

SC2

FLU

RSV

HRV

EV

ADV

PIV

HMPV

HCOV

Does infection with one respiratory virus change your risk of infection with another?

Interactions between respiratory viruses in US adults and children: a prospective cohort study

Kat Hoffman · 4th year Biostatistics PhD student · UW Biostatistics Student Seminar · October 14, 2026

About this work

A research assistantship project

This talk is about my RA work this past year with Dr. Helen Chu's lab at UW: using the CASCADIA cohort to study how respiratory viruses interact.

Chu Lab

www.chulab.org

Data: CASCADIA, a CDC-funded prospective household cohort in Washington and Oregon (Babu et al., BMJ Open 2023)

Paper: Hoffman et al., under review at *Lancet Microbe*.

Jointly supervised by



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A grant deliverable for the Washington State Department of Health (Northwest Pathogen Genomics Center of Excellence; HED29377-2, NU50CK000630), which also funded my PhD.

Roadmap

Part I

Why would viruses interact?

The biology in one picture, a brief history of the evidence, and why existing human data are hard to interpret

Part II

The CASCADIA study

A cohort swabbed weekly; time-varying Cox models with calendar time as the time scale; what we found

Part III

How else could we attack this?

Estimands, behavior as a mediator, self-controlled and trial-emulation designs, informative testing, sparsity, transmission models

Part I

Why would viruses interact?

Biology for statisticians

Respiratory viruses circulate, often at the same time

SC2

SARS-CoV-2

Causes COVID-19; waves year-round

FLU

Influenza A and B

Sharp winter epidemics

RSV

Respiratory syncytial virus

Leading cause of infant hospitalization

HRV

Human rhinovirus

The "common cold"; most frequent by far

EV

Enterovirus

Close relative of rhinovirus

ADV

Adenovirus

Colds, sore throat, pink eye; common in daycare

PIV

Parainfluenza 1–4

Croup in young children

HMPV

Human metapneumovirus

RSV-like illness

HCOV

Endemic coronaviruses

Four seasonal "cold" coronaviruses

Virus–virus interactions: two directions, several mechanisms

Interference: lower risk of B

- 1 **Innate alarm:** interferon from infected cells puts nearby cells into an antiviral state against any virus

HRV blocks FLU and SC2 in airway tissue (Wu 2020; Dee 2021)

- 2 **Fewer entry points:** the first virus occupies or strips the receptors a second virus needs

Influenza neuraminidase removes sialic-acid receptors (Huang 2008)

- 3 **Competition:** viruses compete for the same cells and cellular machinery

Cell-culture co-infection studies (reviewed in Piret & Boivin 2022)

Enhancement: higher risk of B

- 1 **More entry points:** the first virus up-regulates receptors used by the second

FLU increases ACE2, the SC2 receptor (Bai 2021; Schweitzer 2021)

- 2 **Damaged barrier:** injured epithelium and slower mucus clearance let a second pathogen establish

Well known for bacteria after influenza

- 3 **Muted alarm:** viruses that suppress interferon remove the protective effect

SARS-CoV-2 delays the type I interferon response (Blanco-Melo 2020)

Direction-specific

$A \rightarrow B$ need not equal $B \rightarrow A$

Time-dependent

depends on the gap between infections (ferrets: Laurie 2015)

Host-dependent

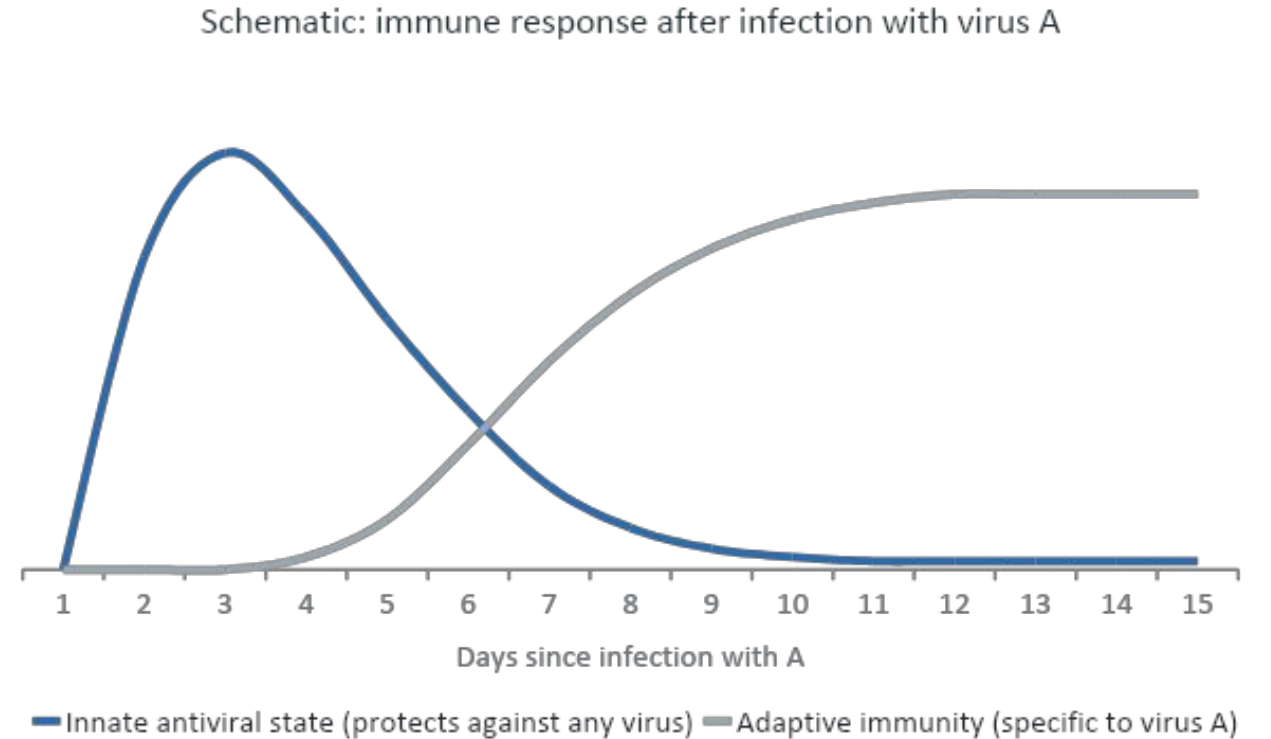
age, prior immunity, and symptom severity

In our terms

does the hazard of B at time t depend on time since A?

The innate "alarm": fast, non-specific, and short-lived

- 1 Sense**
Within hours, an infected airway cell detects viral RNA
- 2 Signal**
It secretes interferons (type I and III), which reach neighboring cells
- 3 Defend**
Neighbors switch on hundreds of antiviral genes that block entry and replication of any virus
- 4 Wane**
Fades within ~2 weeks. Antigen specific antibodies and T cells proliferate later



Illustrative shapes, not data

What this predicts: if interference is innate, protection against B should be strongest in the first 1–2 weeks after A, fade after that, and apply to many virus pairs.

Sixty years of clues, mostly indirect

1960s–70s

Live enterovirus (oral polio) vaccines in children coincide with fewer influenza, PIV, RSV, HRV, ADV detections

Voroshilova 1989

2009

Pandemic H1N1 delayed in France during a rhinovirus wave

Casalegno 2010

2020–21

HRV-induced interferon blocks influenza and SARS-CoV-2 in human airway tissue

Wu, Lancet Microbe; Dee, JID

1982

RSV and influenza outbreaks seem to avoid each other

Anestad, Lancet

2019

Negative HRV–influenza A association in Glasgow surveillance, at the population and individual level

Nickbakhsh, PNAS

2024–25

Transmission models of influenza–RSV; household and records-based cohorts

Kramer, Nat Commun; Heimonen, JID

Evidence types: cell culture · animal models · ecological time series · clinical test records. Few prospective human cohorts.

Why the existing human evidence is hard to interpret

Problem

Clinically indicated testing

Only people sick enough to seek care get tested; mild and asymptomatic infections are missed

No unexposed comparator

No virus-negative person-time, so no incidence comparison with a group that wasn't recently infected

Codetection in a single swab

Two viruses in one sample says nothing about which came first or the gap between them

One pair, one direction

e.g., only SARS-CoV-2 after influenza; ignores other viruses circulating at the same time

What a better design needs

→ **Test on a schedule, regardless of symptoms**

→ **Follow everyone, infected or not, over calendar time**

→ **Repeated longitudinal sampling**

→ **Model all viruses jointly**

Why should a biostatistician care?

1 Epidemic forecasting

If one virus's wave suppresses or boosts another's, forecasting each virus separately is misspecified.

2 Timing of interventions

Vaccination and antivirals could have direct or indirect effects on other viruses.

3 Reading the pandemic era

Distancing and masking reshuffled seasons; interactions may explain some of the unusual post-2020 patterns.

4 A hard inference problem

Time-varying exposures, informative observation, many virus pairs, sparse data.

Part II

The CASCADIA study

Design, outcome definitions, model, and results

CASCADIA: a community cohort that swabbed every week

Design

- Prospective, community-based household cohort
- Washington and Oregon; ages 6 months–49 years
- June 2022 – March 2024
- Weekly symptom surveys; symptoms can be reported any time
- Self-collected nasal swabs mailed in for RT-qPCR
- Powered for SARS-CoV-2 vaccine effectiveness (Babu 2023); this paper is a secondary analysis

3,560

participants

428

aged 6 mo–4 y

4,299

person-years

1.3 y

median follow-up

85%

median weekly swab
adherence

10,838

illness episodes

Two streams of swabs, tested at different levels of detail



• Weekly swab

Taken regardless of symptoms. RT-qPCR for SC2, FLU, RSV; run on the full panel if positive or if symptoms began within 72 h

▼ Symptom-triggered swab

Whenever new or worsening symptoms start more than 72 h after the last swab. Always run on the full 9-virus panel

SC2 shedding substudy

Extra swabs after a SARS-CoV-2 positive. Asymptomatic RSV and FLU found only by this extra swabbing are excluded

Consequence: asymptomatic infections are captured only for SC2, FLU, and RSV. For the other six viruses we only see symptomatic detections.

From swab results to episodes: illness vs. infection

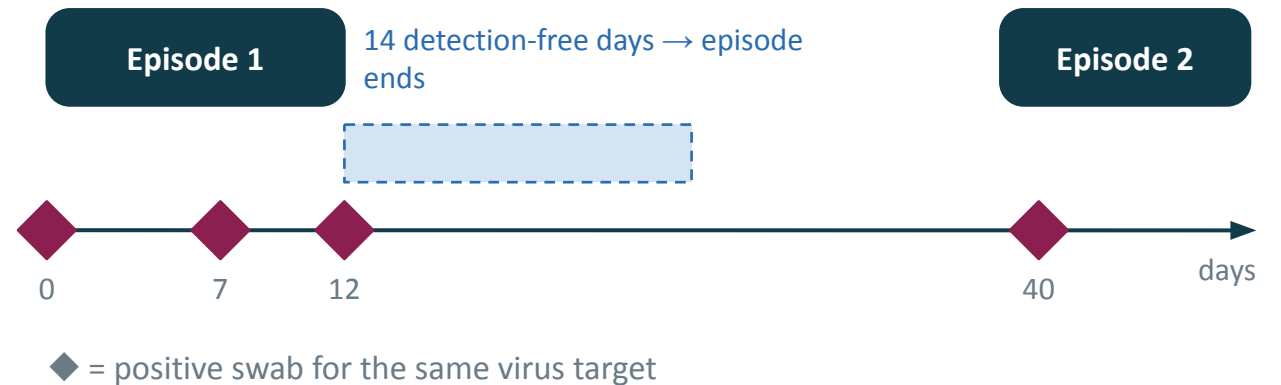
Illness (all 9 viruses)

Symptomatic detection. Primary analysis: exposures and outcomes are both illnesses

Infection (SC2, FLU, RSV only)

Symptomatic or asymptomatic detection. Secondary analysis

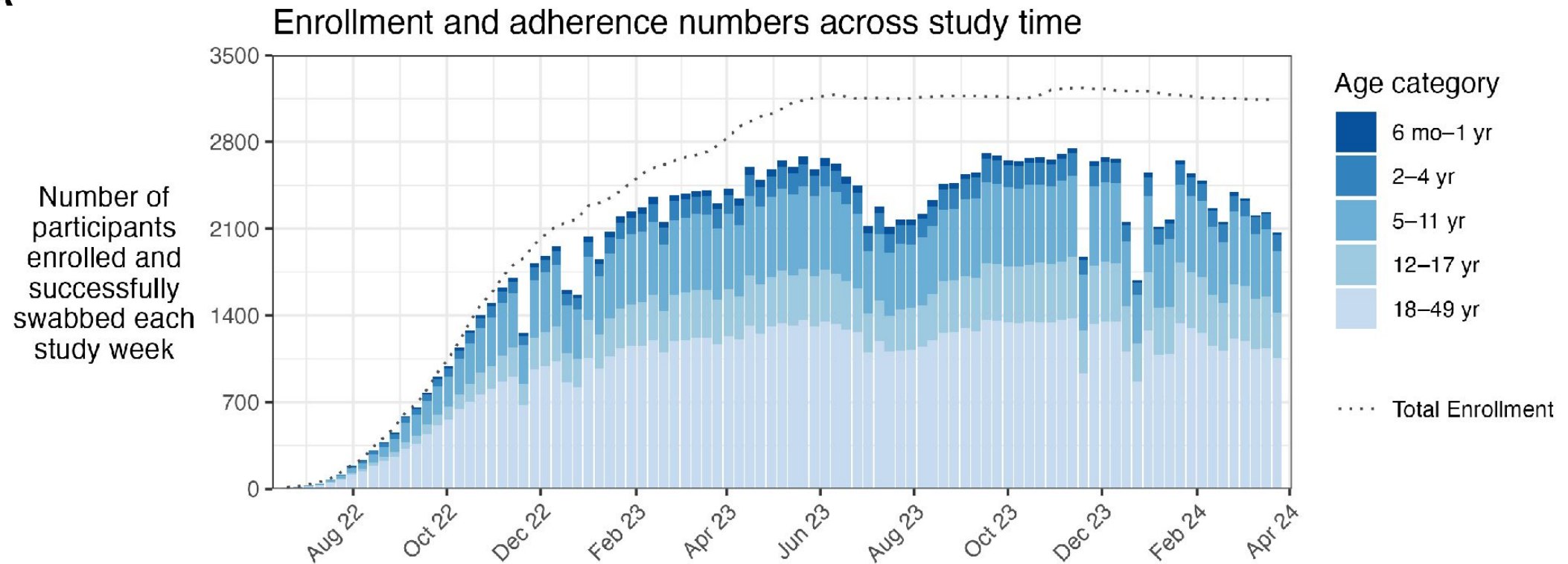
- Defined separately per virus subtype target (e.g., RSV A vs. B)
- Episodes of different viruses may overlap
- Sensitivity: 21- and 28-day gap rules



The episode start date (first positive swab) is the event time for outcomes and the anchor for exposure windows.

Enrollment accrues over time; swab adherence is high overall

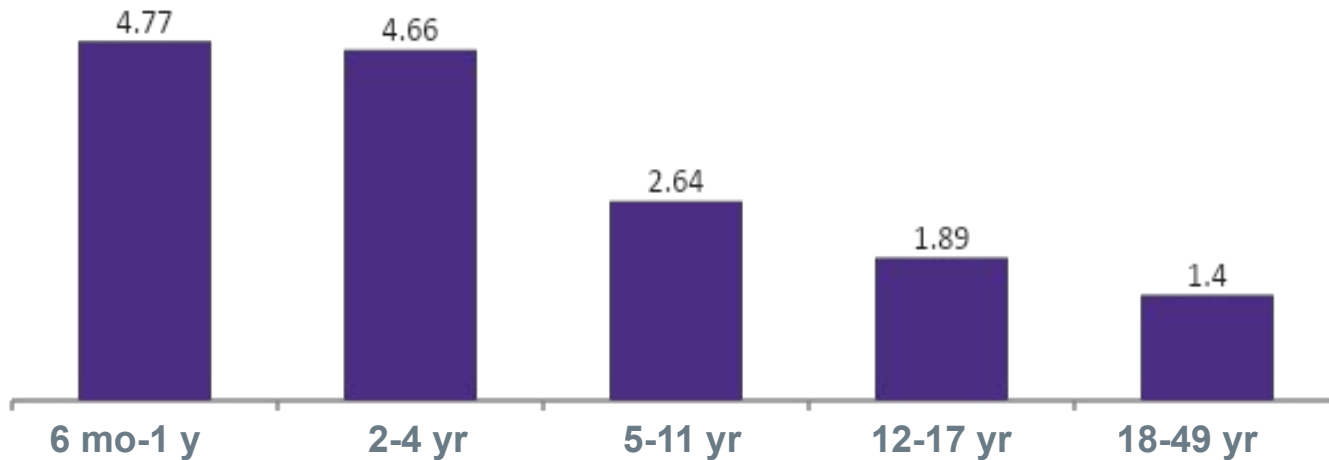
A



Enrollment numbers over time and proportion of each age category with a successful swab submission each week (manuscript Figure 1A).

Illness is common, especially in young children

Median illness episodes per person-year, by age at enrollment



83%

of participants had ≥ 1 illness (92% of children under 5)

$\approx 3\times$

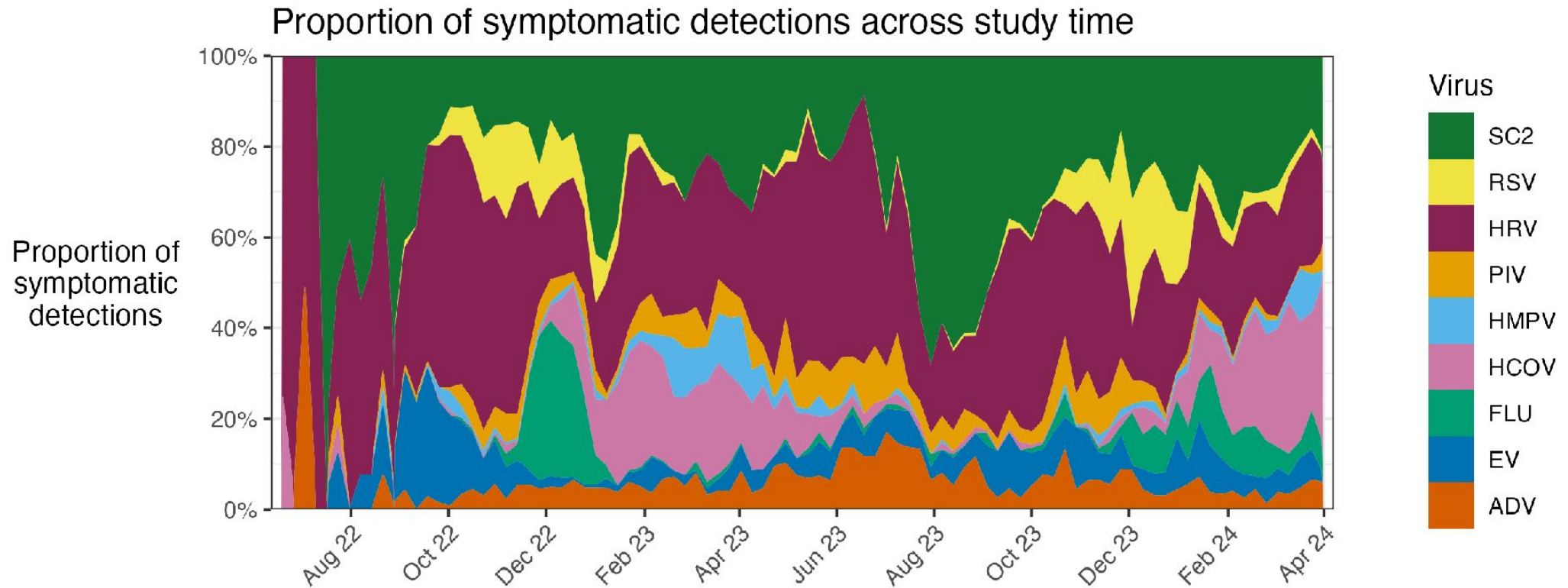
illness rate in children 6 mo–4 y vs. adults (4.7 vs. 1.4 per person-year)

41%

of all illness episodes were rhinovirus (4,454 of 10,838)

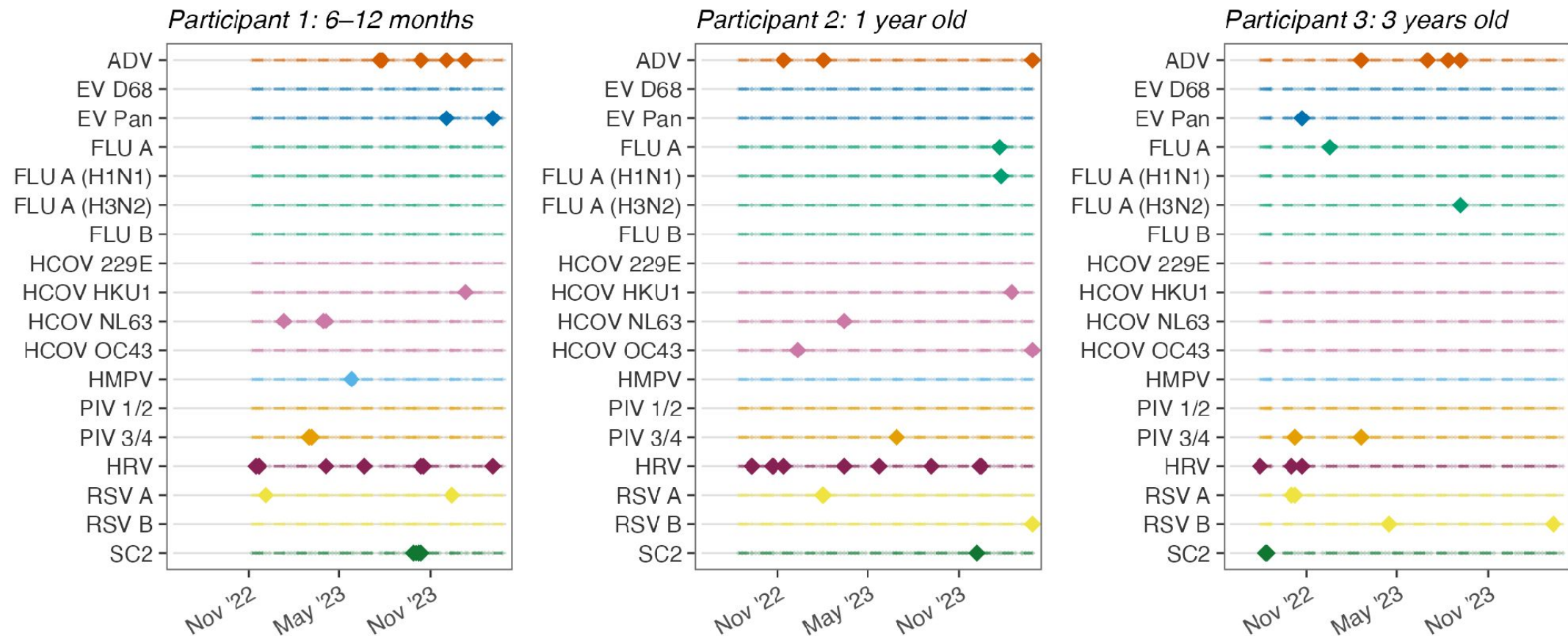
The viruses overlap in calendar time, and the mixture of symptomatic detections shifts rapidly

B



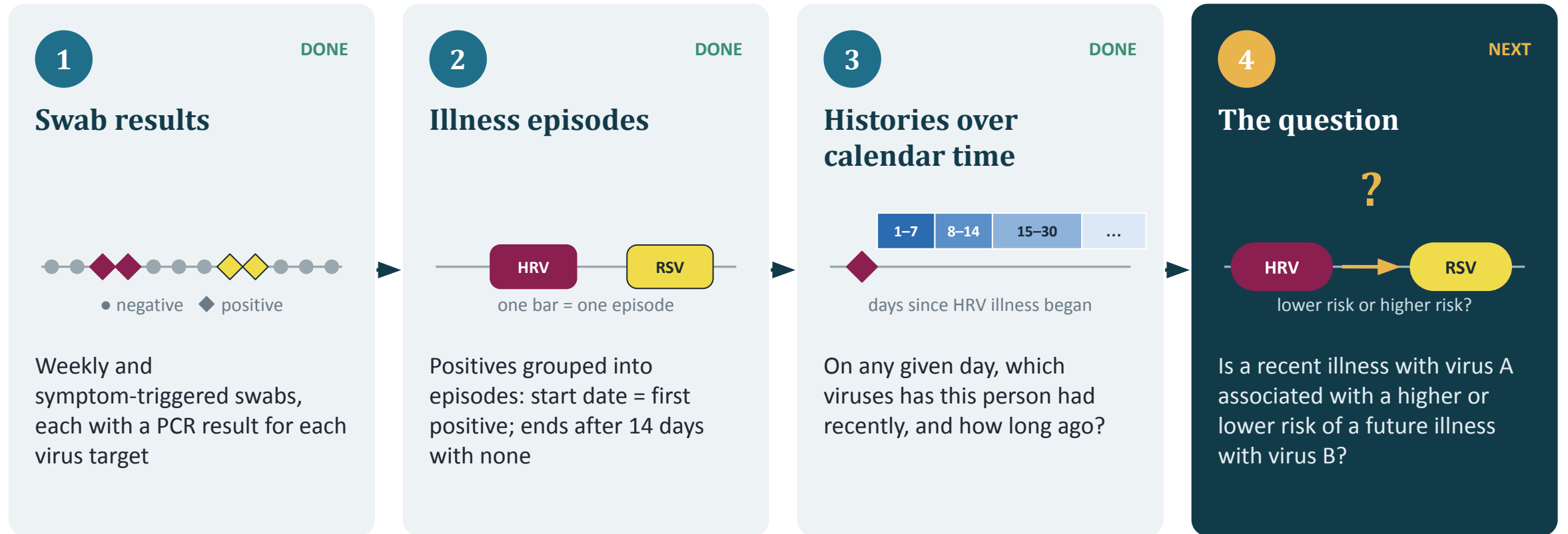
Weekly share of symptomatic detections by virus (manuscript Figure 1B). HRV is common year-round; SC2, FLU, and RSV come in waves.

Young children cycle through many viruses



Three participants under 5 (manuscript Figure 2). Rows are panel targets; diamonds are positive detections.

Where we are: from swabs to a question about timing



The comparison we need: the rate of B among people with a recent A illness vs. people without one, on the same calendar dates. First, a tempting shortcut...

A tempting summary that answers the wrong question

After every type of primary illness, the most common next illness was rhinovirus:

30.7%–47.4%

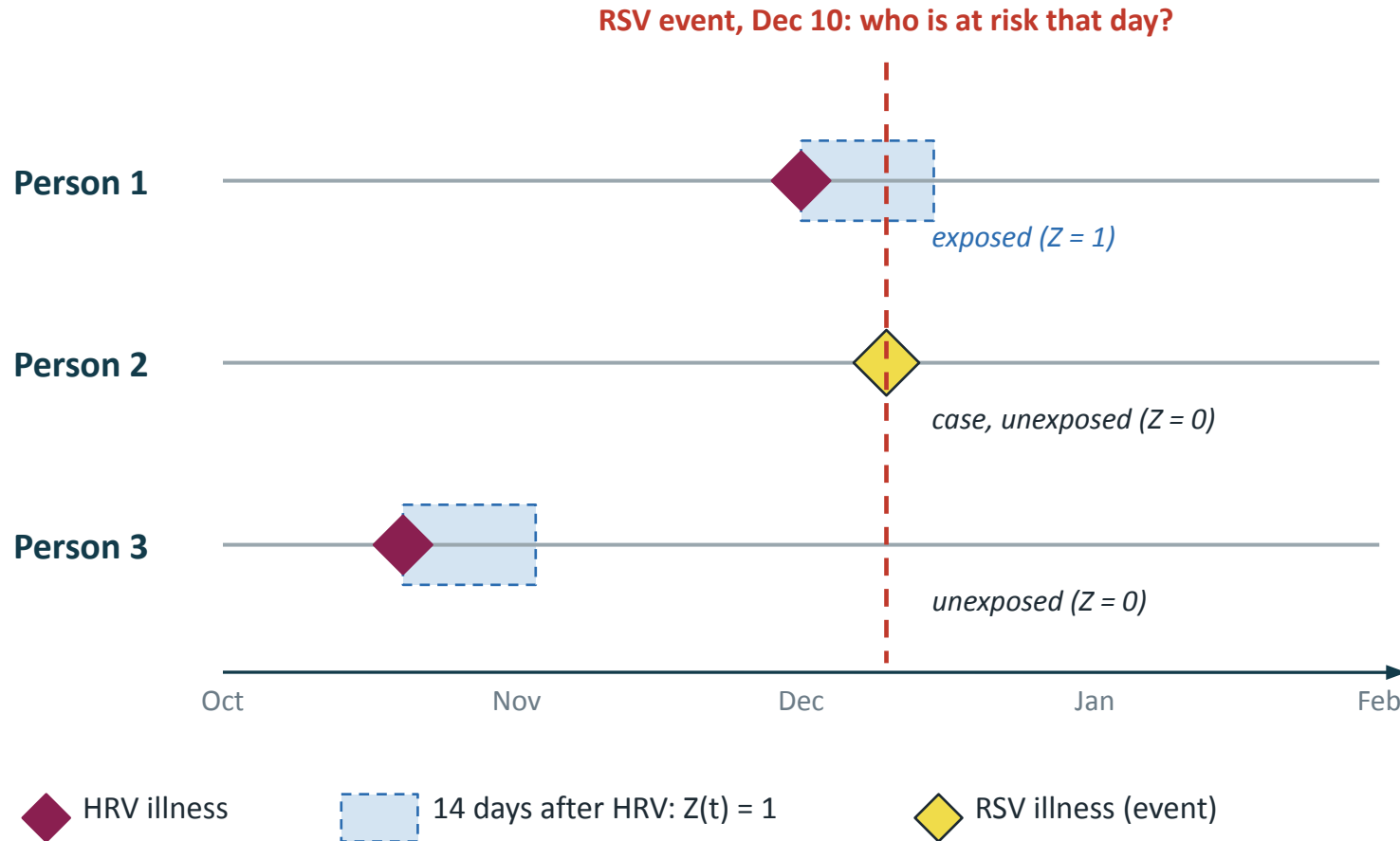
Does everything promote rhinovirus? No.
Rhinovirus is 41% of all illnesses.

What the table is missing

- No comparator: conditions on having a primary illness
- No person-time: longer follow-up means more secondary events
- No calendar time: ignores which viruses were circulating

		Secondary pathogen detected within 180 days, n (%)								
	N	SC2	FLU	RSV	HCOV	ADV	HMPV	PIV	HRV	EV
Primary and secondary illnesses										
SC2	1375	60 (4.4%)	62 (4.5%)	44 (3.2%)	172 (12.5%)	87 (6.3%)	39 (2.8%)	75 (5.5%)	422 (30.7%)	127 (9.2%)
FLU	468	71 (15.2%)	25 (5.3%)	16 (3.4%)	92 (19.7%)	36 (7.7%)	33 (7.1%)	37 (7.9%)	144 (30.8%)	23 (4.9%)
RSV	497	59 (11.9%)	30 (6.0%)	17 (3.4%)	143 (28.8%)	60 (12.1%)	38 (7.6%)	54 (10.9%)	207 (41.6%)	43 (8.7%)
HCOV	1339	129 (9.6%)	15 (1.1%)	20 (1.5%)	114 (8.5%)	115 (8.6%)	78 (5.8%)	110 (8.2%)	417 (31.1%)	96 (7.2%)
ADV	758	75 (9.9%)	31 (4.1%)	55 (7.3%)	140 (18.5%)	231 (30.5%)	35 (4.6%)	122 (16.1%)	359 (47.4%)	103 (13.6%)
HMPV	364	36 (9.9%)	10 (2.7%)	5 (1.4%)	42 (11.5%)	32 (8.8%)	2 (0.5%)	33 (9.1%)	128 (35.2%)	22 (6.0%)
PIV	663	100 (15.1%)	18 (2.7%)	54 (8.1%)	101 (15.2%)	115 (17.3%)	43 (6.5%)	56 (8.4%)	311 (46.9%)	86 (13.0%)
HRV	4454	551 (12.4%)	215 (4.8%)	273 (6.1%)	776 (17.4%)	462 (10.4%)	231 (5.2%)	413 (9.3%)	1767 (39.7%)	424 (9.5%)
EV	920	120 (13.0%)	46 (5.0%)	86 (9.3%)	161 (17.5%)	100 (10.9%)	46 (5.0%)	78 (8.5%)	346 (37.6%)	89 (9.7%)

Start simple: does a recent rhinovirus illness change RSV risk?



Toy data: three participants, one outcome virus, one exposure virus

One exposure, one outcome

$$\lambda_{\text{RSV}}(t) = \lambda_0(t) \cdot e^{\beta \cdot Z(t)}$$

$Z(t) = 1$ if an HRV illness began in the past 14 days

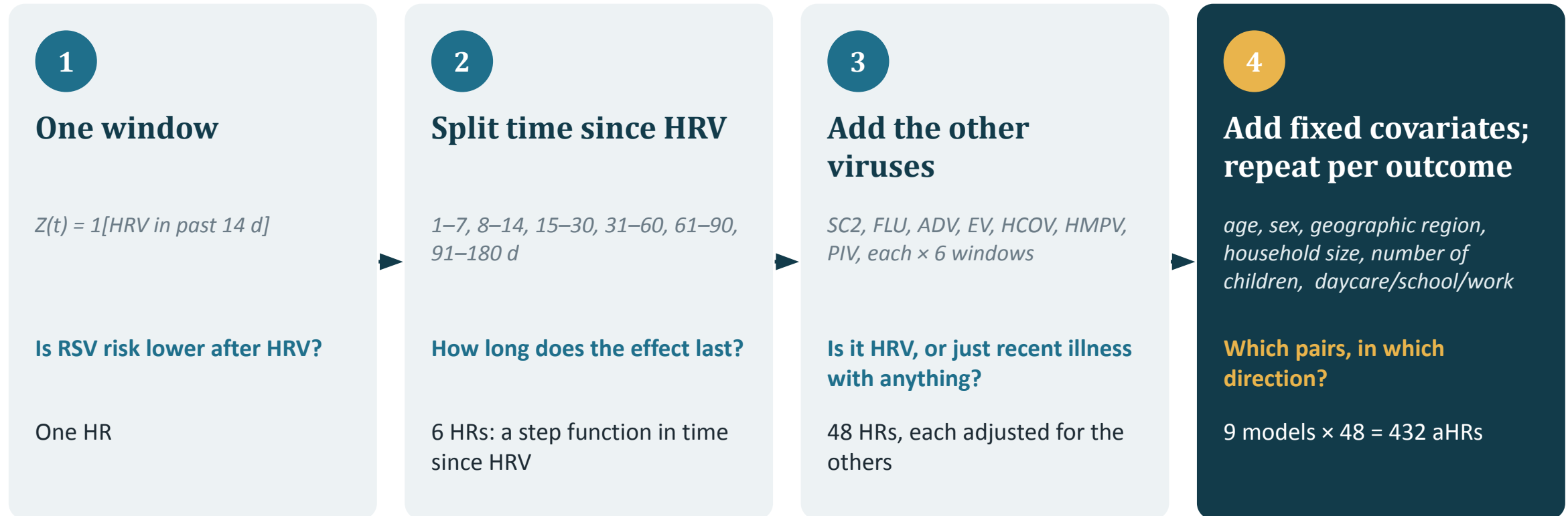
$\lambda_{\text{RSV}}(t)$: hazard for incident RSV illness at time t

$\lambda_0(t)$: baseline hazard for incident RSV illness at time t

$\exp(\beta)$ means...

RSV hazard on the same calendar day for people with vs. without a recent HRV illness.
 $\lambda_0(t)$ absorbs the RSV seasonality

Building up to the full model, one step at a time



The model: one Cox regression per outcome virus

$$\lambda_{ij}(t \mid \mathcal{H}_i(t^-), \mathbf{X}_i) = \lambda_{0j}(t) \exp \left\{ \sum_{k \neq j} \sum_{w=1}^W \beta_{jkw} Z_{ikw}(t) + \boldsymbol{\gamma}_j^\top \mathbf{X}_i \right\}$$

t	calendar date (not time since enrollment)
j	outcome virus: hazard of the first detected illness with j
Z_{ijk}	time-varying indicator that individual i experienced symptomatic illness with virus k within the w -th time interval preceding t .
w	window: 1–7, 8–14, 15–30, 31–60, 61–90, 91–180 days
$\mathbf{X}_i$	vector of fixed baseline covariates: age, sex, geographic region, household size, number of children, daycare/school/work

$\exp(\beta_{ijk}) = \text{adjusted HR}$

Illness with k , w days ago, vs. no k -illness in the prior 180 days, holding $\mathbf{X}$ and other recent illnesses fixed

$$9 \times 8 \times 6 = 432$$

adjusted hazard ratios across 9 outcome models

Design choices and their reasons

1 Calendar time scale

The baseline hazard absorbs seasonality nonparametrically. Each risk set compares people on the same date

2 Left truncation

Participants enter the risk set at enrollment (delayed entry), not at the study start

3 First event only

Outcome is the first detected illness with j , which avoids assumptions about dependence between recurrences

4 All viruses at once

Each aHR is conditional on recent illness with the other seven viruses; a pairwise model can't do this

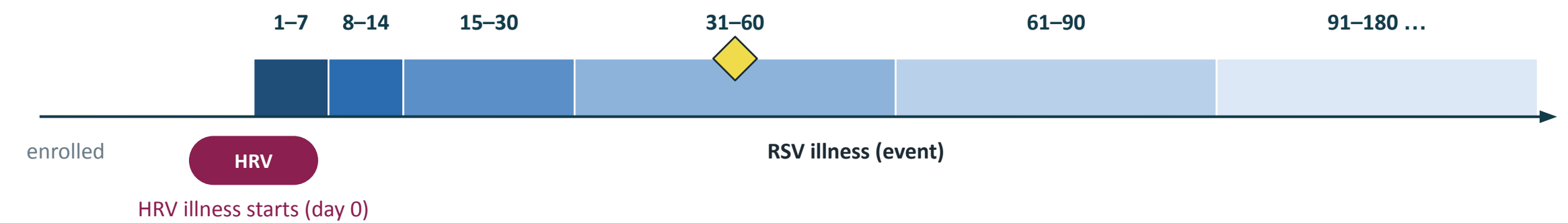
5 Household-clustered SEs

Robust sandwich variance, since household members share exposures

6 BH within each model

False discovery rate controlled at 5% across the 48 coefficients per outcome model

Exposure is time-varying: one participant's data

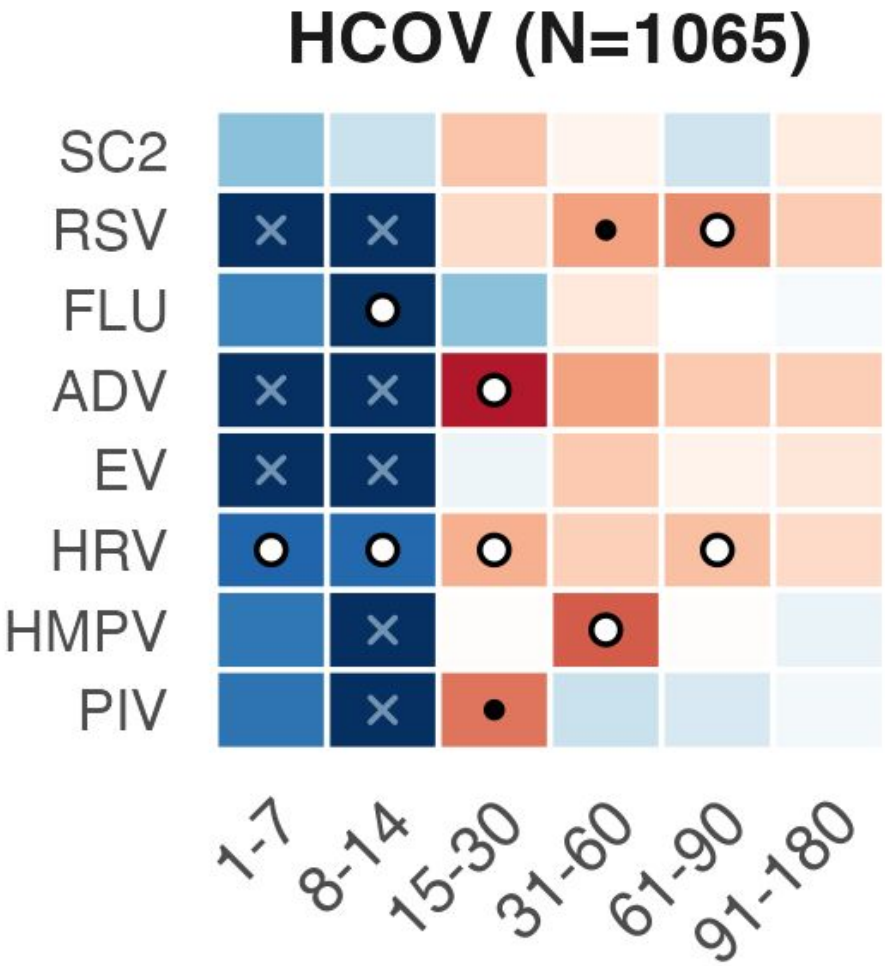


start	stop	HRV window	other viruses ...	RSV event
0	20	(not yet enrolled)	—	—
20	40	none (ref)	...	0
40	47	1–7	...	0
47	54	8–14	...	0
54	70	15–30	...	0
70	100	31–60	...	1

Counting-process format

Each row is an interval with constant covariates; split at every window boundary for every virus (survival::tmerge). Days relative to the HRV illness; in the model, t is the calendar date

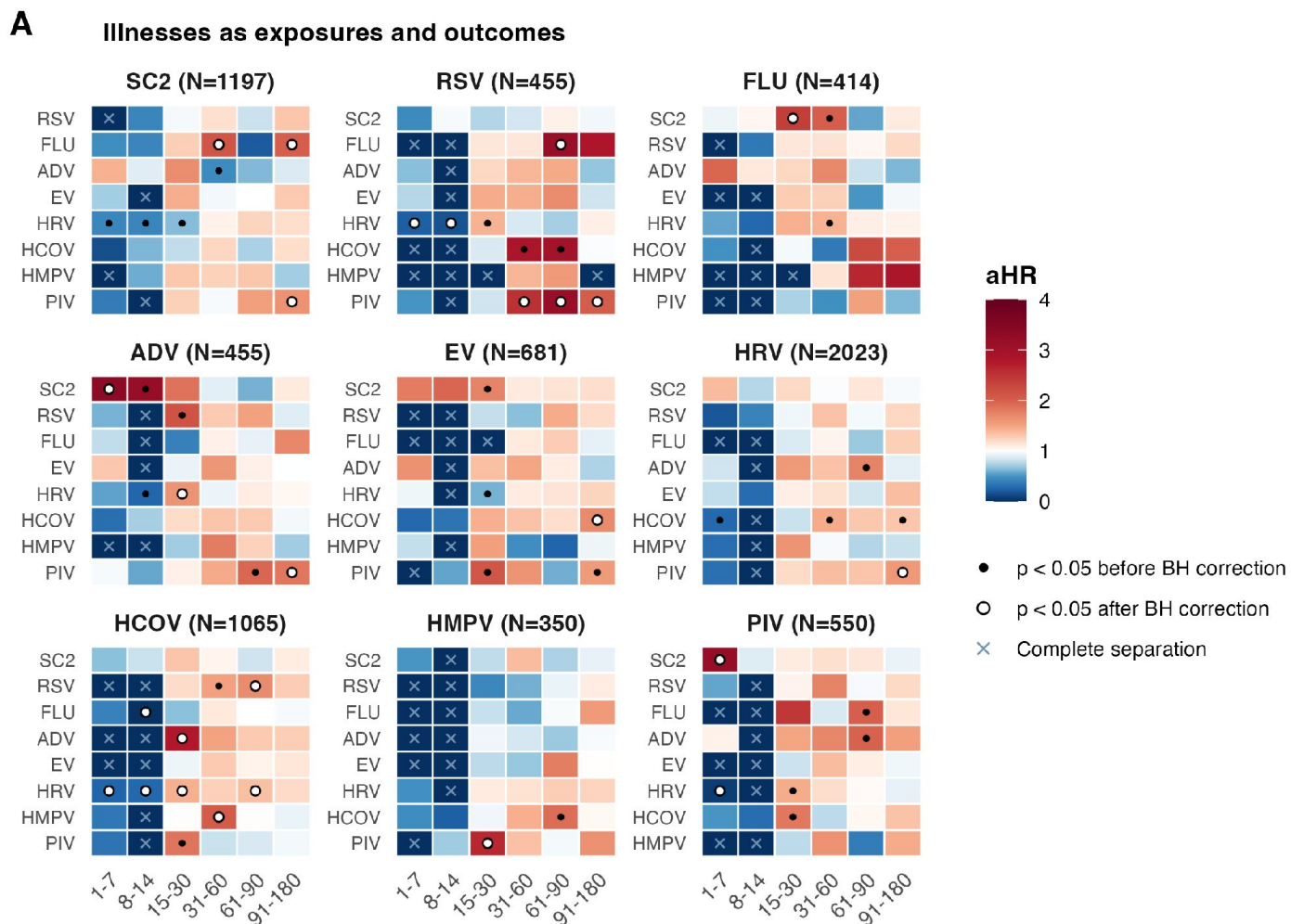
How to read the results heatmap



- Panel** one outcome virus (here HCOV illness, N = 1,065 events) = one Cox model
- Rows** prior (exposure) virus
- Columns** days since that prior illness began
- Color** aHR: blue < 1 (lower risk), red > 1 (higher risk), scale 0–4
- significant after BH; ● p < 0.05 before BH only
- ✕ not estimable: zero outcome events in exposed person-time

Example: HRV row, columns 1–7 and 8–14 are dark blue with ○

Short term: a recent illness usually means lower risk of the next



aHR 0.07–0.27



Recent rhinovirus illness (≤ 14 days) $\rightarrow$ much lower risk of RSV, HCOV, PIV illness; consistent across ages

aHR 3.20–3.33



The exception: SC2 illness 1–7 days earlier $\rightarrow$ higher ADV and PIV risk. But people swabbed more for new symptoms after SC2

Beyond two weeks, estimates move to the null and then above it

1–14 days

Mostly < 1

Consistent with transient innate interference, or with people changing their behavior while sick

15–60 days

Mixed, near 1

The pattern a short-lived innate effect would predict as it wears off

61–180 days

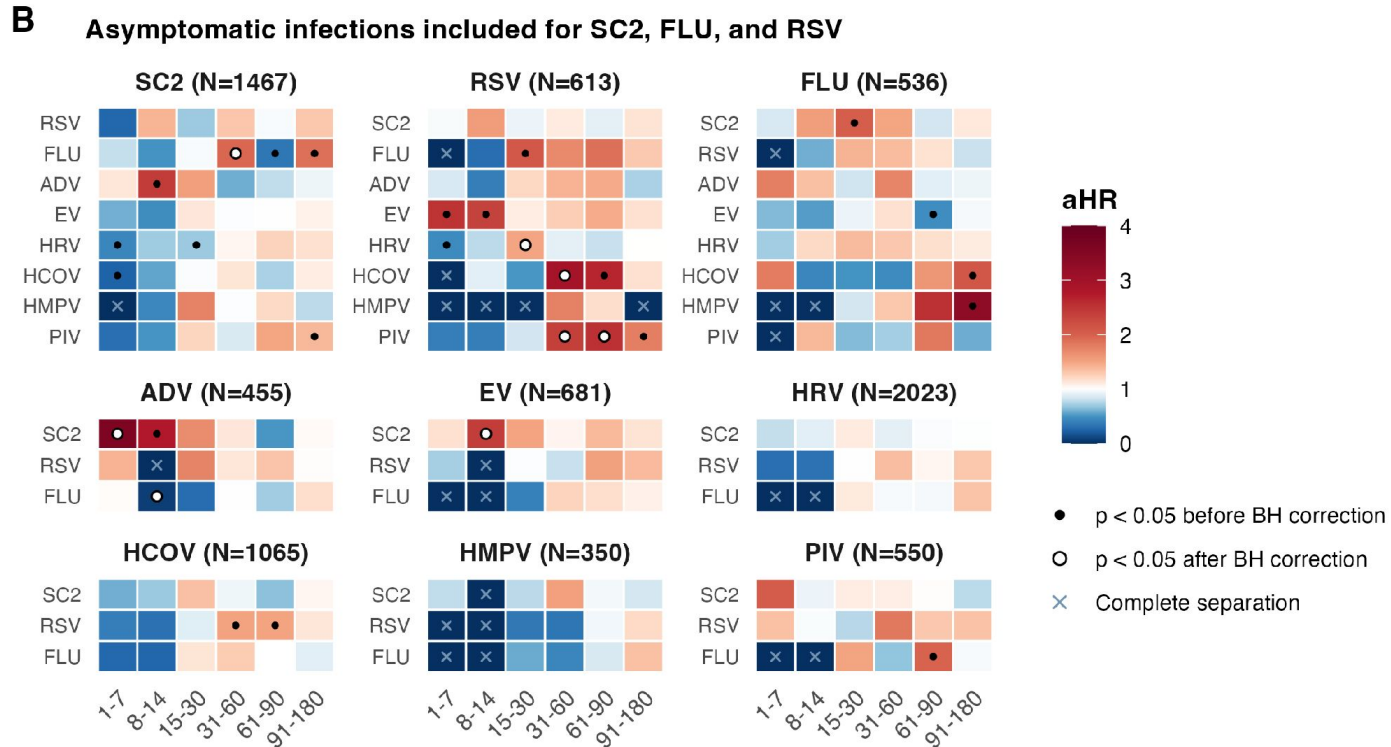
Significant: > 1

e.g., FLU (61–90 d) or PIV (31–180 d)
→ RSV, aHR 2.54–3.17; several others 1.59–1.95

time since prior illness →

Why > 1 later? Probably not biology. More likely shared exposure or susceptibility: households, daycare, and social networks that pass viruses along one after another.

Adding asymptomatic infections weakens the protective signal



- Short-term aHRs generally attenuated
- HRV → RSV infection: now > 1 (not significant after BH)
- SC2 infection 8–14 d → EV illness: aHR 2.42 (1.36–4.28)
- Long-term windows: qualitatively similar

Two readings

Biology: symptomatic infections trigger stronger innate responses.

Measurement: a second infection is less likely to be caught as a "new" symptomatic illness.

Manuscript Figure 4B: SC2, FLU, RSV defined as infections (symptomatic or not)

Age may modify interactions (exploratory)

Age group	Prior → outcome	Window	aHR
6 mo–4 y	FLU → SC2 (illness / infection)	1–7, 31–60 d	5.50–15.92
6 mo–4 y	ADV → SC2 infection; FLU	< 30 d	4.52–10.35
6 mo–4 y	SC2 → PIV illness	≤ 14 d	3.43–9.54
5–17 y	ADV → SC2 infection or FLU; HMPV → EV	≤ 14 d	3.63–18.26
18–49 y	PIV or SC2 → ADV; EV → RSV	1–7	4.69–8.67
All ages	HRV → HCOV, PIV, RSV	≤ 14 d	< 1, consistent

Read with care

Age × exposure interactions; wide CIs; more non-estimable cells; 6 mo–1 y and 2–4 y collapsed for sparsity

Biologically plausible

Young children may mount different innate responses; clinical reports describe enhanced susceptibility in children

Robustness checks and limitations

Sensitivity analyses

- 21- and 28-day episode gap rules: nearly identical
- Delay entry until 180 days of history are observed: directionally similar
- Infections instead of illnesses: attenuated (previous slide)

Limitations

- Post-illness behavior (staying home, masking) and residual confounding
- Detection times are not infection times; order of detection may differ from order of acquisition
- Asymptomatic data for 3 of 9 viruses only
- Complete separation: many short-window aHRs not estimable
- First event per outcome only
- Mostly higher-income Pacific Northwest households; no adults ≥ 50

Study takeaways

- 1 In the two weeks after a viral illness, the risk of a different viral illness tends to be lower, most strongly after rhinovirus.
- 2 There are exceptions with higher risk: SC2 → ADV/PIV, and in children under 5, FLU → SC2.
- 3 Associations depend on symptom status, on age, and on how infections are observed.

Part III · Discussion

How else could we attack this problem?

Estimands, causal structure, measurement, sparsity, and mechanistic models

What is our estimand, really?

Current target: a conditional hazard ratio. Among people still free of virus j on date t , compare those with a k -illness w days ago with those without one in the prior 180 days.

HRs are not risk contrasts

Conditioning on survival to t builds in selection (Hernán 2010). An HR in the 8–14 day window compares groups already filtered by days 1–7

"Infection" is not an intervention

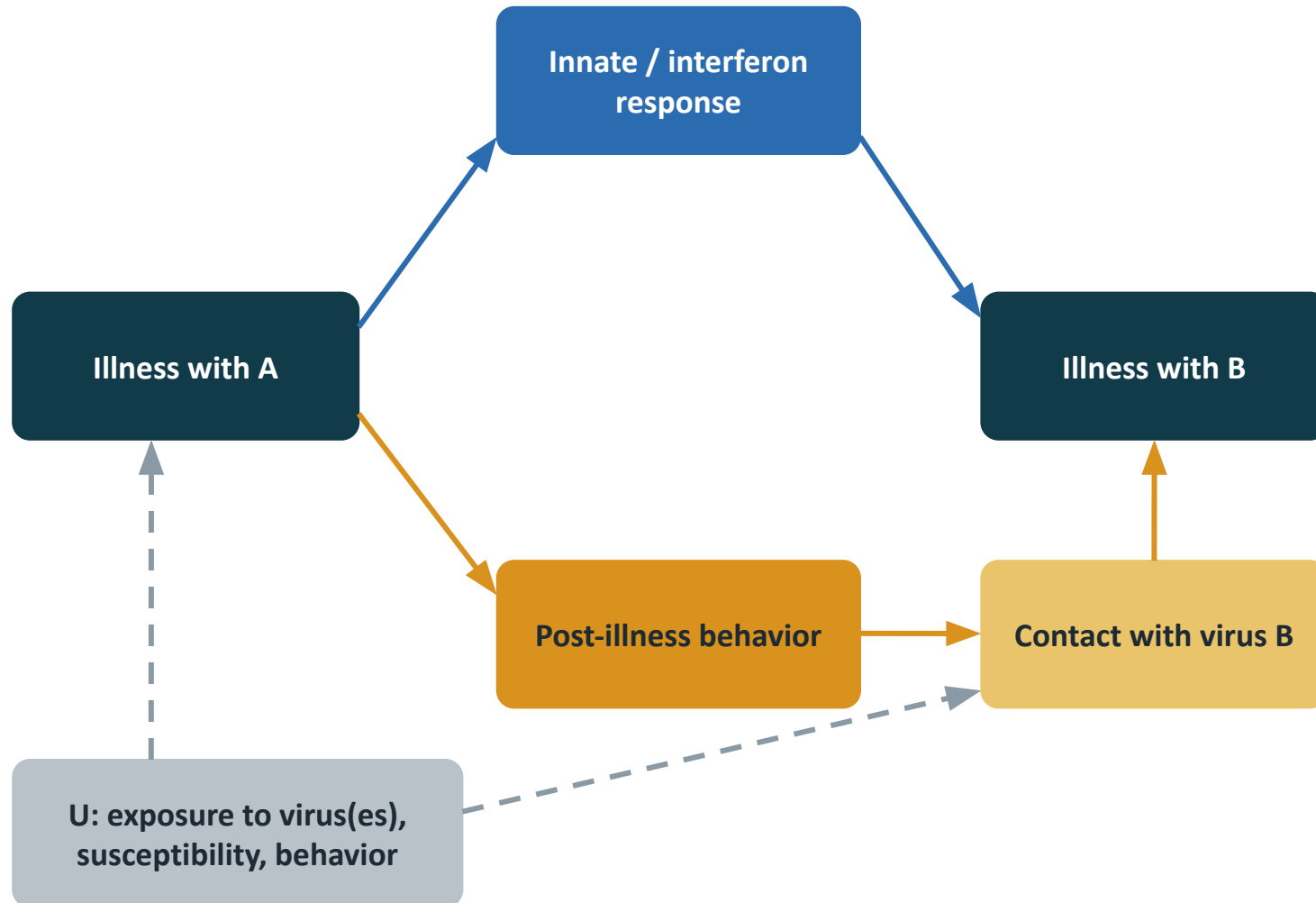
What hypothetical trial do we have in mind? Assigning infection? A challenge study? Live-attenuated vaccines (OPV, LAIV) are a real, randomizable stand-in

Alternative targets

14- or 30-day risk difference after a k -illness vs. matched non-ill people; a smooth curve over time since the illness; marginal vs. conditional on other viruses

Up for discussion: which estimand would a virologist want? An epidemic modeler? A parent deciding about daycare?

Biology, behavior, or shared exposure?



Blue path: interference

Roughly the direct effect not through behavior: what virologists mean

Amber path: behavior

A mediator. Real for epidemics, but not immunology. HRV is mild, yet it gives the strongest effect

Grey: shared exposure

Confounding that changes over time. Could explain late aHRs > 1; baseline Z only partly captures it

Other designs, each answering a slightly different question

Self-controlled case series

Cases of B only; compare B incidence in risk windows after A vs. other times within the same person. Removes time-invariant confounding. Needs care with seasonality and with B changing later exposure

Wang et al. 2026 (influenza)

Case-crossover

Compare A-exposure in the window before B with earlier reference windows for the same person. Exposure trends (seasons) bias it

Classic for transient exposures

Test-negative design

Among symptomatic people tested: A-history in B-positives vs. B-negatives. Cheap with surveillance data, but conditions on being tested

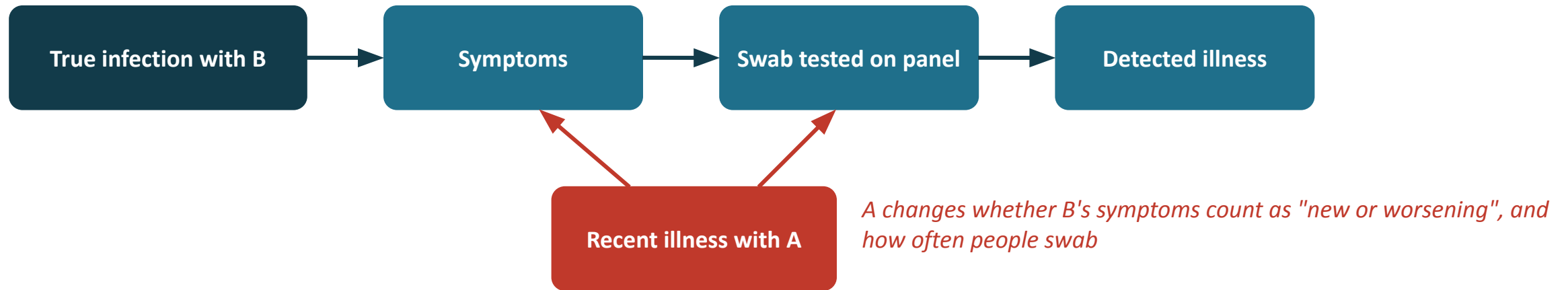
Stowe et al. 2021 (SC2/FLU)

Sequential target-trial emulation

Each day, "newly ill with A" vs. matched not-ill people (same date, age, household size); follow 14/30 days for B. Gives risk curves and avoids immortal time. Still can't handle lack of 'exposure' data (not a well-defined intervention)

Natural fit for cohort data

The observation process is part of the data



Informative testing

Testing depends on symptoms, which depend on A (more swabs after SC2). Options: model the testing intensity and weight by its inverse (Lin, Scharfstein & Rosenheck 2004)

Onset is interval-censored

We see detection, not infection, and PCR stays positive for a while after. Options: interval-censored survival; uncertainty in onset

Partially hidden states

Weekly swabs suggest a hidden Markov / multi-state model: latent infection states with misclassified observations

Many cells, few events: sparsity and multiplicity

432

coefficients from 9 models

Many short-window cells have 0 events among exposed person-time: complete separation, $\beta^* \rightarrow -\infty$

Is separation evidence of protection, or of too little overlap in circulation?

1

Penalized likelihood

Firth-type bias reduction for Cox (Heinze & Schemper 2001) gives finite estimates under separation

2

Hierarchical shrinkage

Partial pooling across pairs and windows, e.g. $\beta_{ijw} \sim N(\mu_w, \tau^2)$; borrows strength across sparse pairs

3

Smooth in time

Replace 6 bins with a spline in days since illness; fewer parameters and no arbitrary cut-points

4

Poisson GLMM

Cox $\approx$ Poisson on split person-time (Whitehead 1980; Laird & Olivier 1981), which opens up random effects and Bayesian tools

5

Error-rate family

BH within each outcome model, or across all 432? Hierarchical FDR (outcome $\rightarrow$ exposure)?

Approaches at a glance

Approach	Target	Handles well	Struggles with
Cox on calendar time (ours)	Conditional HR by time since A	Seasonality; all viruses jointly	Behavior, informative testing, sparsity
Self-controlled (SCCS, case-crossover)	Within-person rate or odds ratio	Time-invariant confounding	Seasonality; event-dependent exposure
Test-negative design	OR among those tested	Uses routine surveillance	Selection into testing
Target-trial emulation	Risk difference at 14/30 d	Clear time zero; absolute risk	Still needs no unmeasured confounding
Hierarchical / Bayesian	Shrunken pair-specific effects	Sparsity, multiplicity	Sensitivity to priors and exchangeability
Transmission models	Interaction strength θ , duration $1/\delta$	Population dynamics, forecasting	Ecological; structural assumptions

Questions for discussion

- 1 Which estimand would you report: conditional HR, risk difference, or a mechanistic θ ?
- 2 How would you separate biological interference from post-illness behavior?
- 3 Symptom-triggered testing depends on prior illness. How would you correct for it?
- 4 With 432 coefficients and many empty cells: shrink, smooth, or aggregate?
- 5 If we could redesign CASCADIA, what should we measure?

Thank you

Questions and discussion

Paper: MedRxiv

Analysis code: github.com/kathoffman/viral-int

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