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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.

**Sarah Temmam**<sup>1</sup>, Khamsing Vongphayloth<sup>2</sup>, Tran Cong Tu<sup>3</sup>, Béatrice Regnault<sup>1</sup>, Massimiliano Bonomi<sup>4</sup>, Eduard Baquero<sup>5</sup>, Cécile Hérat<sup>6</sup>, Sandie Munier<sup>7</sup>, Flora Donati<sup>8</sup>, Delphine Chrétien<sup>1</sup>, Thomas Bigot<sup>9</sup>, Léa Vendramini<sup>1</sup>, Philippe Pérot<sup>1</sup>, Yasaman Karami<sup>4</sup>, Océane Dehan<sup>8</sup>, Faustine Amara<sup>7</sup>, Bounsavane Douangboubpha<sup>10</sup>, Daosavanh Sanamxay<sup>10</sup>, Vilakhan Xayaphet<sup>10</sup>, Phetphoumin Paphaphanh<sup>10</sup>, Somphavanh Somlor<sup>2</sup>, Khaithong Lakeomany<sup>2</sup>, Nothasin Phommavanh<sup>2</sup>, Mikael Attia<sup>7</sup>, Laurine Conquet<sup>11</sup>, Grégory Jouvion<sup>12</sup>, Juliana Pipoli Da Fonseca<sup>13</sup>, Thomas Cokelaer<sup>13</sup>, Tran Nhu Duong<sup>3</sup>, Tran Vu Phong<sup>3</sup>, Nguyen Thi Yen<sup>3</sup>, Hoang Ngoc Anh<sup>3</sup>, Tran Hai Son<sup>3</sup>, Pham Tuan Anh<sup>3</sup>, Vu Dinh Thong<sup>14</sup>, Francis Relouzat<sup>6</sup>, Thibaut Naninck<sup>6</sup>, Julien Lemaître<sup>6</sup>, Nathalie Derreudre-Bosquet<sup>6</sup>, Quentin Pascal<sup>6</sup>, Michael Nilges<sup>4</sup>, Vincent Lacoste<sup>2</sup>, Xavier Montagutelli<sup>11</sup>, Vu Sinh Nam<sup>3</sup>, Roger Le Grand<sup>6</sup>, Félix A. Rey<sup>5</sup>, Sylvie van der Werf<sup>7</sup>, Paul T. Brey<sup>2</sup>, Marc Eloit<sup>1</sup>.

contact: [sarah.temmam@pasteur.fr](mailto:sarah.temmam@pasteur.fr) / [marc.eloit@pasteur.fr](mailto:marc.eloit@pasteur.fr)

- Institut Pasteur, Université de Paris, Pathogen Discovery Laboratory, Paris, France.
- Institut Pasteur du Laos, Vientiane, Lao People's Democratic Republic.
- National Institute of Hygiene and Epidemiology, Hanoi 100000, Vietnam.
- Institut Pasteur, Université de Paris, CNRS UMR 3528, Structural Bioinformatics Unit, Paris, France.
- Institut Pasteur, Université de Paris, CNRS UMR 3569, Structural Virology Unit, Paris, France.
- Center for Immunology of Viral, Auto-immune, Hematological and Bacterial Diseases (IMVA-HB/IDMIT), Université Paris-Saclay, Inserm, CEA, Fontenay-aux-Roses, France.
- Institut Pasteur, Université de Paris, CNRS UMR 3569, Molecular Genetics of RNA Viruses Unit, Paris, France.
- Institut Pasteur, Université Paris Cité, National Reference Center for Respiratory Viruses, Paris, France.
- Bioinformatic and Biostatistic Hub - Computational Biology Department, Institut Pasteur, Université Paris Cité, Paris, France.
- Faculty of Environmental Sciences, National University of Laos, Vientiane, Lao People's Democratic Republic.
- Institut Pasteur, Université Paris Cité, Mouse Genetics Laboratory, Paris, France.
- Ecole Nationale Vétérinaire d'Alfort, Unité d'Histologie et d'Anatomie Pathologique, Maisons-Alfort, France.
- Biomics Platform, CZRT, Institut Pasteur, Université Paris Cité, Paris, France.
- Institute of Ecology and Biological Resources, Vietnam Academy of Science and Technology (VAST), Hanoi 70072, Vietnam.

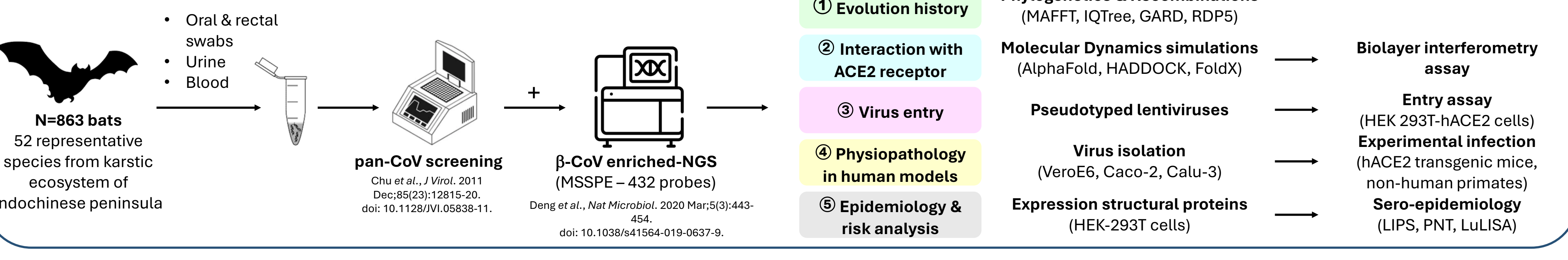
## Background

- 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; Zhou et al., 2021 Cell. DOI: 10.1016/j.cell.2021.06.008; Sanchez et al., 2022 Nat. Comm. DOI: 10.1038/s41467-022-31860-w

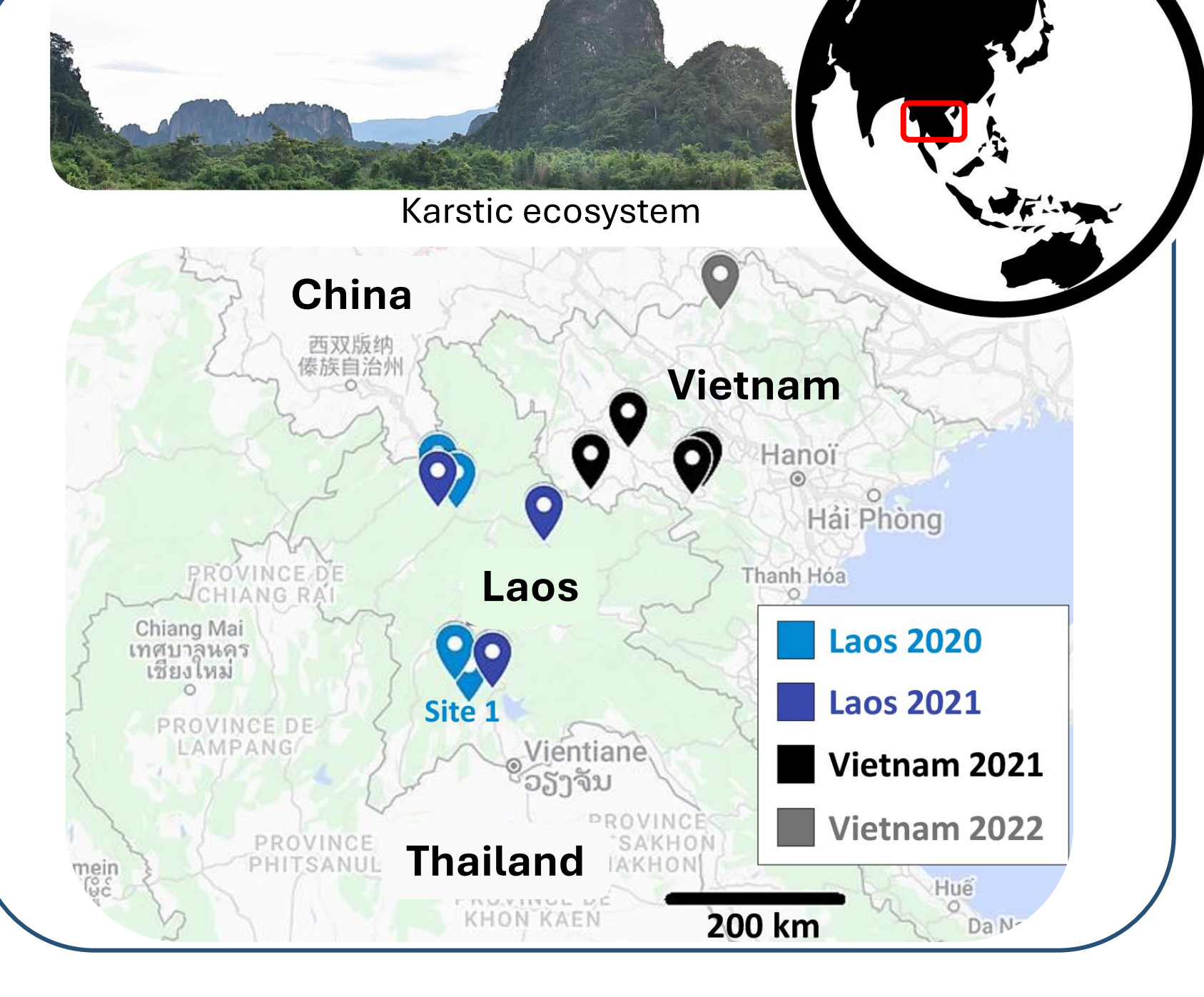
## Objectives

- 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

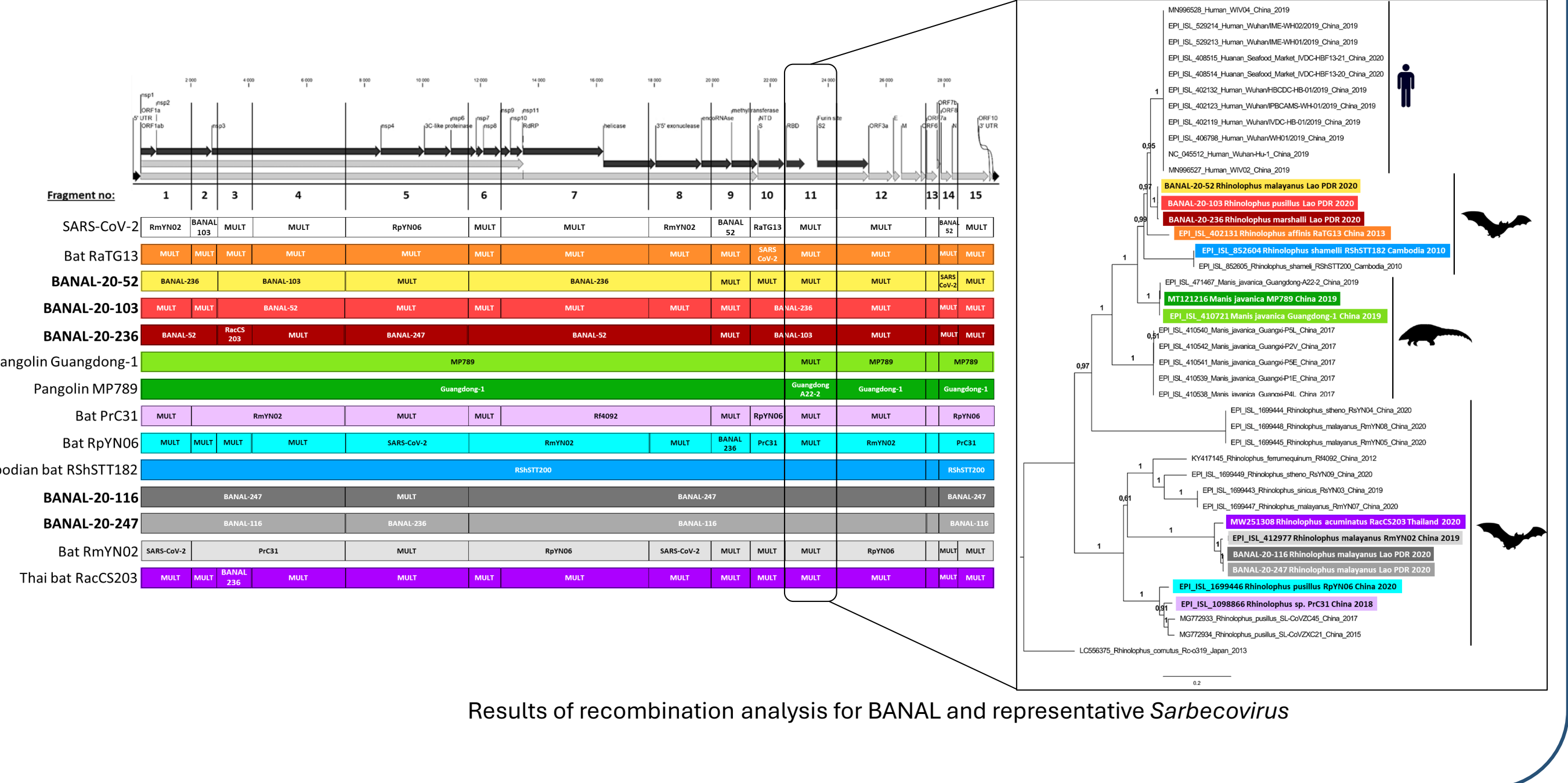
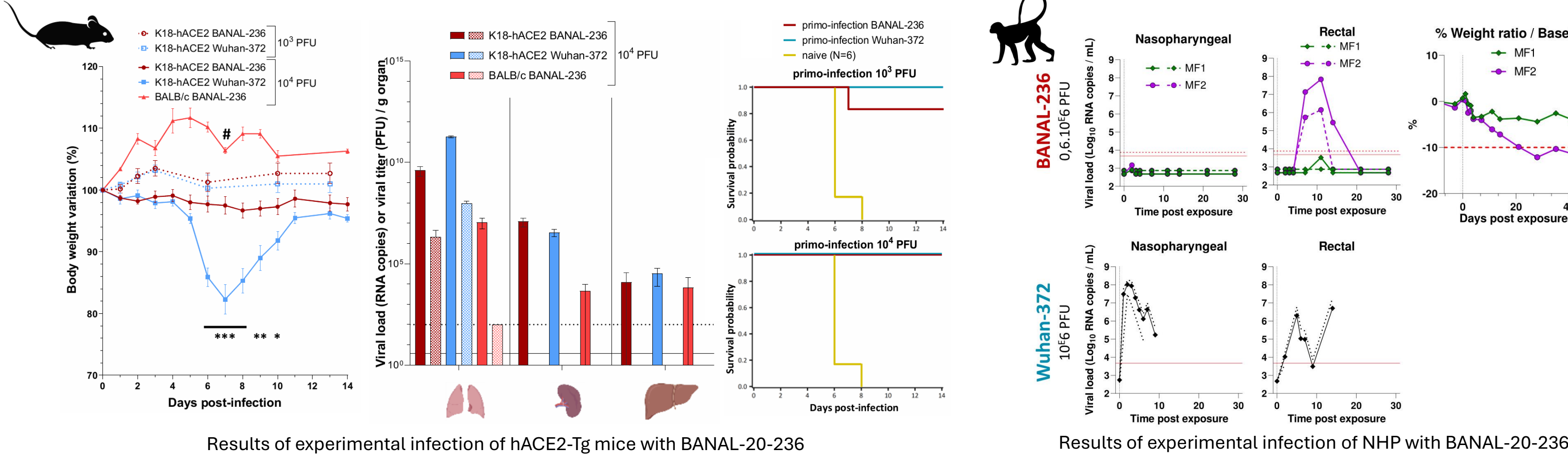
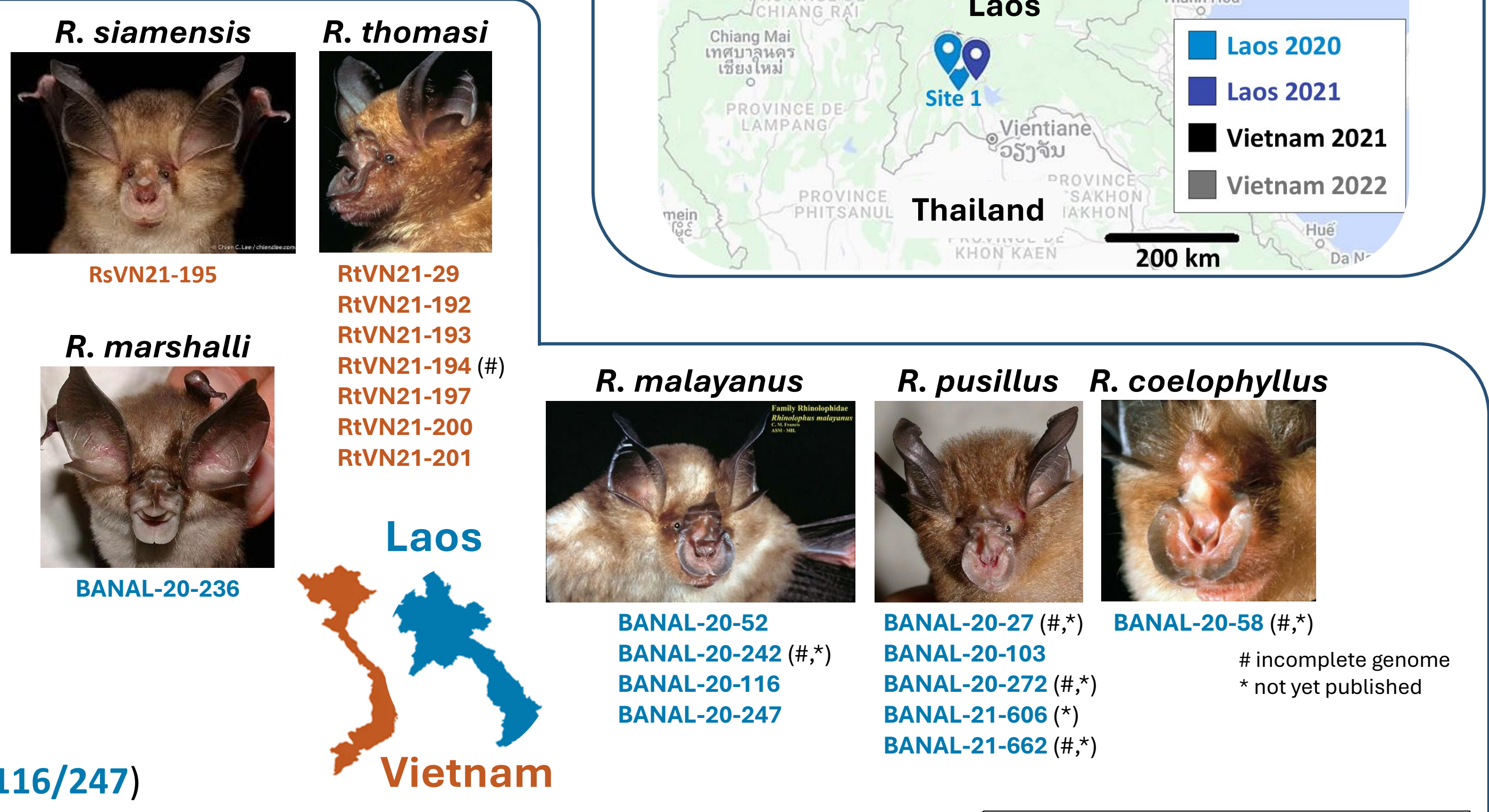


## Study sites



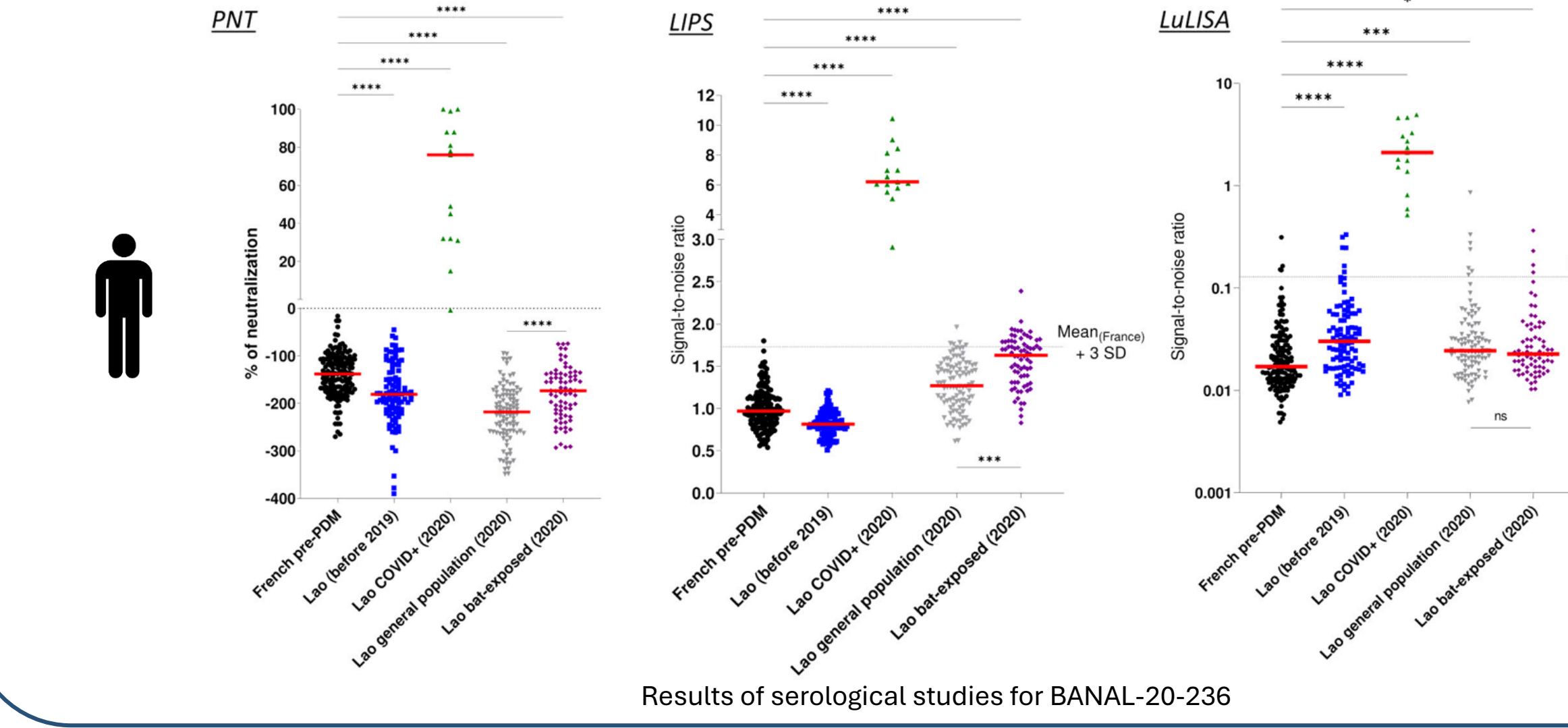
## Results

- 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



## 5. 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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