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Sarah Temmam, Khamsing Vongphayloth, Tran Cong Tu, Béatrice Regnault, Massimiliano Bonomi, Eduard Baquero, Cécile Hérate, Sandie Munier, Delphine Chrétien, Flora Donati, et al.

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# Horseshoe bats from Southeast Asia host a high diversity of Sarbecoviruses, including close ancestors of SARS-CoV-2.

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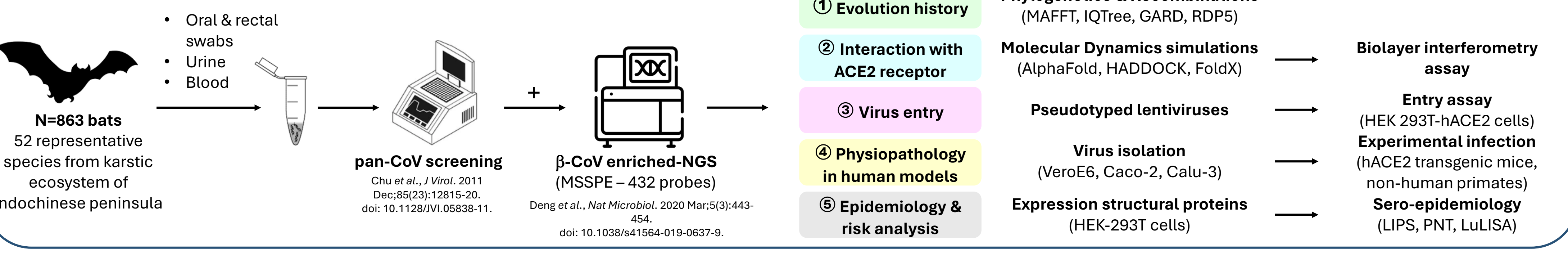
## Background

- Bats are **reservoirs** of many alpha- & beta-CoVs
- > **4000 CoVs** identified in **14 bat species** Ruiz-Aravena et al., 2022 Nat. Rev. Microbiol. DOI: 10.1038/s41579-021-00652-2
- SE Asia: huge richness of horseshoe bat species
- Many **outbreaks** due to CoVs, *Sarbecovirus* at the origin of the last human pandemic Keusch et al., 2022 PNAS. DOI: 10.1073/pnas.2202871119

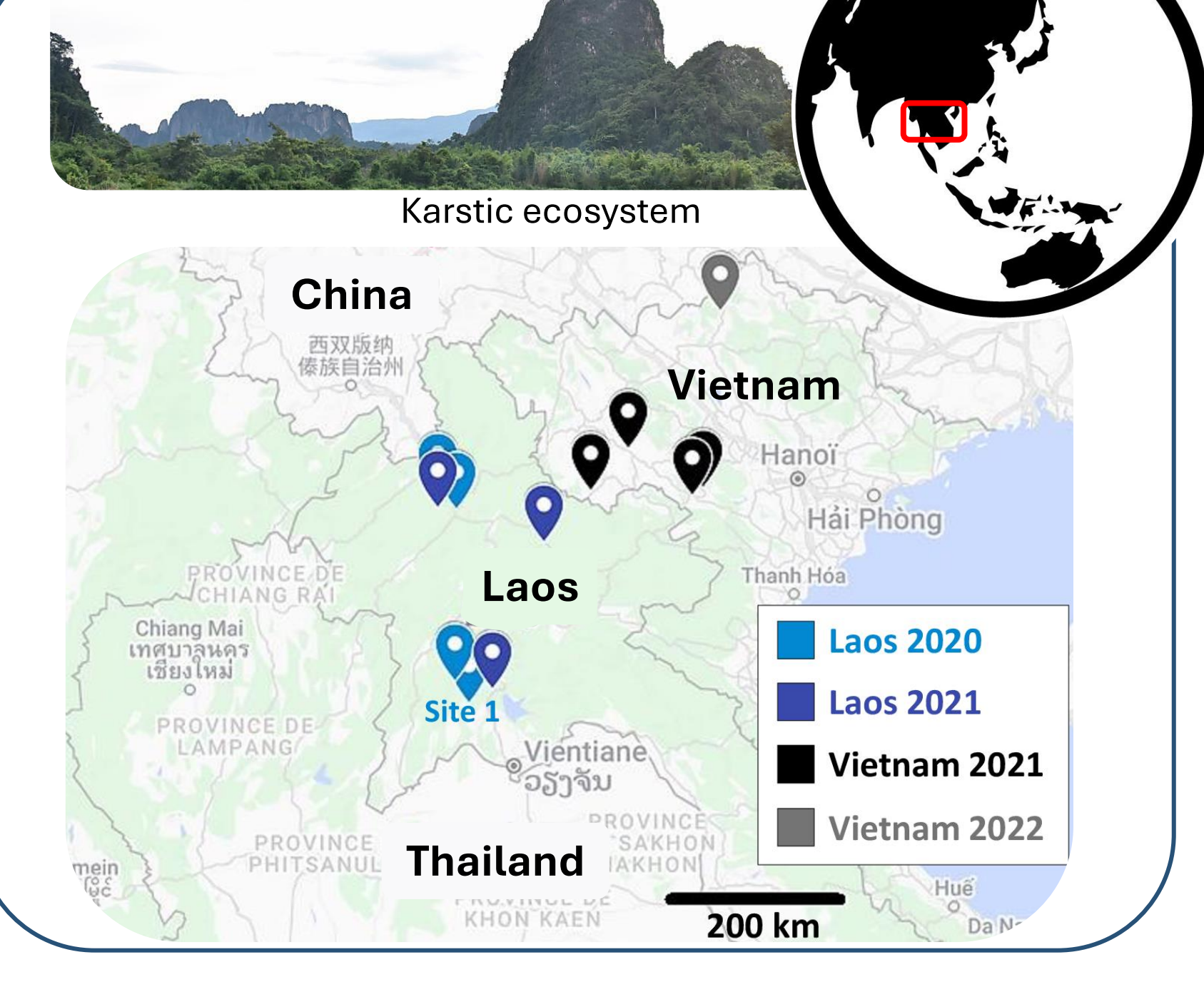
## Objectives

- Understanding of the origins, natural history & dissemination of *Sarbecovirus*
  - Identify **natural reservoirs** of *Sarbecovirus*
  - Decipher **interspecies transmission** (bat-to-bat, bat-to-mammals, bat-to-humans)
- Study the **pathogenicity** of bat *Sarbecovirus* in human-relevant models
- Detect past CoV infections in humans
  - Identify **early circulation** of *Sarbecovirus* before global spread

## Methods

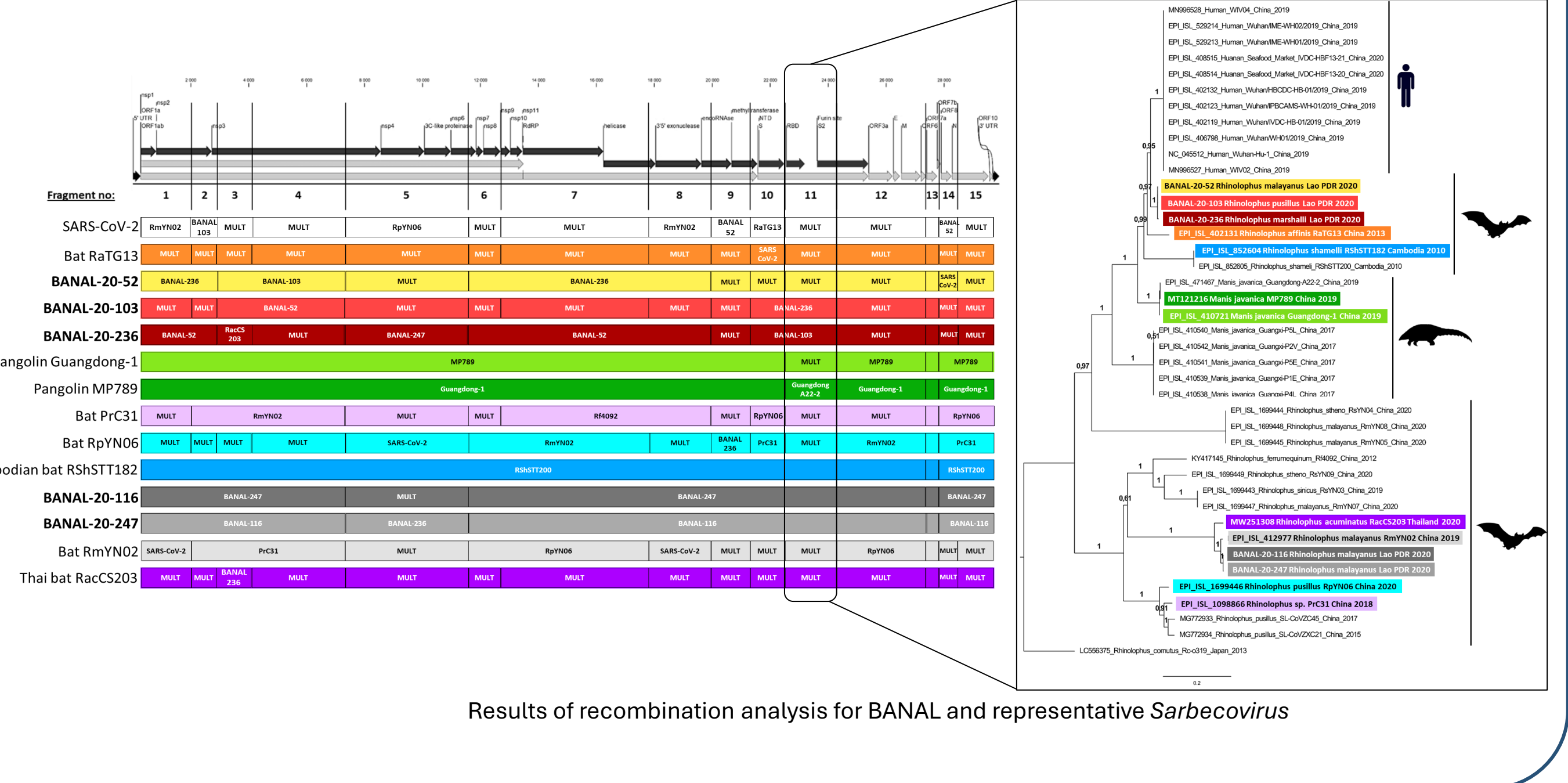
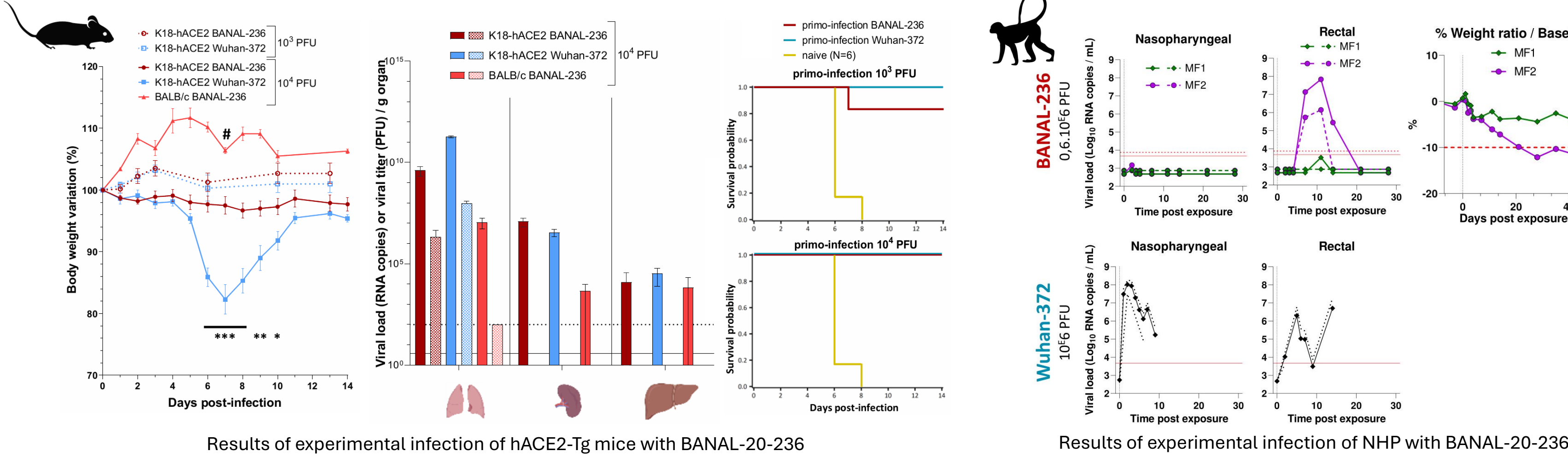
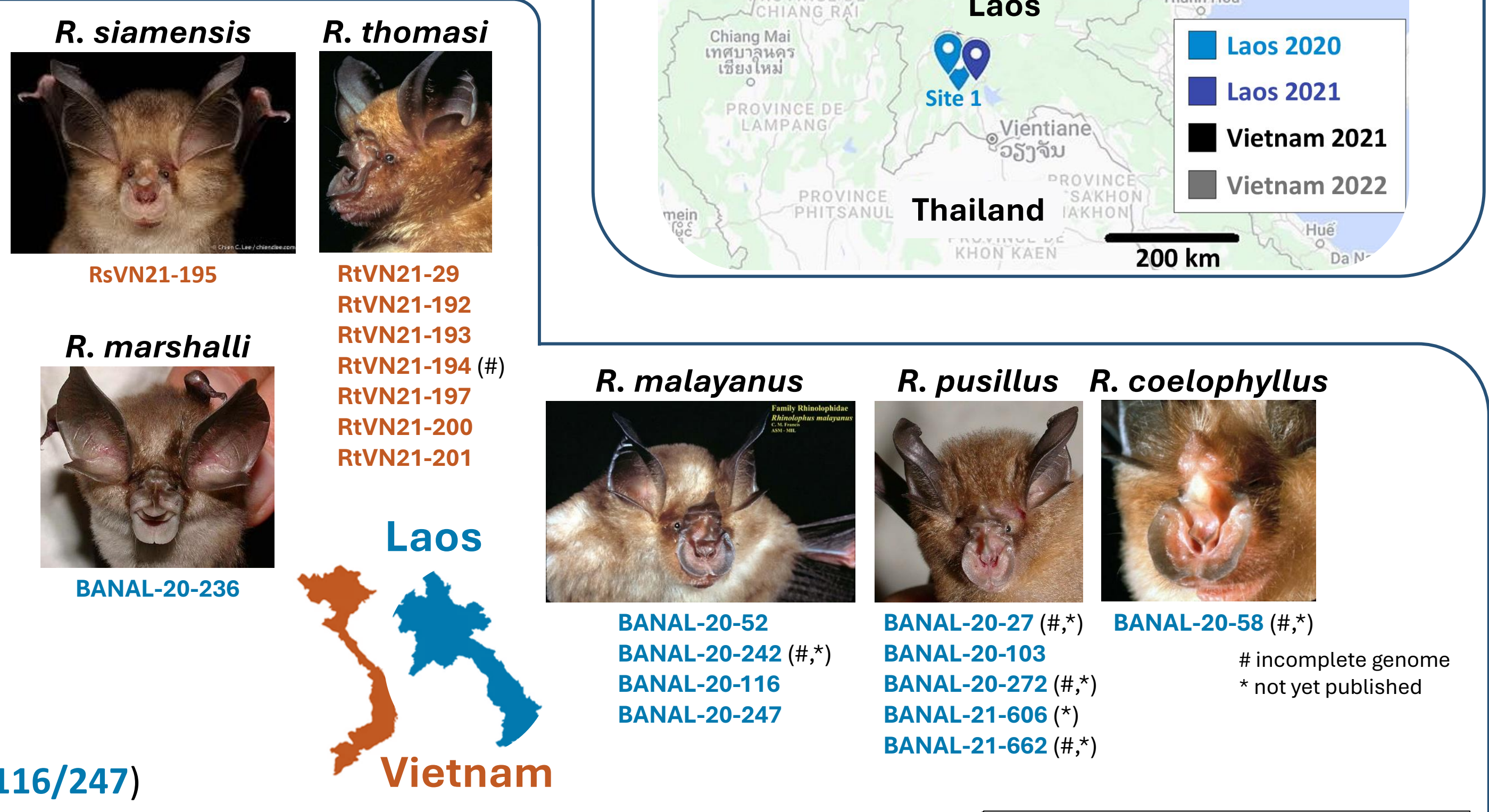


## Study sites



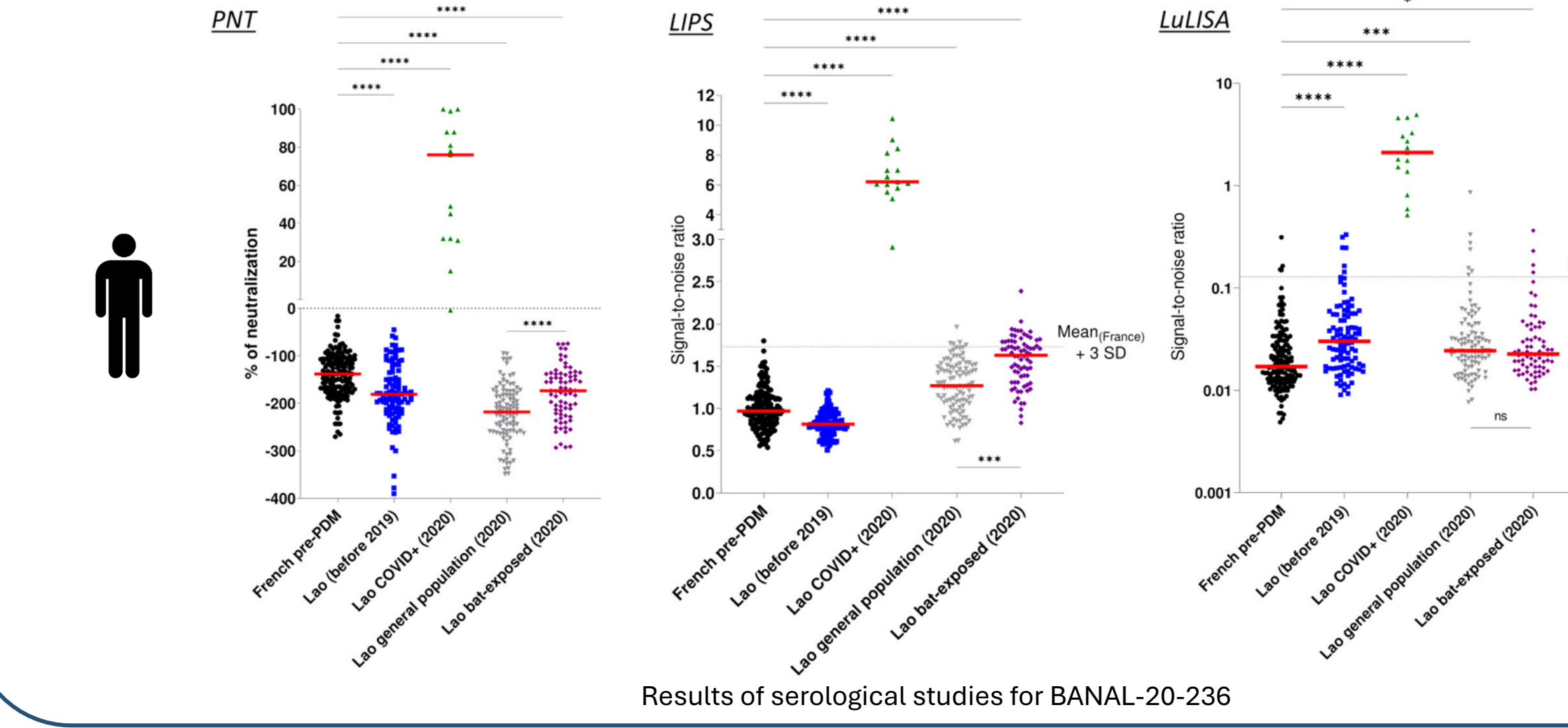
## Results

- Identification of **19 novel Sarbecovirus** in 6 *Rhinolophus* sp. bat species:
  - R. siamensis* & *R. thomasi* in Vietnam
  - R. marshalli*, *R. malayanus*, *R. pusillus* & *R. coelophyllus* in Laos
  - Rhinolophus* sp. are the **natural reservoirs** of *Sarbecovirus*
  - No *Sarbecovirus* identified in other bat species
  - No furin site in Spike protein of bat *Sarbecovirus*
- Recombination and cross-species transmission are major drivers of virus evolution:
  - Concomitant circulation of ≠ lineages in same cave → risk of recombination
  - Same *Sarbecovirus* strain identified in ≠ bat species → **cross-species transmission** between bats that live in **sympatry**
- Host range of bat *Sarbecovirus* partly driven by ability to interact with ACE2 receptor:
  - Genomic signature of Receptor-Binding Domain in Spike protein
    - Deletion** in RBD = **inability** to interact with ACE2 (**RsVN21-195, RtVN21-29 to -201 + BANAL-20-116/247**)
    - Conservation** of contact residues = **ability** to interact with ACE2 (**BANAL-20-52/103/236, -21-606**)
  - Interaction with hACE2 receptor
    - No interaction & no entry in human cells (**RsVN21-195, RtVN21-29 to -201 + BANAL-20-116/247**) → involvement of another receptor?
    - High affinity & ACE2-dependant entry in human cells (**BANAL-20-52/103/236, -21-606**) → **risk of spillover?**
- Pathogenicity of bat *Sarbecovirus* in human-relevant models (e.g. BANAL-20-236):
  - Tg mice**: no significant body weight loss & virus load in lungs << SARS-CoV-2 (Wuhan strain) **cross-protection** against SARS-CoV-2 <sup>614</sup> challenge
  - NHP**: no clinical signs & transient virus load in the **enteric route** compared to SARS-CoV-2



- Past Sarbecovirus exposure** of humans highly exposed to bat feces
  - Lack of serological detection in bat guano collectors (Laos)
  - Only cross-reactive Ab detected for COVID-19 patients

- Enterotropism of bat *Sarbecovirus*
- No/few circulation of bat *Sarbecovirus* in humans



Acquisition of a furin site & transmission by aerosol route in intermediate host?

## Conclusion & perspectives

- Ecological factors** contributing to a possible emergence of *Sarbecovirus*:
  - Bat species richness → horseshoe bats are natural reservoirs
  - Bat lifestyle → colonies with mixed species more prone to exchange viruses through feco-oral route
  - Co-circulation of different virus strains in same ecosystem → risk of recombination
  - Human exposure → ↑ risk of contact with bat feces for guano collectors, religious communities, tourists visiting caves
- Emergence of SARS-CoV-2**: questions to be solved
  - Origin of furin cleavage site → likely acquired through recombination
    - Origin of donor sequence (virus genome, host transcript, etc.)?
    - Host for recombination (bat, intermediate host, etc.)?
  - Route of transmission to human populations
    - Furin acquisition = unique event to explain shift from enteric to respiratory tropism?
- Proof-of-concept** to study the emergence of CoVs in Indochinese peninsula
- Perspectives**: New collections from Vietnam, at the border with China

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