

# Evaluating neutralizing immune responses to potential pan-sarbecovirus vaccines

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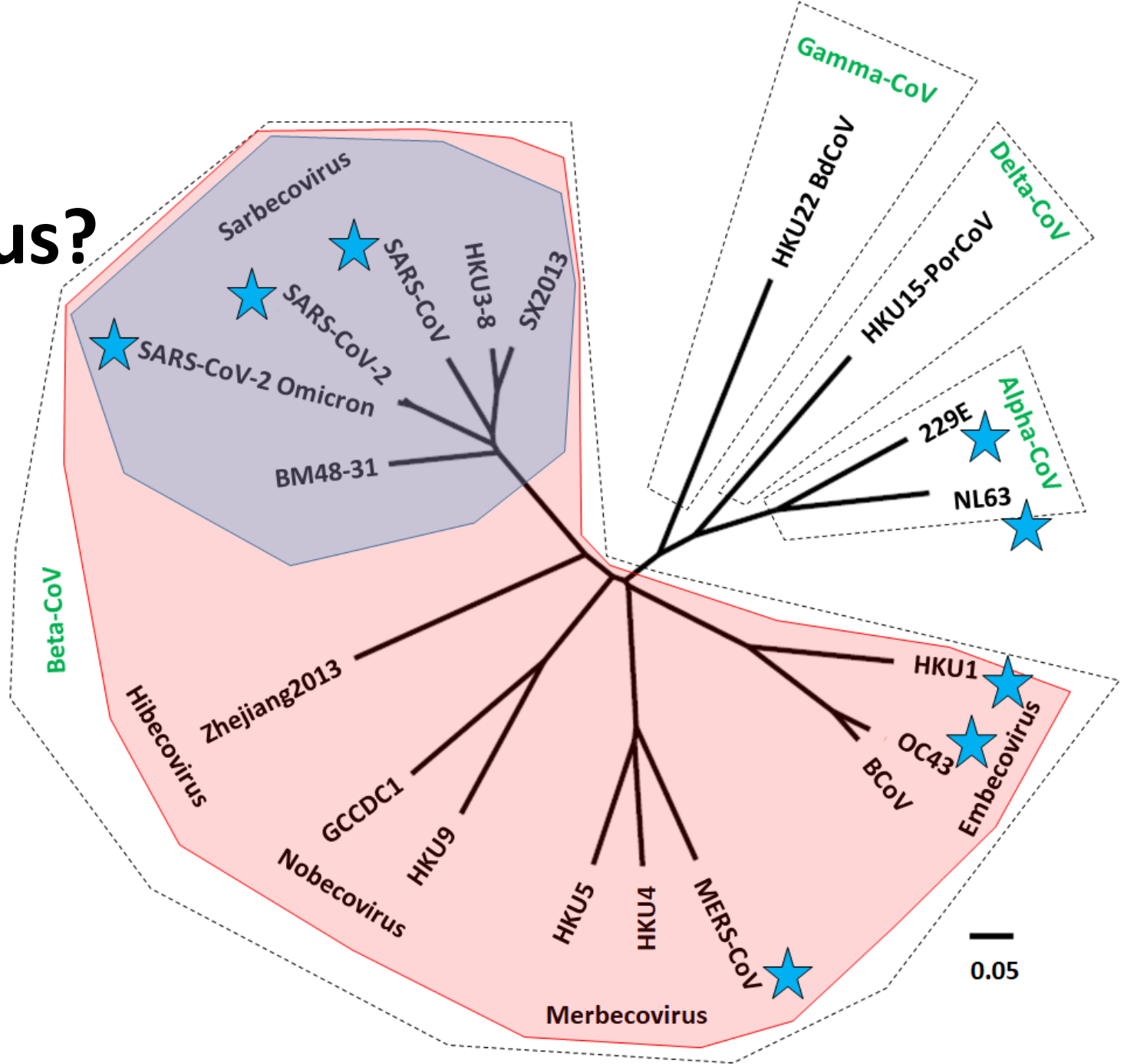
WHO Global Consultation - Why do we need a pan-sarbecovirus vaccine?

January 28<sup>th</sup>, 2022

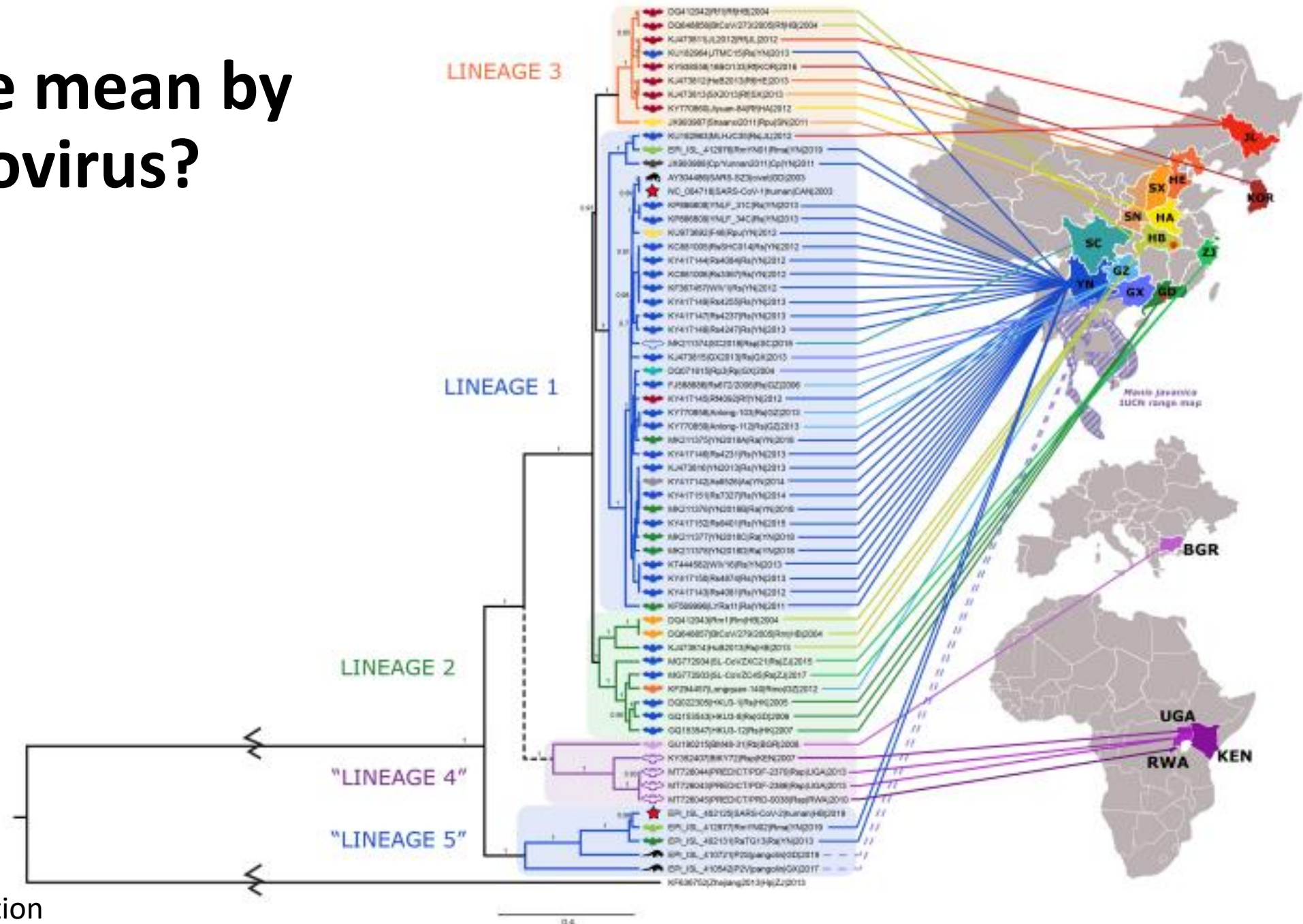


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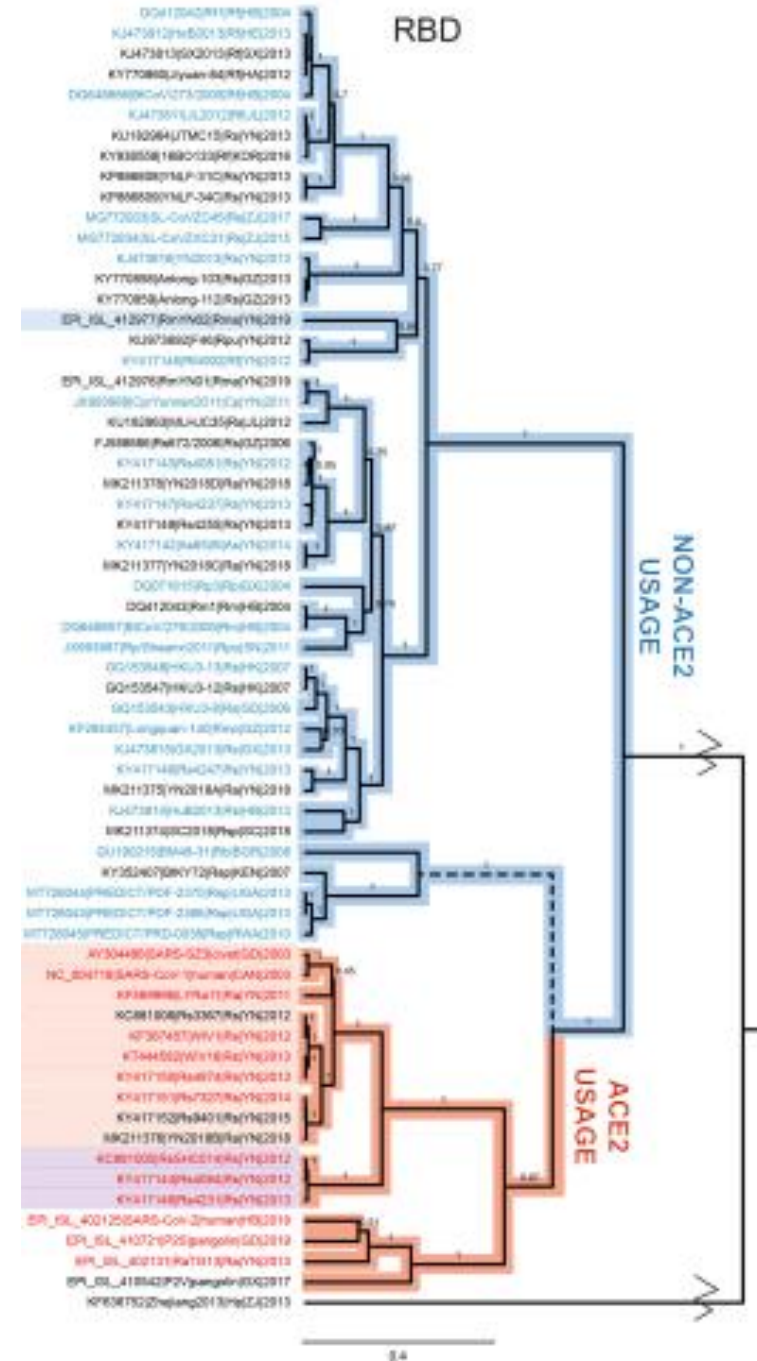
# What do we mean by pan-sarbecovirus?



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# Building a panel for measuring virus neutralization

## Variant-proof SARS-CoV-2 vaccine

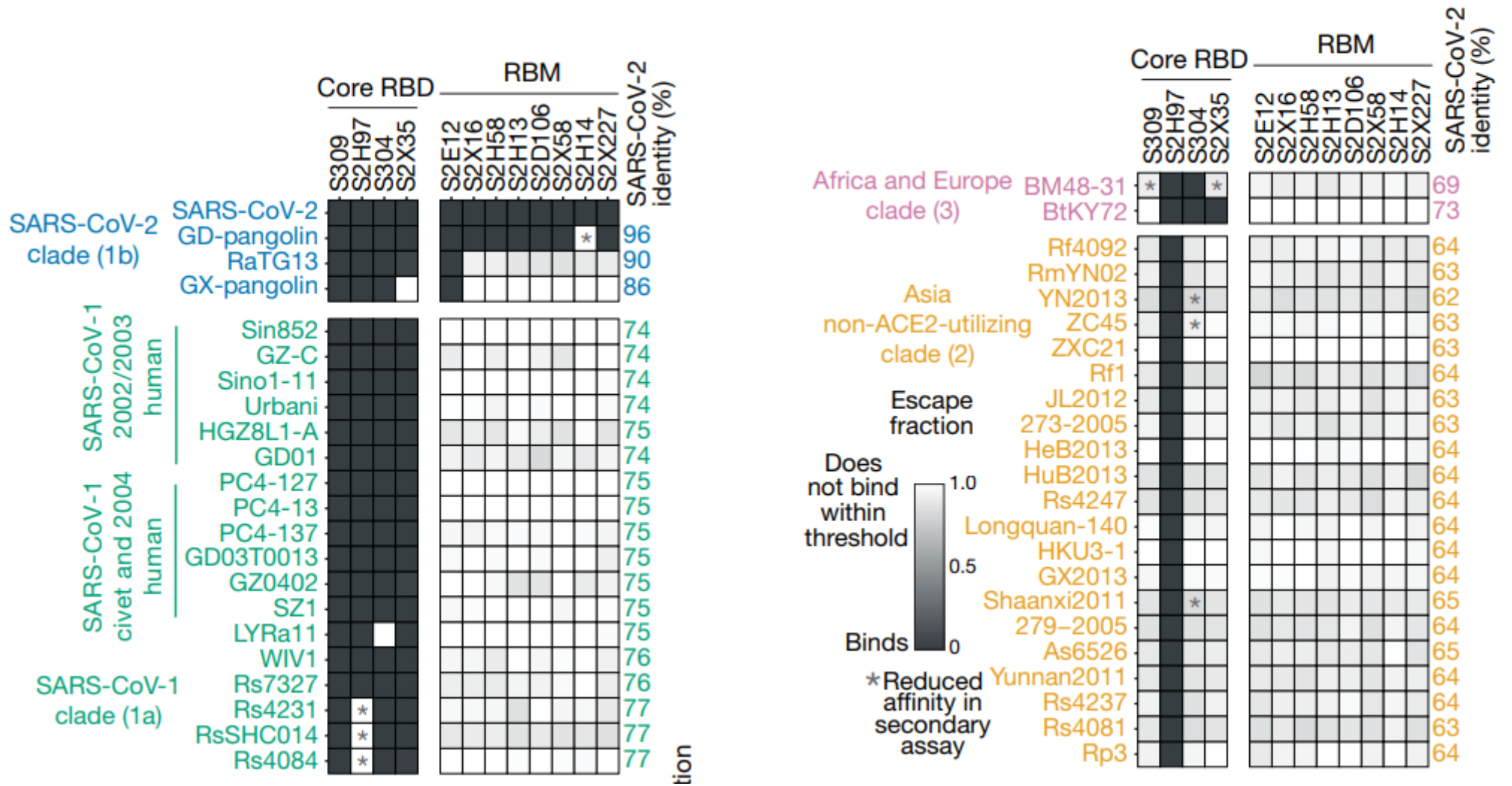
- Wild type SARS-CoV-2
- A selection of VoCs and Vols
- BA.1 and BA.2 (Omicron)
- To probe the extremes
  - SARS-CoV-1
  - RaTG13
  - WIV
- Artificial escape mutants
  - E.g. PMS20 (Schmidt *et al.*, NEJM, 2021)
  - Mutants from yeast libraries (Jesse Bloom lab)
  - Etc.

## Pan-sarbecovirus vaccine

- A selection of sarbecoviruses from all clades (ACE2 and non-ACE2 binding)
- Wild type SARS-CoV-2
- A selection of VoCs and Vols
- BA.1 and BA.2 (Omicron)
- To probe the extremes
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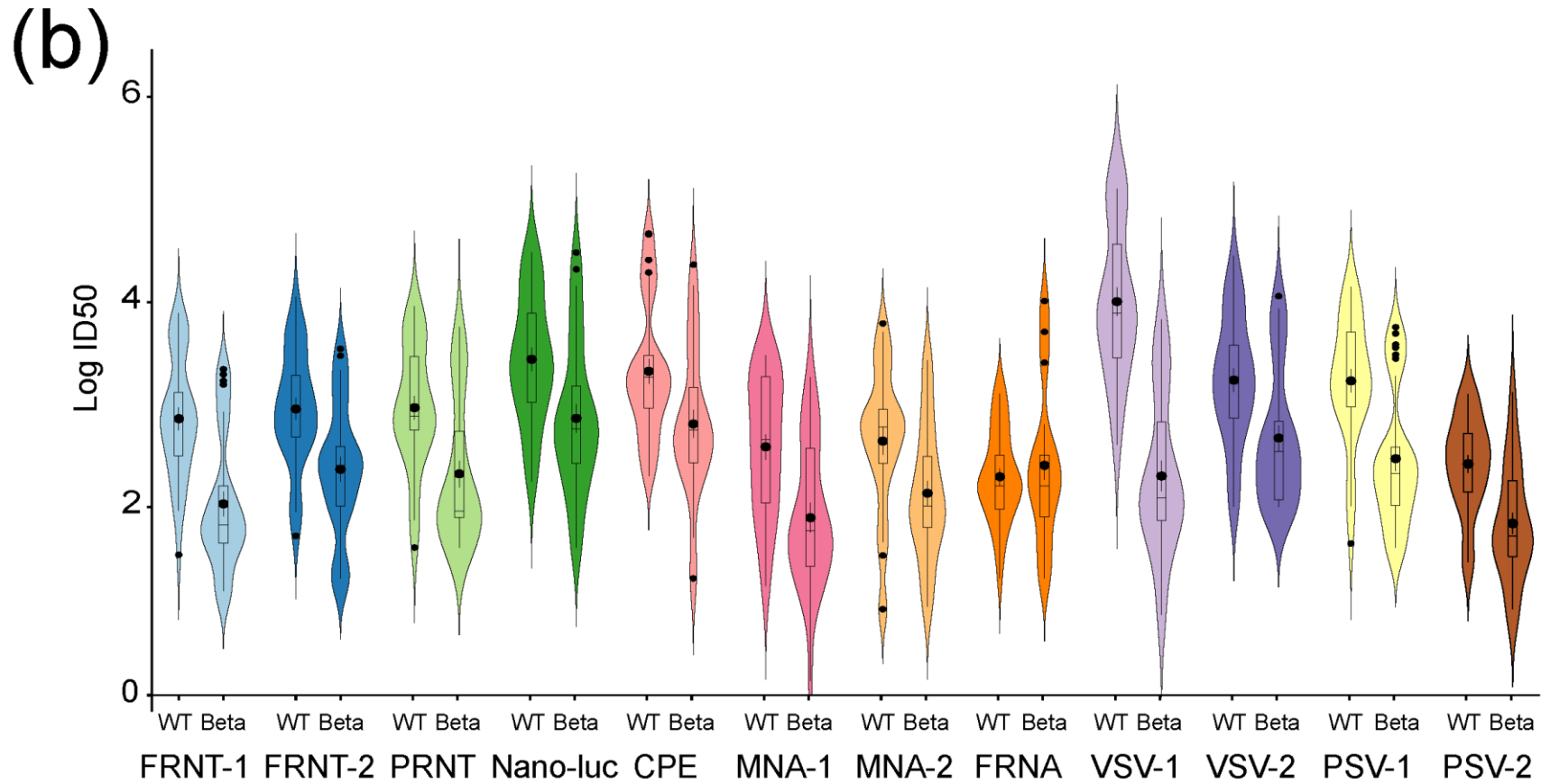
# Example of panels (here for RBD binding assays)



# Available neutralization assays

- **Live virus neutralization assays**
  - **Plaque reduction neutralization test (PRNT)**
  - **Focus reduction neutralization test (FRNT)**
  - **Microneutralization assay (MN)**
- **Pseudotyped particle assays**
  - **Lentiviral systems**
  - **VSV-based systems**
    - **Single cycle**
    - **Multi-cycle (replication competent)**
- **ACE2-RBD interaction inhibition assay (ARIIA)**

# Assessing neutralization





# Assessing neutralization

- For SARS-CoV-2, VoC and Vol authentic virus could be used in PRNT/FRNT/MN
- For SARS-CoV and related viruses authentic virus could be used as well but may fall under e.g. Select Agent regulations or similar
- For many sarbecoviruses, only sequences are known but viruses have not be isolated
  - Could be used in pseudotyped particles (VSV, lentiviral systems etc.)
  - Could be rescued in e.g. SARS-CoV-2 backbones → likely GoF and therefore not recommended
- Artificial escape mutants can also safely be used in pseudotyped particle assays
- RBD-ACE2 interaction inhibition assays are likely less helpful (especially for non-ACE2 using sarbecoviruses)

# Conclusions/needs

- **A carefully curated panel of diverse sarbecovirus constructs for pseudotyped entry inhibition assays would be very helpful**
- **The panel could be distributed as plasmids e.g. by NIBSC for global use**
- **Reagents for assay standardization would be helpful**
  - **We would likely need to rely on mAbs like S2H97 are needed for this**
- **More research into non-ACE2 binding sarbecoviruses is needed to identify receptors and suitable cell lines for neutralization assays**