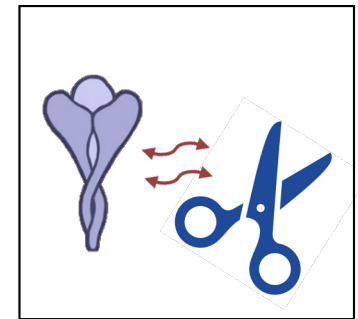
Evasion of nAb
(T19R, S45F?, T95I? G142D,
E156G/Δ157-158)



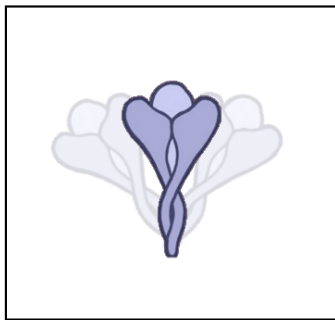
Increased ACE2
affinity
(L452R, T478K)



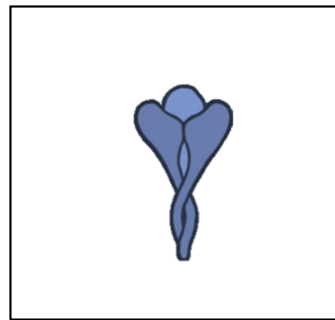
Increased Furin
affinity/cleavage
(P681R, Q675H)



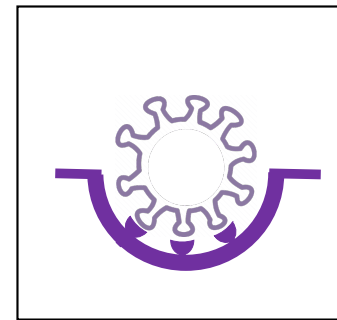
Decreased TMPRSS2
affinity
(P812S)



Decreased spike
protein stability
(Q675H, A846S, P1162L)

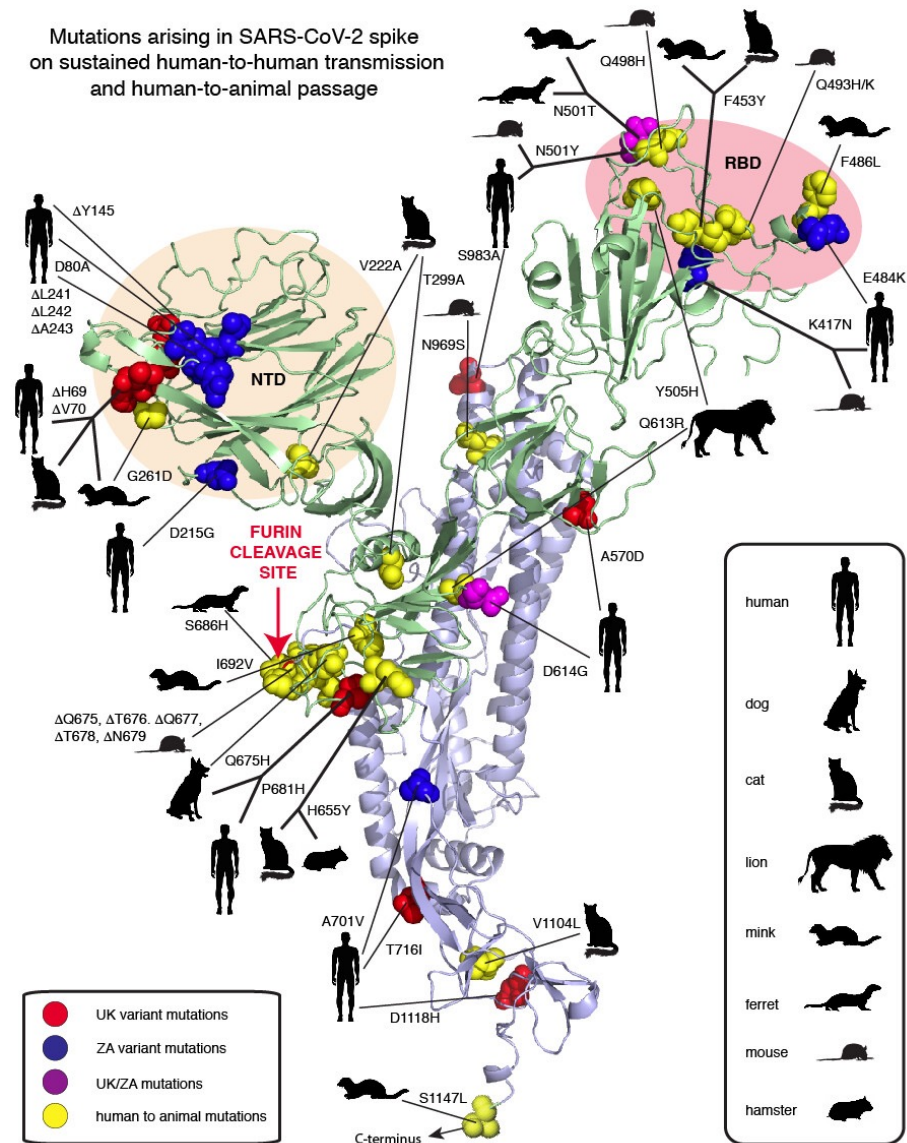


Increased spike protein
stability
(A647S, A845V)

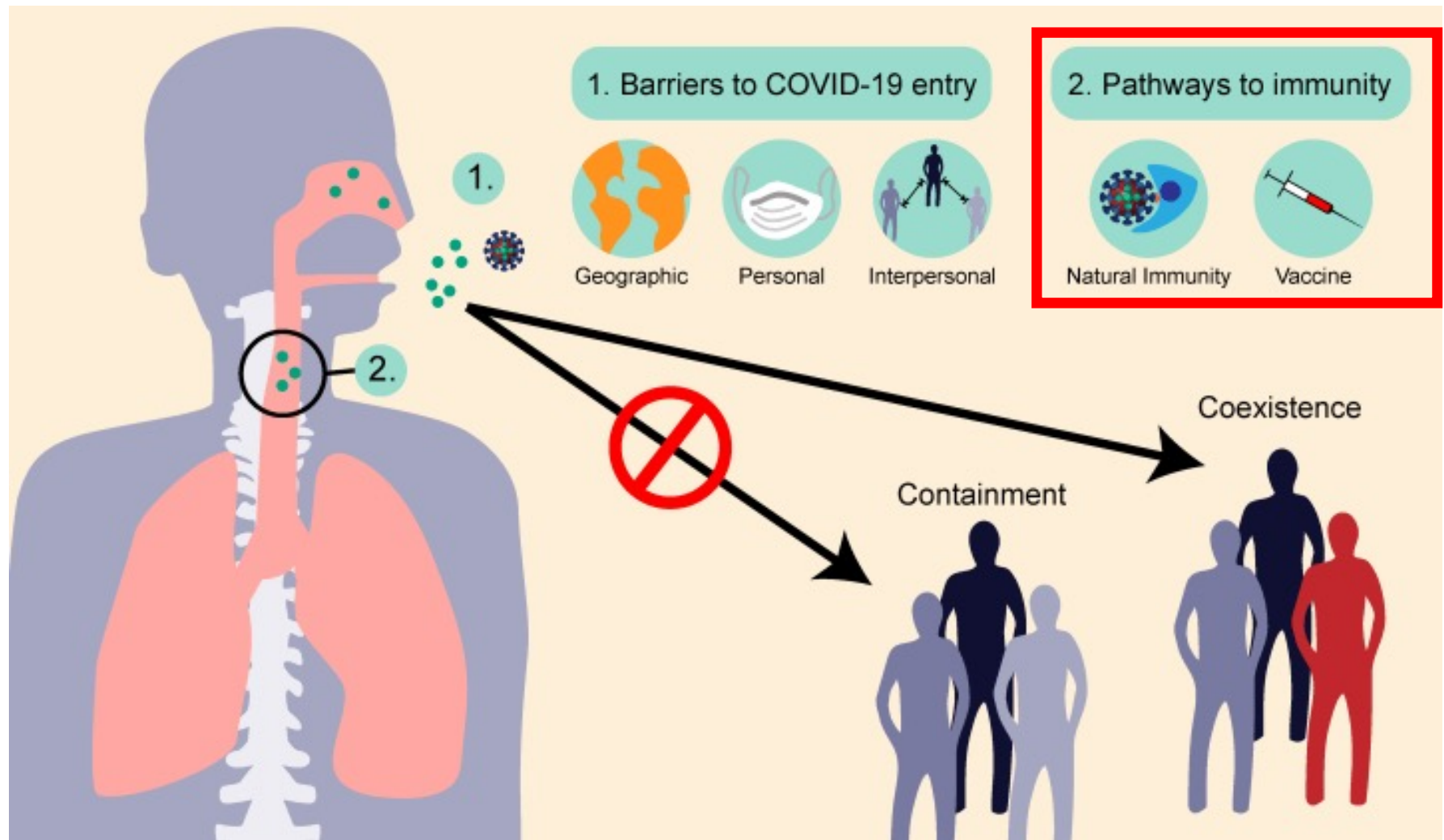


Increased fusion?
(P812S, A846S D950N, P1162L)

Mutations arising in SARS-CoV-2 spike
on sustained human-to-human transmission
and human-to-animal passage

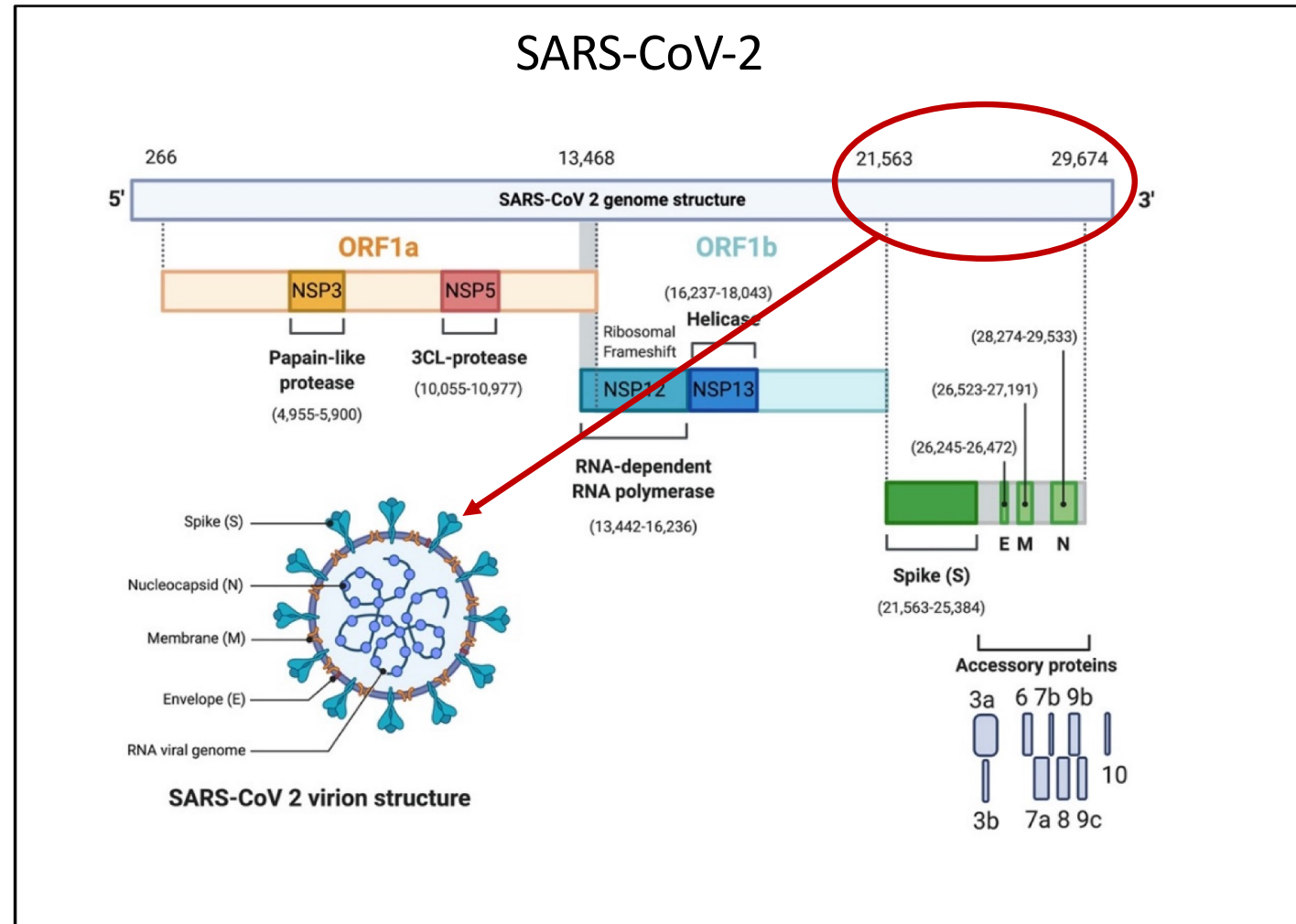


Robert F. Garry, Virological.org 2022



Chen and Senft, Covid-19 and emerging viral disease: the journey from Animals to humans 2020

- **Pathways to immunity occur either from infection which can have severe consequences or vaccination!**
- Immune response targets both structural & non-structural proteins
- Both antibody (Ab) & cell mediated immunity (CMI) are imp. for viral control
- Ab is easier to measure



Where is it going?

We need to use genomics/molecular biology to create vaccines that protect against emerging variants & related viruses!

- Optimize current vaccines – regimens/boosters, mix & match
- Develop
 - “Variant specific” vaccines – combine different strains, multivalent
 - Next generation broadly protective SARS-CoV-2 vaccines which are able to protect against existing/future variants
 - “Universal” coronavirus vaccines – protect against betacoronaviruses/pan-coronaviruses

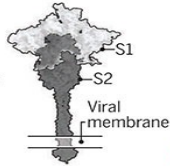
Finding the best shot

Aiming to prevent a future pandemic like COVID-19, scientists are looking for ways to immunize people against many, if not all, coronaviruses. Several strategies for these pancoronavirus vaccines focus on spike, the surface protein common to all members of the viral family.

The crown's jewel

Spike initiates an infection when part of its head (S1) binds to a human cellular receptor and a human enzyme cleaves spike so its stem (S2) can fuse with the cell. Spike varies between coronaviruses and the most conserved regions of its head or stem may serve as a broadly protective vaccine.

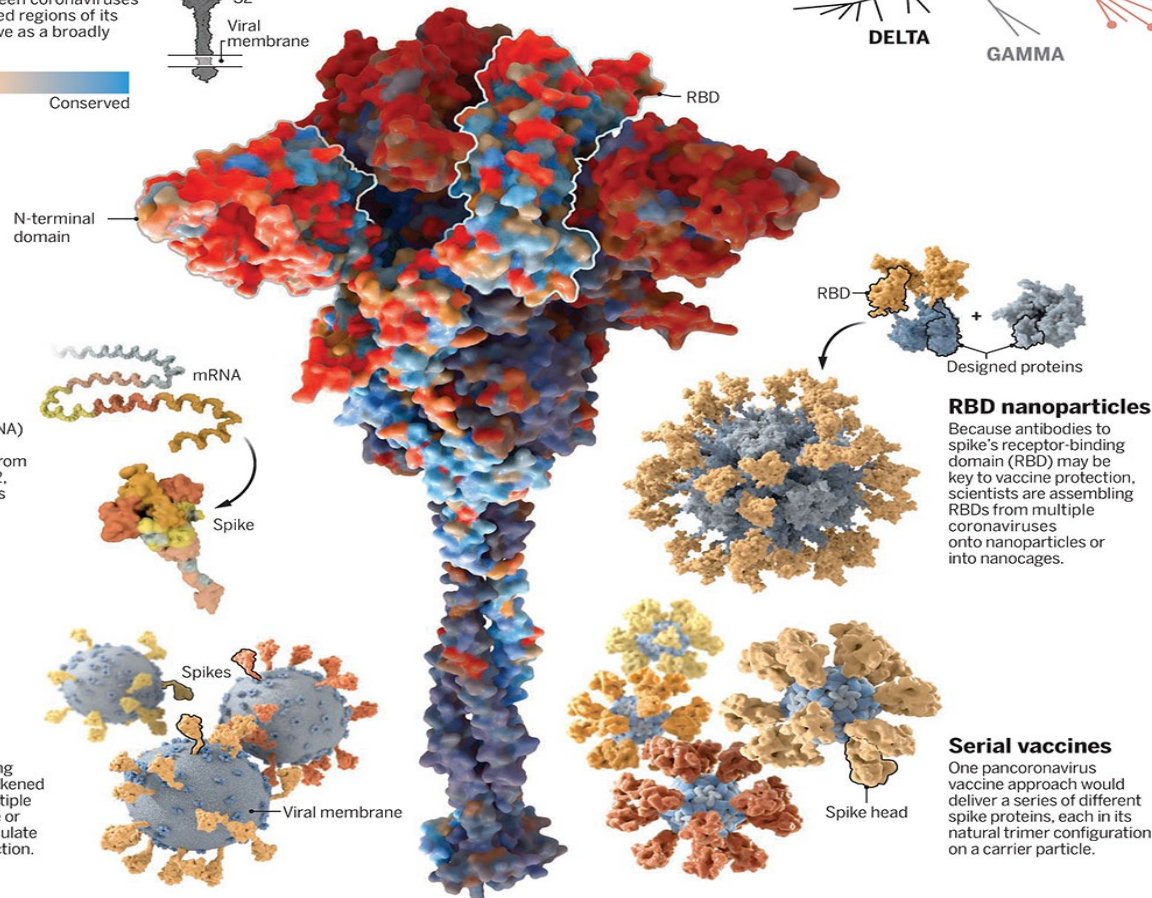
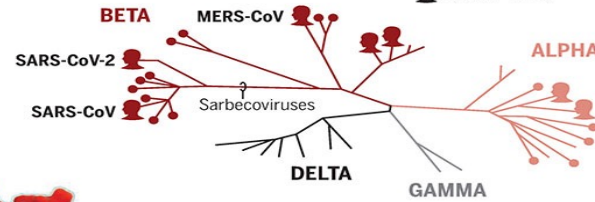
Variable Conserved



Family matters

Coronaviruses are grouped into four genera. They infect many species, although most have been found in bats. Of the seven known to infect people, four cause mild colds and three can be lethal.

Human Bat



Chimeric spike

A messenger RNA (mRNA) vaccine that combines spike gene sequences from SARS-CoV, SARS-CoV-2, and other coronaviruses can produce a mix of protein domains that may confer broad immune protection.

Whole virus

Vaccinologists have long used inactivated or weakened viruses. Combining multiple coronaviruses from one or more genera could stimulate broader immune protection.

RBD nanoparticles

Because antibodies to spike's receptor-binding domain (RBD) may be key to vaccine protection, scientists are assembling RBDs from multiple coronaviruses onto nanoparticles or into nanocages.

Serial vaccines

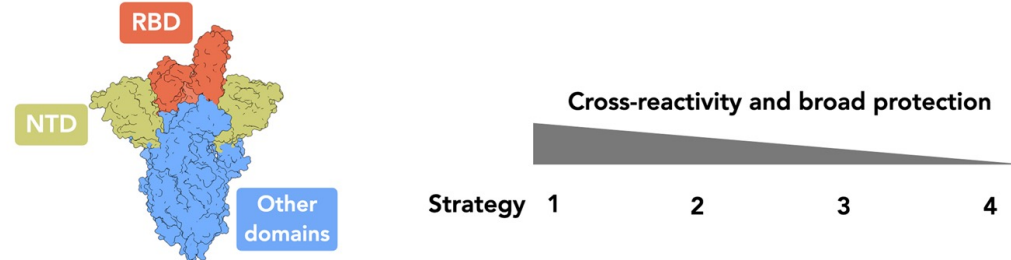
One pancoronavirus vaccine approach would deliver a series of different spike proteins, each in its natural trimer configuration on a carrier particle.

Jon Cohen Science 2021

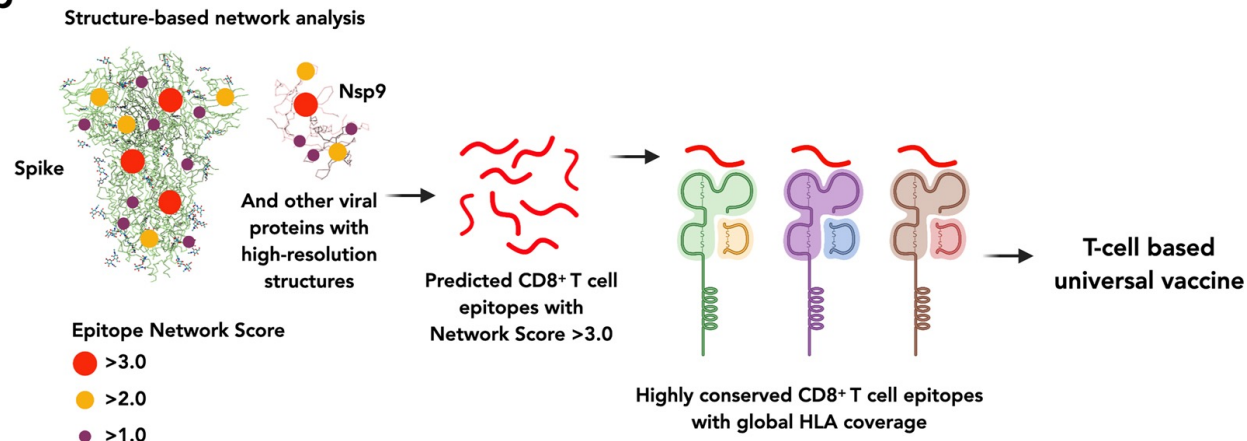
Liu et al. A novel STING agonist-adjuvanted pan-sarbecovirus vaccine elicits potent and durable neutralizing antibody and T cell responses in mice, rabbits and NHPs. Cell Res 2022

a

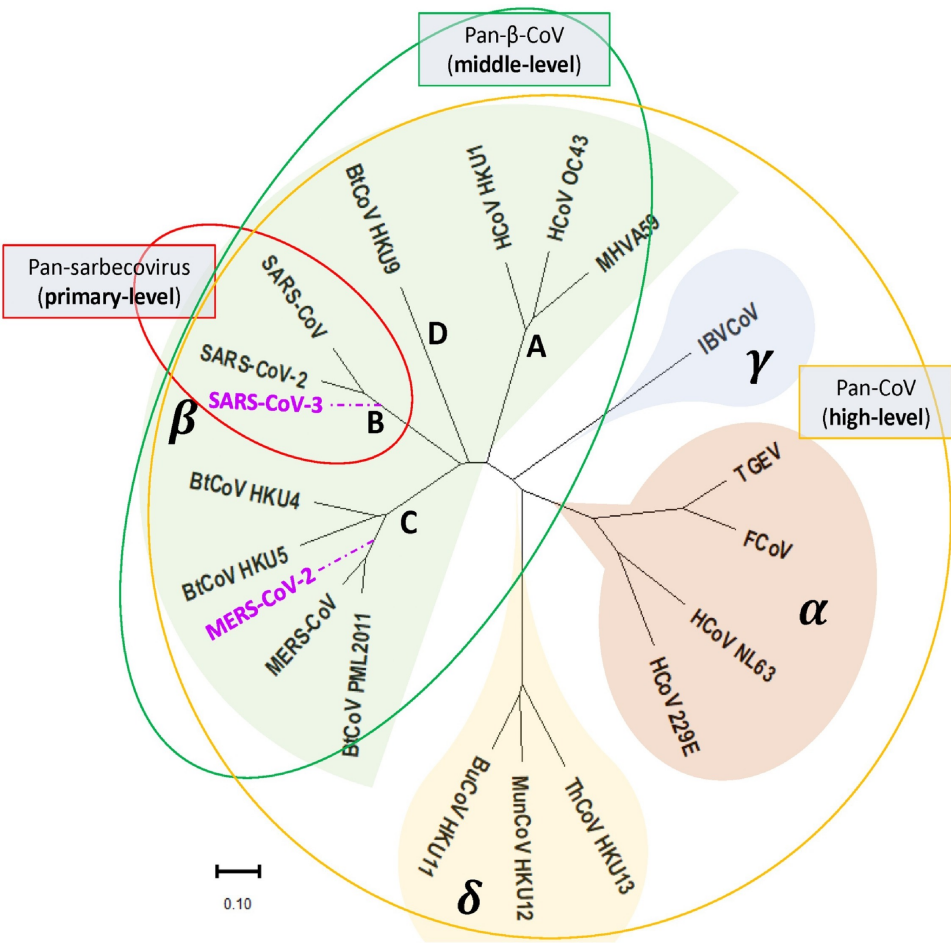
Chimeric spike design				Vaccination strategies			
Spike	NTD	RBD	Other domains	Strategy-1	Strategy-2	Strategy-3	Strategy-4
Chimera-1	HKU3-1	SARS-CoV	SARS-CoV-2	Prime/Boost	Prime	N/A	N/A
Chimera-2	SARS-CoV	SARS-CoV-2	SARS-CoV	Prime/Boost	Prime	N/A	N/A
Chimera-3	SARS-CoV-2	SARS-CoV	SARS-CoV-2	Prime/Boost	Boost	N/A	N/A
Chimera-4	SARS-CoV-2	RsSHC014	SARS-CoV-2	Prime/Boost	Boost	Prime/Boost	N/A
SARS-CoV-2	SARS-CoV-2			N/A	N/A	N/A	Prime/Boost



b

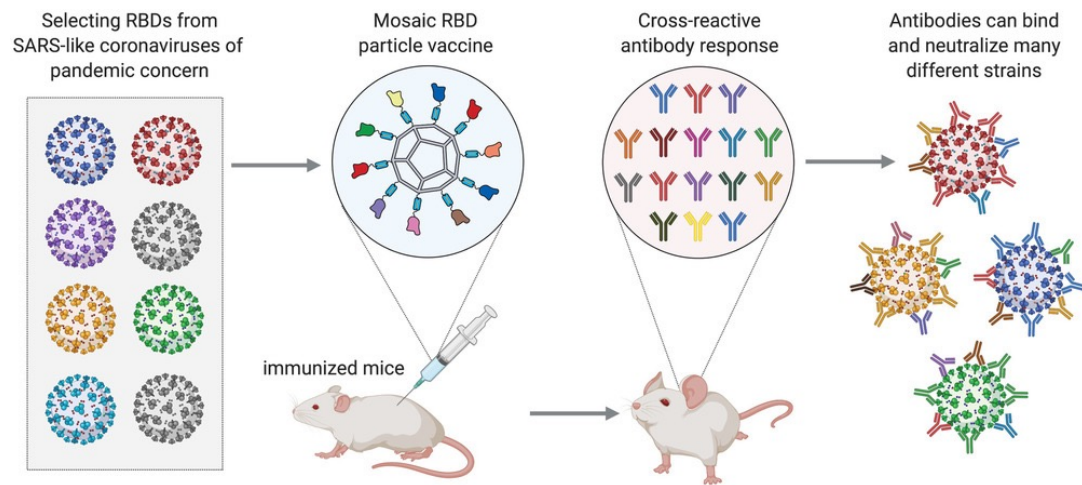


Li, H., Saphire, E.O. Novel attempts launched toward universal Sarbecovirus vaccine. *Cell Res* **31**, 1226–1227 (2021).



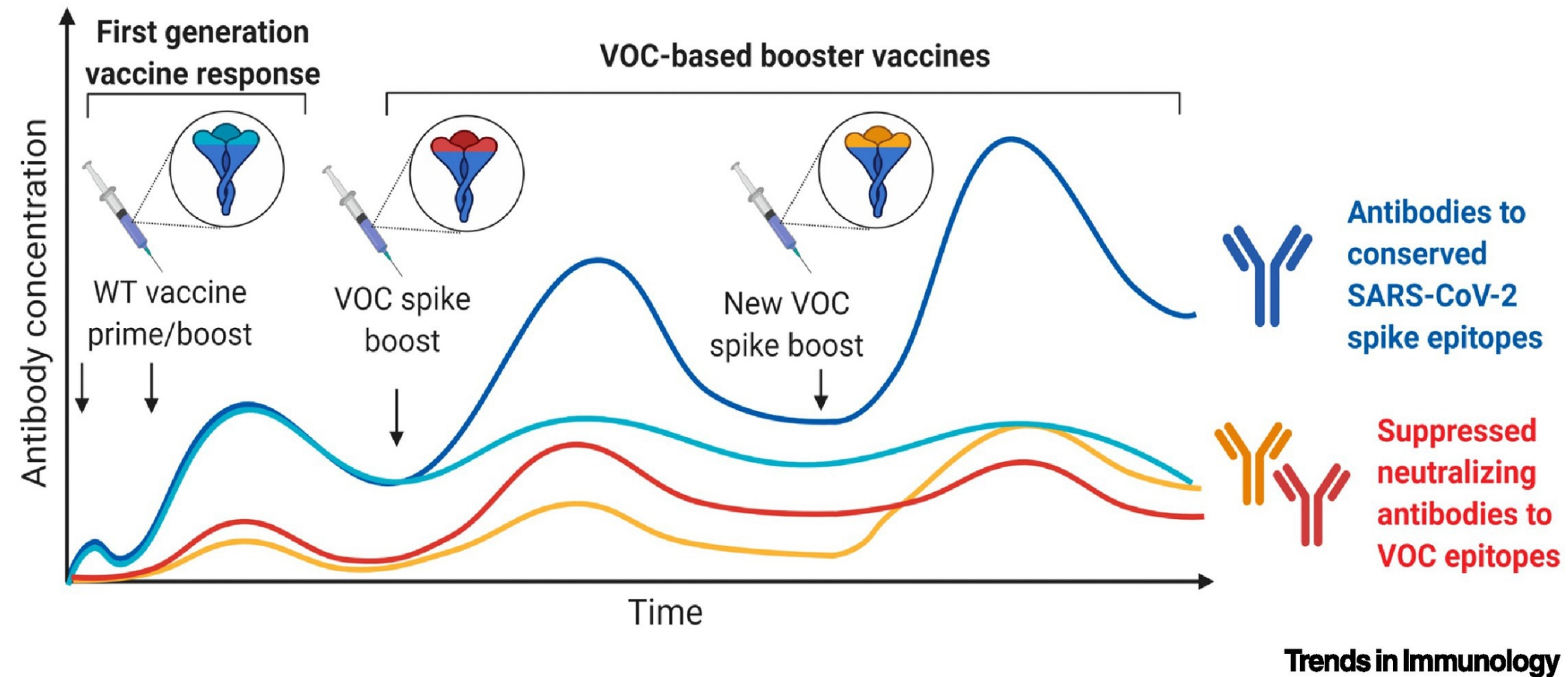
Trends in Immunology

Su et al. Developing pan-β-coronavirus vaccines against emerging SARS-CoV-2 variants of concern 2022.



Cable et al. Innovative vaccine approaches – a Keystone Symposia Report. Ann New York Acad of Sci 2022





Wheatley et al. Immune imprinting and Sars-CoV-2 vaccine design. Trends in Immunology 2021

SARS-CoV-2 Conclusions

- **What is it?**

- It's a Betacoronavirus that is here to stay!
- We are viewing this pandemic with genomic, molecular biology, & epidemiological tools that were unheard of in the past

- **Where did it come from?**

- It started as a zoonosis & decided that it likes humans & other animals
- Its survival depends on its ability to breed variants – more will emerge
- It has relatives that pose a risk for future pandemics!

- **Where is it going?**

- Current spike-based vaccines protect against severe disease but not omicron acquisition – vaccine durability & what happens with waning immunity remains a big unknown
- **We need better current and ongoing epidemiological population level correlates between vaccination status, infection status, & immunity**
- Climate change & globalization will impact the interface between humans, animals, & the environment – we need inter-sectoral "One Health" approaches that build global pandemic resiliency



SARS-CoV-2 is the Pandemic's Pandemic



everything I say

“A lie gets halfway around the world before the truth has a chance to get its pants on”

Winston Churchill