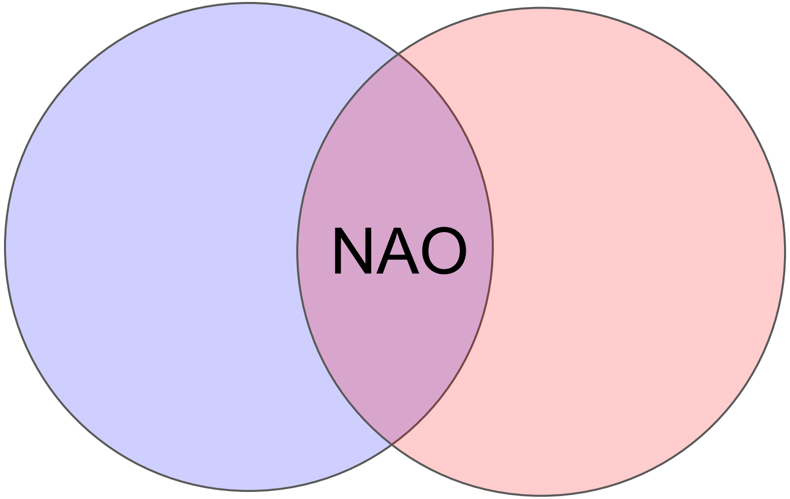
Predicting Relative Abundance

Jeff Kaufman

2023-10-18

Wastewater Biosurveillance Workshop

Background



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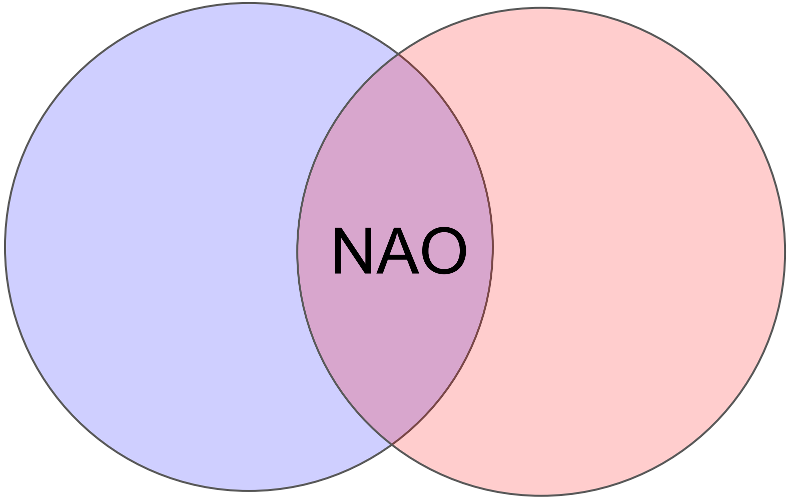

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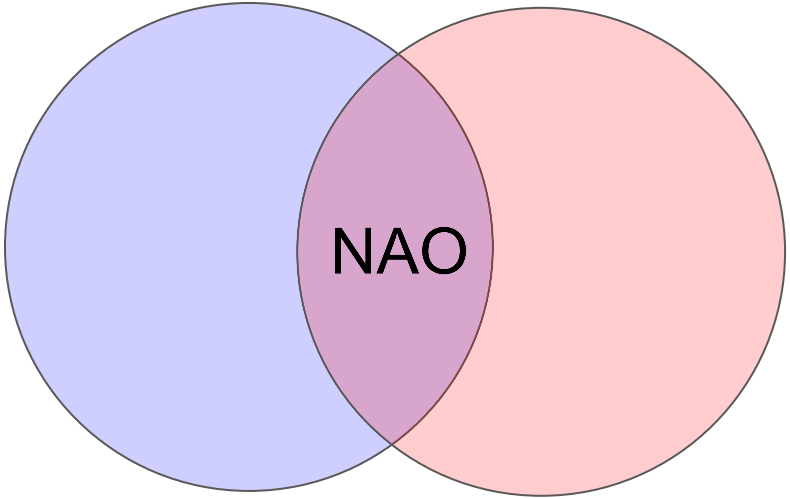

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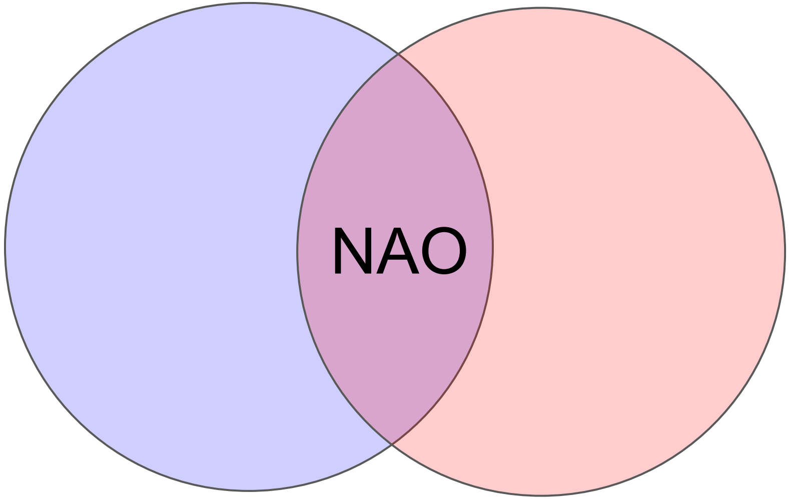

Background

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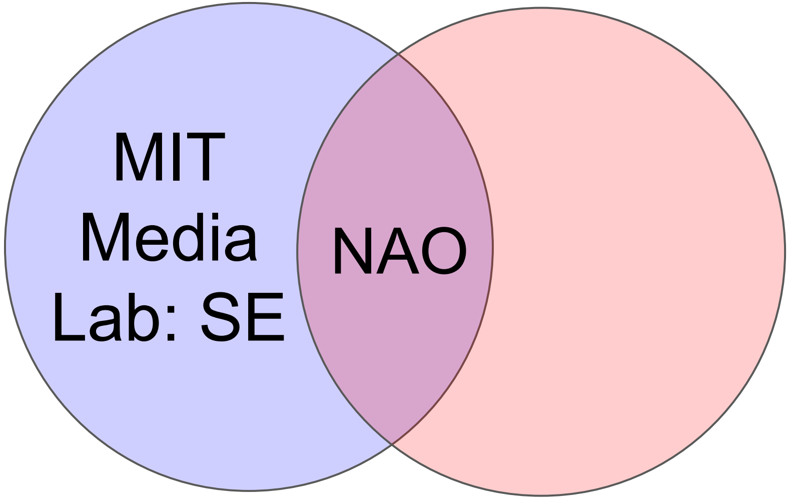
  - MIT Media Lab: Sculpting Evolution (Esvelt Lab)



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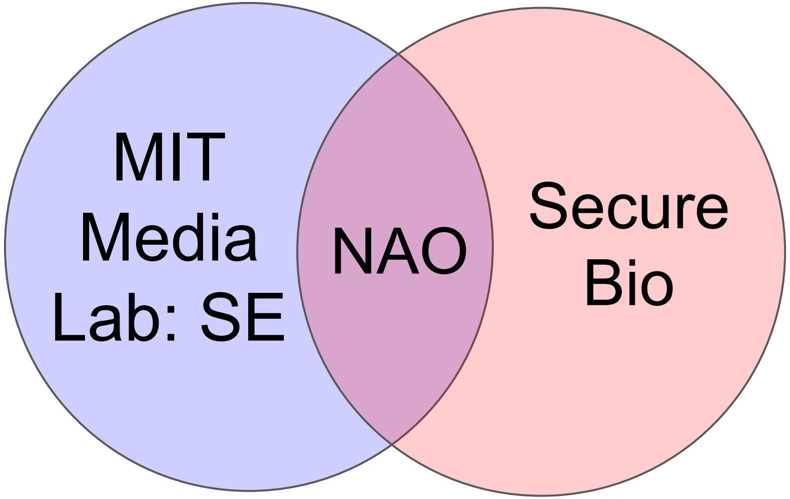
  - SecureBio



Background

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- Presenting work from a team

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Mike McLaren

Simon Grimm

Dan Rice

Jeff Kaufman

Background

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- Summary of an NAO report

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    - 2023-08-10, "Predicting Virus Relative Abundance in Wastewater"

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  - `data.securebio.org/p2ra`

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  - Doesn't require pre-selecting pathogens

Background

- NAO Goal: detect pandemics
  - Even if they don't look like previous ones
  - Even one that's intentionally "stealth"
- Wastewater
  - Millions of people → one sample
- Metagenomic sequencing
  - Doesn't require pre-selecting pathogens
  - But most reads won't match a pathogen

Key question

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- At a given stage of a future viral pandemic, what fraction of wastewater metagenomic sequencing reads match the virus?

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- $\mathrm{RA}(1\%)$: relative abundance of virus, when:
  - 1% currently infected (prevalence), or
  - 1% became infected this week (incidence)

Key question

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  - How deep to sequence?

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- Knowing $\mathrm{RA}(1\%)$ for many viruses would help us estimate:
  - How deep to sequence?
  - What would it cost?

Approach

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- Link public health data to sequencing data

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  - Collect metagenomic wastewater data

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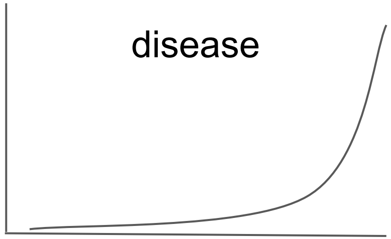
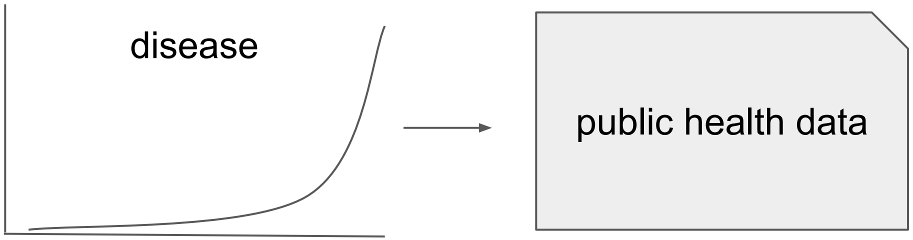
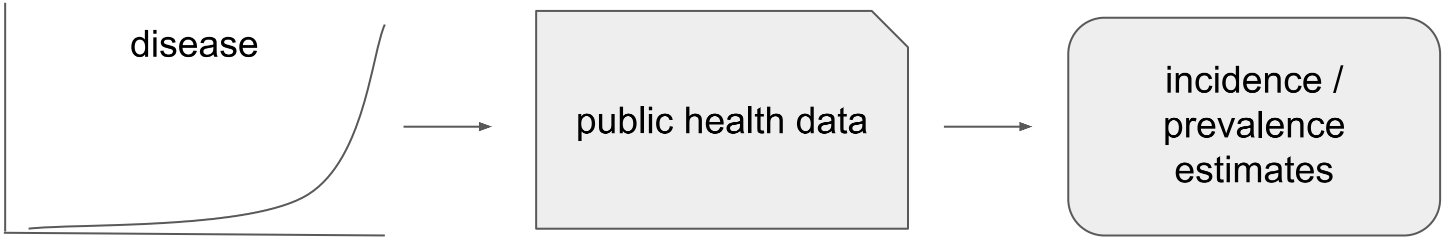
  - Estimate $\mathrm{RA}(1\%)$


disease



disease

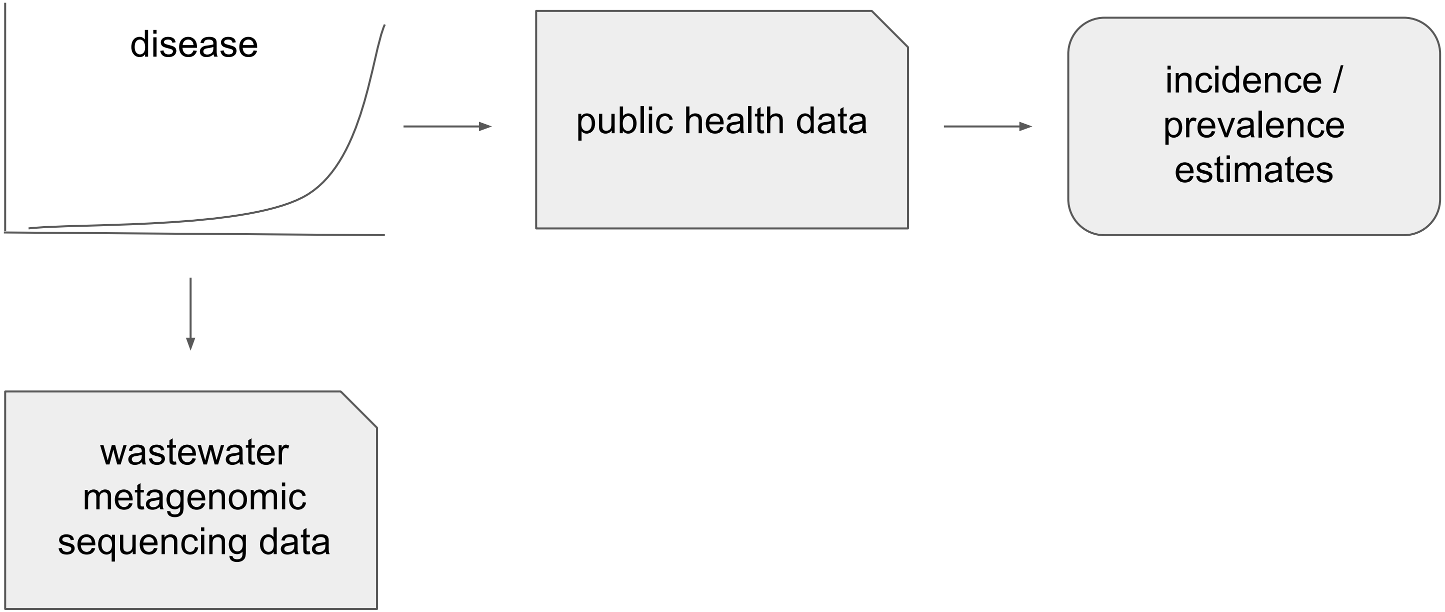
public health data



disease

public health data

incidence / prevalence estimates



disease

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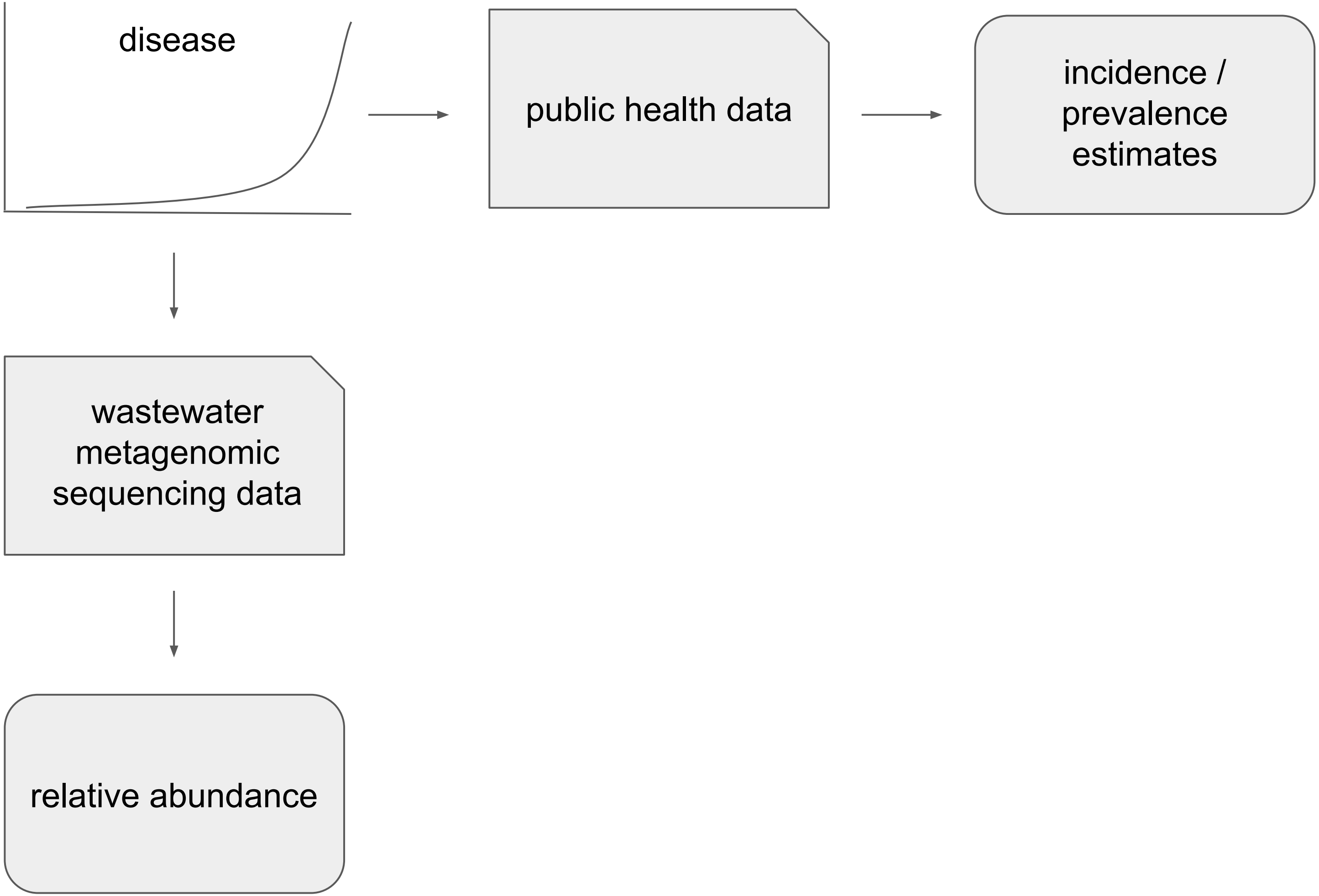
wastewater metagenomic sequencing data



disease

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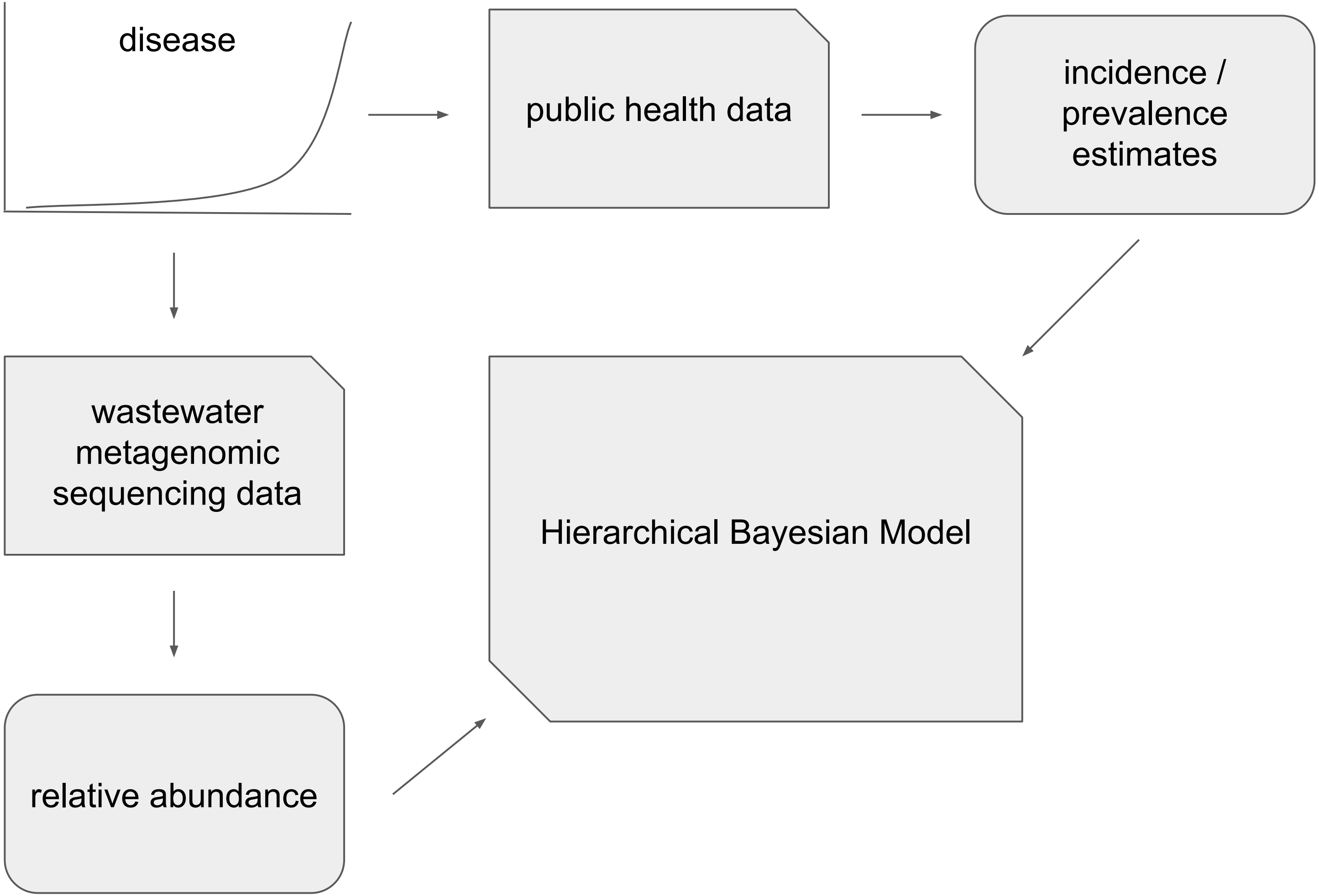
relative abundance


disease
public health data
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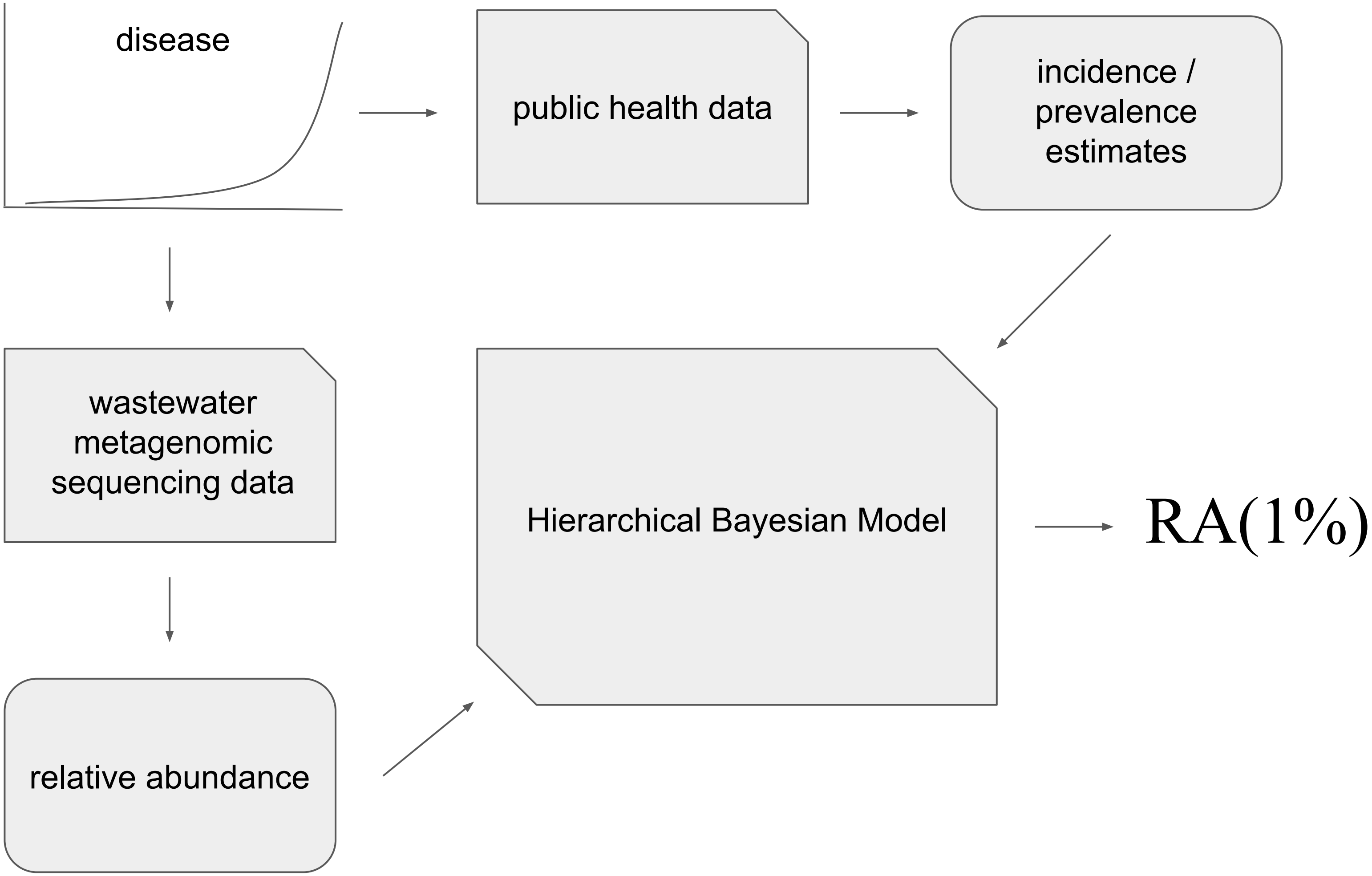
Hierarchical Bayesian Model
relative abundance



disease

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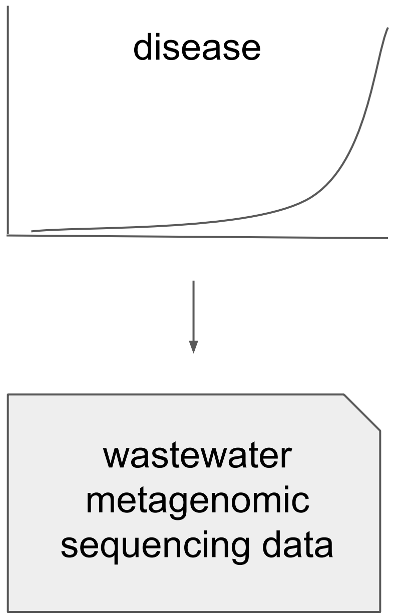
Hierarchical Bayesian Model

RA(1%)

Sequencing Data

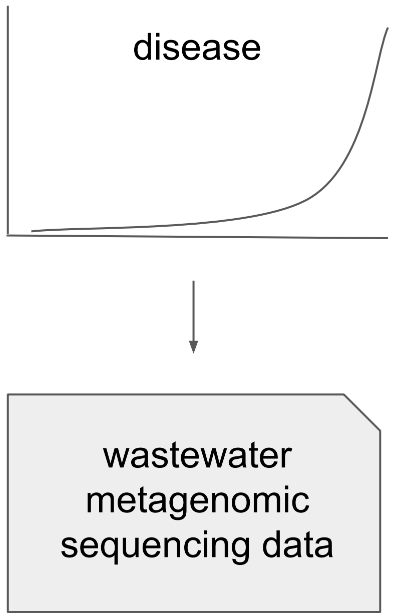


disease

wastewater metagenomic sequencing data

Sequencing Data

- RNA (2.8B read pairs)



disease

wastewater metagenomic sequencing data

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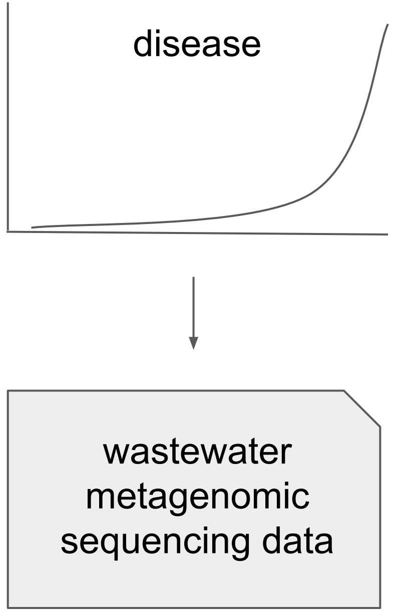

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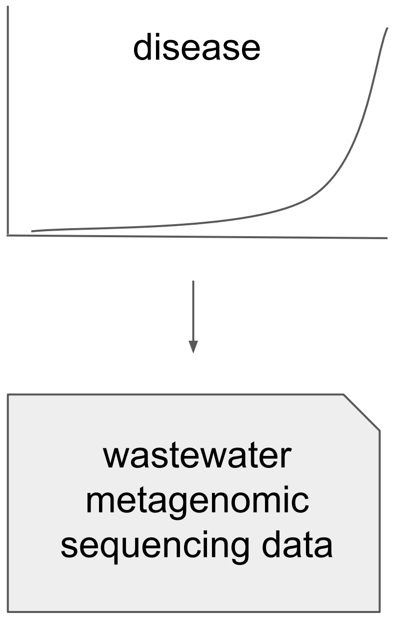

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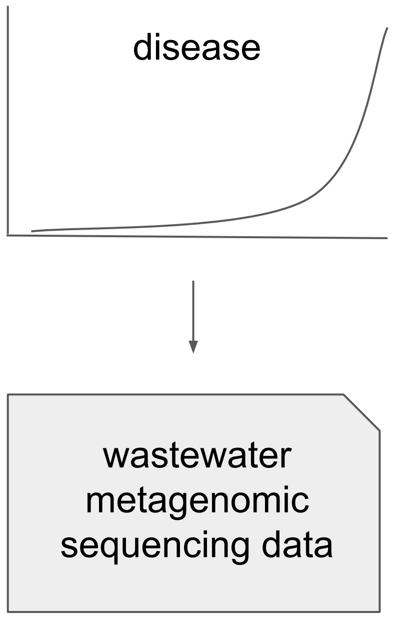

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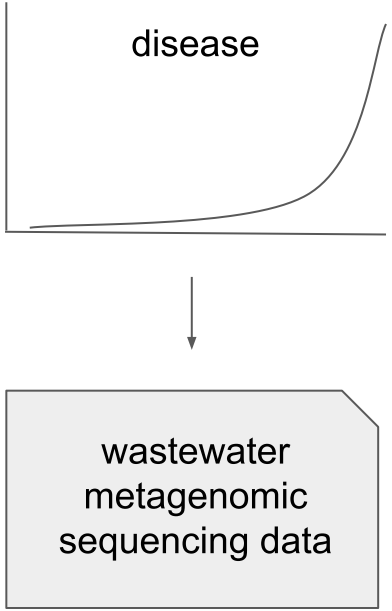
- DNA (4.4B read pairs)



disease

wastewater metagenomic sequencing data

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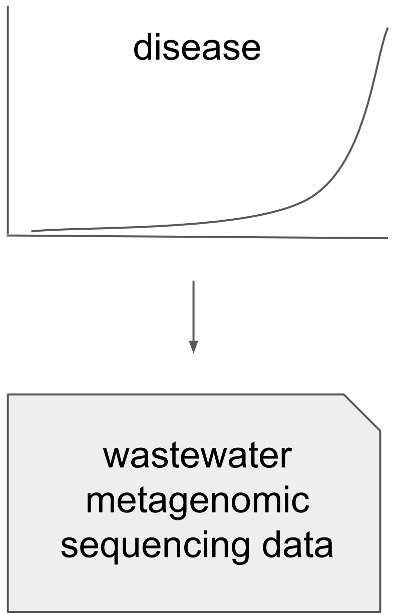
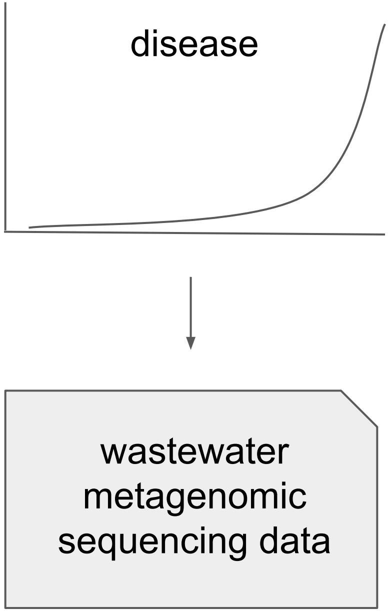


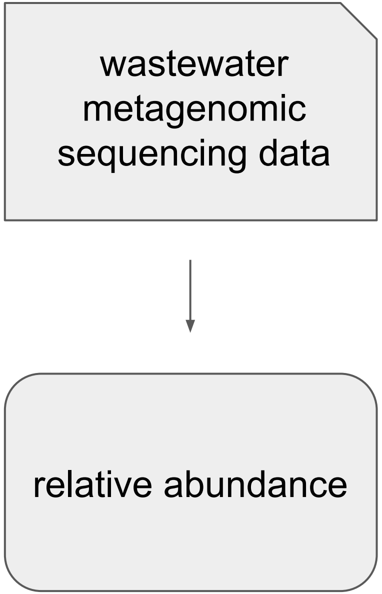
wastewater metagenomic sequencing data

Sequencing Data

- RNA (2.8B read pairs)
  - SF: Crits-Christoph et al. (2021)
  - LA: Rothman et al. (2021)
  - Ohio: Spurbeck et al. (2023)
  - *All during Covid-19*
- DNA (4.4B read pairs)
  - Copenhagen: Brinch et al. (2020)
  - *Pre-Covid-19*

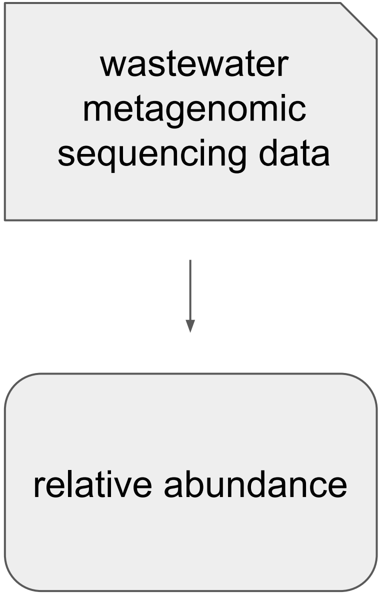


Determine Relative Abundances



Determine Relative Abundances

- Kraken2 to assign reads to species



wastewater metagenomic sequencing data

relative abundance

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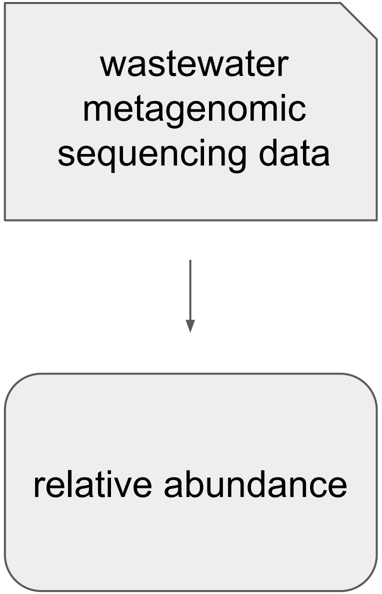
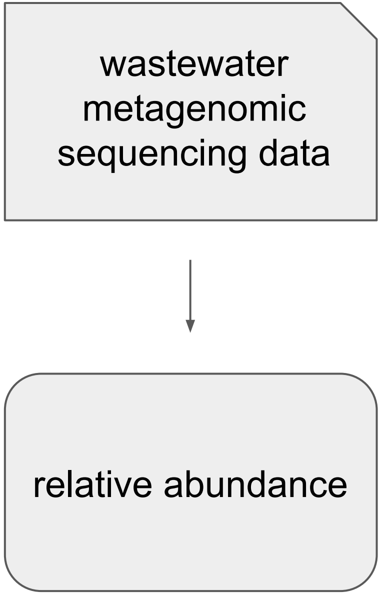


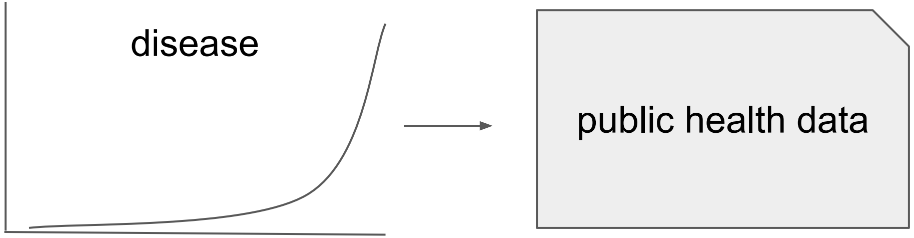
Determine Relative Abundances

- Kraken2 to assign reads to species
- Alignment to reference genomes to remove false positives

- relative abundance = $\frac{\text{reads matching virus}}{\text{reads in sample}}$



Target Viruses

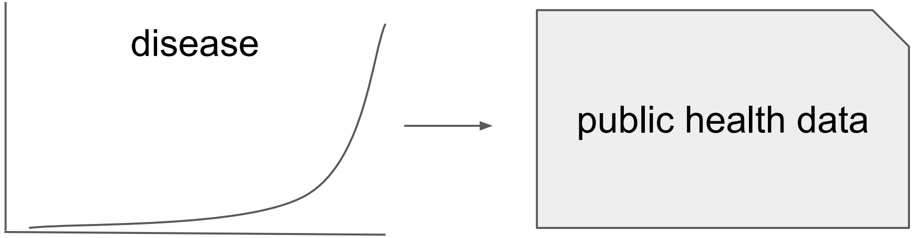


disease

public health data

Target Viruses

- Viruses where we can get public health estimates matching where and when sequencing samples were collected



disease

public health data

Target Viruses

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- Acute

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- Acute
  - Sars-CoV-2

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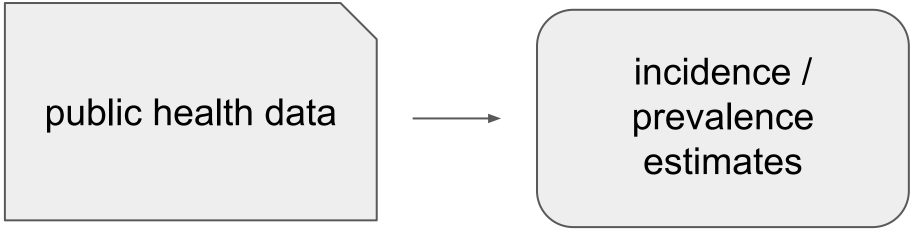
  - Herpes viruses: HSV-1, EBV, CMV

Target Viruses

- Acute
  - Sars-CoV-2
  - Influenza A and B
  - Norovirus: genogroups I and II
- Chronic
  - HIV
  - Herpes viruses: HSV-1, EBV, CMV
  - ... eight others

Public Health Data

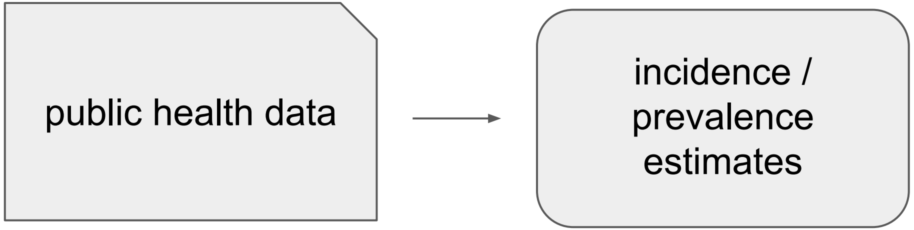


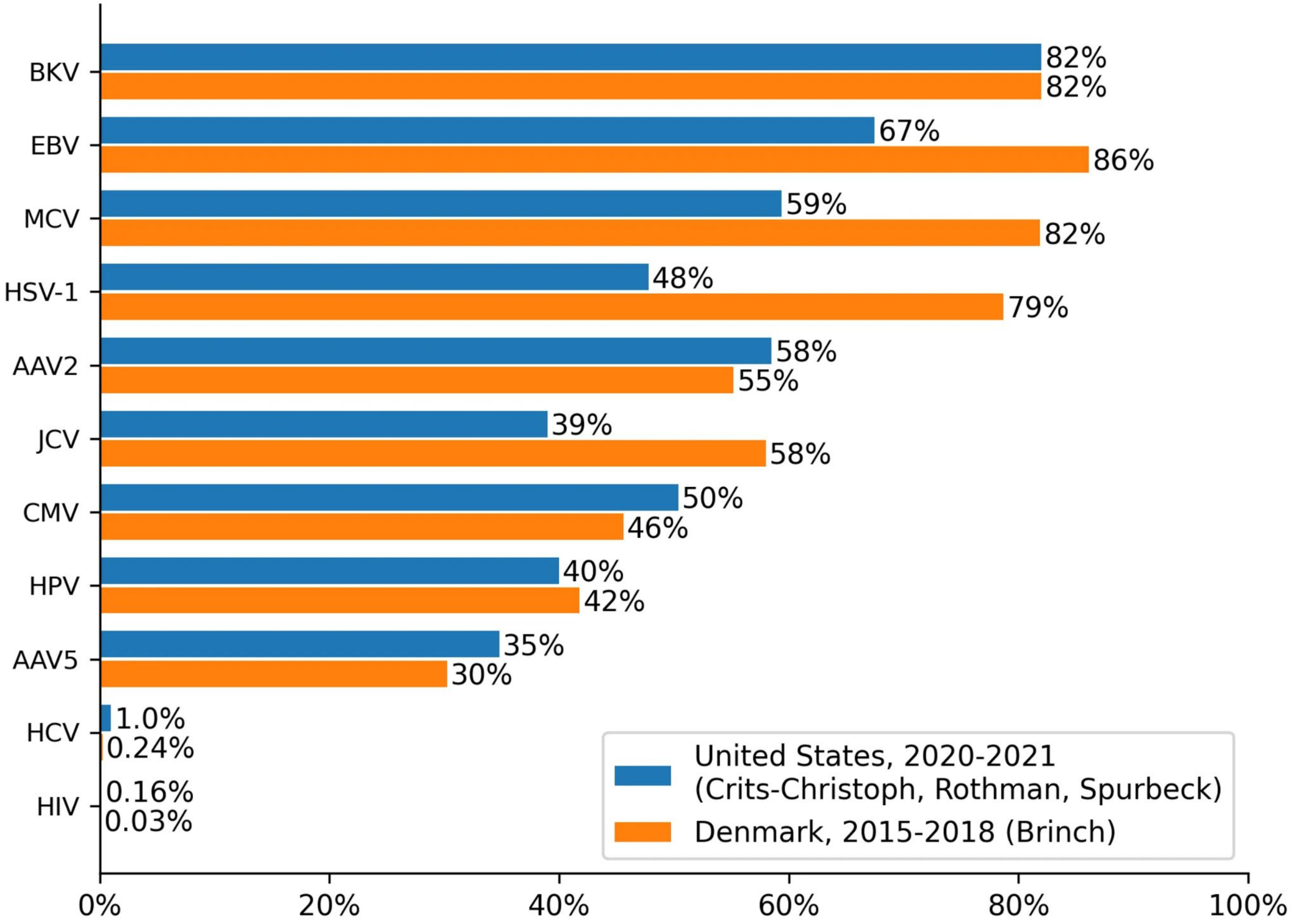
public health data

incidence / prevalence estimates

Public Health Data

- Chronic: estimate prevalence

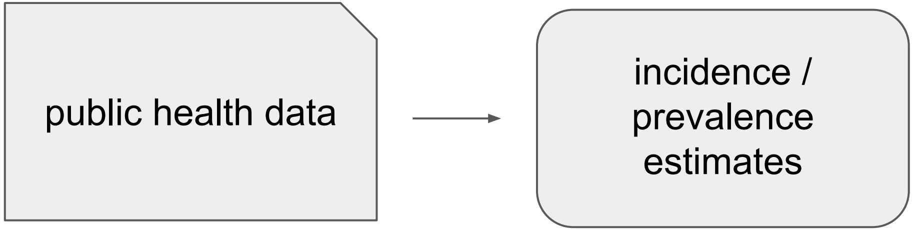




Estimated prevalence of persistent viral infections

Public Health Data

- Chronic: estimate prevalence



public health data

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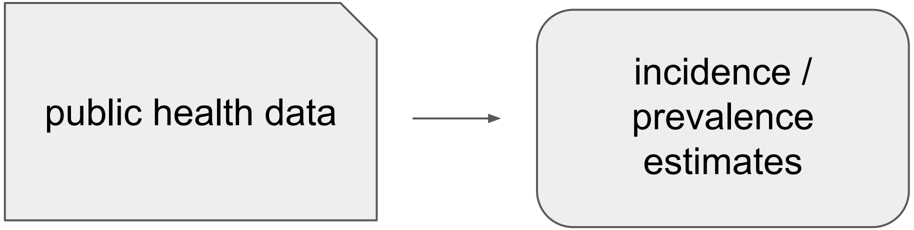
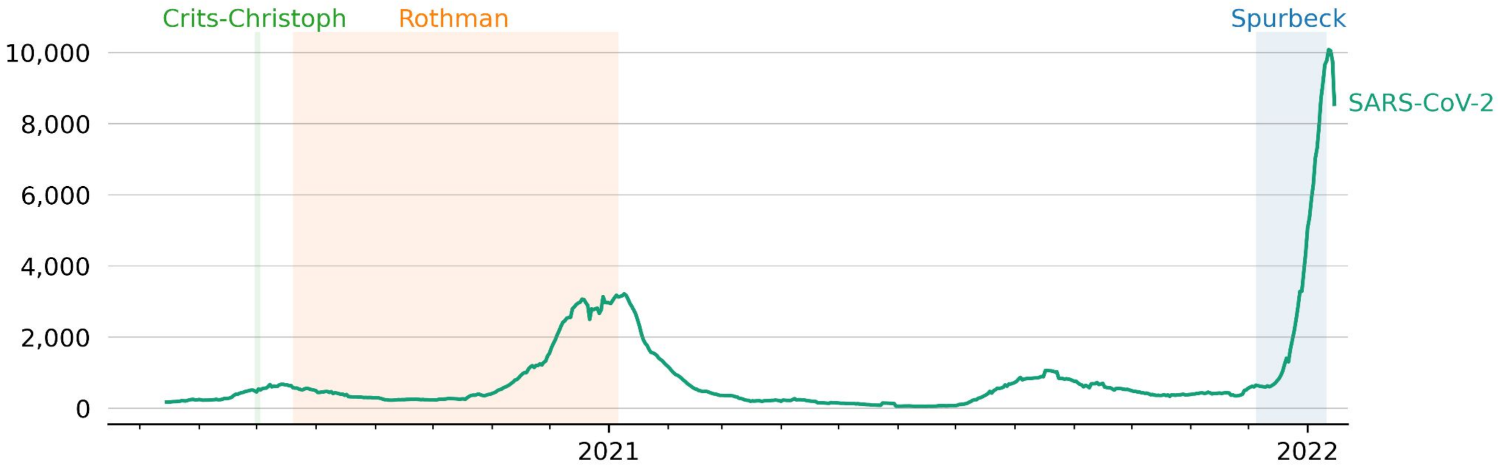
Public Health Data

- Chronic: estimate prevalence
- Acute: estimate incidence



Weekly Infections per 100,000 people



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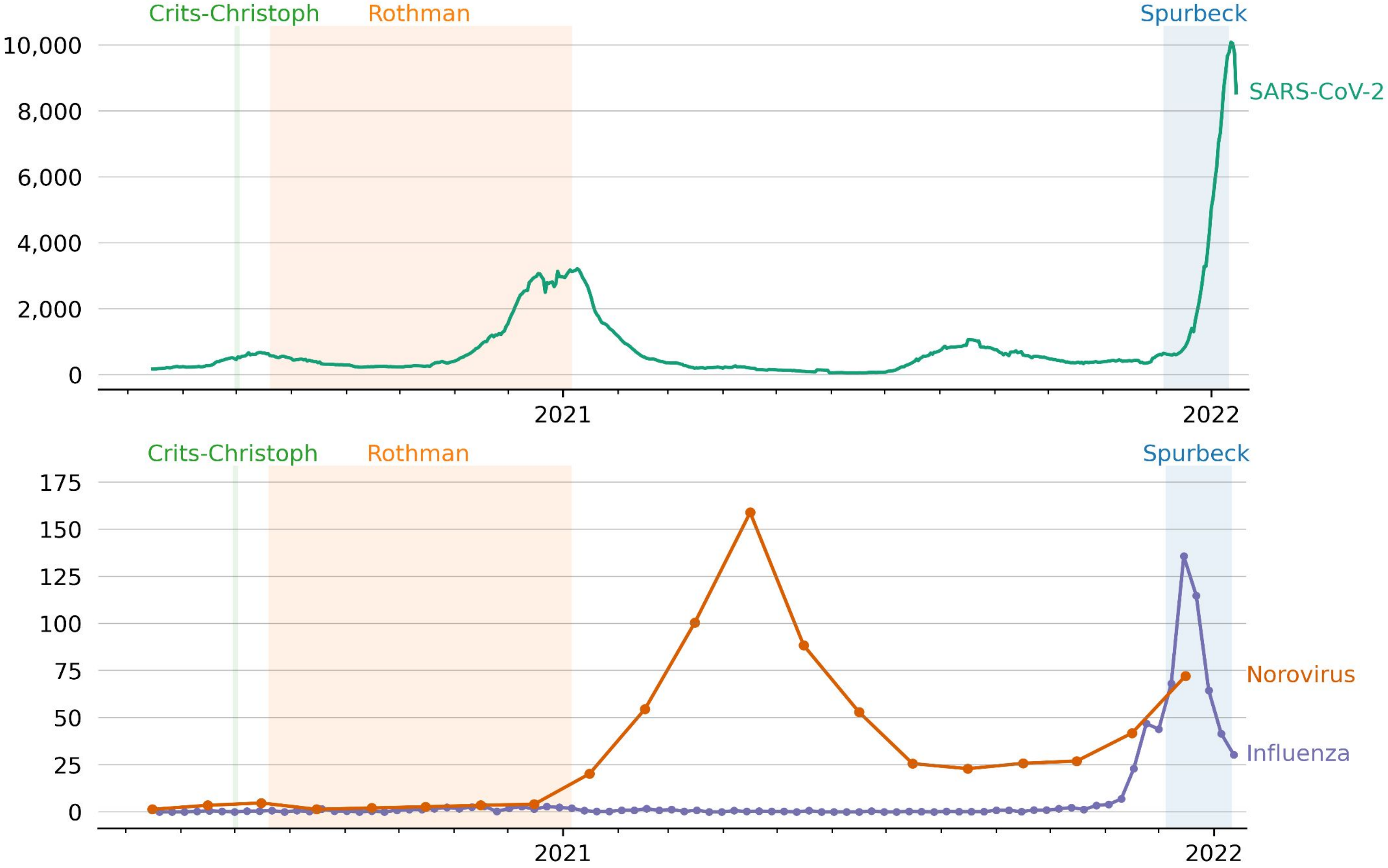
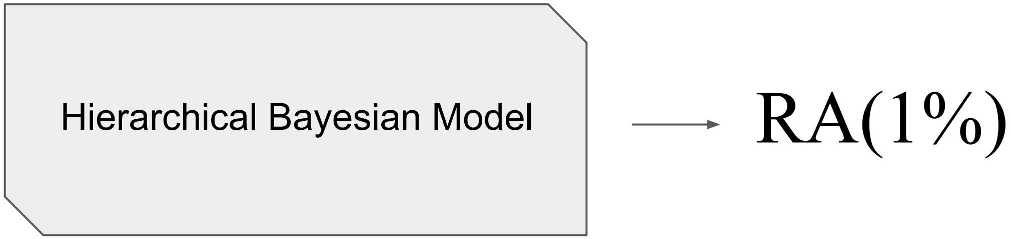


Estimating RA(1%)

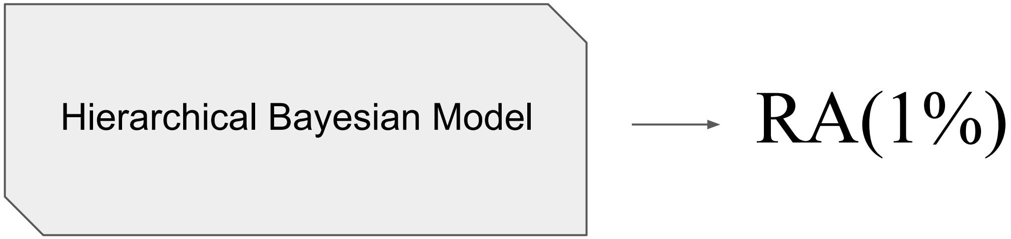


Hierarchical Bayesian Model

RA(1%)

Estimating RA(1%)

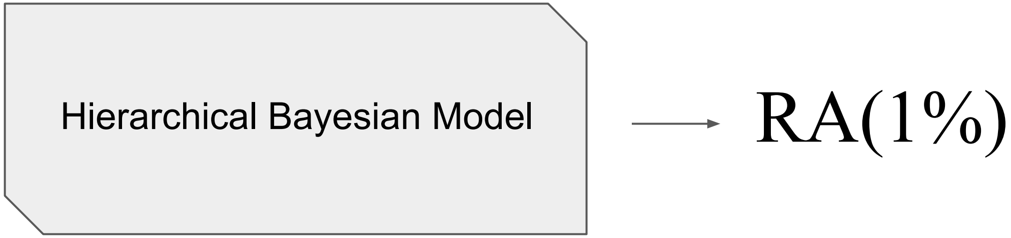
- Chronic: RAp(1%)



Hierarchical Bayesian Model → RA(1%)

Estimating $\mathrm{RA}(1\%)$

- Chronic: $\mathrm{RA}p(1\%)$
  - Relative abundance at 1% prevalence



Hierarchical Bayesian Model

$\mathrm{RA}(1\%)$

Estimating $\mathrm{RA}(1\%)$

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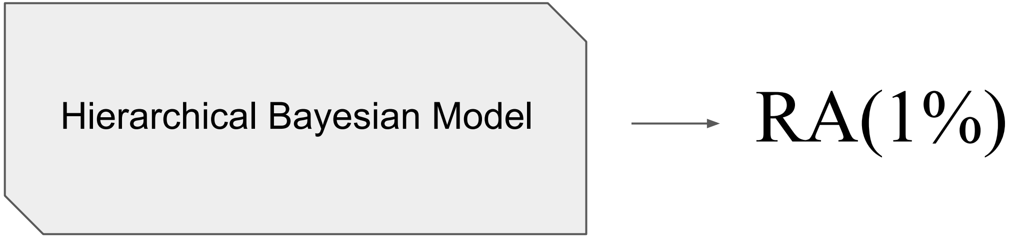

Hierarchical Bayesian Model → $\mathrm{RA}(1\%)$

Estimating $\mathrm{RA}(1\%)$

- Chronic: $\mathrm{RA}p(1\%)$
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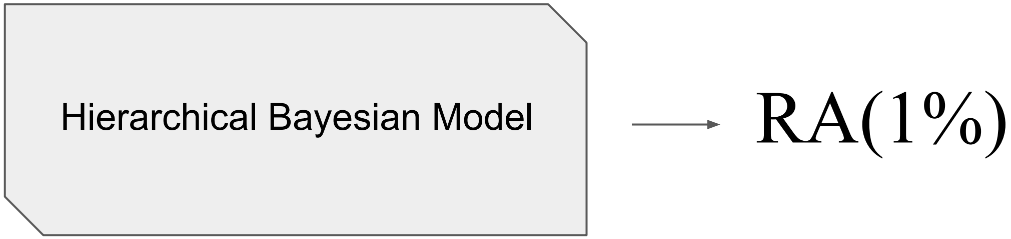
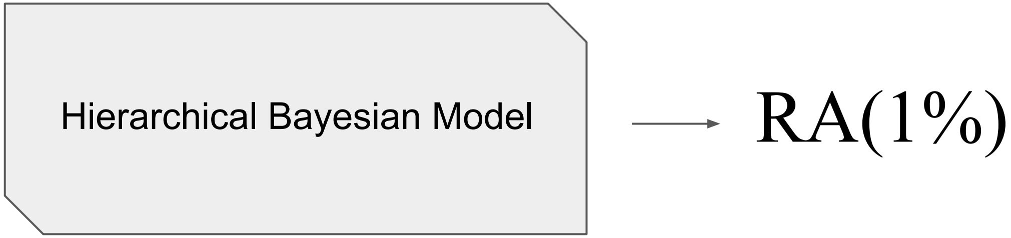
- Acute: $\mathrm{RA}i(1\%)$
  - Relative abundance at 1% weekly incidence

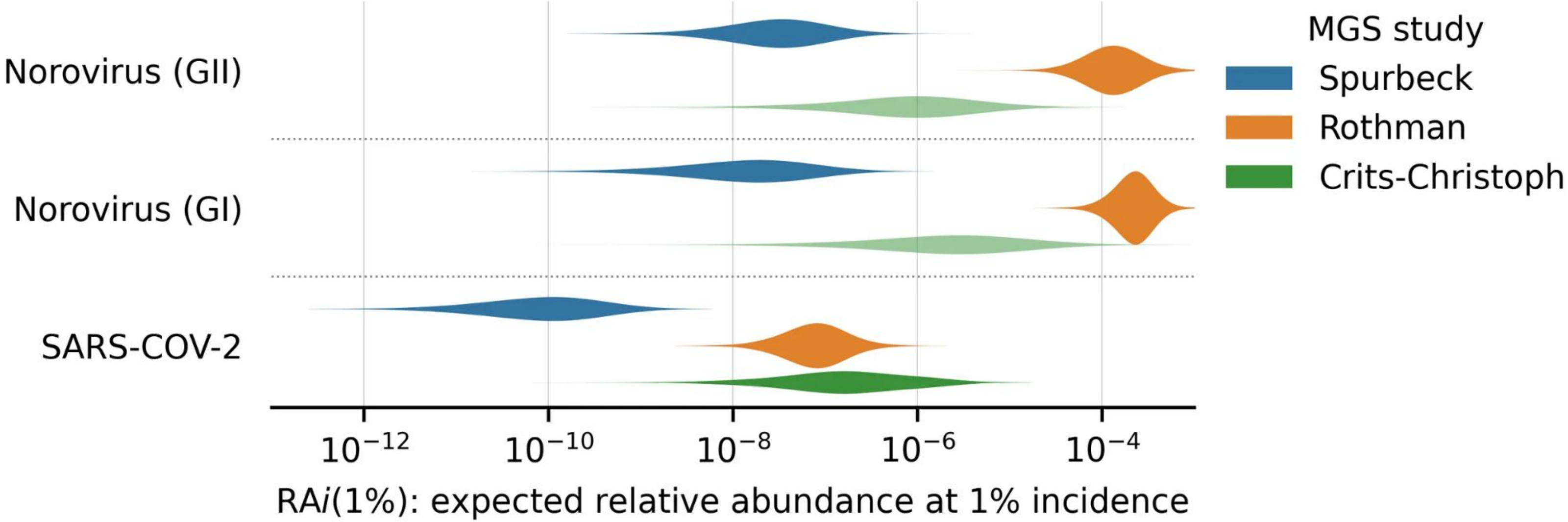


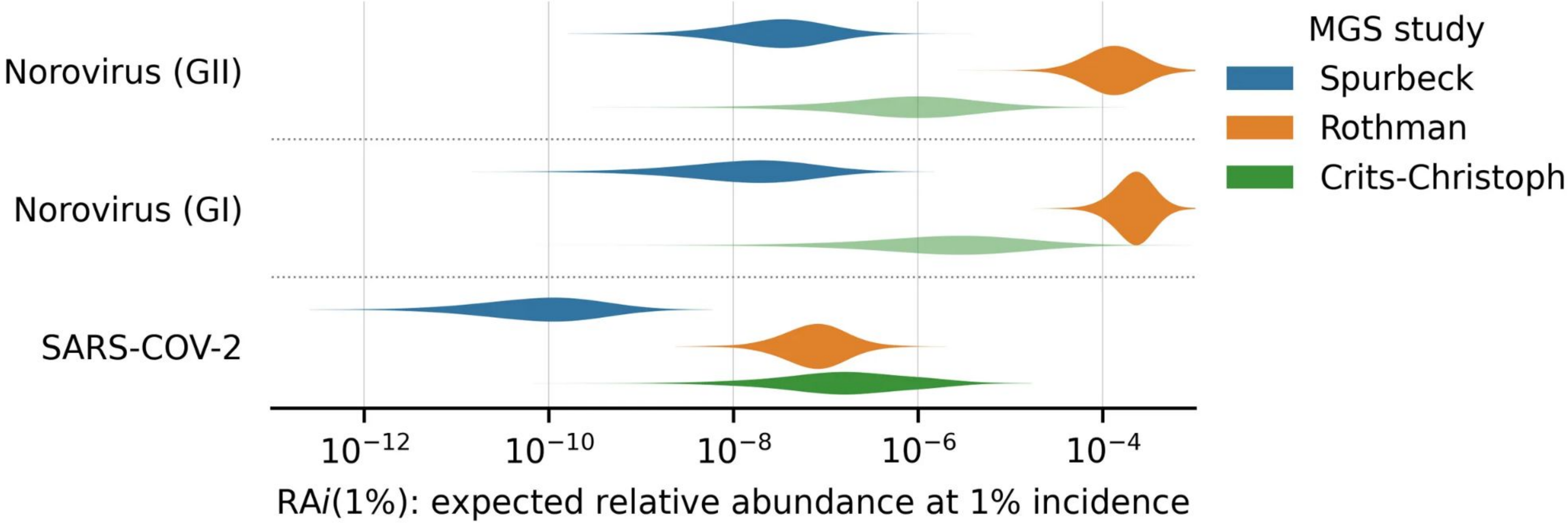
Hierarchical Bayesian Model → $\mathrm{RA}(1\%)$

Estimating $\mathrm{RA}(1\%)$

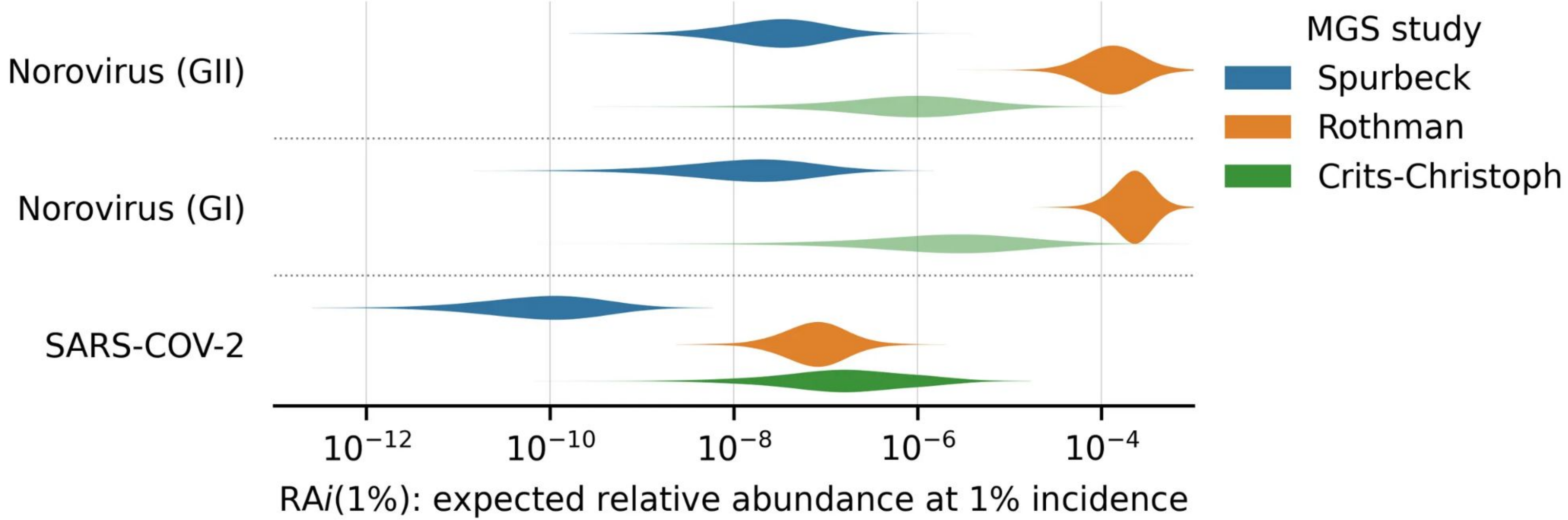
- Chronic: $\mathrm{RA}p(1\%)$
  - Relative abundance at 1% prevalence
- Acute: $\mathrm{RA}i(1\%)$
  - Relative abundance at 1% weekly incidence
- Hierarchical Bayesian logistic regression model




Norovirus (GII)
Norovirus (GI)
SARS-COV-2
MGS study
Spurbeck
Rothman
Crits-Christoph
10^{-12}
10^{-10}
10^{-8}
10^{-6}
10^{-4}
RA*i*(1%): expected relative abundance at 1% incidence



- Lots of variation by virus



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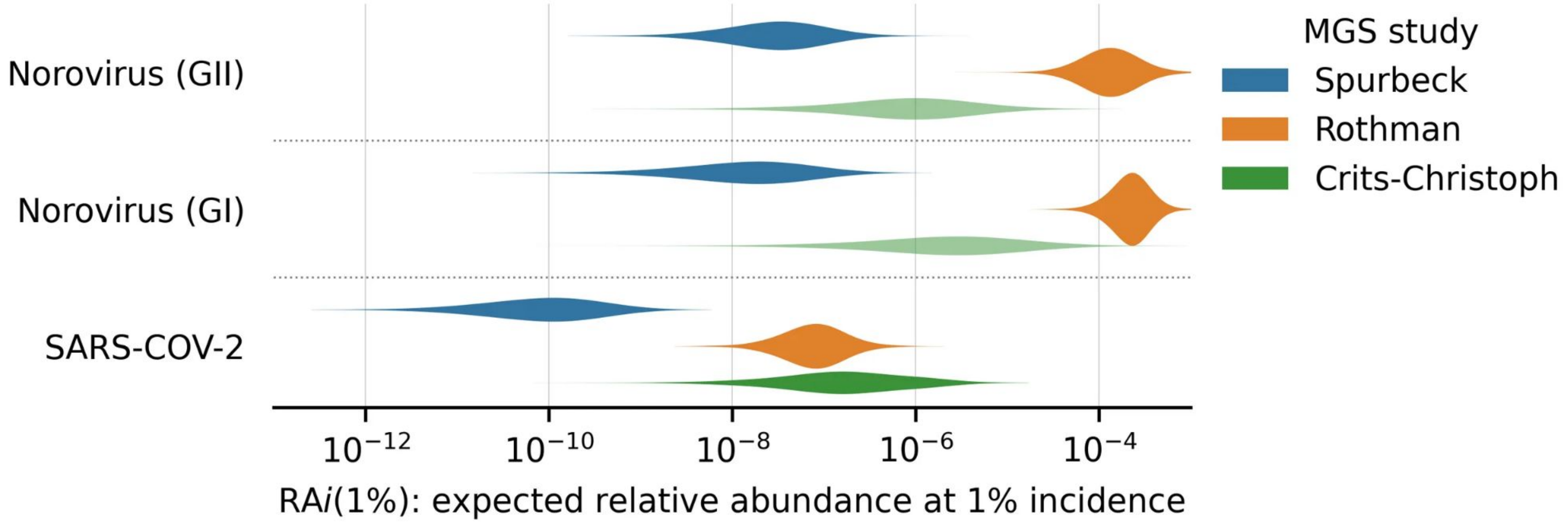
  - Norovirus (~1e-4) vs Sars-Cov-2 (~1e-7) in Rothman



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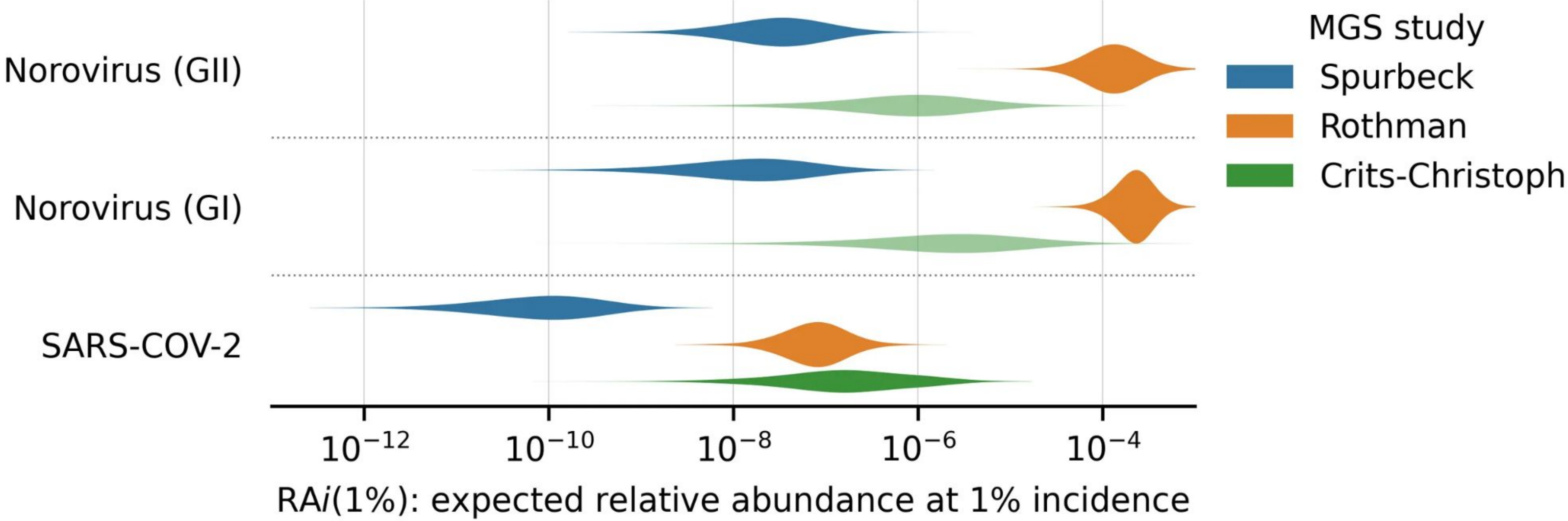

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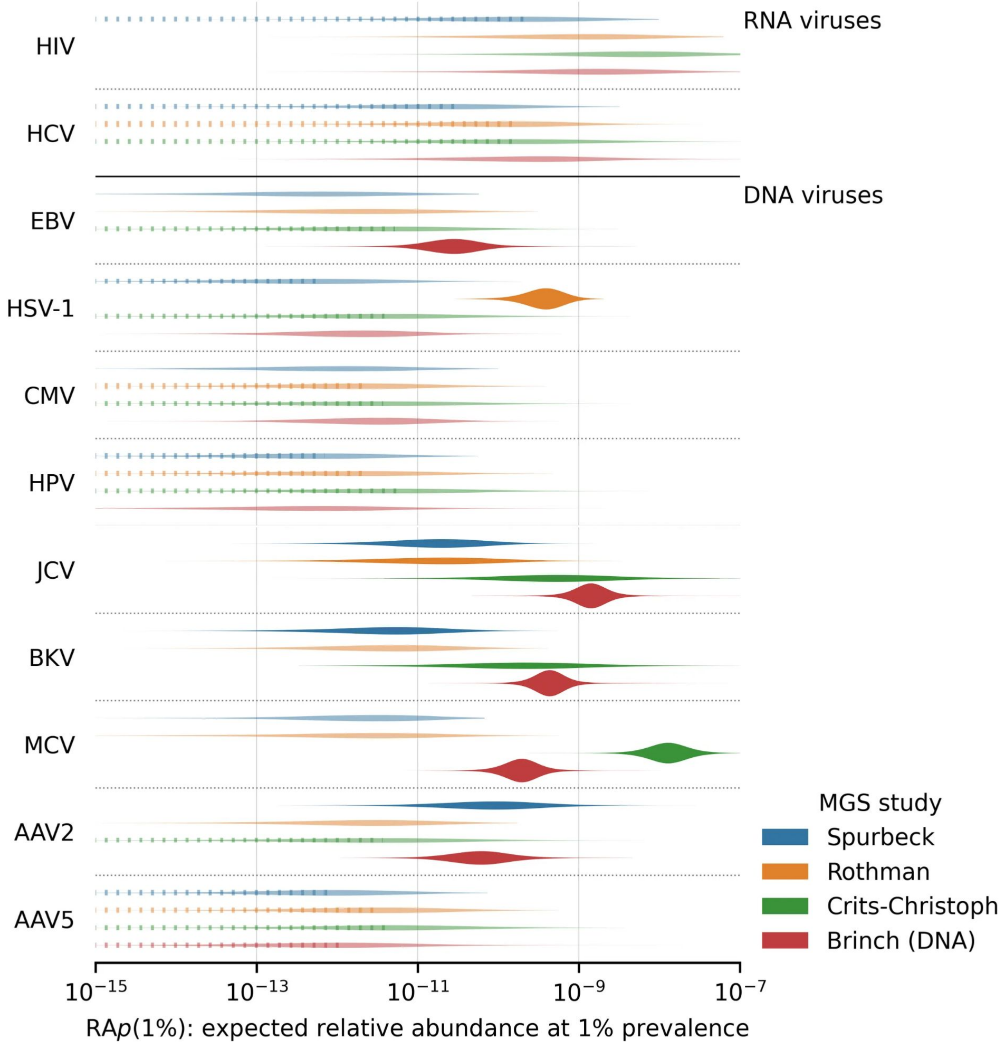
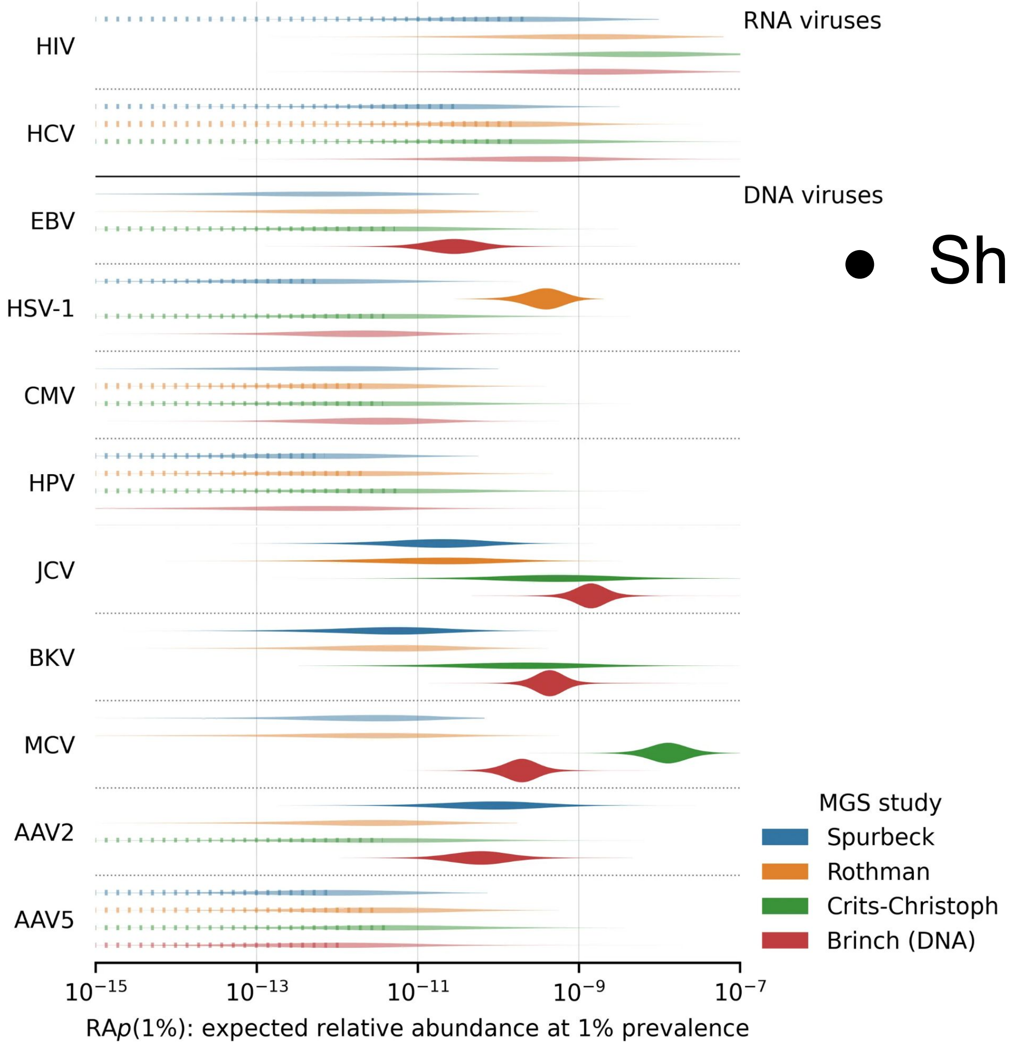
- And by study
  - Spurbeck is consistently lower


RNA viruses
HIV
HCV
DNA viruses
EBV
HSV-1
CMV
HPV
JCV
BKV
MCV
AAV2
AAV5
10^{-15}
10^{-13}
10^{-11}
10^{-9}
10^{-7}
RAp(1%): expected relative abundance at 1% prevalence
MGS study
Spurbeck
Rothman
Crits-Christoph
Brinch (DNA)



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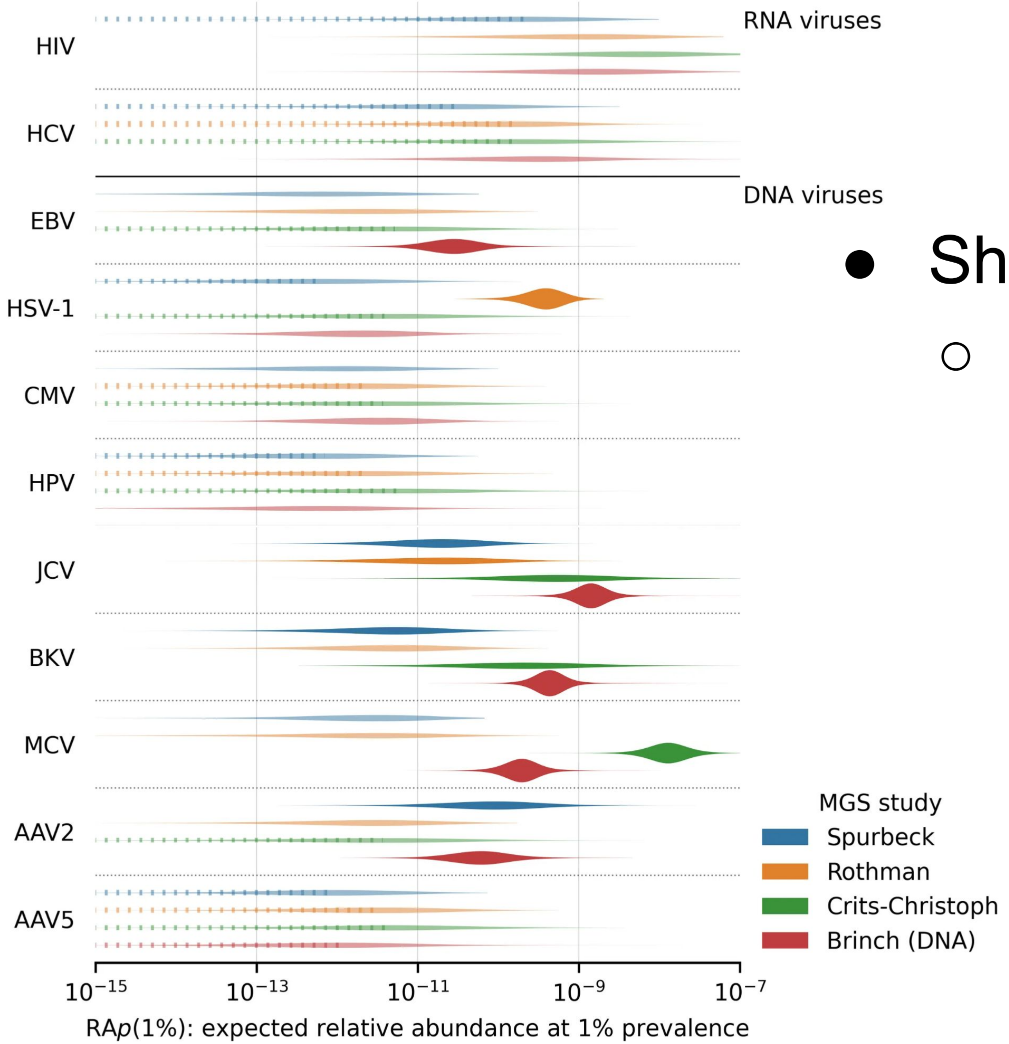

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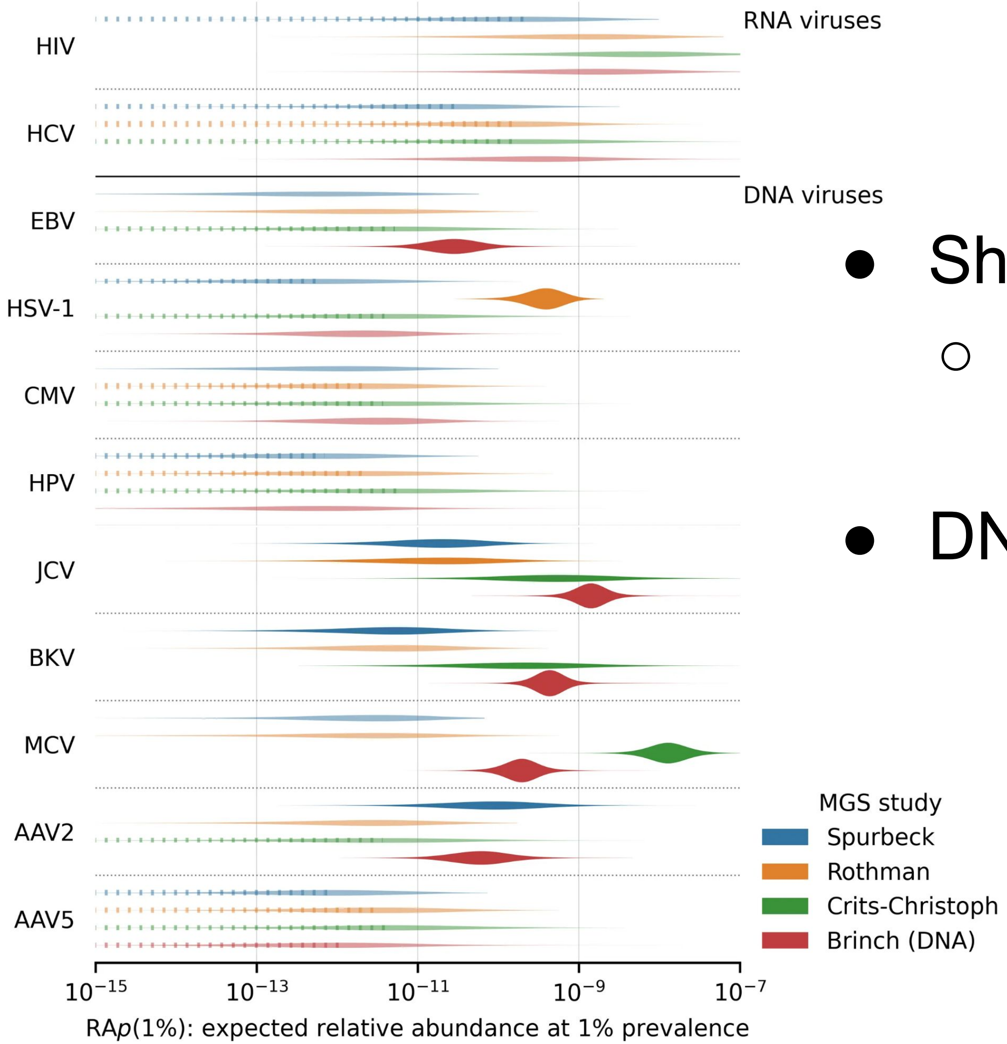

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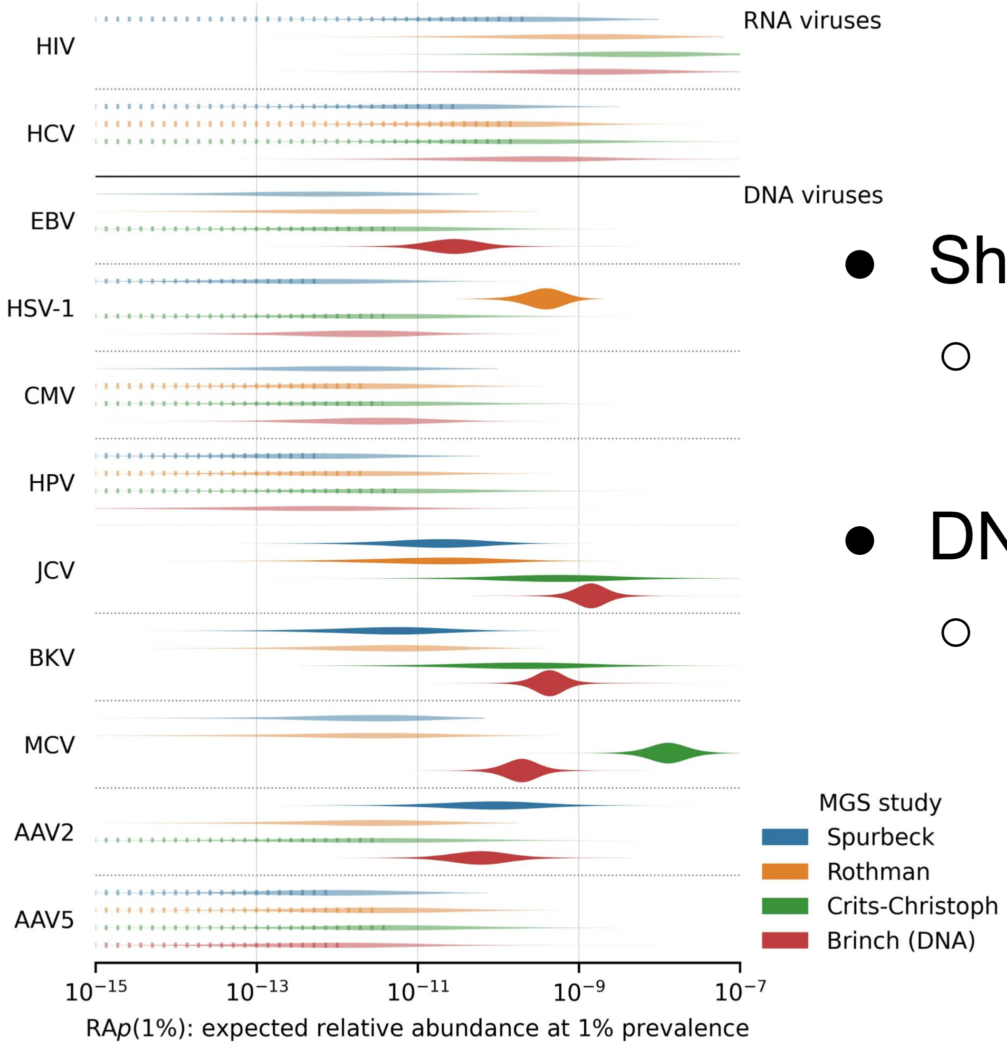

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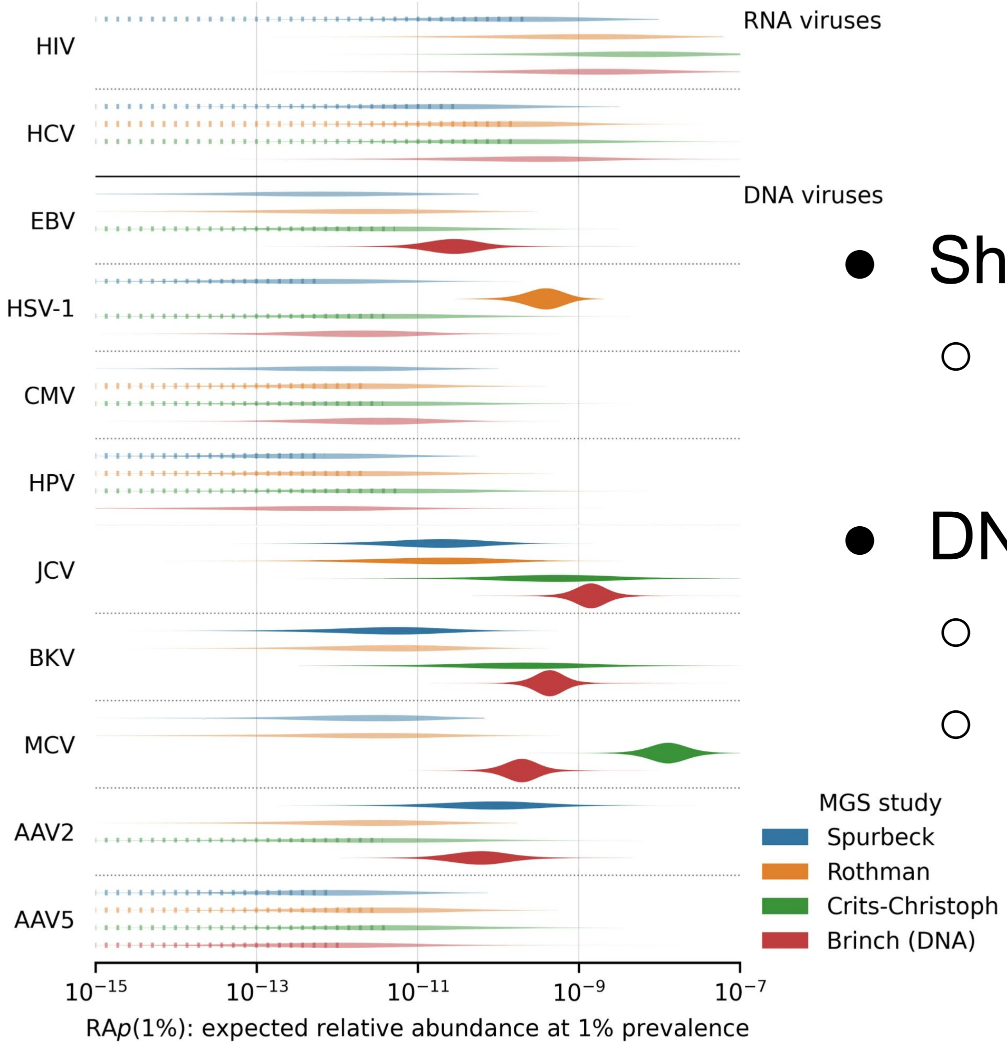

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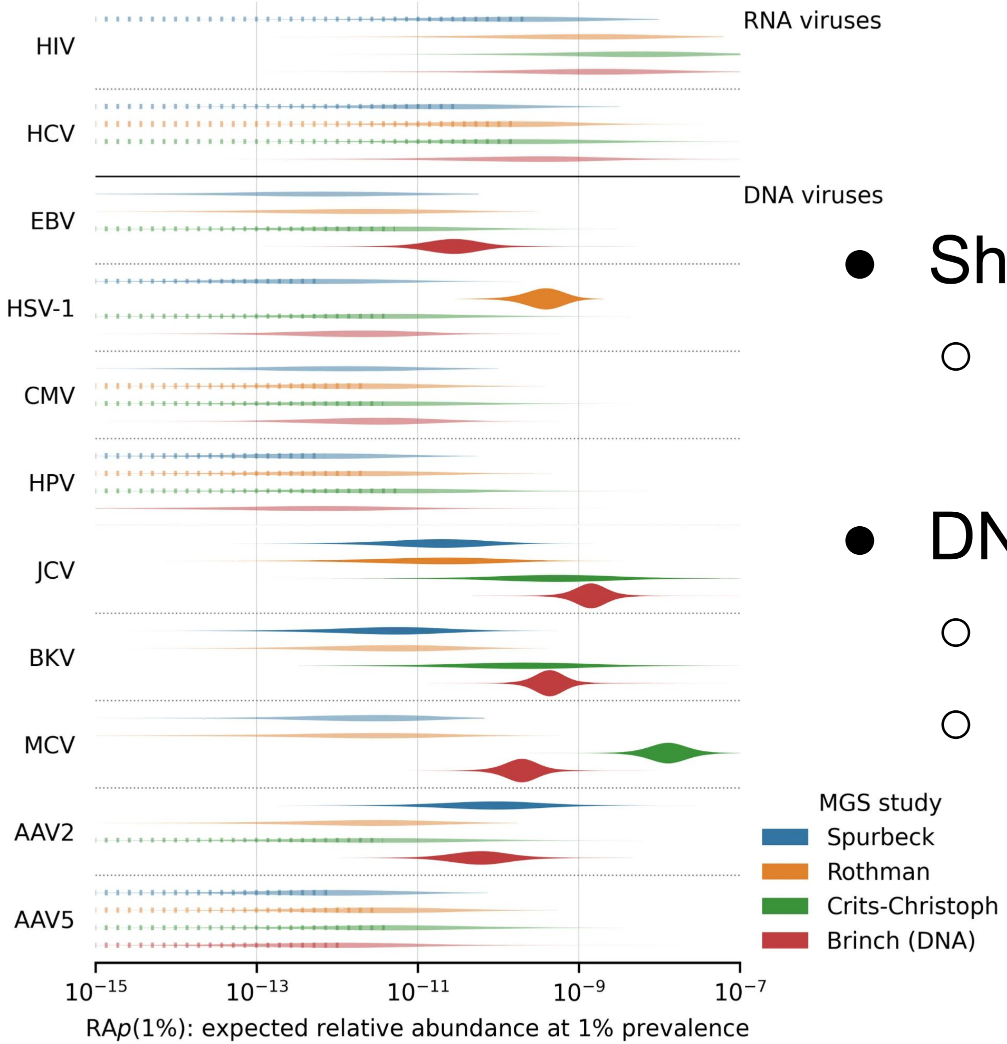

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    - ex: MCV and HSV-1

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    - Deep sequencing (more reads) during a higher-infection time would allow better estimates

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- Full report: `data.securebio.org/p2ra`