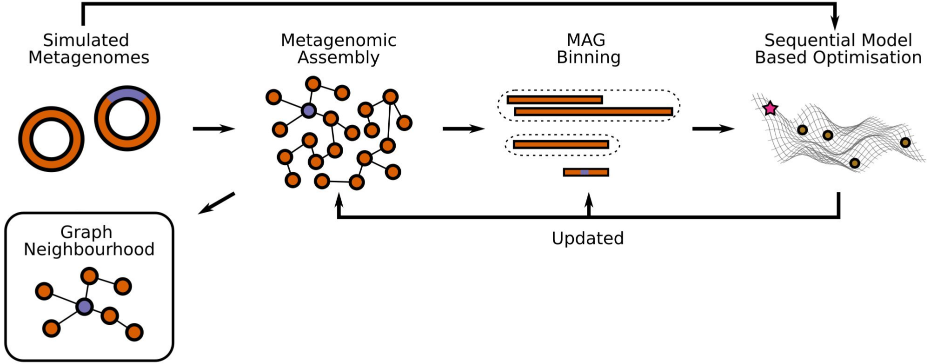
There and back again: characterising SARS-CoV-2 wildlife spillover and spillback

(Pre-Print:10.1101/2022.02.22.481551v3)

Finlay Maguire
Computer Science and Community Health & Epidemiology, Dalhousie University
Shared Hospital Laboratory, Toronto
Sunnybrook Research Institute, Toronto

Maguire Lab: 2022-

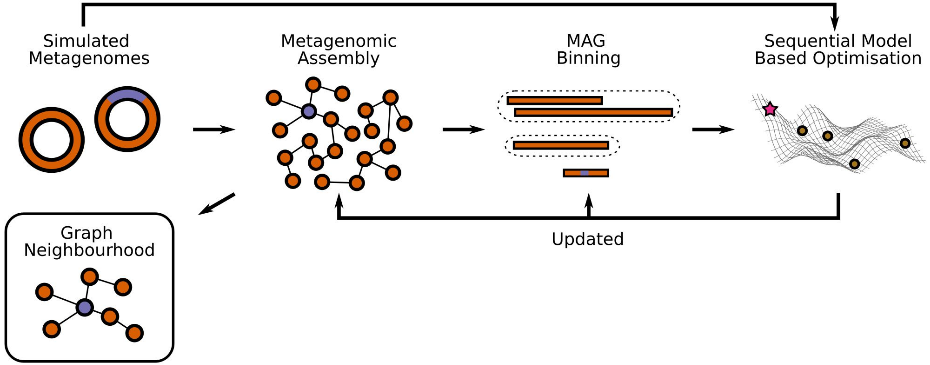
Genomic Epidemiology of Infectious Diseases



- **SARS-CoV-2**
  - *CIHR PG*: genotype to phenotype
  - *NSERC CANMOD*: creating genomic SIR models
- **Antimicrobial resistance**
  - *NSERC DG*: LGT via metagenomic graphs
  - *PHA4GE:* Emerging threats & public health bioinformatics

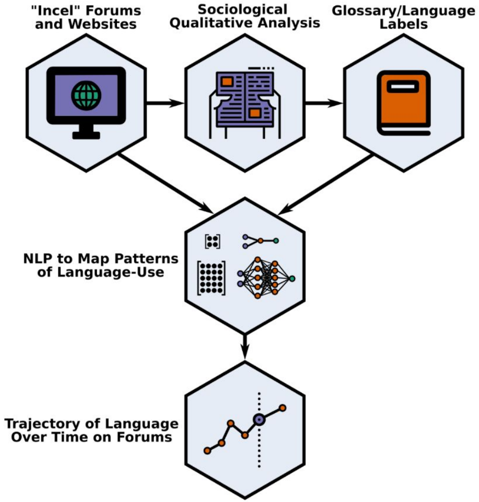
Maguire Lab: 2022-

Genomic Epidemiology of Infectious Diseases


Simulated Metagenomes
Metagenomic Assembly
MAG Binning
Sequential Model Based Optimisation
Graph Neighbourhood
Updated

- **SARS-CoV-2**
  - *CIHR PG*: genotype to phenotype
  - *NSERC CANMOD*: creating genomic SIR models
- **Antimicrobial resistance**
  - *NSERC DG*: LGT via metagenomic graphs
  - *PHA4GE:* Emerging threats & public health bioinformatics

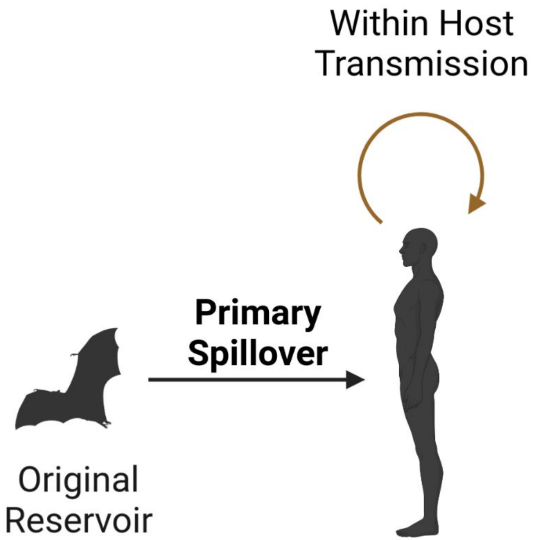
Collaborative Health Data Science


"Incel" Forums and Websites
Sociological Qualitative Analysis
Glossary/Language Labels
NLP to Map Patterns of Language-Use
Trajectory of Language Over Time on Forums

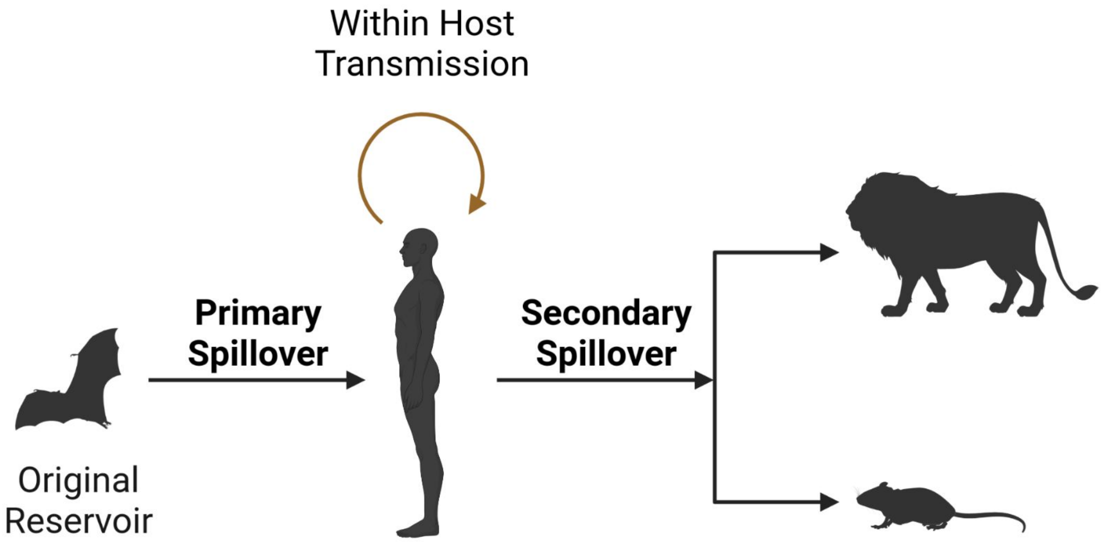
- **Social disconnection**
  - *SSHRC IDG*: online "Incel" radicalisation
- **Health inequality**
  - *SSHRC IDG*: modelling interplay of "luck" + frailty/resilience on health outcomes

Why monitor pathogens in non-human animals?

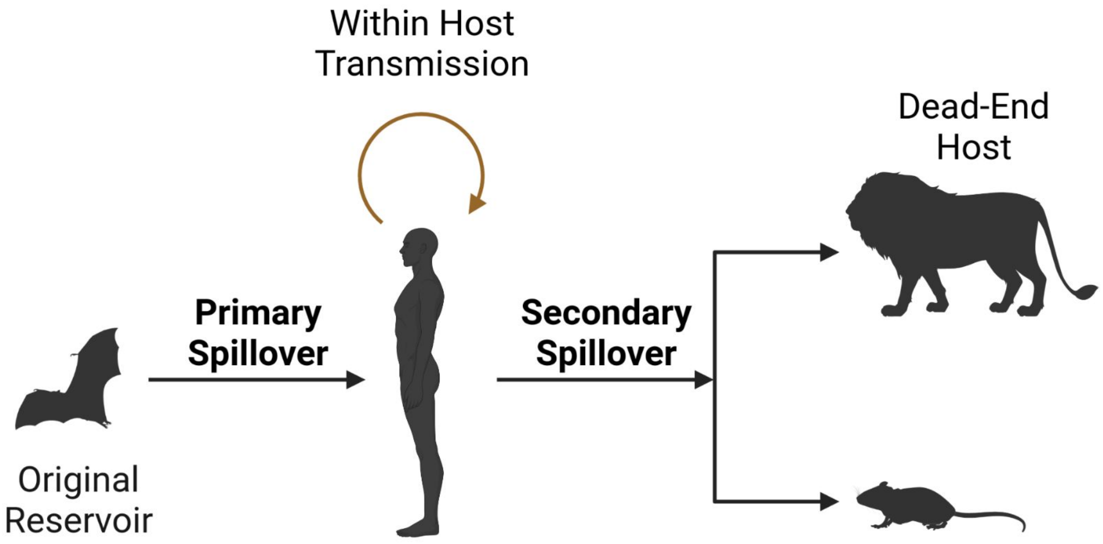
Animal infections can impact evolution of pathogens



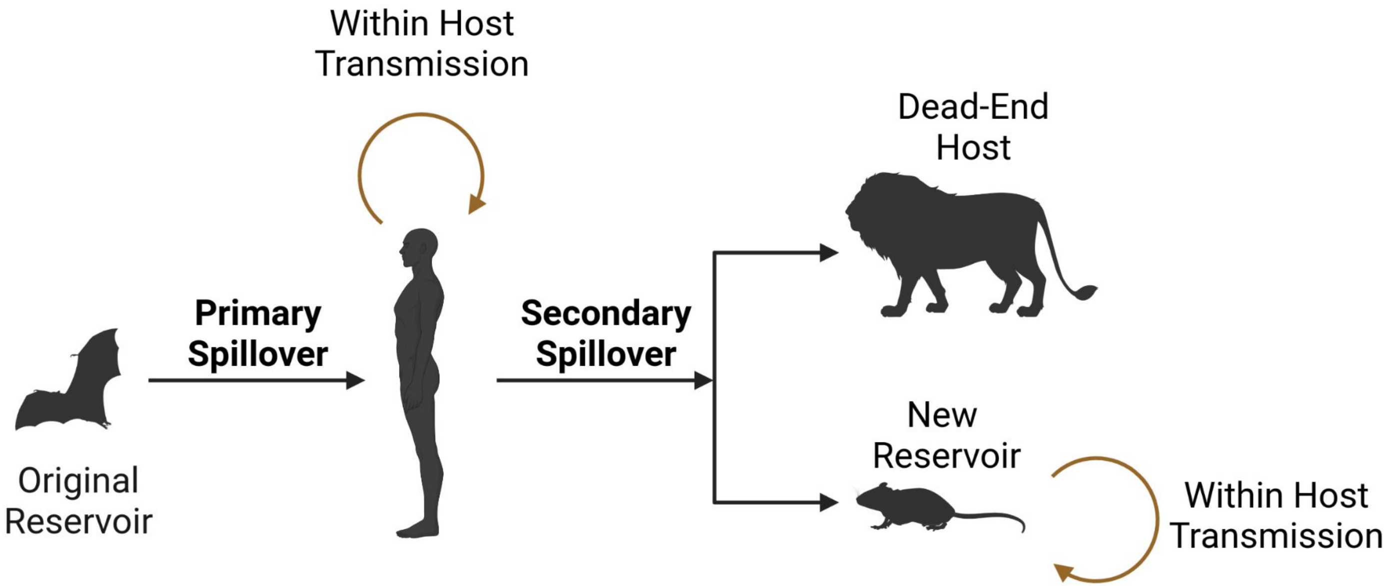
Animal infections can impact evolution of pathogens



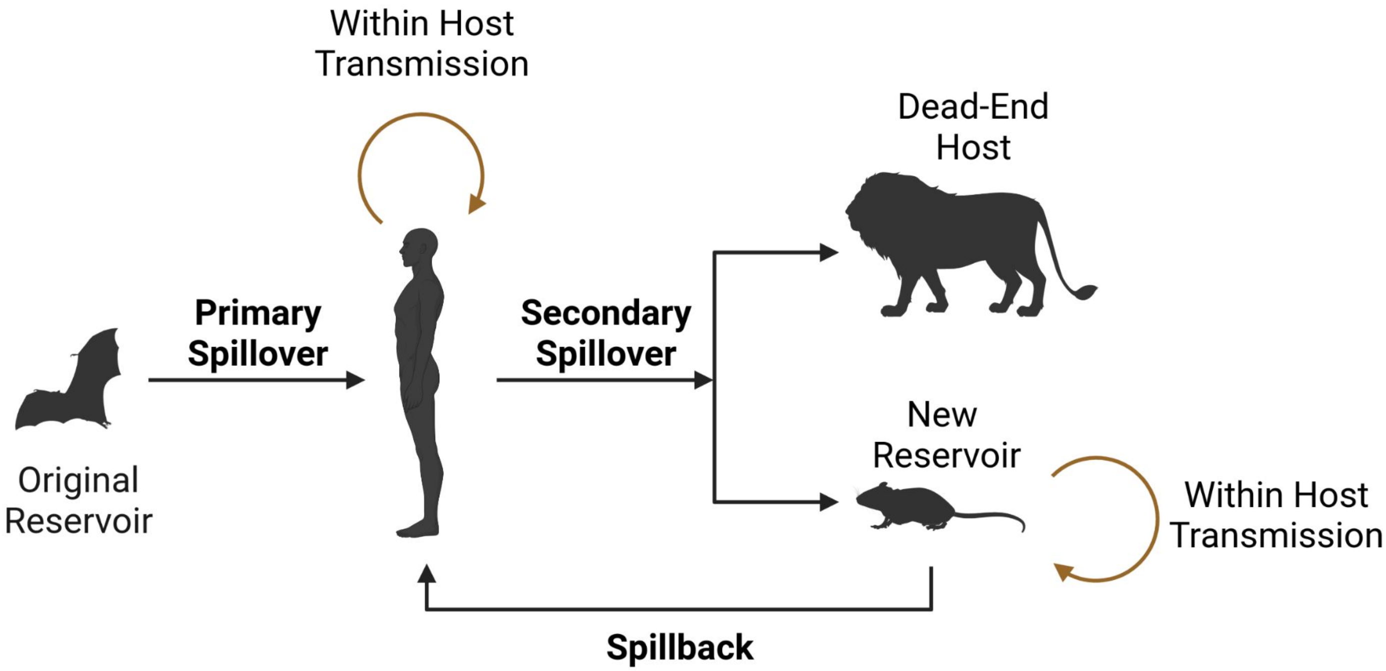
Animal infections can impact evolution of pathogens



Animal infections can impact evolution of pathogens



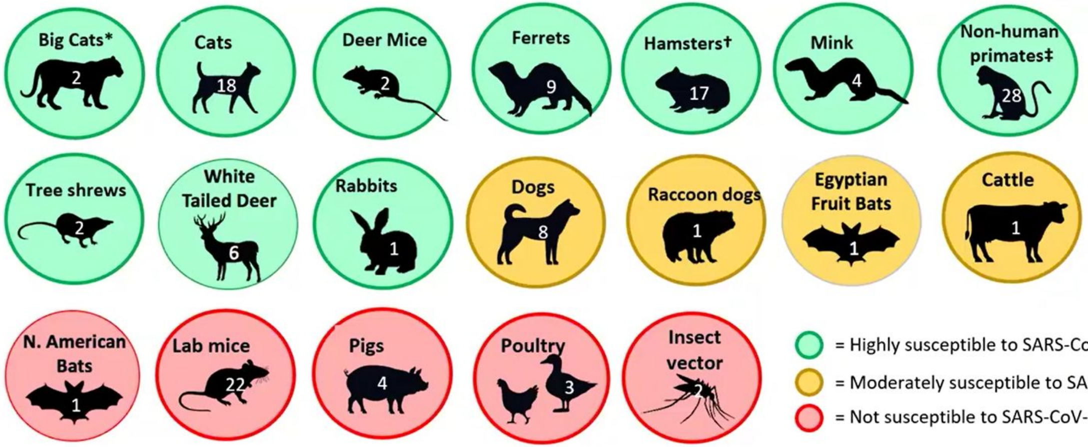
Animal infections can impact evolution of pathogens



Are secondary animal reservoirs a problem in SARS-CoV-2?

SARS-CoV-2 can infect ~50 non-human mammals

Published or pre-print articles – SARS-CoV-2 experimental or natural infection in animals



🟩 = Highly susceptible to SARS-CoV-2 infection

🟨 = Moderately susceptible to SARS-CoV-2 infection

🟥 = Not susceptible to SARS-CoV-2 infection

*Big cats include: lions, tigers and puma

†Hamster species include: Chinese hamsters and golden Syrian hamsters

‡Non-human primate species include: African green monkeys, baboons, common marmosets, cynomolgus macaques, pigtail macaques, rhesus macaques, and savanna monkeys

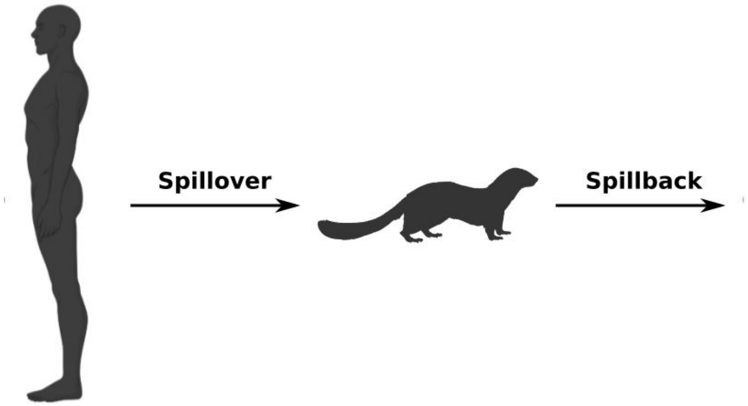
2021-01-18: CDC

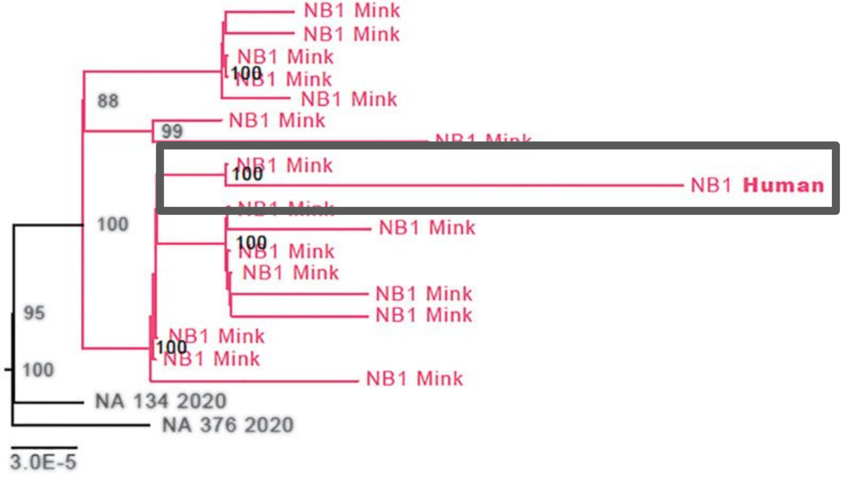
Secondary Spillback into humans has been observed

Transmission of SARS-CoV-2 on mink farms between humans and mink and back to humans

BAS B. OUDE MUNNINK, REINA S. SIKKEMA, DAVID F. NIEUWENHUIJSE, ROBERT JAN MOLENAAR, EMMANUELLE MUNGER, RICHARD MOLENKAMP, ARCO VAN DER SPEK, PAULIEN TOLSMA, ARIENE RIETVELD, [...] MARION P. G. KOOPMANS +13 authors Authors Info & Affiliations

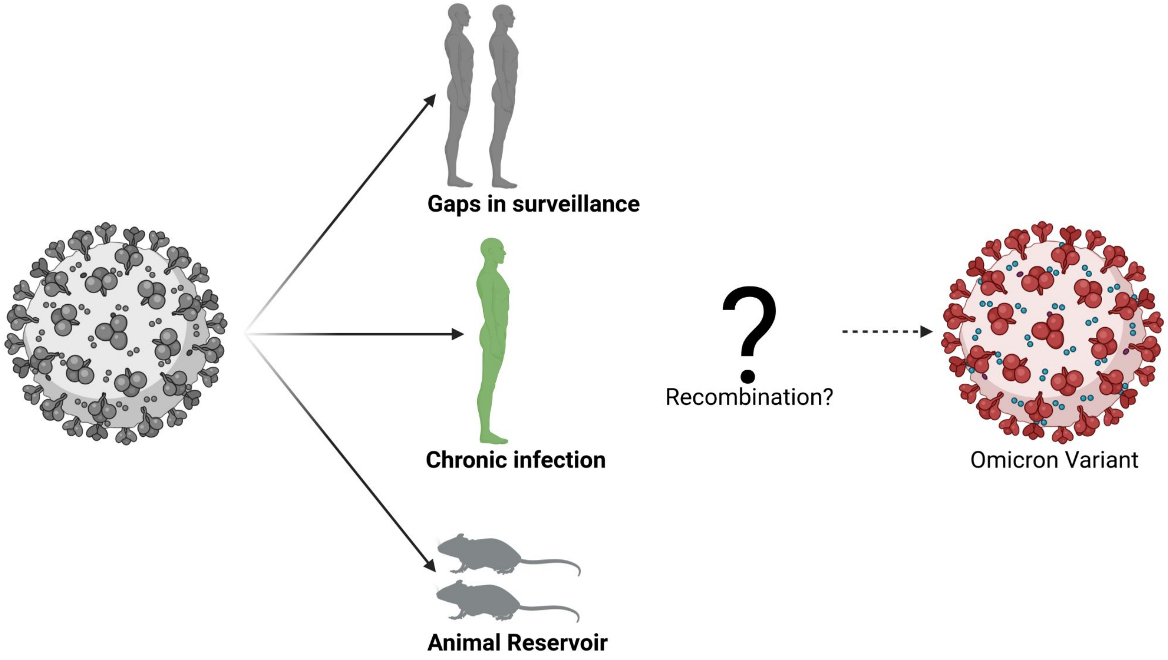
SCIENCE • 10 Nov 2020 • Vol 371, Issue 6525 • pp. 172-177 • DOI: 10.1126/science.abe5901





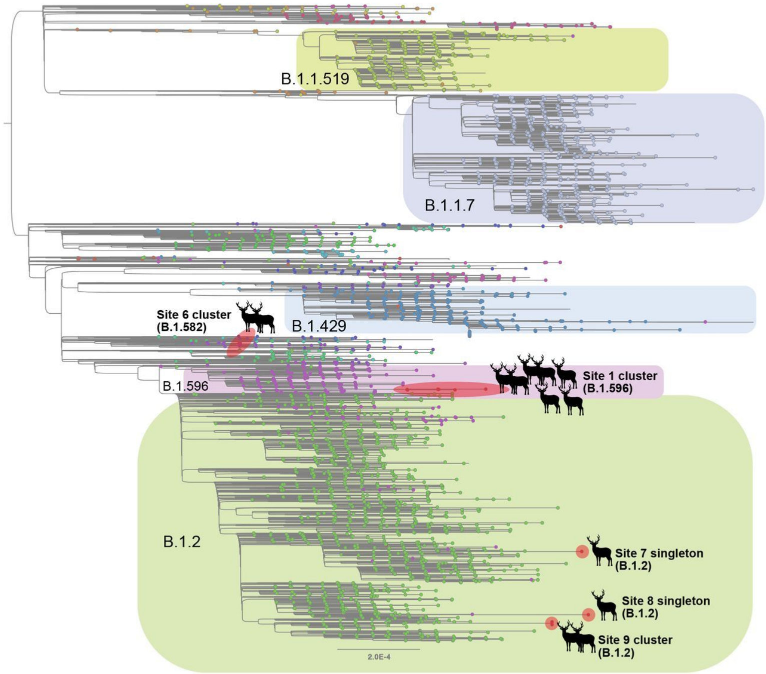
10.1126/science.abe5901

Omicron may have originated in animal reservoirs

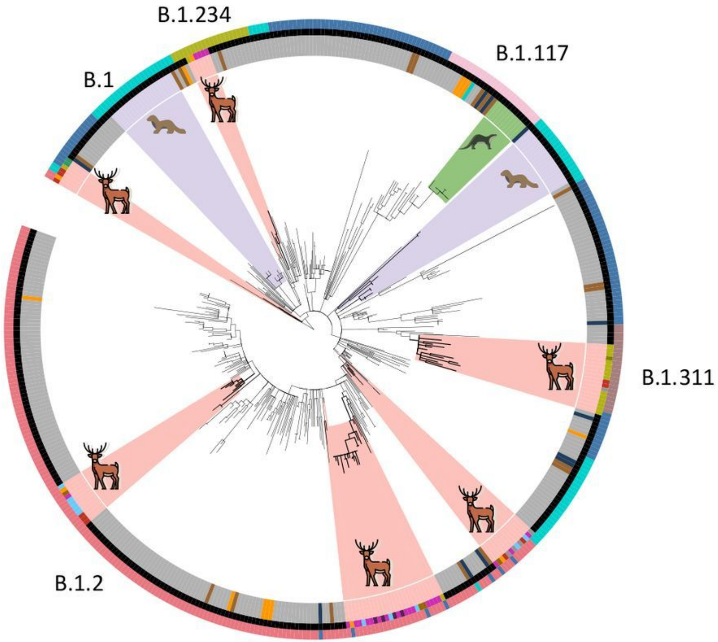


Why are White-Tailed Deer a priority?

White-Tailed Deer are susceptible

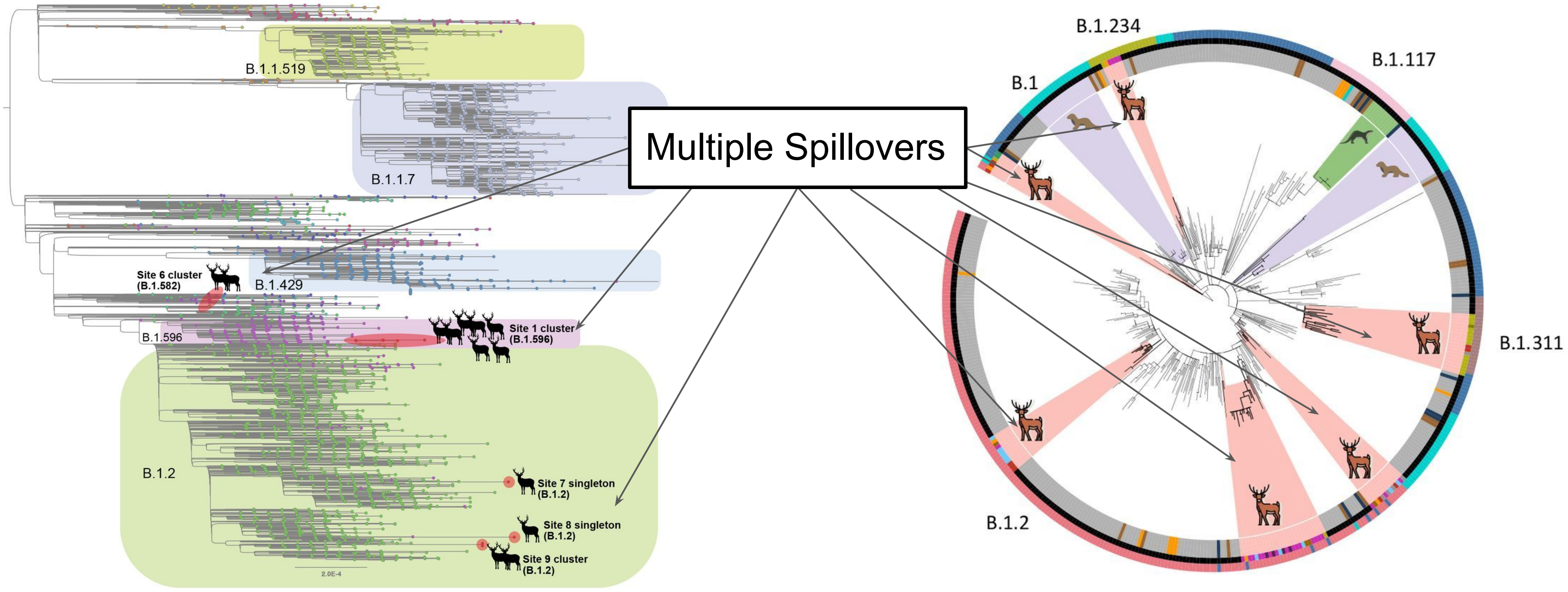


(Hale, 2021) 10.1101/2021.11.04.467308



(Kuchipudi, 2021) 10.1101/2021.10.31.466677

White-Tailed Deer are susceptible



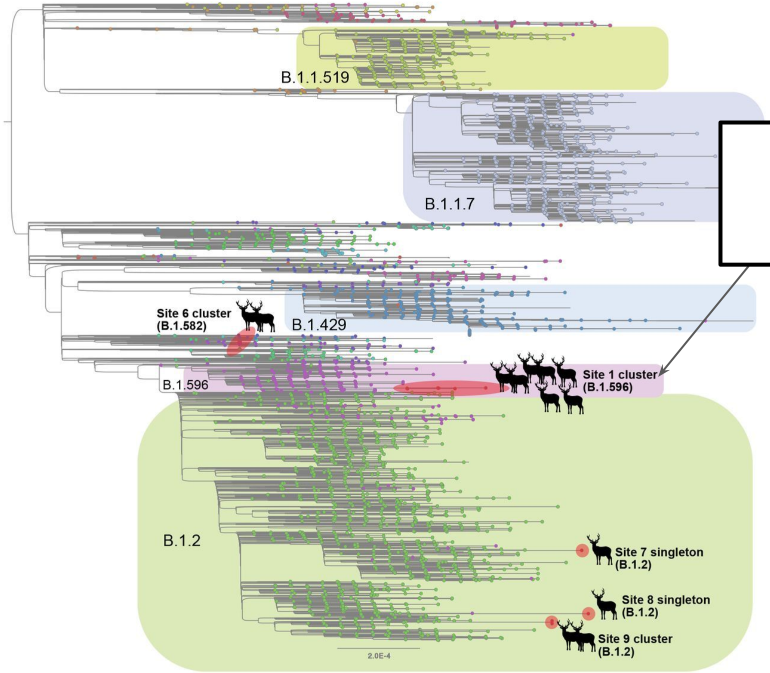
Multiple Spillovers

(Hale, 2021) 10.1101/2021.11.04.467308

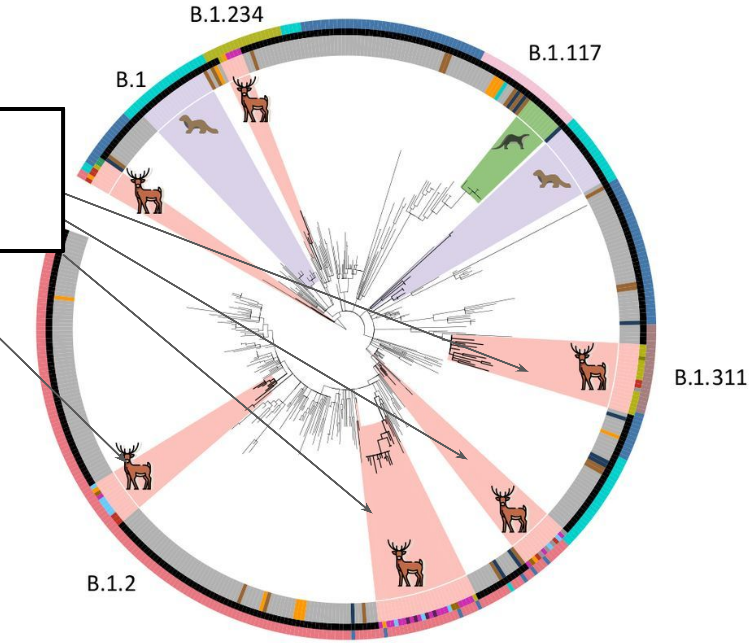
(Kuchipudi, 2021) 10.1101/2021.10.31.466677

White-Tailed Deer are susceptible

Deer to Deer Transmission

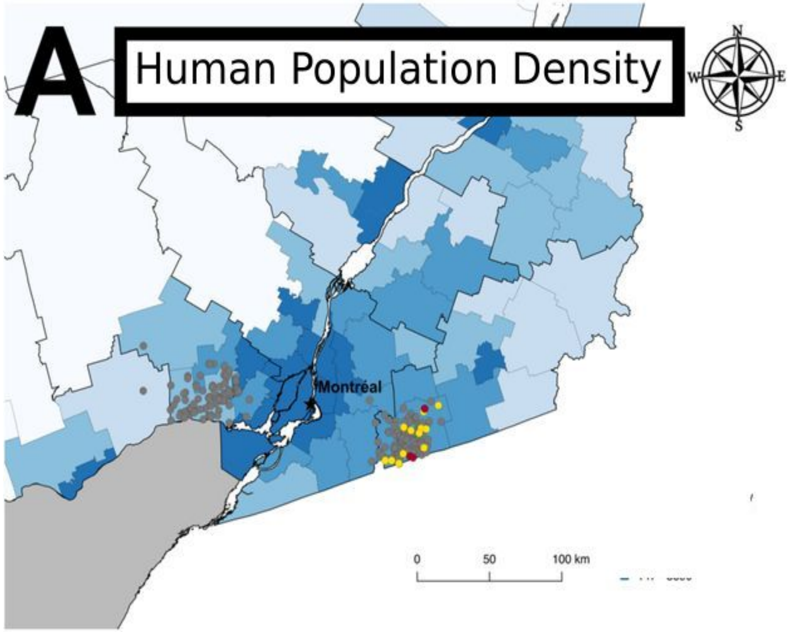


(Hale, 2021) 10.1101/2021.11.04.467308



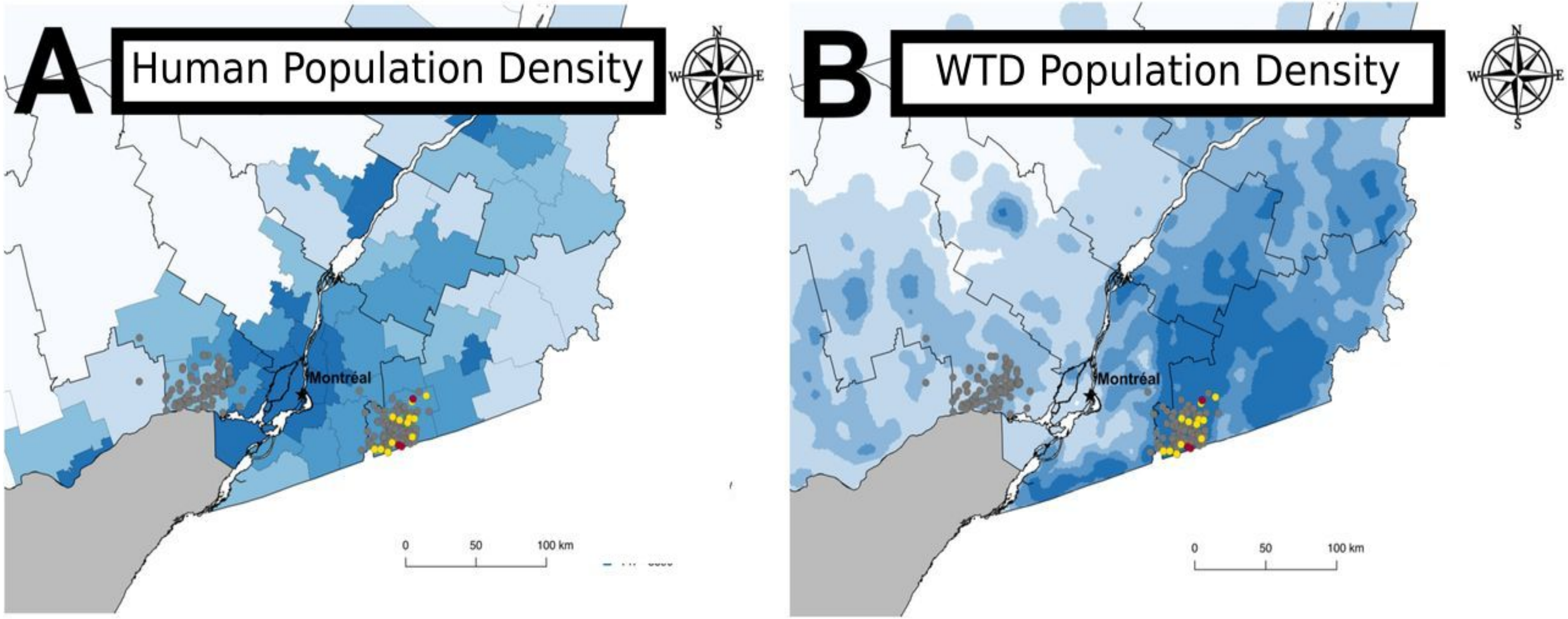
(Kuchipudi, 2021) 10.1101/2021.10.31.466677

White-Tailed Deer: large/mobile populations near humans



(Kotwa, 2022) 10.1101/2022.01.20.476458

White-Tailed Deer: large/mobile populations near humans



(Kotwa, 2022) 10.1101/2022.01.20.476458

How can we monitor SARS-CoV-2 evolution in White-Tailed Deer?

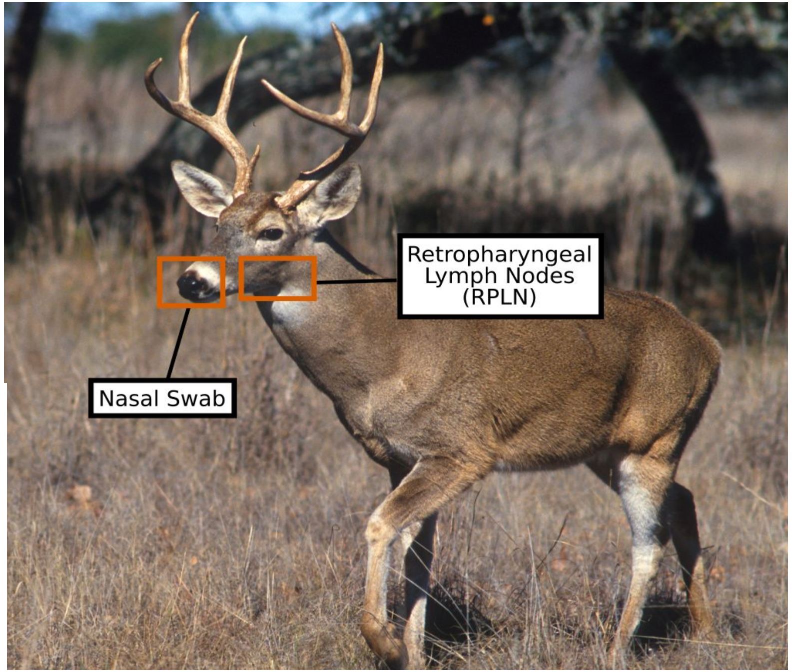
Use pre-existing surveillance programs for WTD

- SARS-CoV-2 sampling added to Chronic Wasting Disease surveillance program (Nov 1st - Dec 31st 2021)

USDA photo by Scott Bauer - Image Number: K5437-3

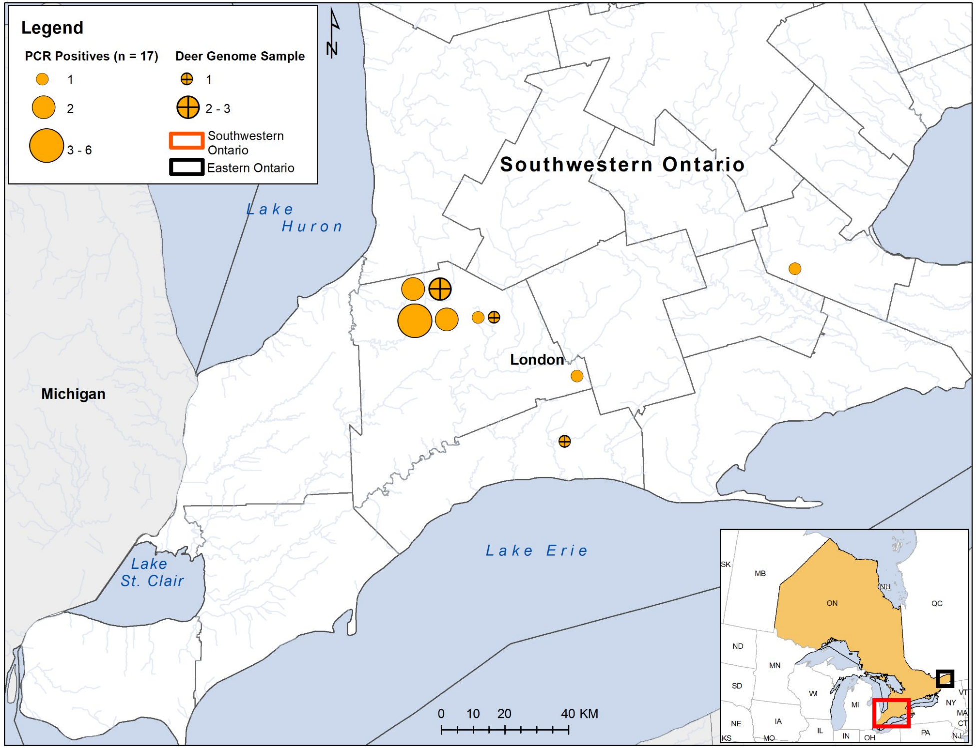
Use pre-existing surveillance programs for WTD

- SARS-CoV-2 sampling added to Chronic Wasting Disease surveillance program (Nov 1st - Dec 31st 2021)
- Nasal swabs and RPLN samples from hunter-harvested carcasses



USDA photo by Scott Bauer - Image Number: K5437-3

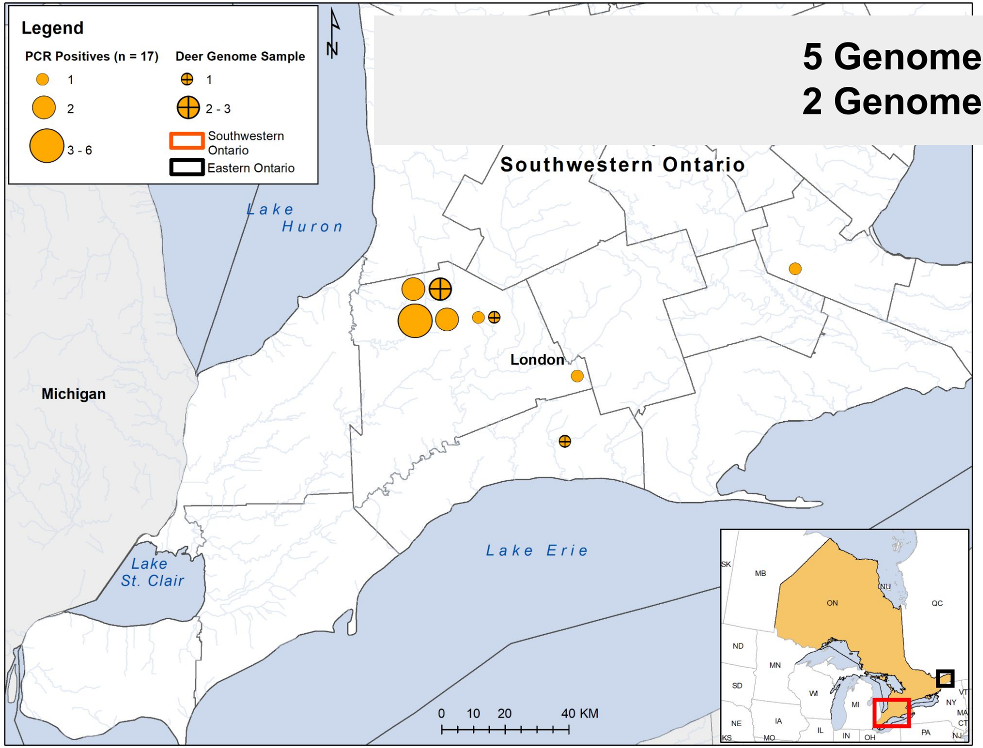
17/298 White-Tailed Deer were positive for SARS-CoV-2



No positive samples from Eastern Ontario

- Independent extraction qRT-PCR (UTR+E, N+E) and serology at separate institutes.
- Viral sequencing attempted for confirmed positive samples.

17/298 White-Tailed Deer were positive for SARS-CoV-2



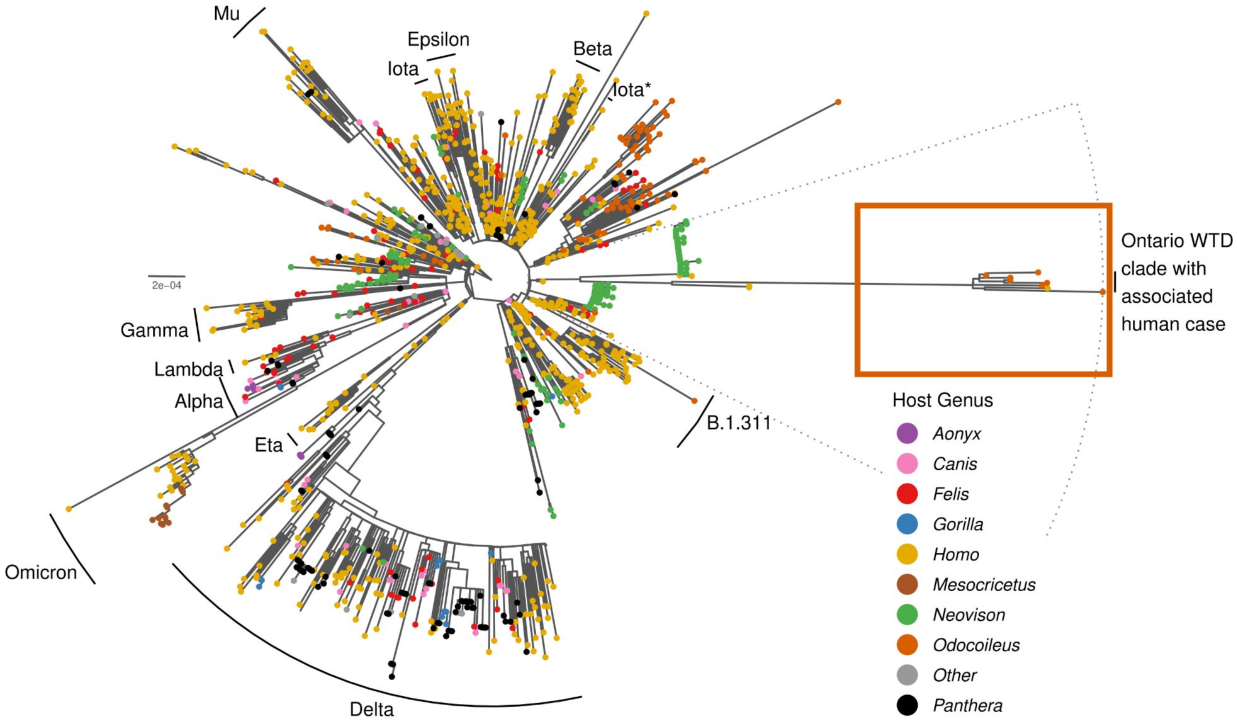
No positive samples from Eastern Ontario

5 Genomes: >99% complete
2 Genomes: >75% complete

- Independent extraction qRT-PCR (UTR+E, N+E) and serology at separate institutes.
- Viral sequencing attempted for confirmed positive samples.

Another recent spillover from local human infections?

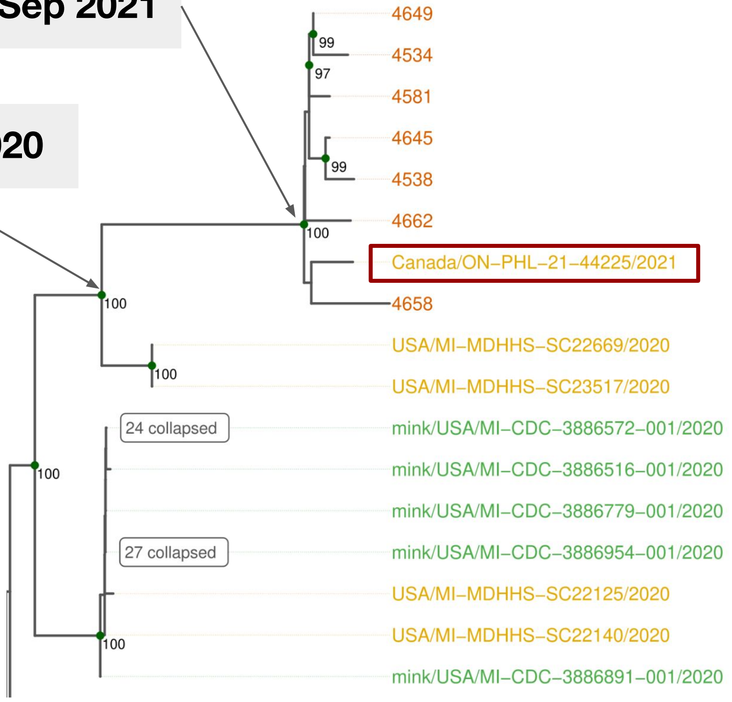
Samples formed a highly divergent B.1 lineage



Possible Deer-to-Human transmission

Dec 2020 - Sep 2021

Apr-Oct 2020

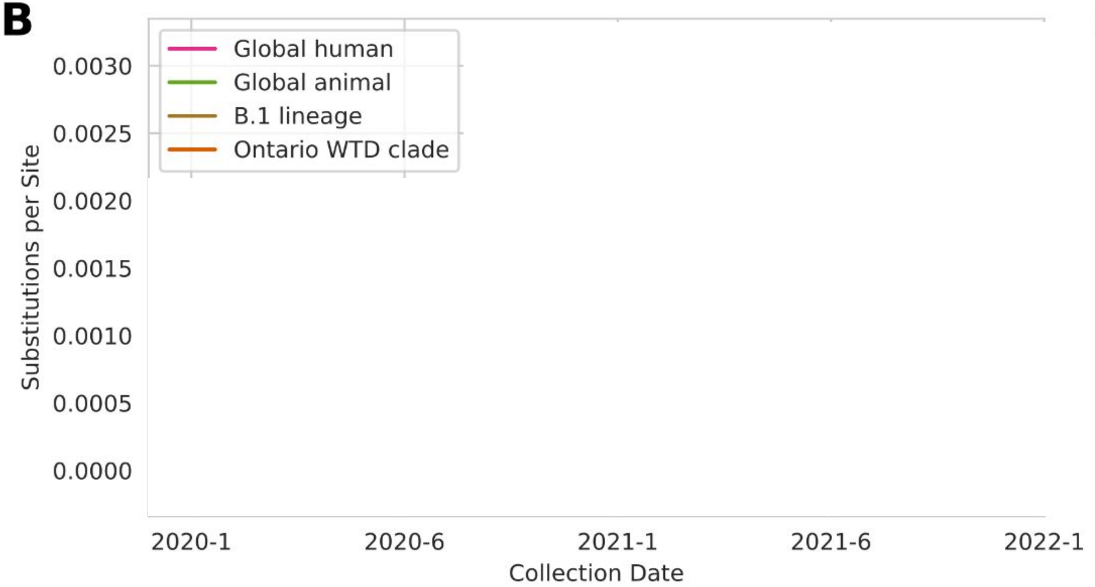


Supporting Circumstantial Evidence:

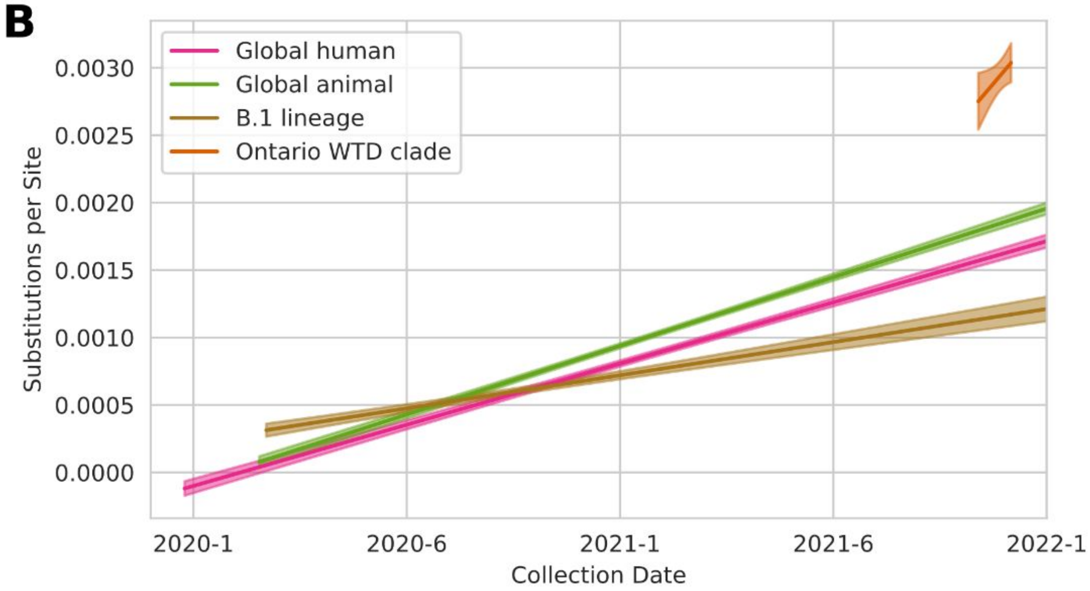
- Spatially congruent
- Temporally congruent
- Plausible Epidemiological Link

How did all this diversity evolve?

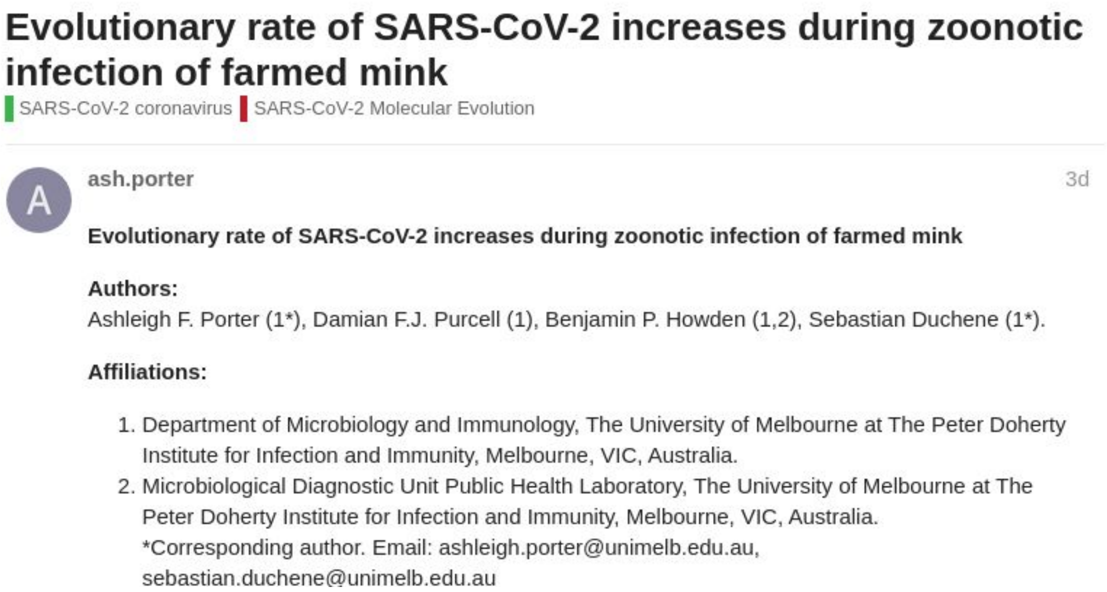
No recombination but possible elevated mutation rate



No recombination but possible elevated mutation rate



No recombination but possible elevated mutation rate



Evolutionary rate of SARS-CoV-2 increases during zoonotic infection of farmed mink

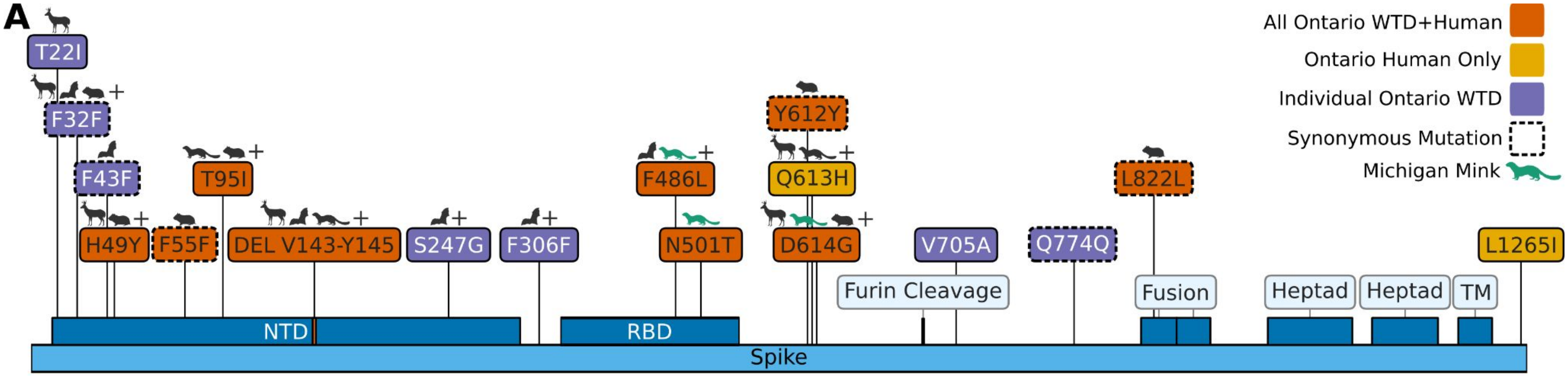
Evolutionary rate of SARS-CoV-2 increases during zoonotic infection of farmed mink

Authors:
Ashleigh F. Porter (1*), Damian F.J. Purcell (1), Benjamin P. Howden (1,2), Sebastian Duchene (1*).

Affiliations:

1. Department of Microbiology and Immunology, The University of Melbourne at The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia.
2. Microbiological Diagnostic Unit Public Health Laboratory, The University of Melbourne at The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia.
   *Corresponding author. Email: ashleigh.porter@unimelb.edu.au, sebastian.duchene@unimelb.edu.au

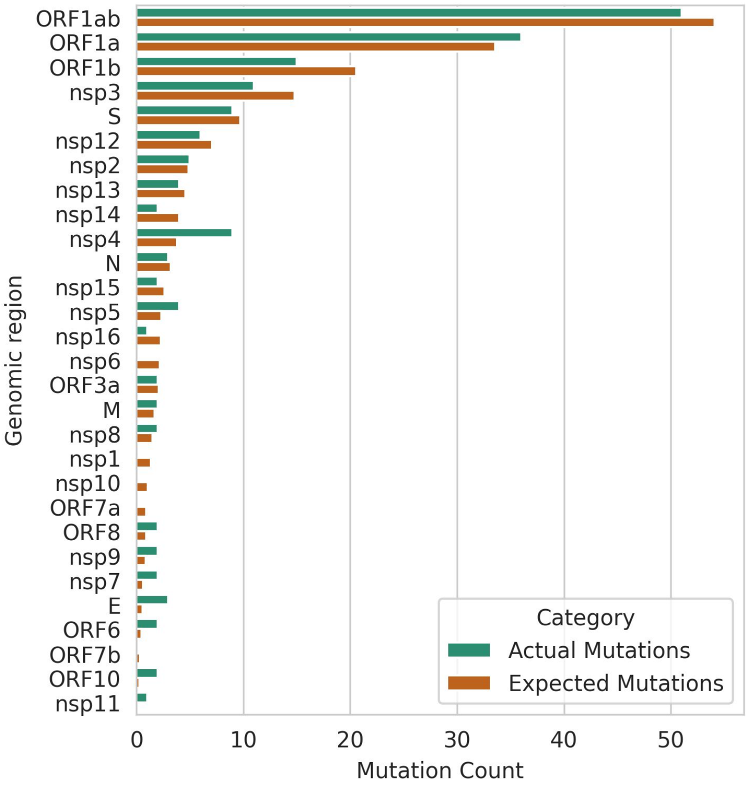
Genomic signs of host adaptation



- 37/49 previously associated with non-human animal hosts (23 new to WTD)
- Elevated C>U mutation rate (APOBEC3)
- Codon usage patterns

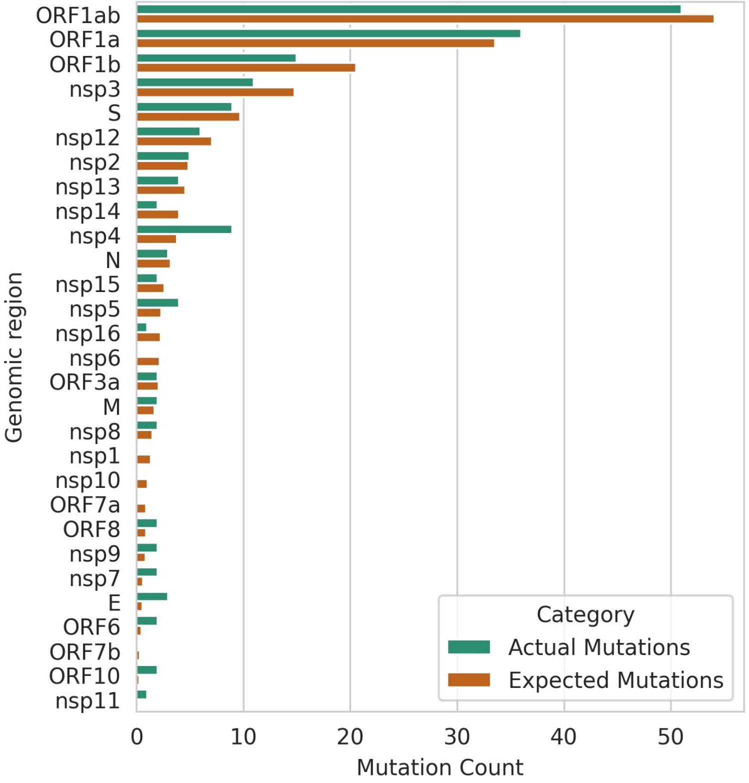
No detectable positive selection

- Mutations distributed proportionally to gene length



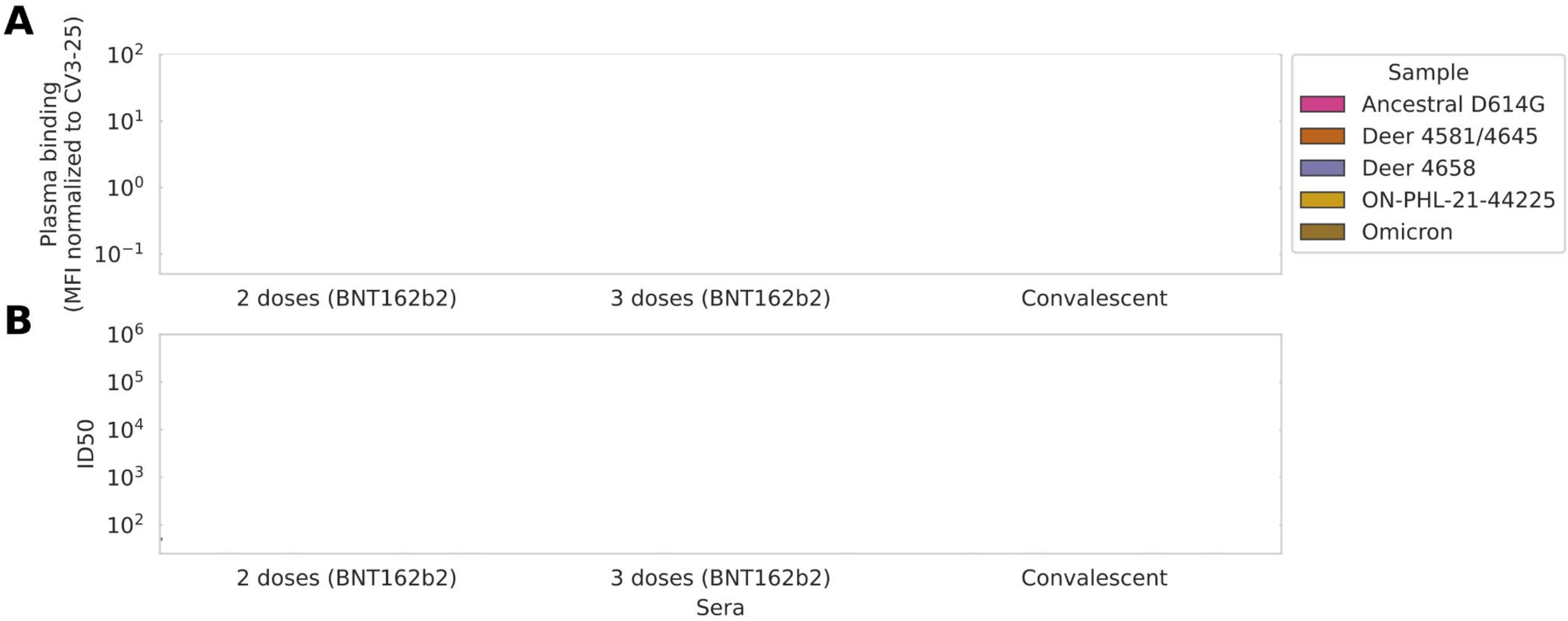
No detectable positive selection

- Mutations distributed proportionally to gene length
- Per-gene dN/dS phylogenetic analysis:
    - No significant positive selection or intensification
    - Relaxation of selection on ORF1ab

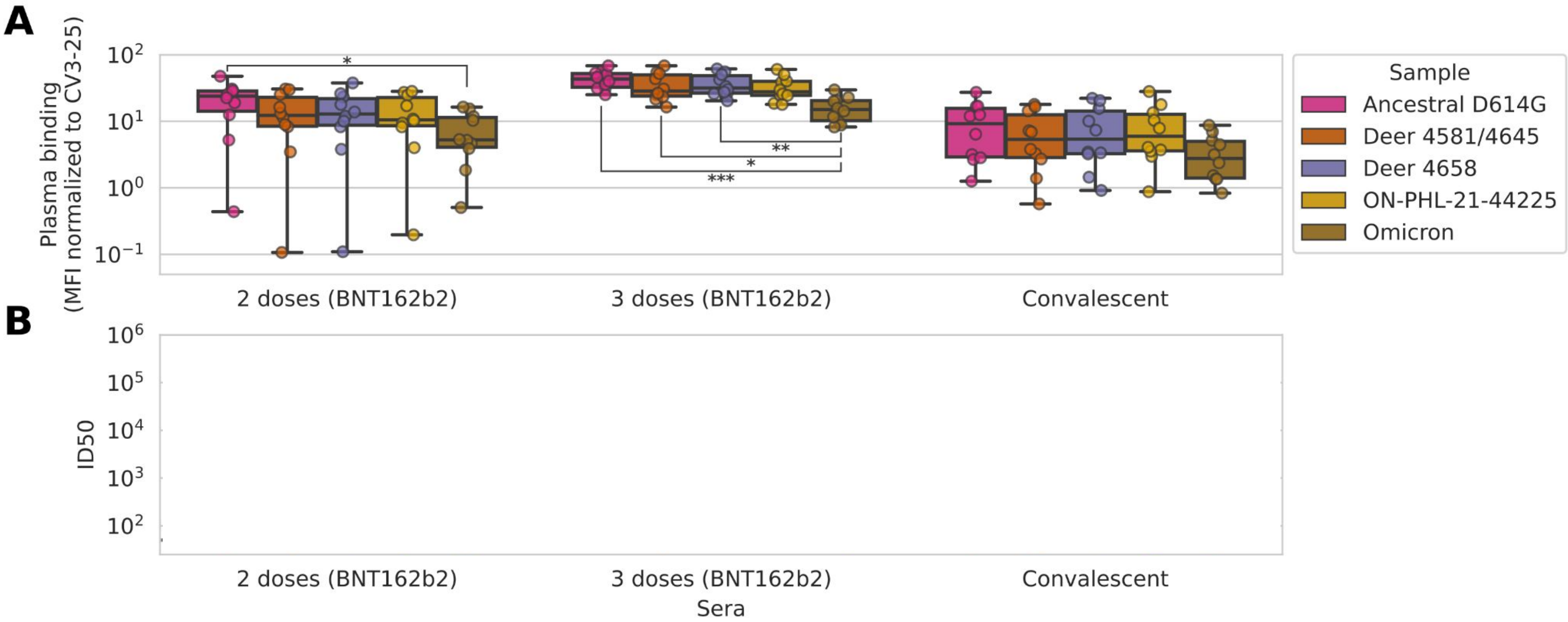


Does this diversity impact phenotype?

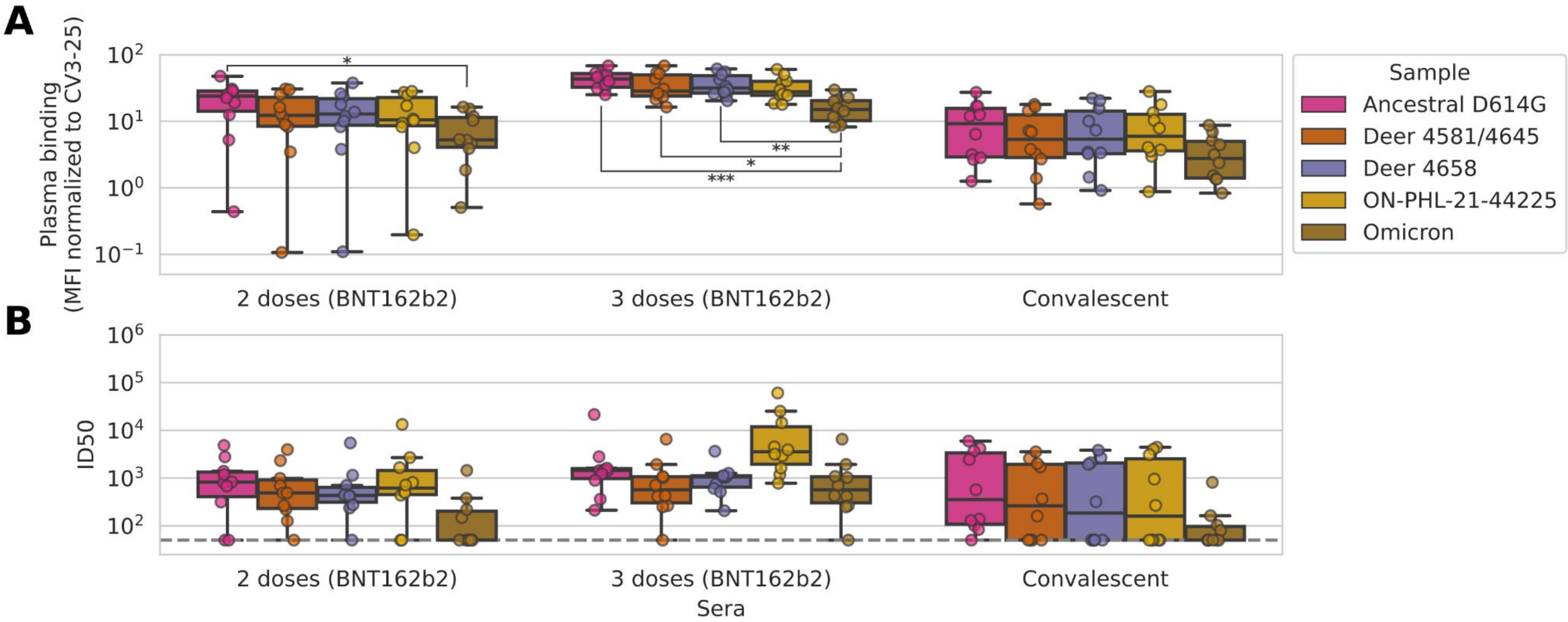
No change of spike antigenicity



No change of spike antigenicity

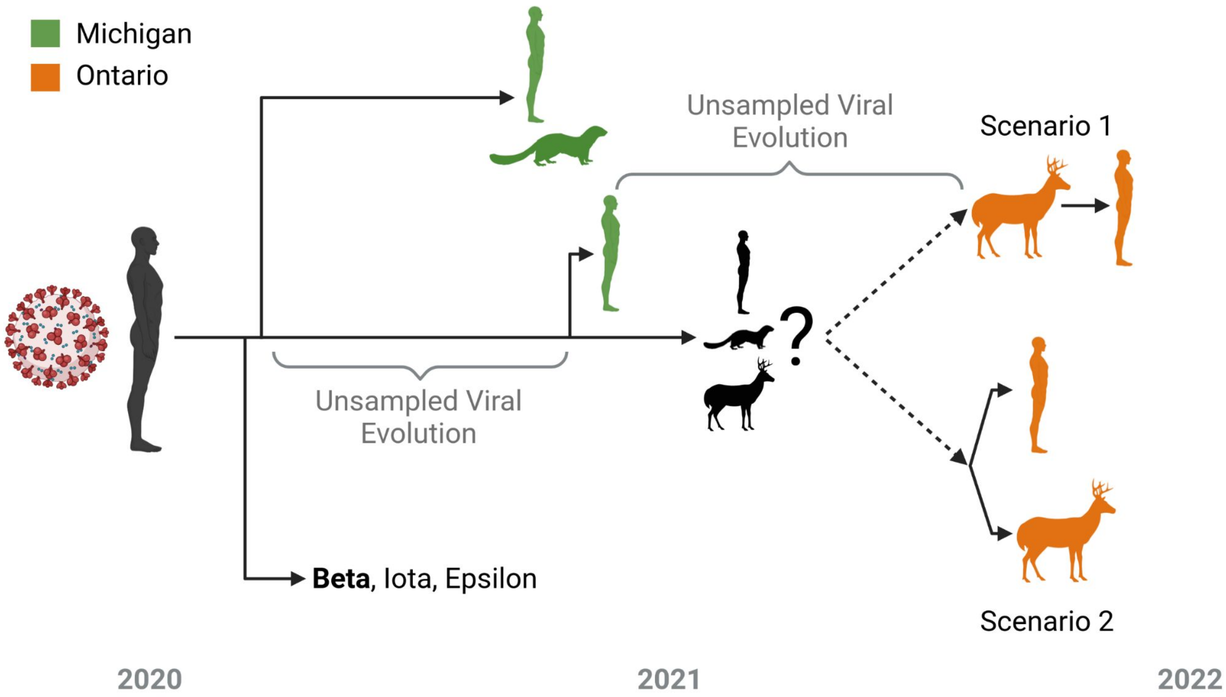


No change of spike antigenicity



Are WTD a secondary reservoir?

Limited “One Health” surveillance means lots of uncertainty



Take-aways

- Highly divergent SARS-CoV-2 in WTD with likely deer-to-human transmission
- Signs of genomic adaptation to animal host (animal-associated mutations, C>U, codon usage, elevated mutation rate)
- No indication of strong selection or change of antigenicity (*c.f.* Omicron)

Take-aways

- Highly divergent SARS-CoV-2 in WTD with likely deer-to-human transmission
- Signs of genomic adaptation to animal host (animal-associated mutations, C>U, codon usage, elevated mutation rate)
- No indication of strong selection or change of antigenicity (*c.f.* Omicron)

- Need to better understand the interplay of virus, disease, and immune selection in non-human animals (and impact on pathogen evolution)
- Similar scenarios could generate future variants of concern
- Therefore, clear need for broader “One-Health” surveillance

“WILD-CoV”

Canadian Food Inspection Agency

National Centre for Foreign Animal Disease

- Bradley Pickering (Iowa State/Manitoba)
- Oliver Lung (Manitoba)
- Peter Kruczkiewicz
- Melissa Goolia, Matthew Suderman, Mathieu Pinette, Greg Smith, Daniel Sullivan, Josip Rudar, Michelle Nebroski

DALHOUSIE UNIVERSITY

Computer Science / Epidemiology

- Finlay Maguire

Public Health Ontario

- Jennifer Guthrie (Western)
- Alex Marchand-Austin

Sunnybrook HEALTH SCIENCES CENTRE

Sunnybrook Research Institute

- Samira Mubareka (Toronto)
- Jonathan Kotwa
- Bryan Griffin
- Kuganya Nirmalarajah, Juliette Blais-Savoie, Hsien-Yao Chee, Emily Chien, Winfield Yim, Andra Banete, Lily Yip

Shared Hospital Laboratory

- Patryk Aftanas

Ontario

Ministry of Northern Development, Mines, Natural Resources and Forestry

- Jeff Bowman (Trent)
- Tore Buchanan
- Larissa Nituch
- Elizabeth Adey

uOttawa

- Marceline Côté
- Geneviè Laroche
- Ardeshir Ariana, Brett Vahkal

Sinai Health

- Allison McGeer (Toronto)

Université de Montréal

CANADIAN WILDLIFE HEALTH COOPERATIVE

Forêts, Faune et Parcs Québec

Ontario MINISTRY OF HEALTH

Guillaume Goyette, Andrés Finzi, Claire Jardine, Ariane Massé Heather McClinchey

CIHR IRSC
Canadian Institutes of Health Research Instituts de recherche en santé du Canada

CoVaRR-Net

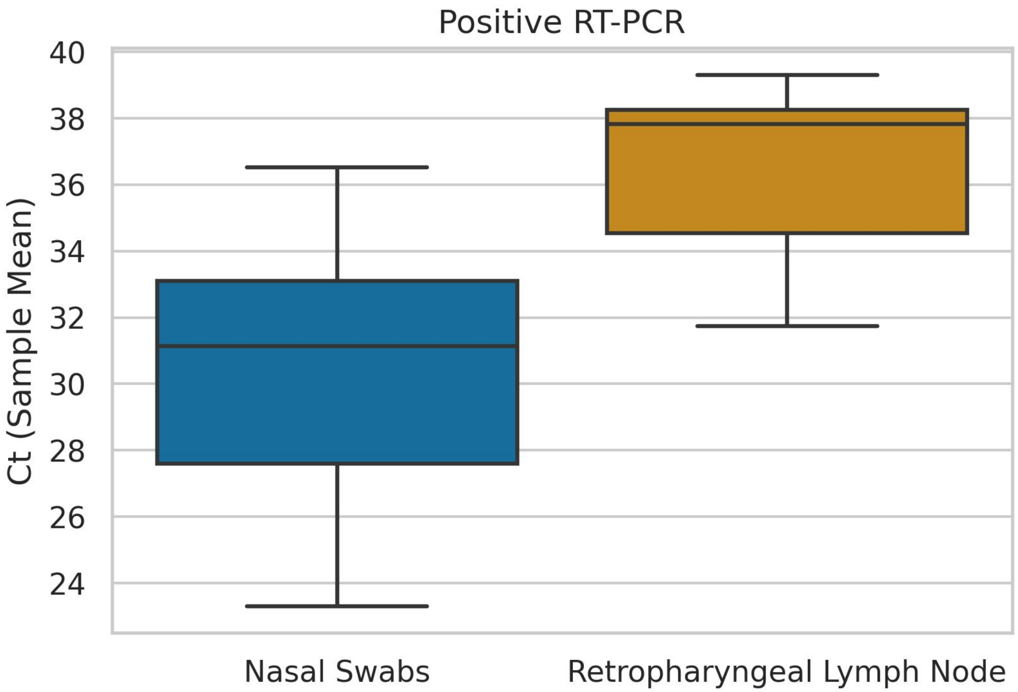
CanCOGeN

CANADIAN WILDLIFE HEALTH COOPERATIVE

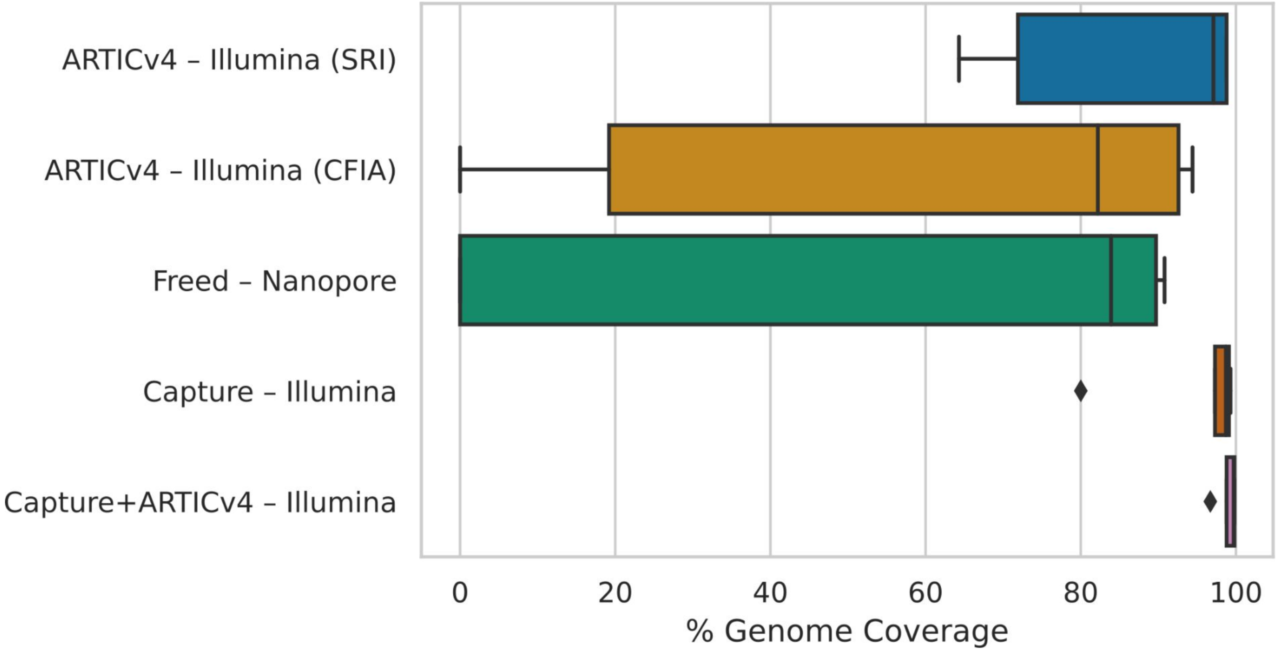
Canadian Safety and Security Program
Programme canadien pour la sûreté et la sécurité

Backup

Challenging to sequence due to Ct

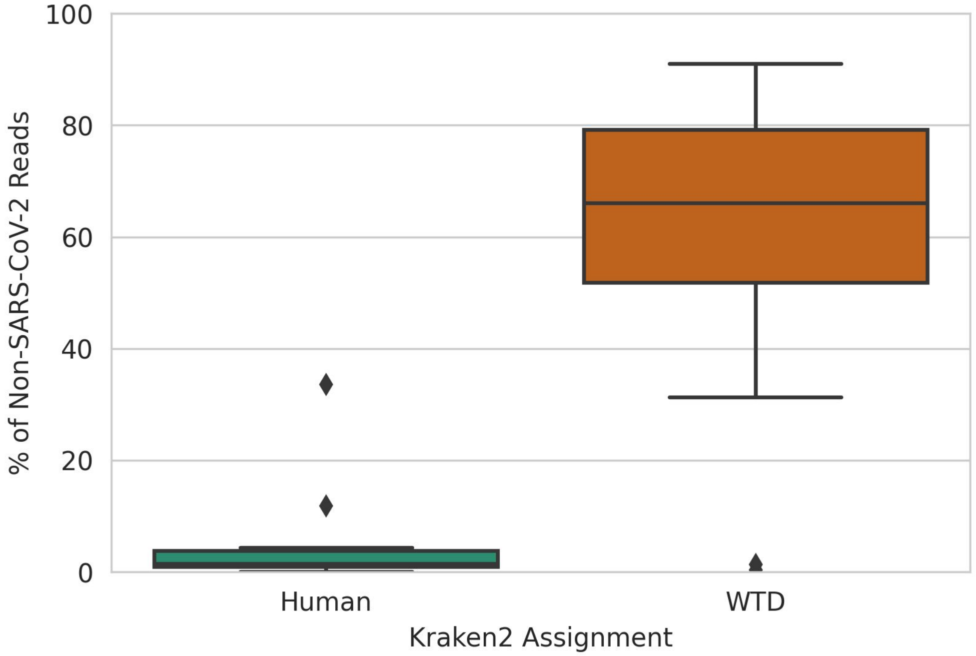


Combining approaches to maximise coverage



Ruling out contamination from human SARS-CoV-2

- Independent RNA extractions + qRT-PCR
- Independent sequencing efforts
- Two sample sites: RPLN and Nasal swabs
- Negative Human RNAase PCR
- Taxonomic read profiling (ARTICv4)



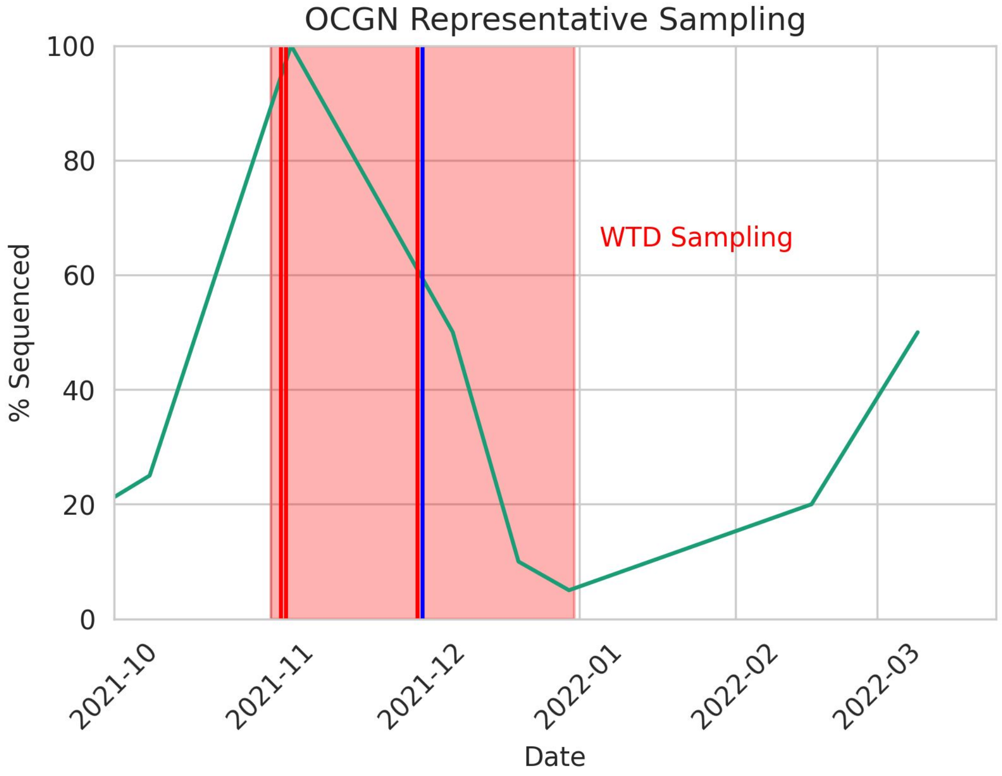
76 Mutations: 49 since MRCA with Michigan Human

- Rare:
    - ORF1a:insertion2038N/MRASD (n=32, including 31 mink from Michigan, USA)
    - ORF1b:V373L (n=425, all human sequences)
    - S:F486L (n=439)
    - ORF3a:L219V (n=805)
    - ORF10:L37F (n=0)

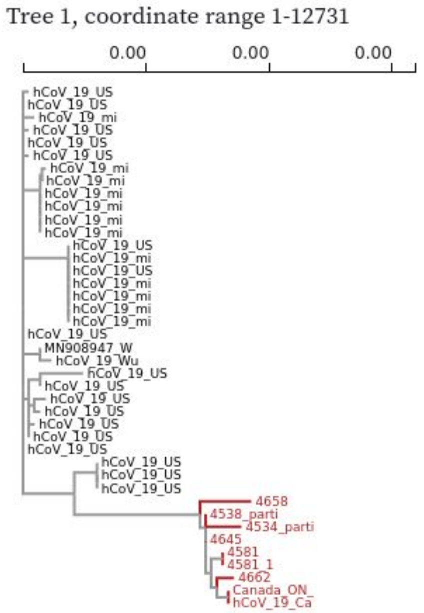
No sign of additional human cases

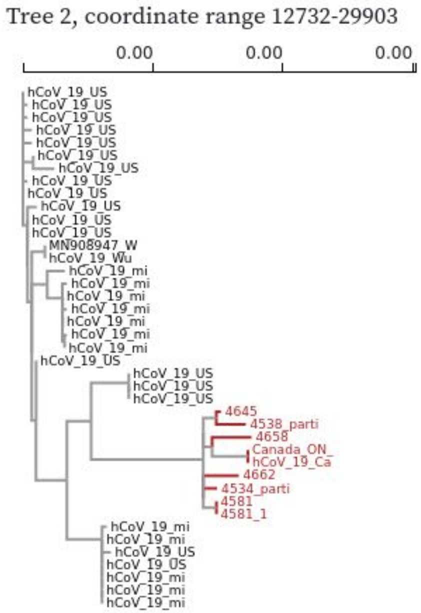
Caveats:

- Omicron induced drop in human surveillance levels
- End of deer hunting season/deer sampling



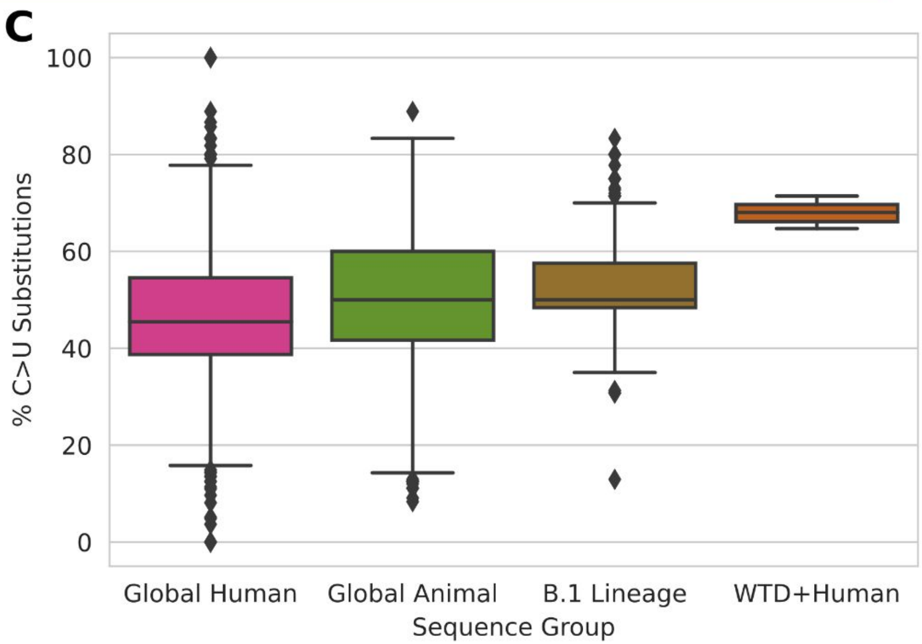
No indication of recombination


Tree 1, coordinate range 1-12731

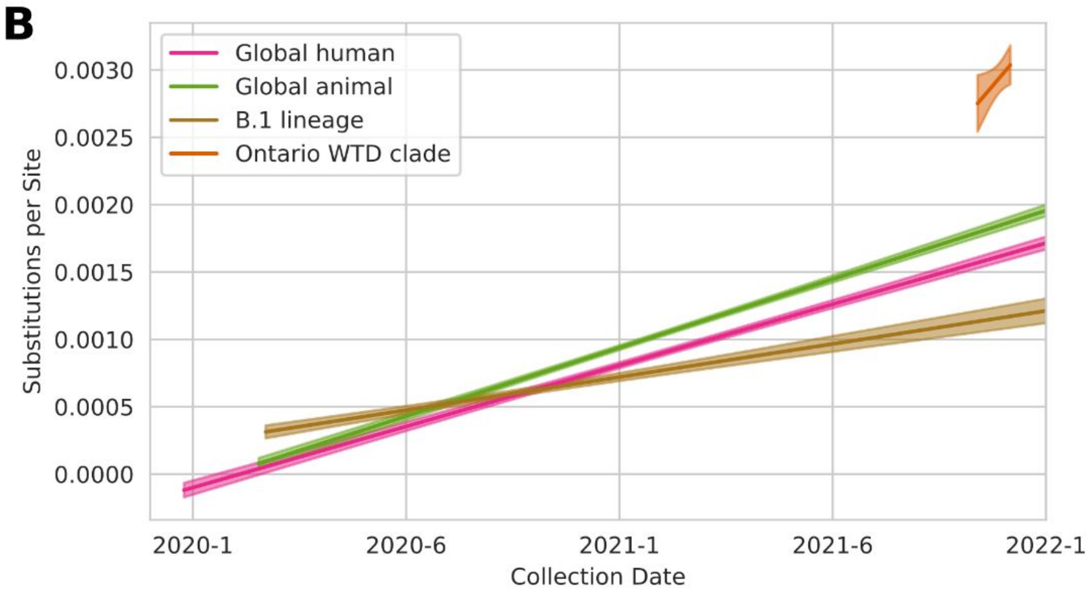

Tree 2, coordinate range 12732-29903

- SNP tables (**sc2rf**)
- Mosaicism (**3Seq**)
- Phylogenetic incongruence (**Hyphy-GARD**)

Signs of host adaptation: C>U and codon usage



No recombination but possible elevated mutation rate



Global human: 0.9×10^{-3} to 1.0×10^{-3}

Global animal: 1.0×10^{-3} to 1.1×10^{-3}

B.1 lineage: 0.4×10^{-3} to 0.6×10^{-3}

Ontario WTD: 0 to 8×10^{-3}

Mink: *3.18×10^{-3} to 10.6×10^{-3}*

Viral cultures