Reassessment of HIV-1 Acute Phase Infectivity

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MIDAS Meeting

Conclusion: HIV-1 acute infectivity has been substantially overestimated

PLOS | MEDICINE

RESEARCH ARTICLE

Reassessment of HIV-1 Acute Phase Infectivity: Accounting for Heterogeneity and Study Design with Simulated Cohorts

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McMaster University

Alison Galvani
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Outline

1. Relevance: Treatment as Prevention (TasP)
2. Measuring excess infectivity with EHM_{acute}
3. Literature review of past estimates
4. Re-estimation of EHM_{acute} from viral load
5. Re-estimation of EHM_{acute} from the Rakai cohort

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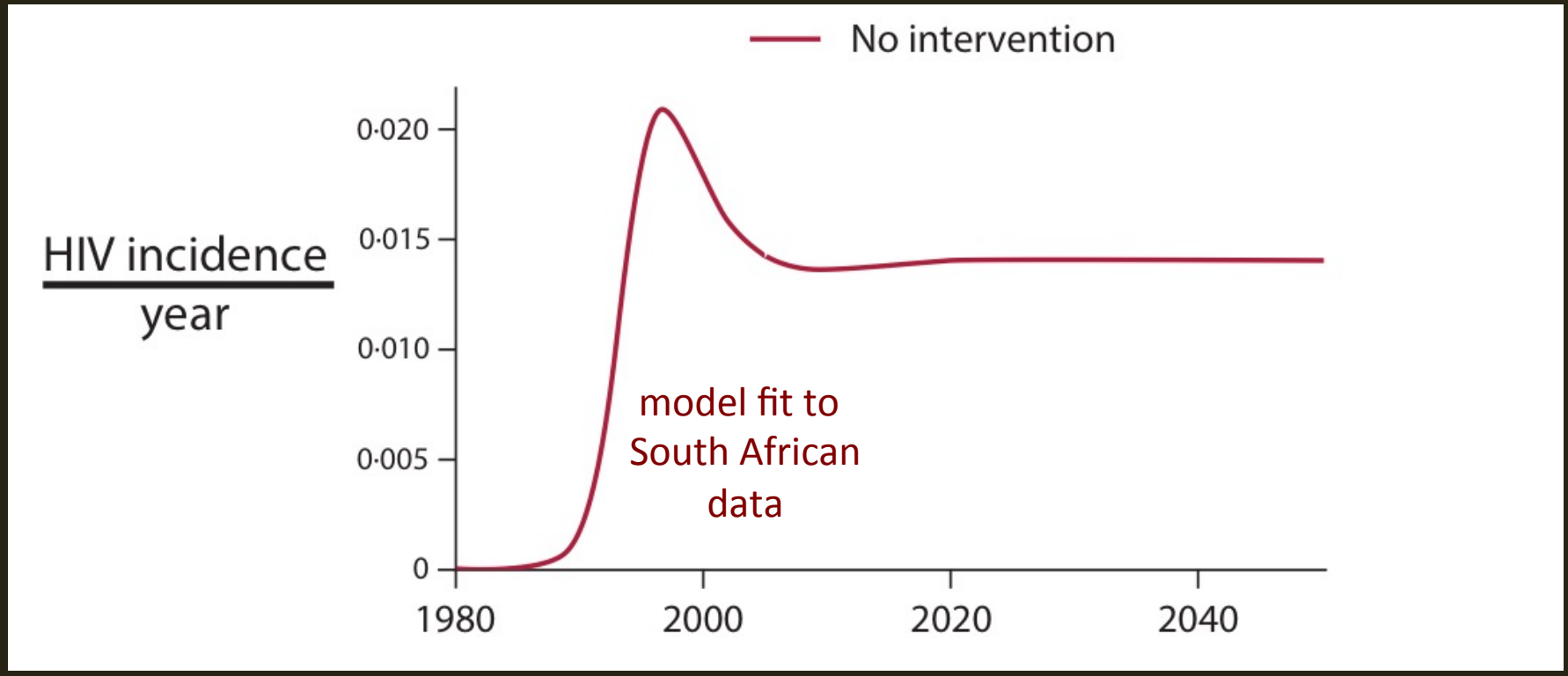
Treatment as Prevention (TasP)

Treated HIV-infected individuals transmit 96% less than untreated HIV-infected individuals

Cohen et al. (2011). *NEJM*.

Treatment as Prevention (TasP)



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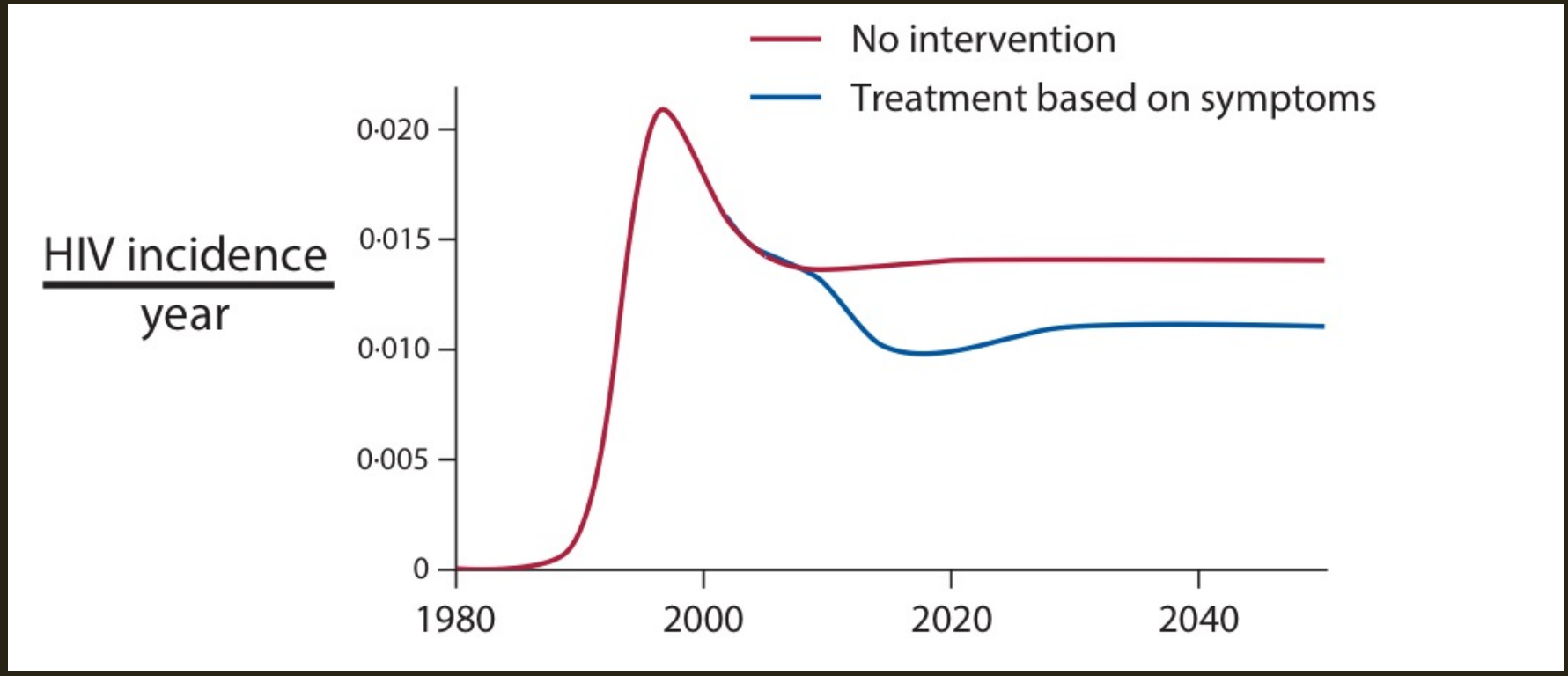

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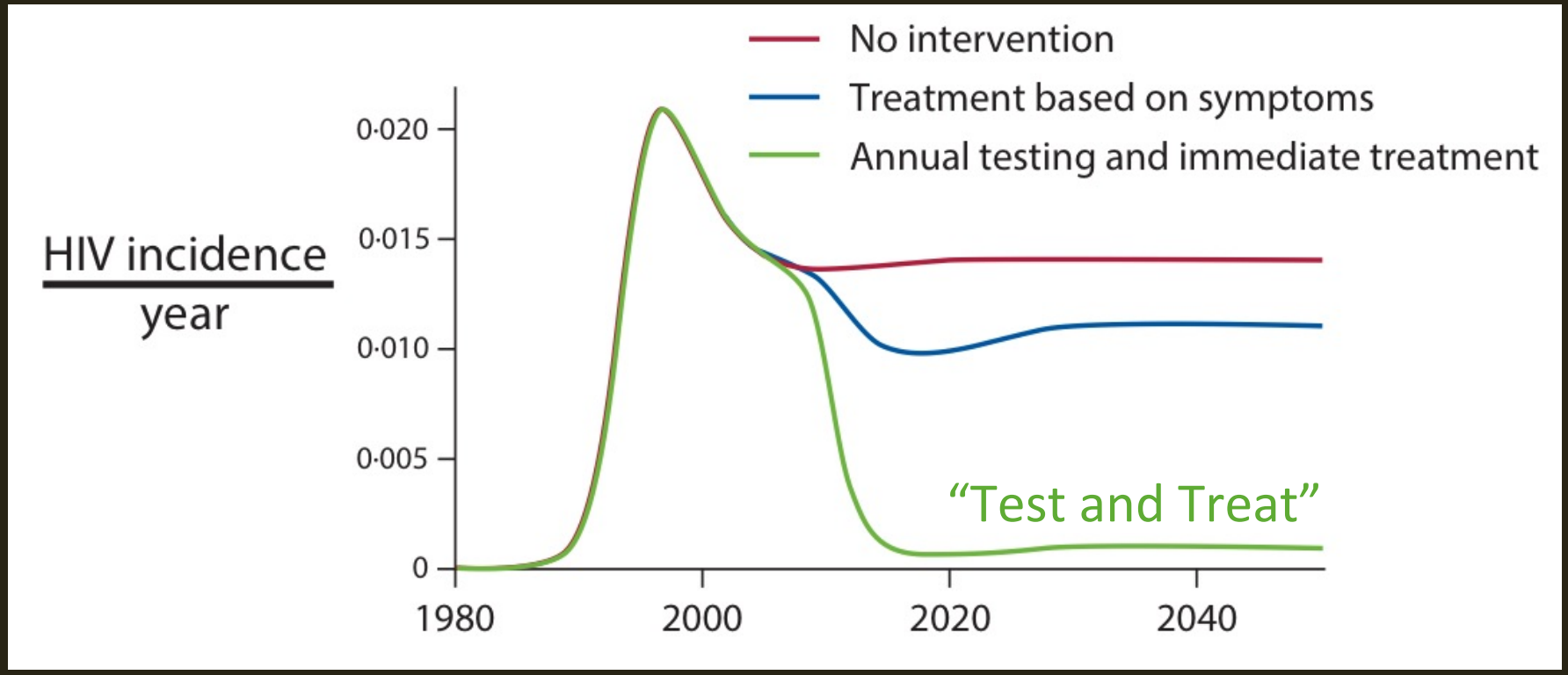
Universal Testing and Treatment



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cluster randomized controlled trials underway

Will "Test and Treat" work?

- Logistics
- Uptake and adherence
- Drug Resistance
- Early Transmission

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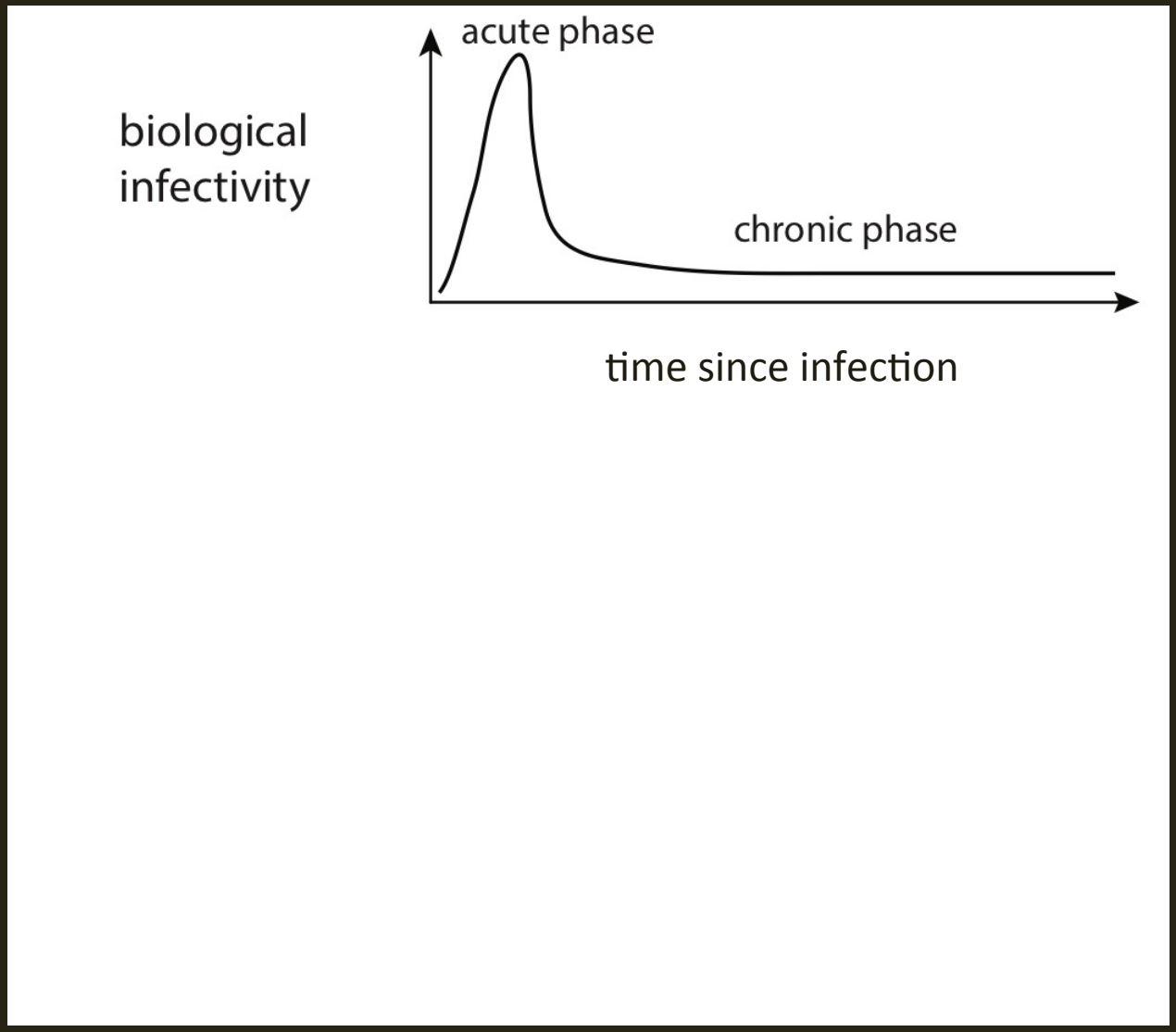
Review

HIV Treatment as Prevention: Debate and Commentary—Will Early Infection Compromise Treatment-as-Prevention Strategies?

Myron S. Cohen[1,2,3¶], Christopher Dye[4¶], Christophe Fraser[5¶*], William C. Miller[2,3¶], Kimberly A. Powers[2,3¶*], Brian G. Williams[6¶*]

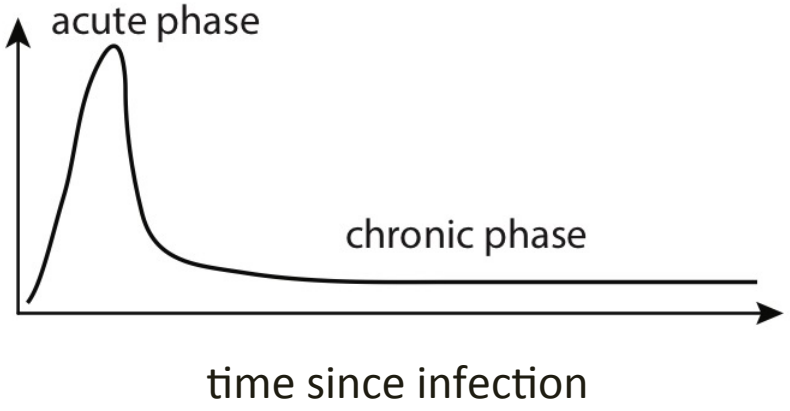
How much transmission happens before diagnosis and treatment?

What proportion of transmission occurs early?



What proportion of transmission occurs early?

(biological infectivity) × (sexual contacts with *susceptible* partners) = rate of new infections generated



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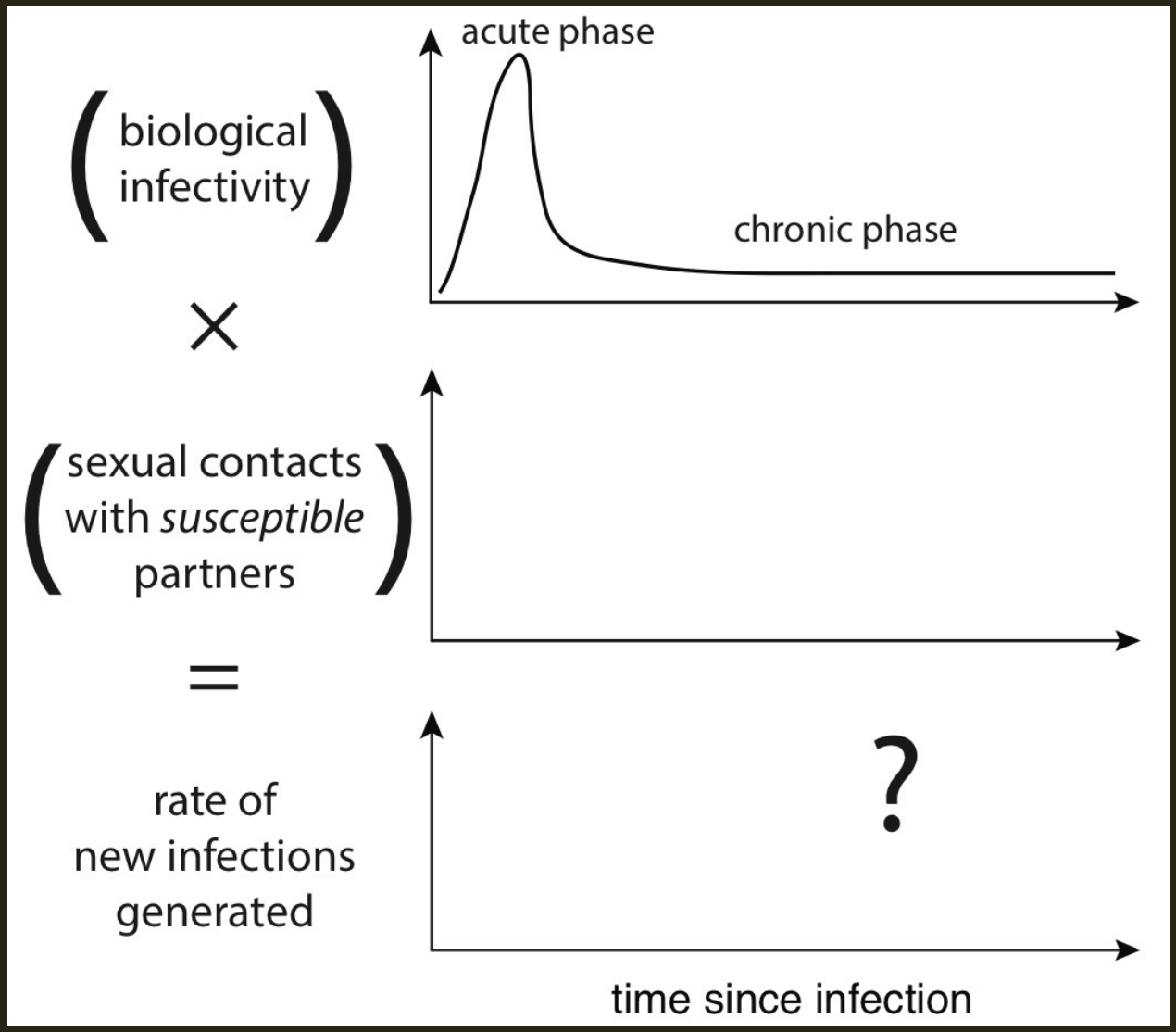

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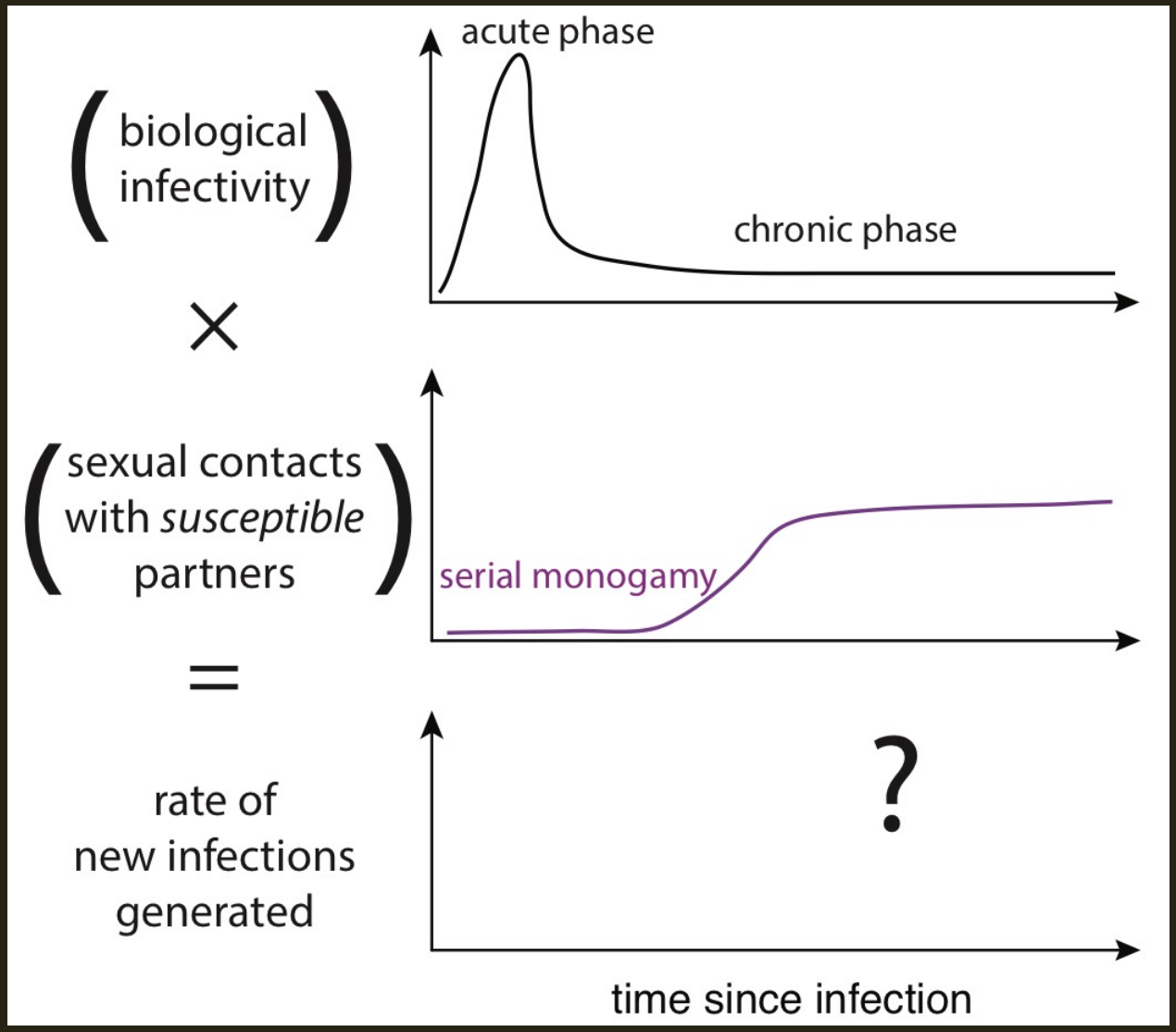

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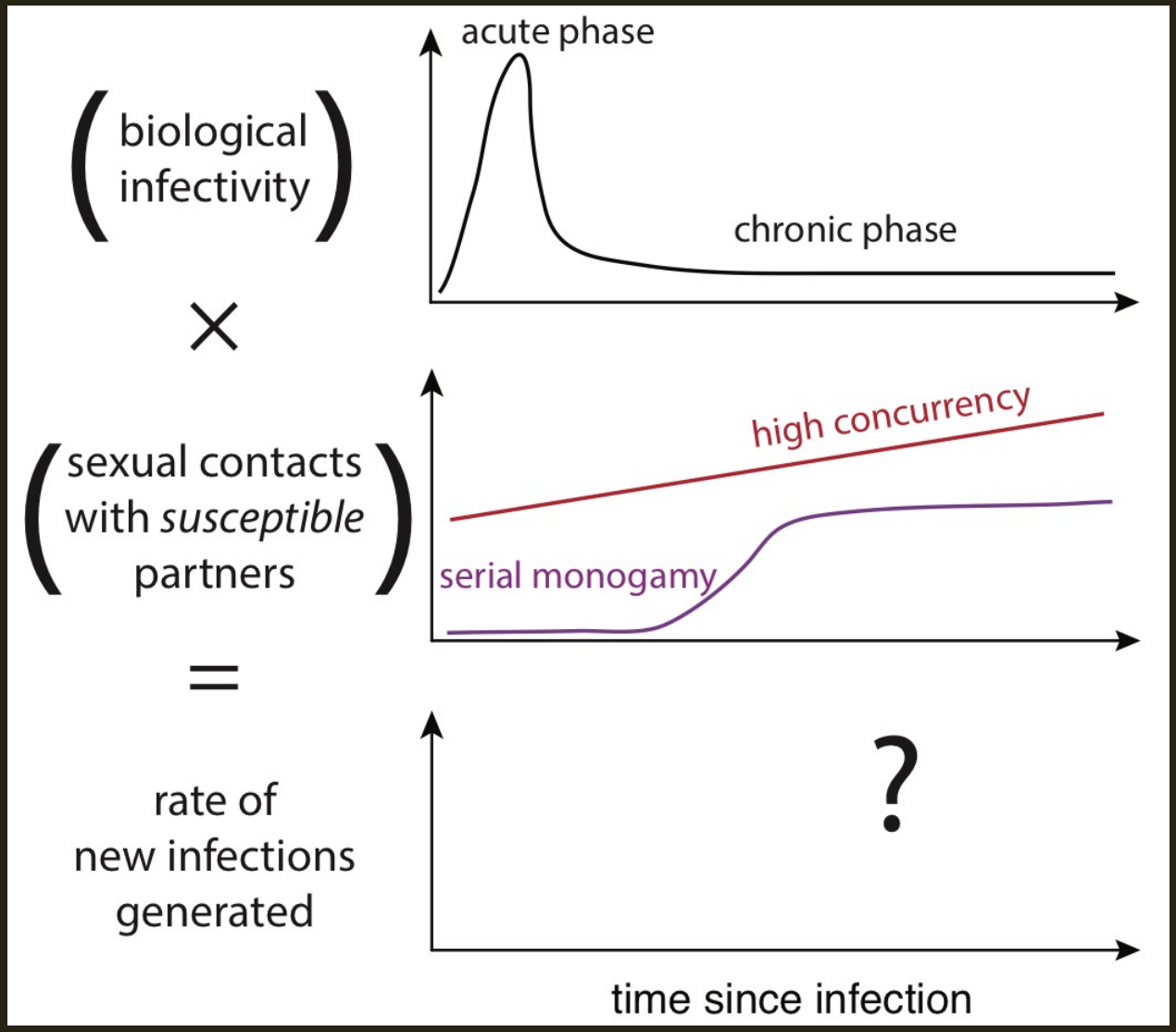

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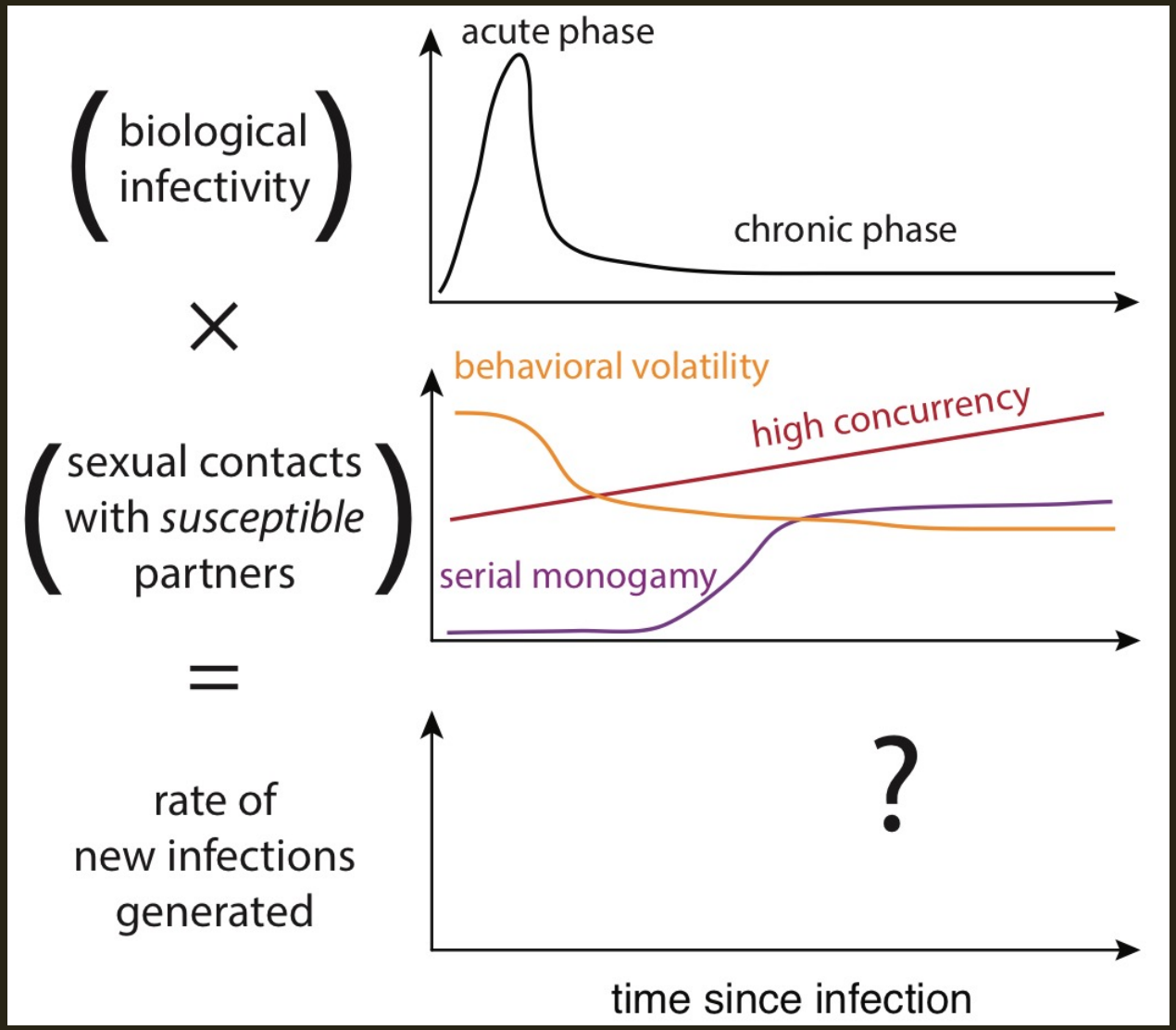

Eaton et al. 2011. *AIDS & Behavior*.

Alam et al. 2013. *Epidemics*.

Romero-Severson et al. 2013. *Epidemiolgy*.

Henry & Koopman. 2015. *Sci Reports*.

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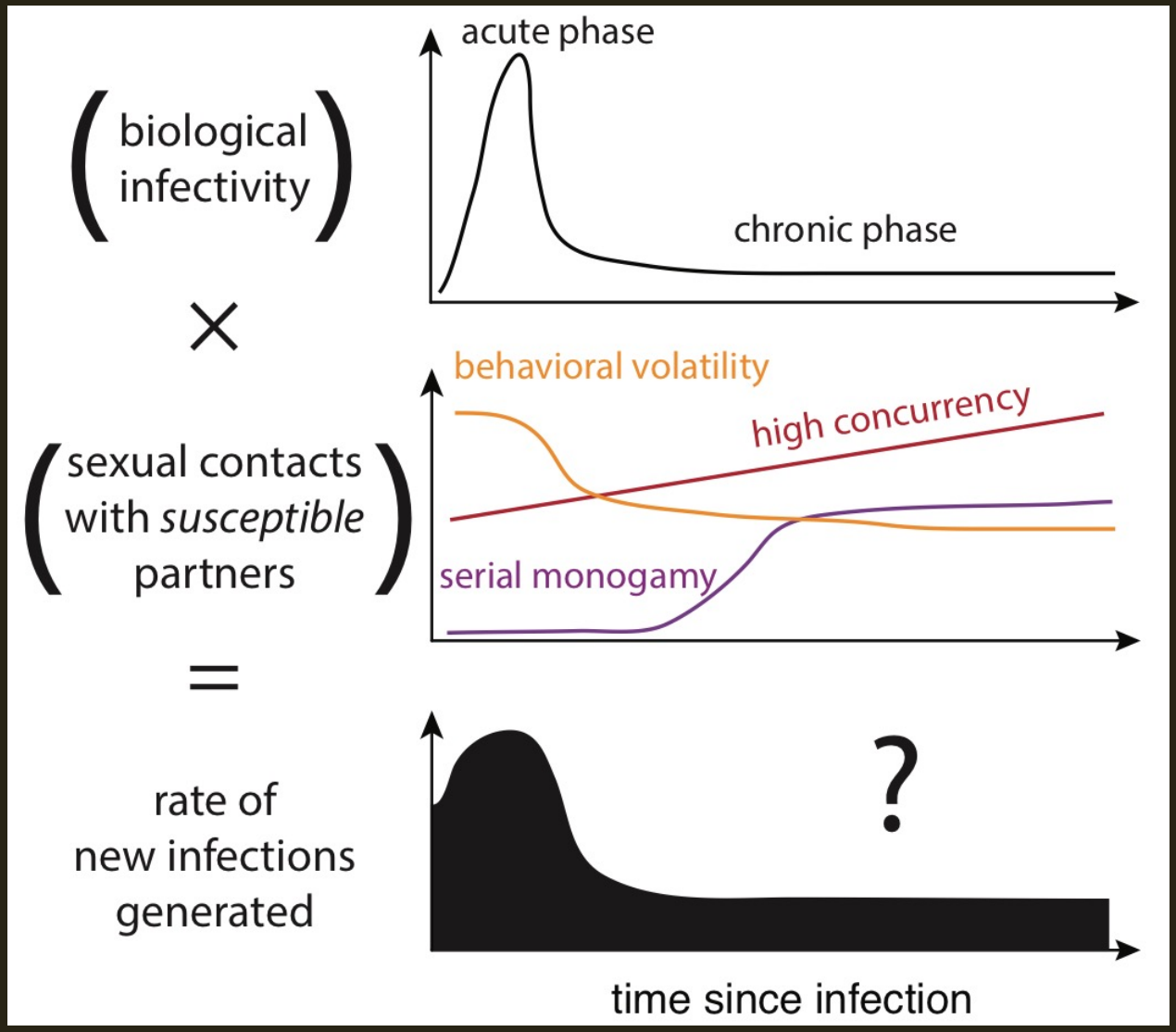

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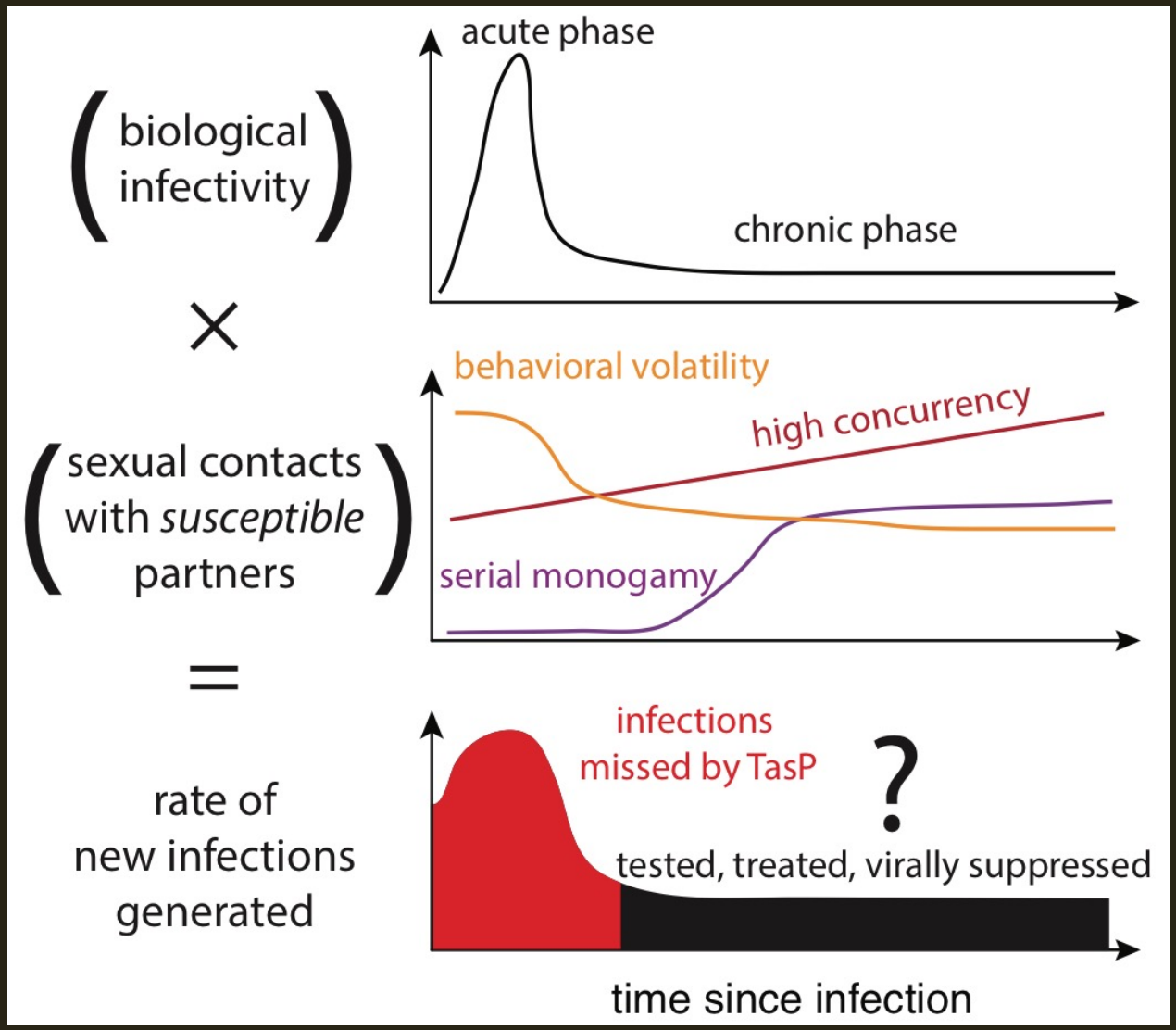

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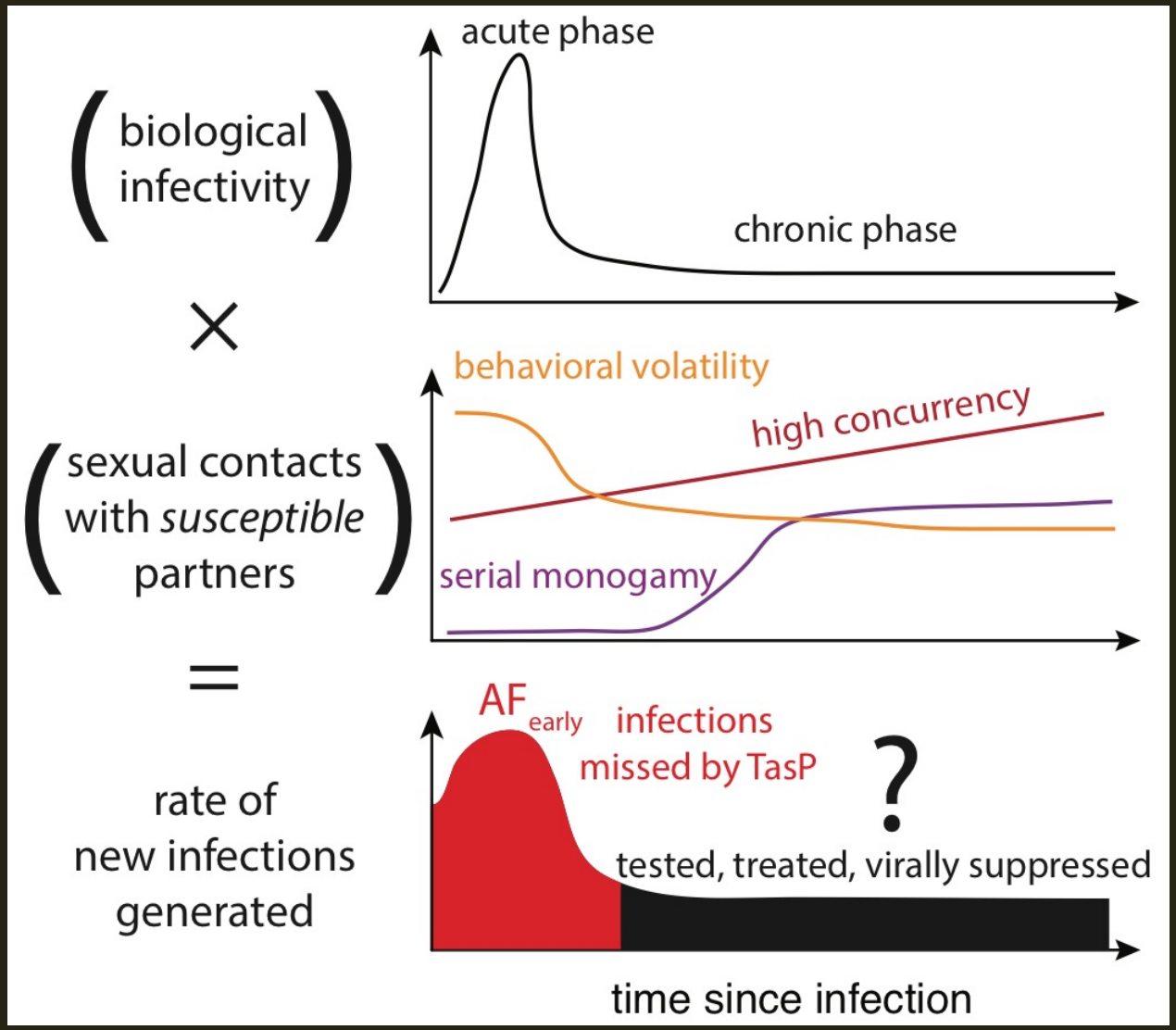
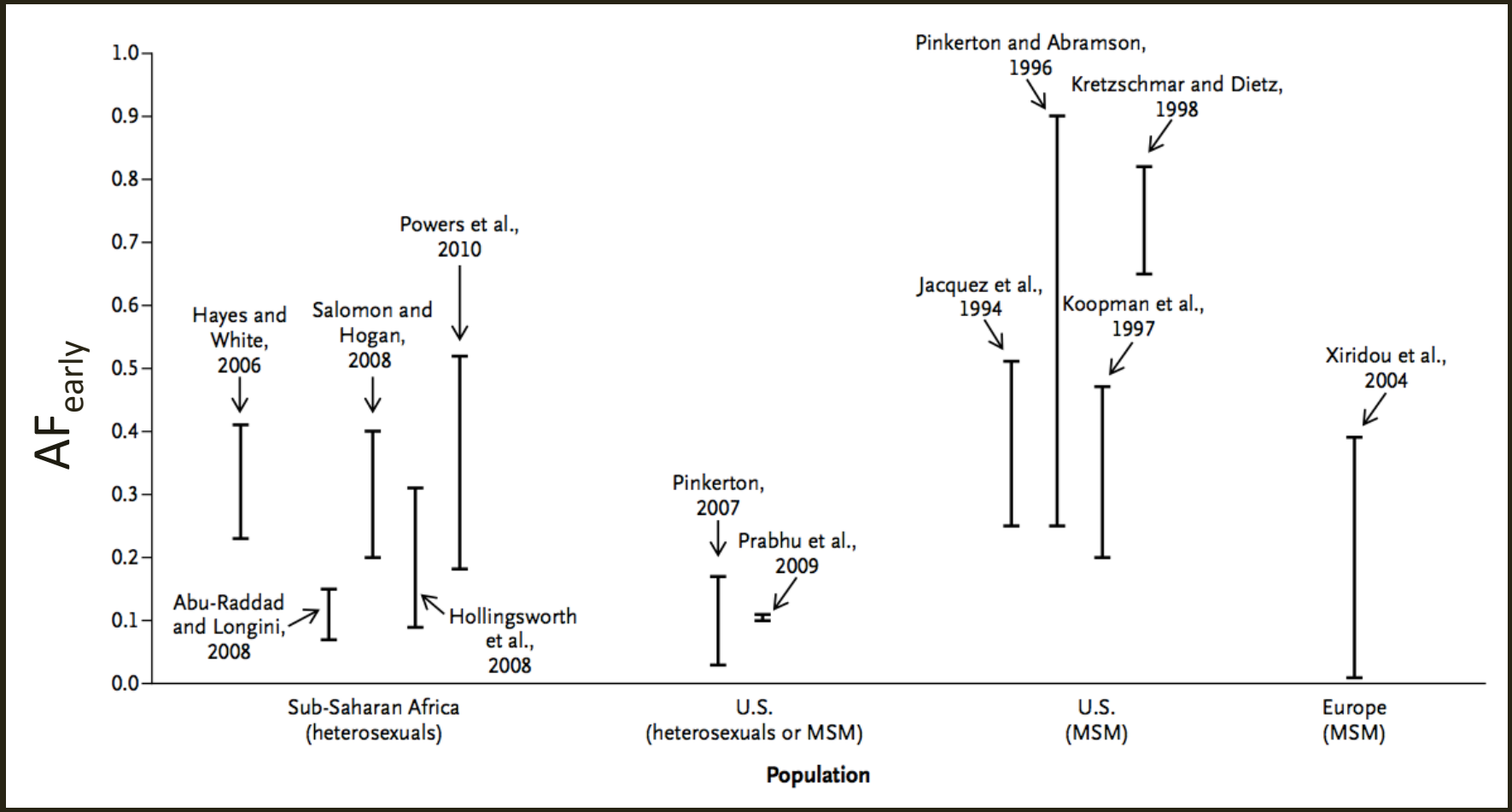


Estimates of AF_{early}: proportion of transmission < 1 yr post-infection



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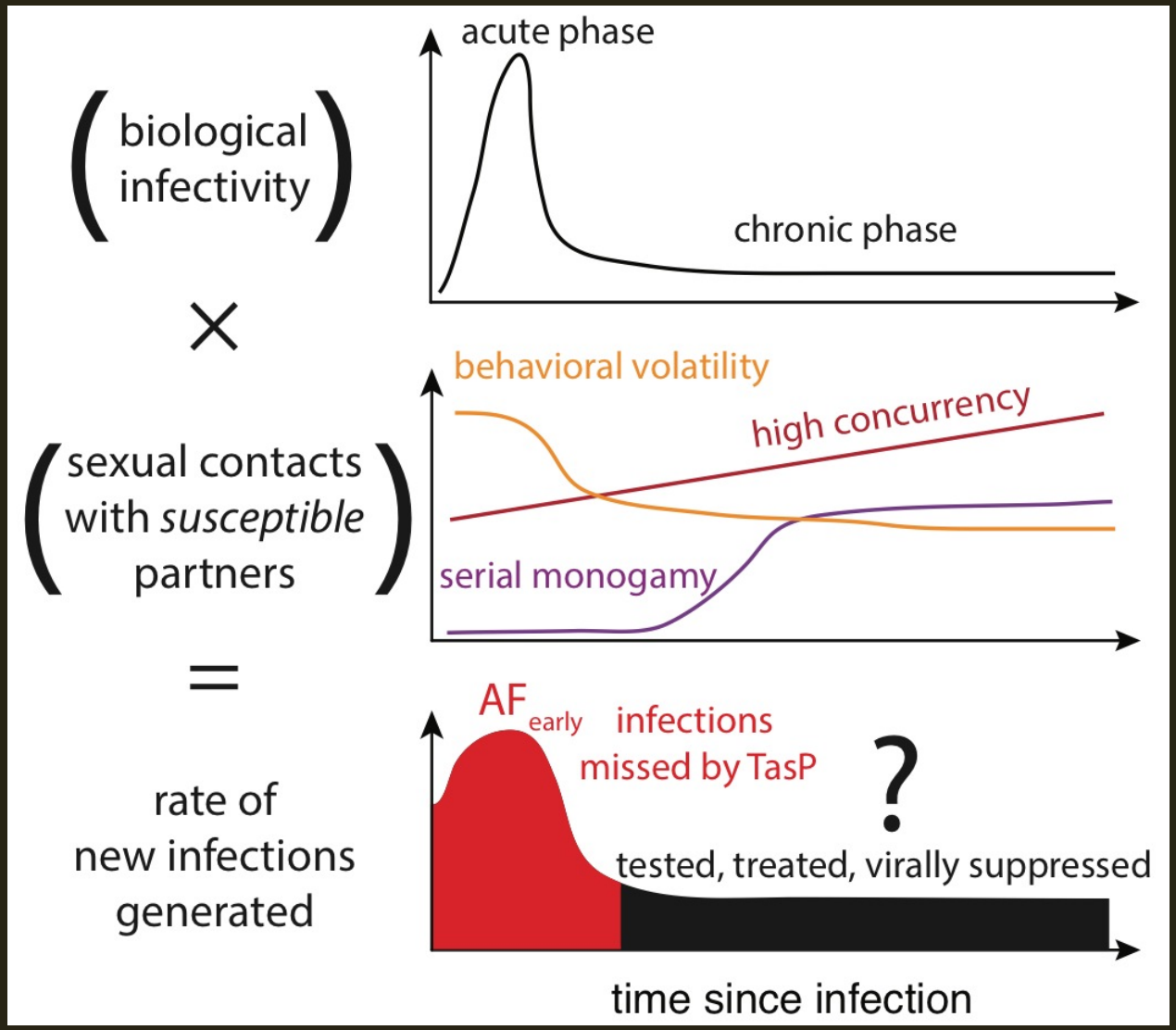

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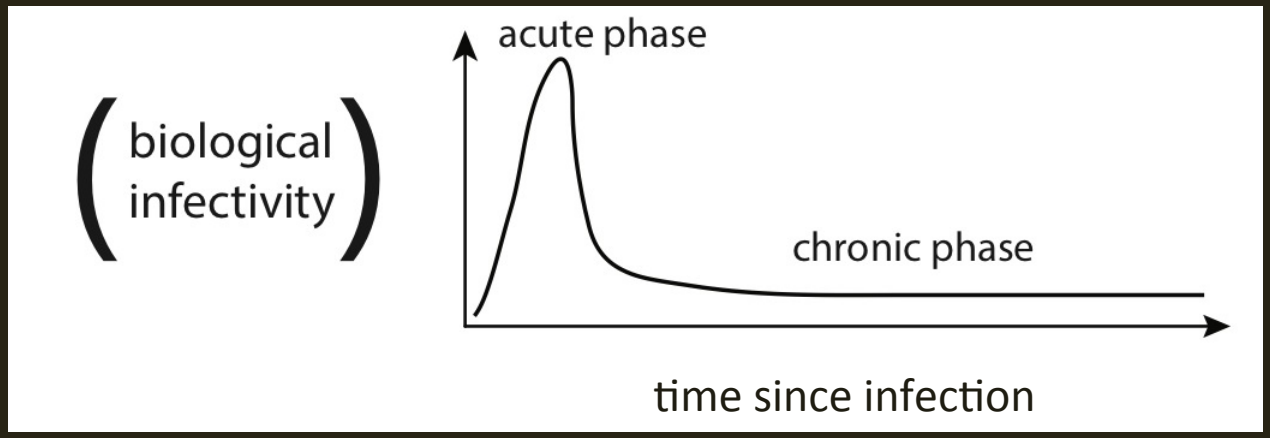

Here, we focus only on biological infectivity.

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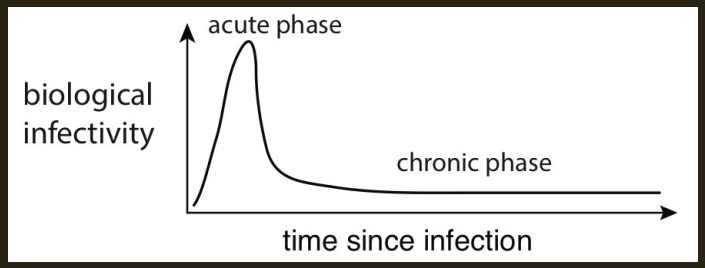

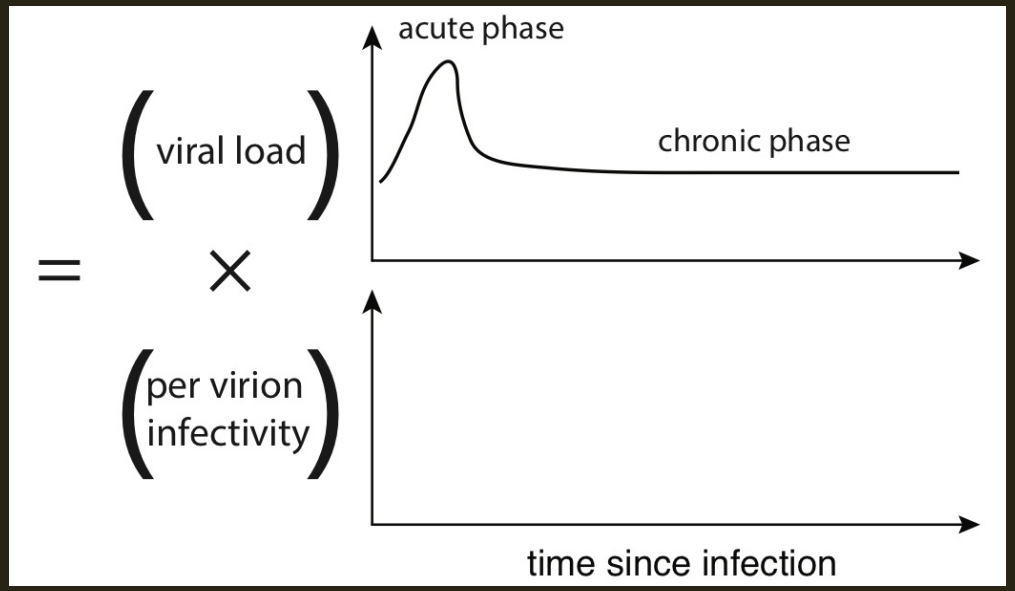

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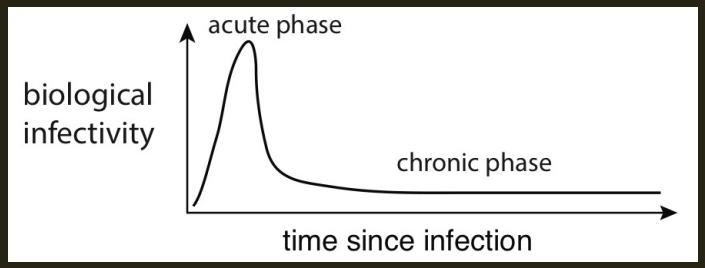

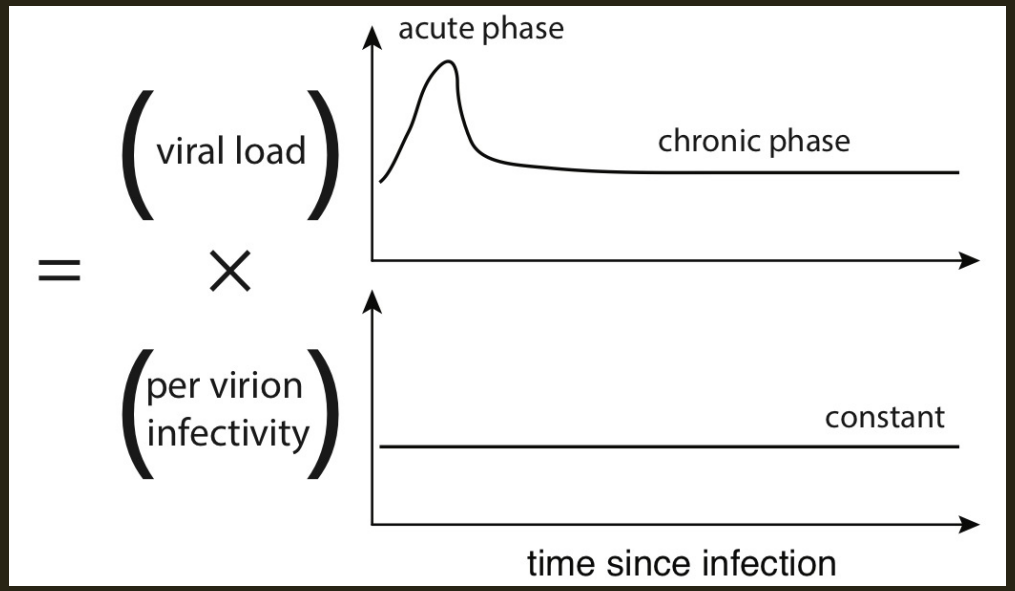

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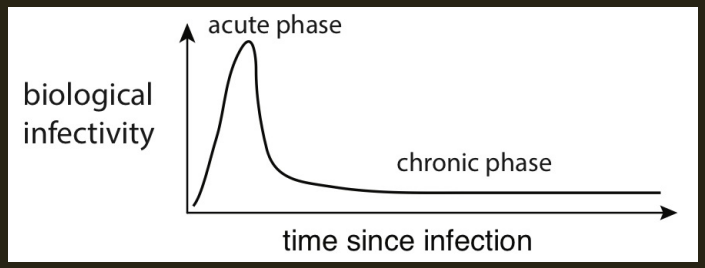
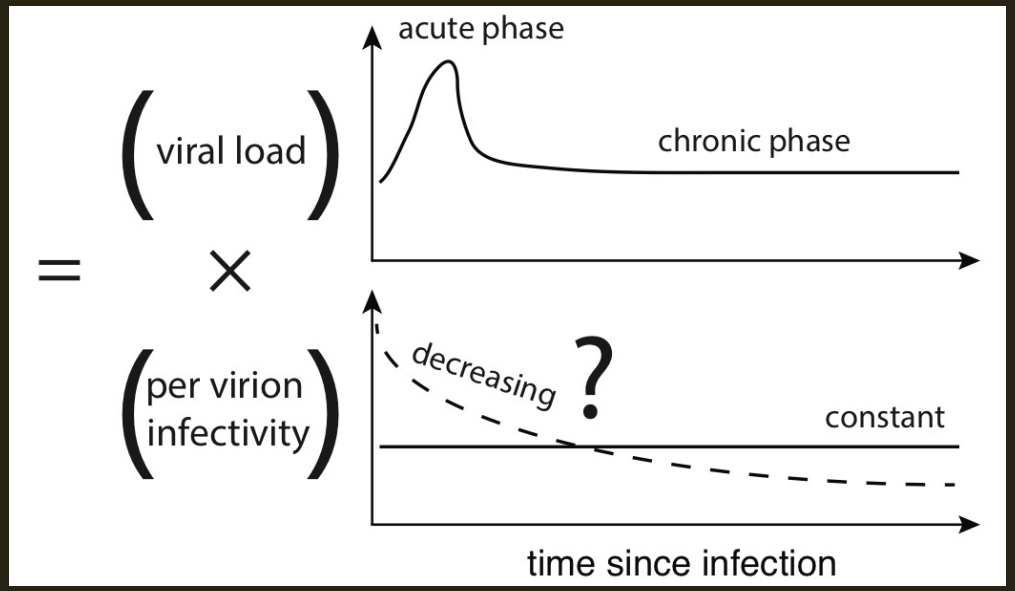


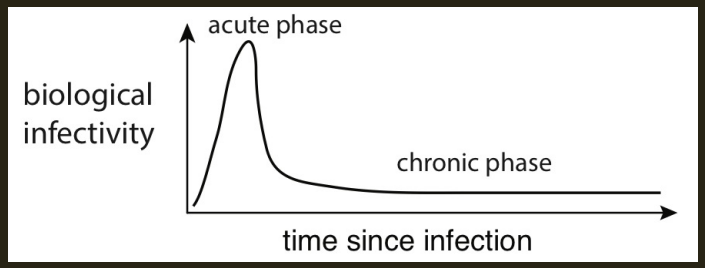


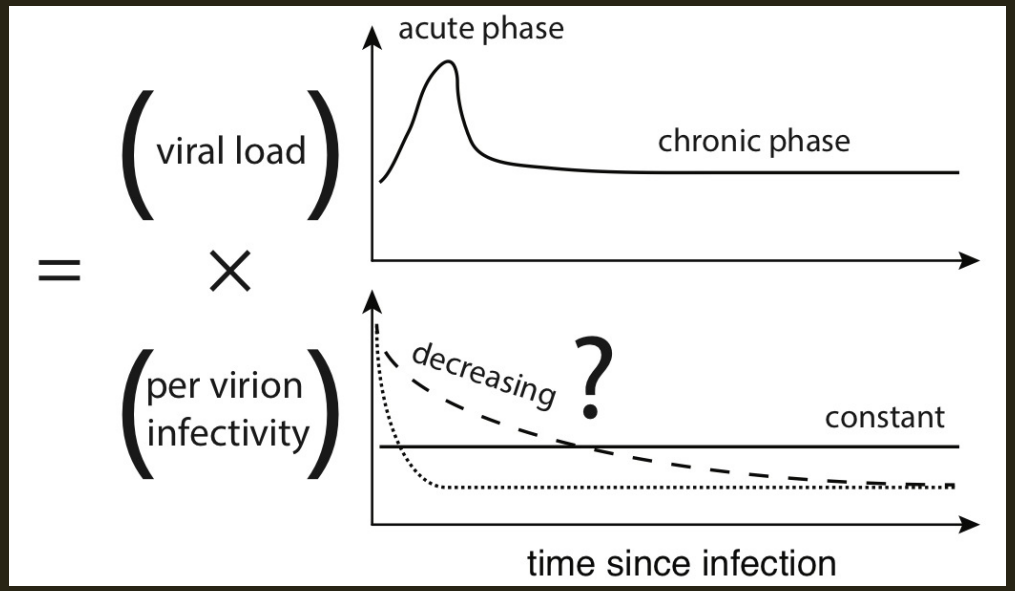
Maybe
recently transmitted virus
is more infectious?

Evidence from macaque-SIV

Ma et al. (2009). *Virology*.

What affects biological infectivity?





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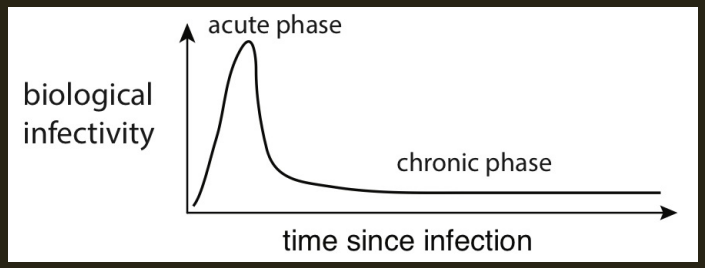
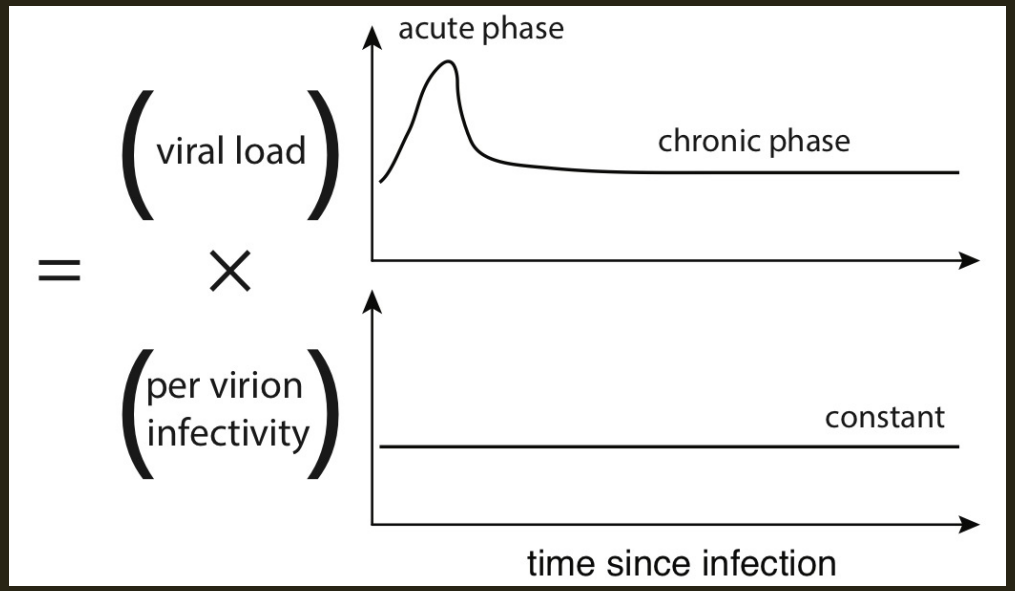
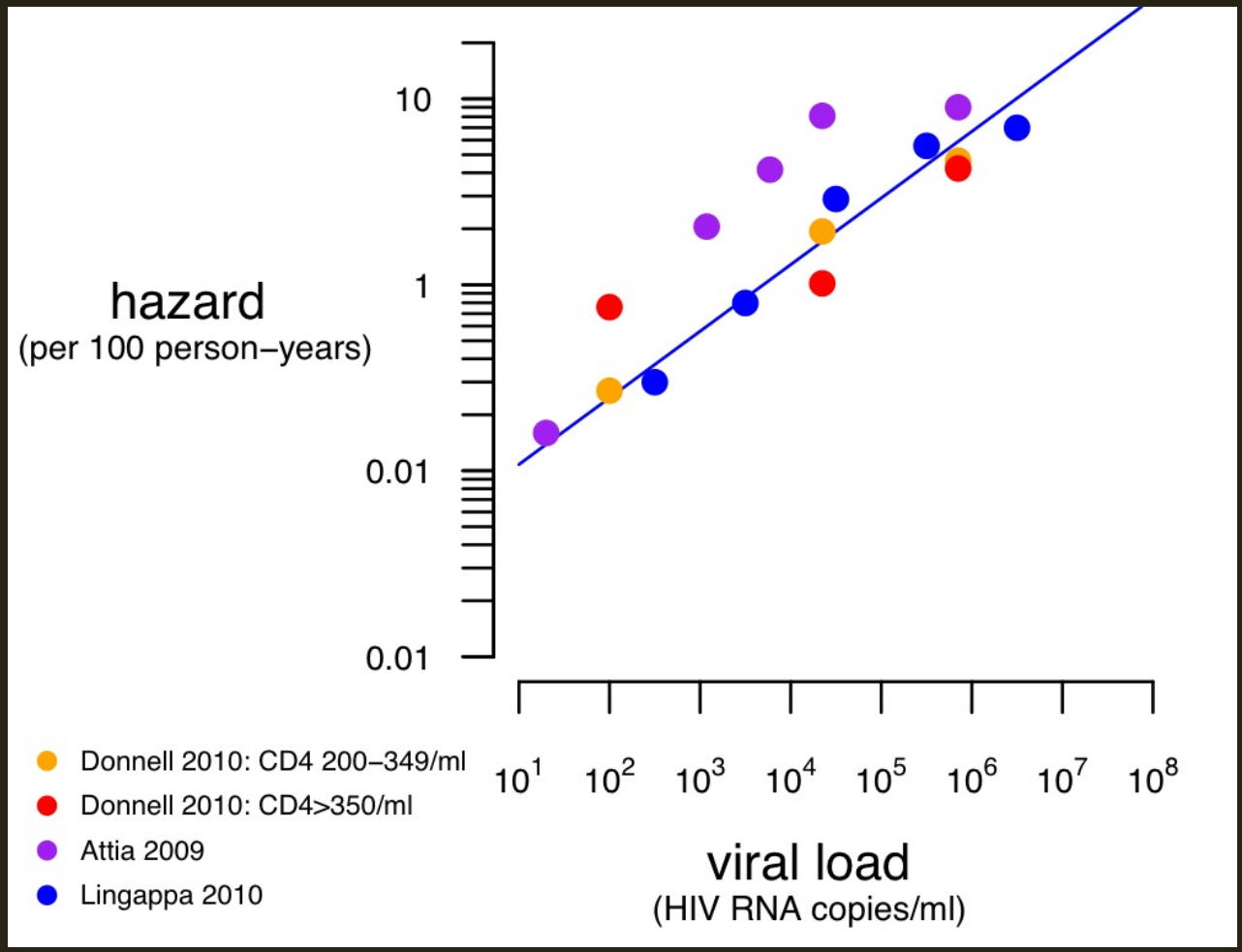




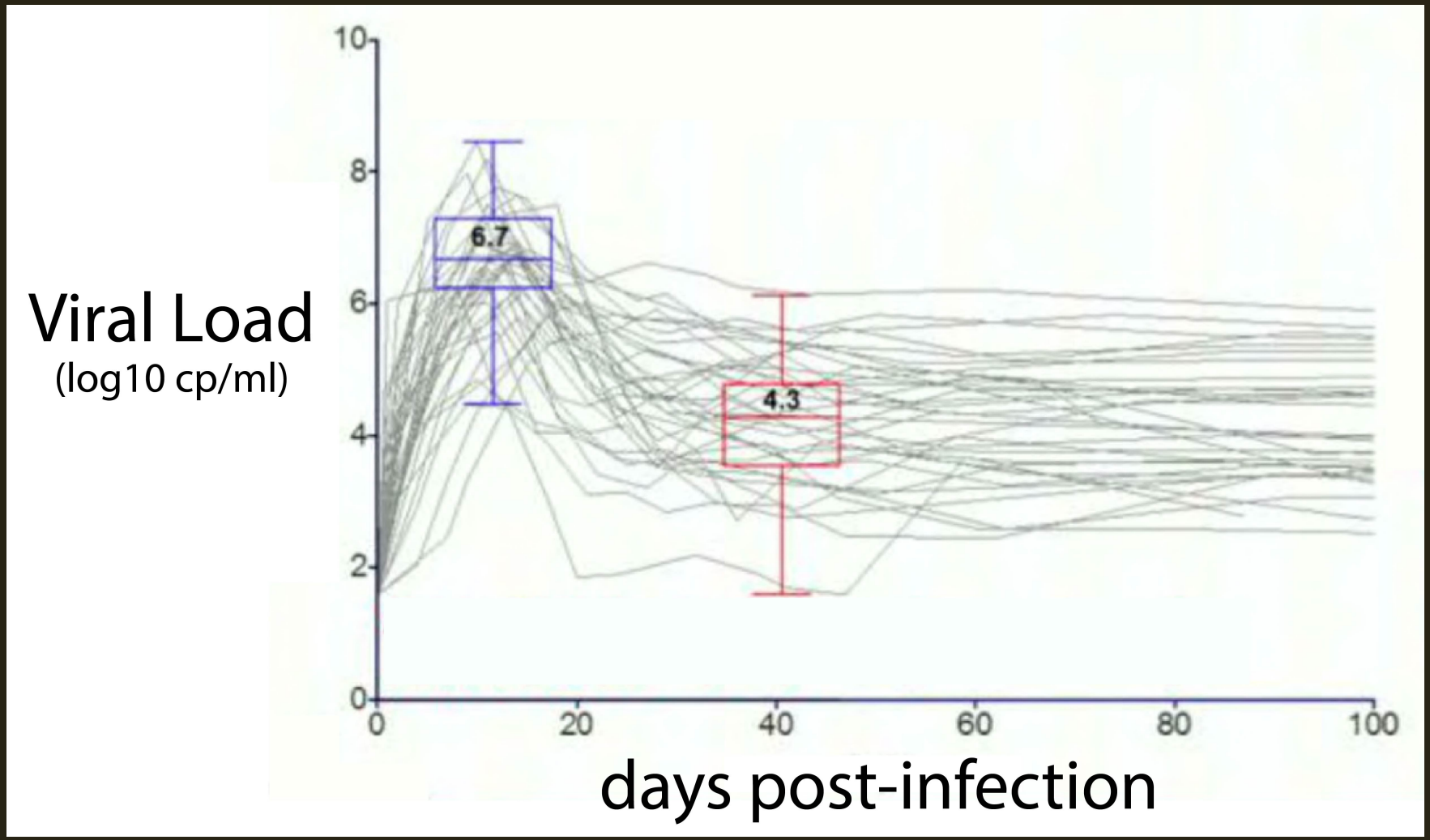
Assume constant strain infectivity for now.

Infectivity-Viral Load Relationship

2.5X infectivity / log10 viral load



Let’s take the average viral load trajectory



Robb (2012). *AIDS Vaccine 2012*. PL02.02.

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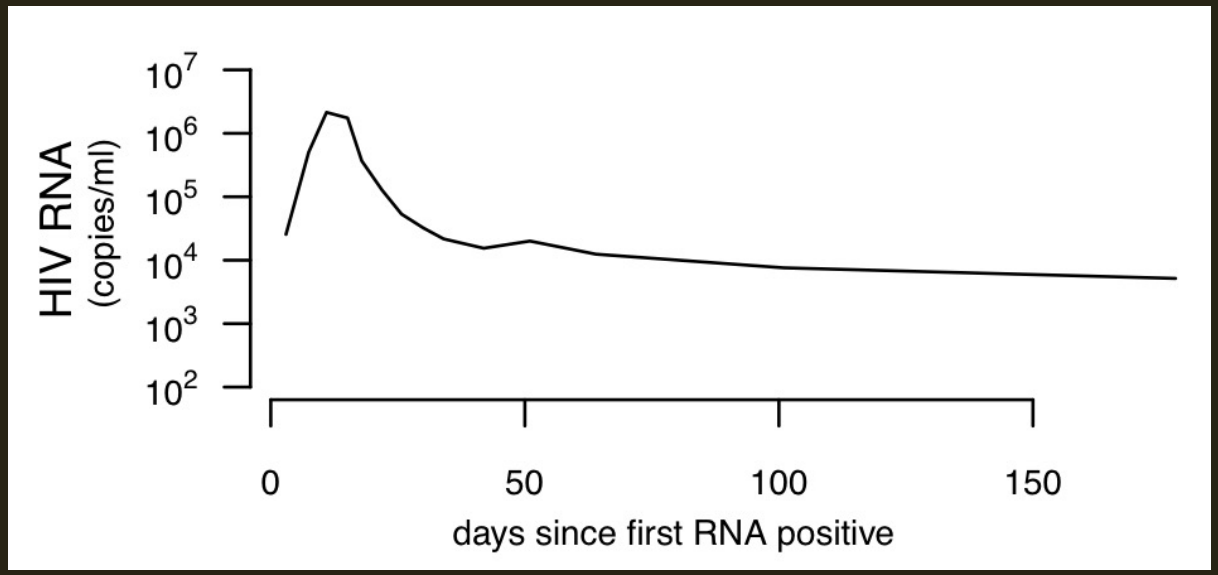
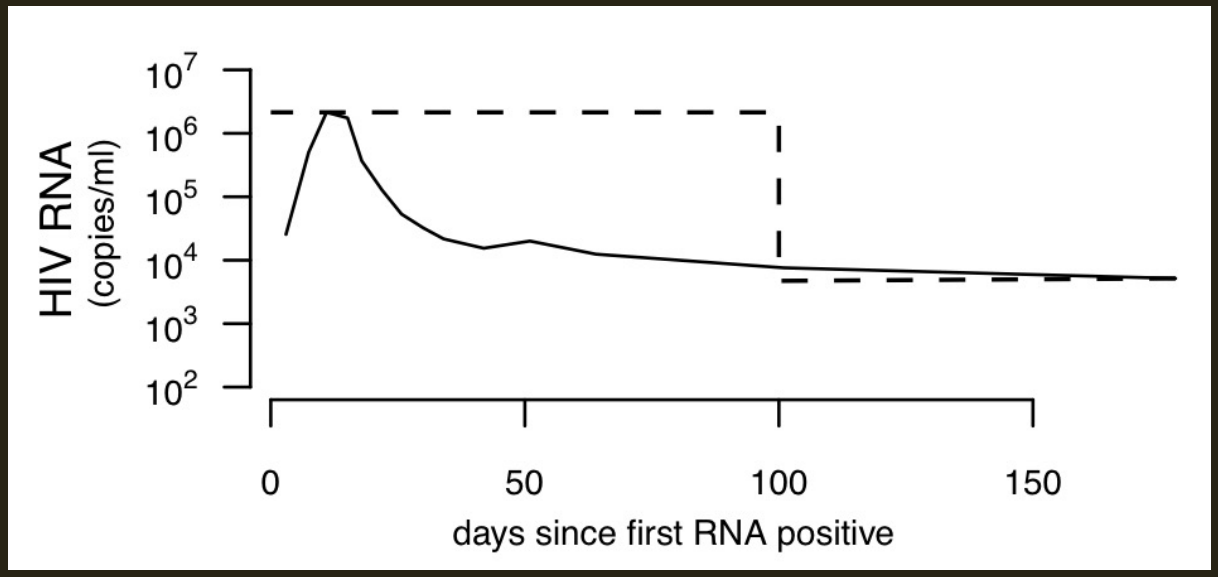


Determining a biological infectivity profile



All previous studies assumed discrete phases…

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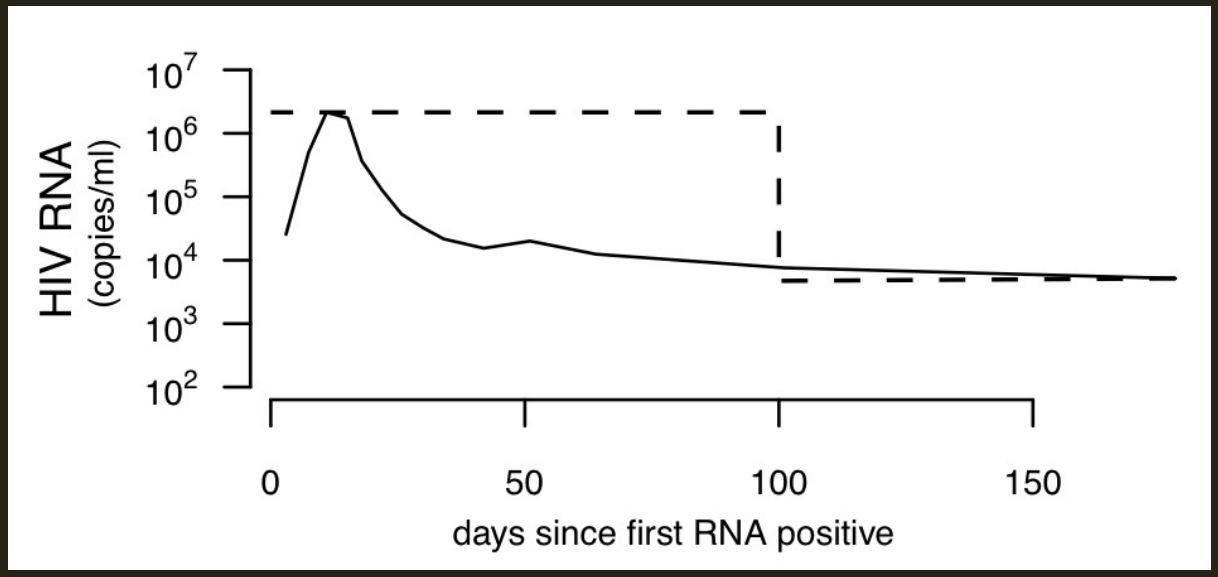

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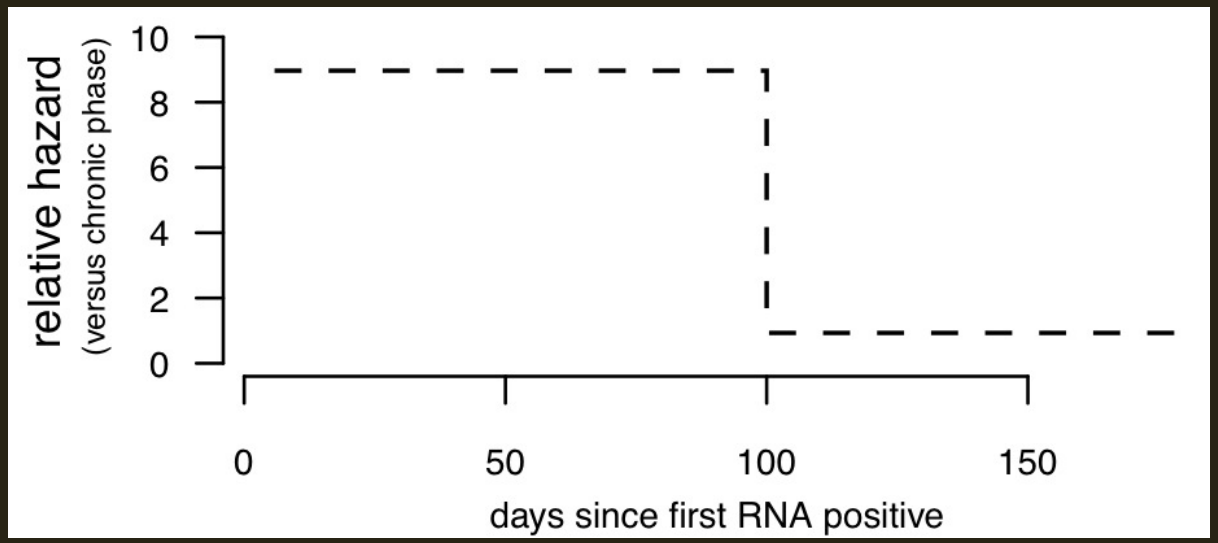
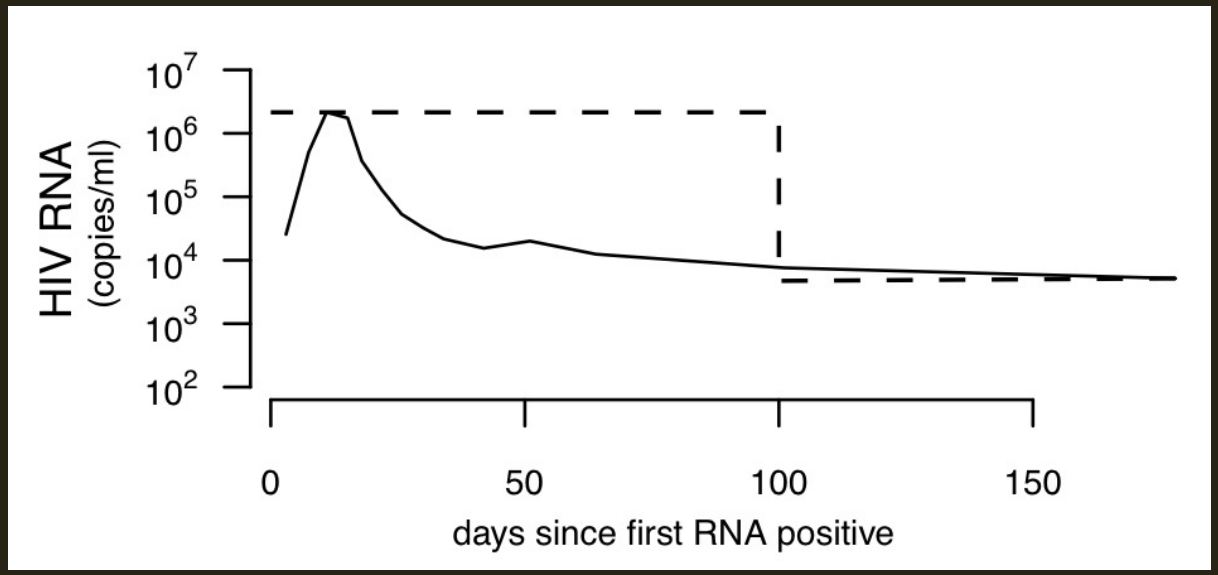


$$\frac{\text{2.5X infectivity}}{\text{log10 viral load}}$$

Determining a biological infectivity profile



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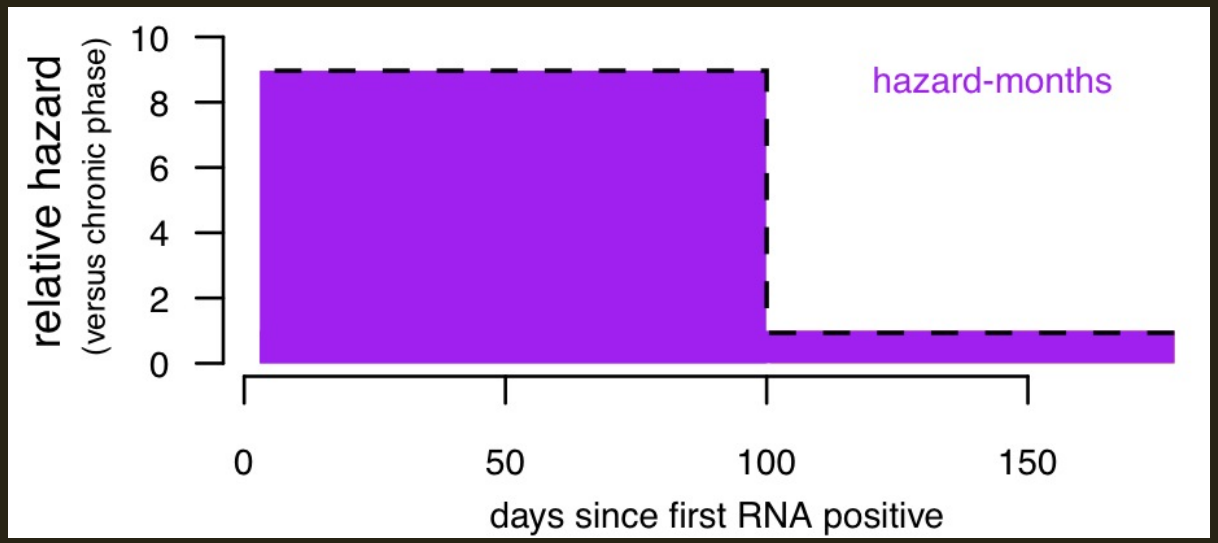

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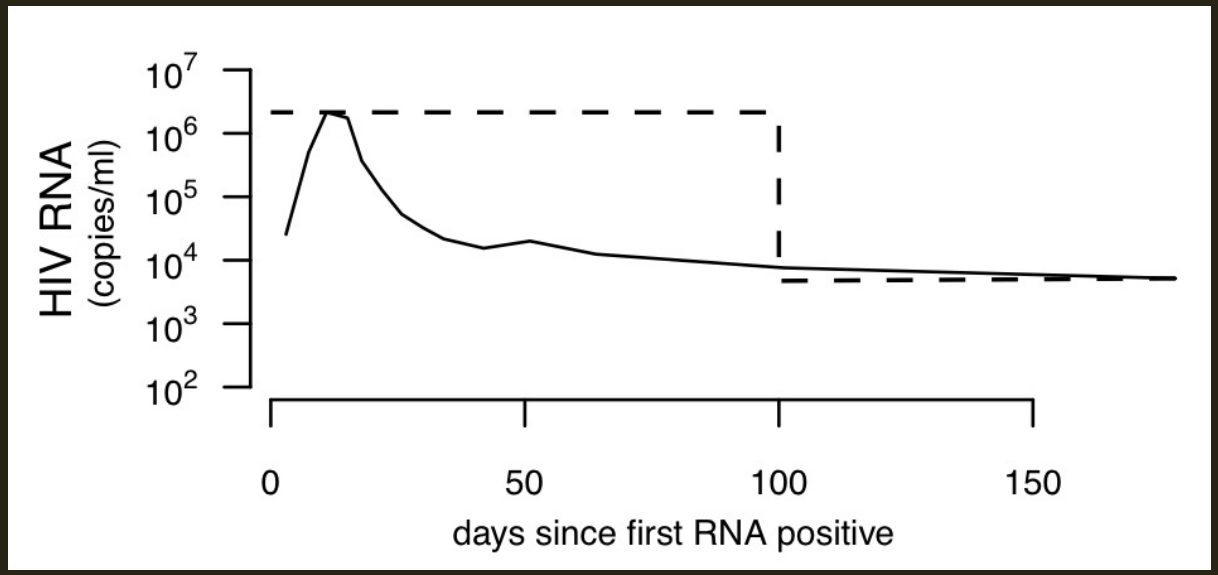

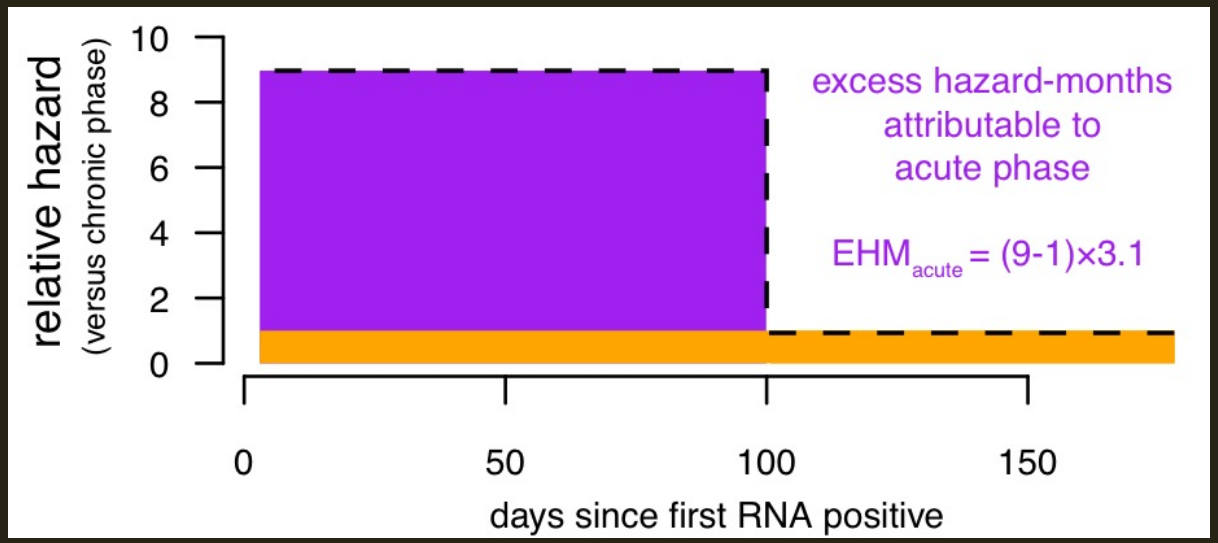

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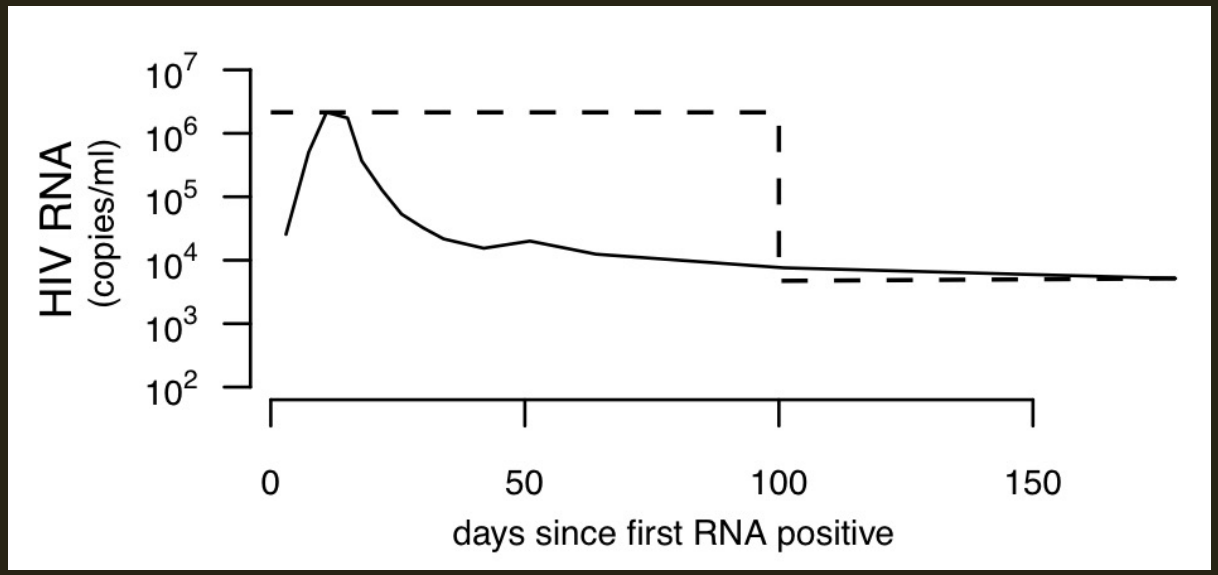
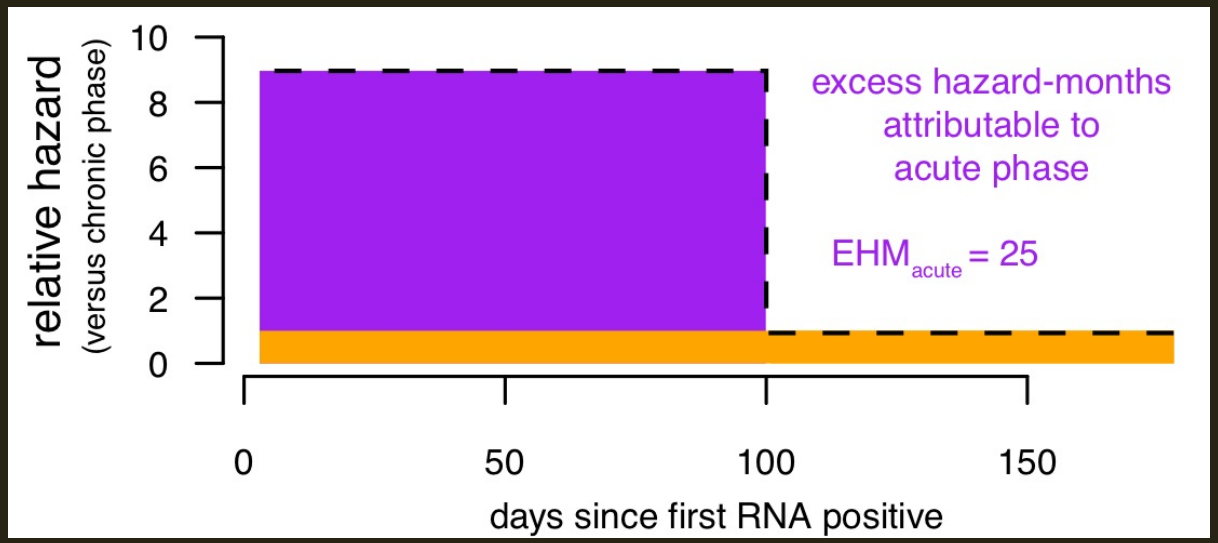
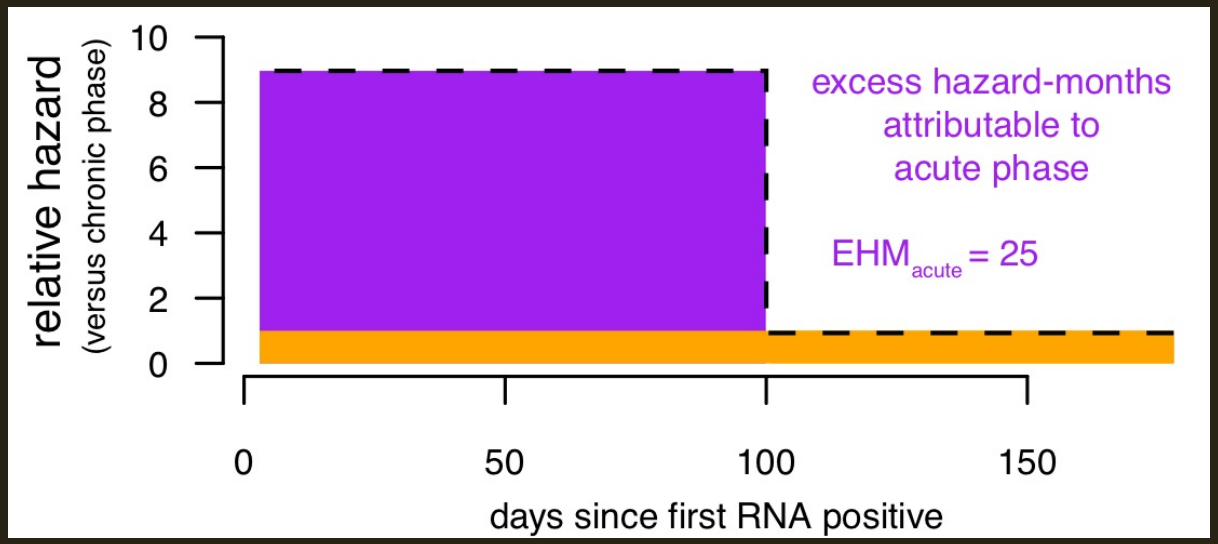




EHM_{acute}

25 compare to 120 hazard-months during 10 years of infection



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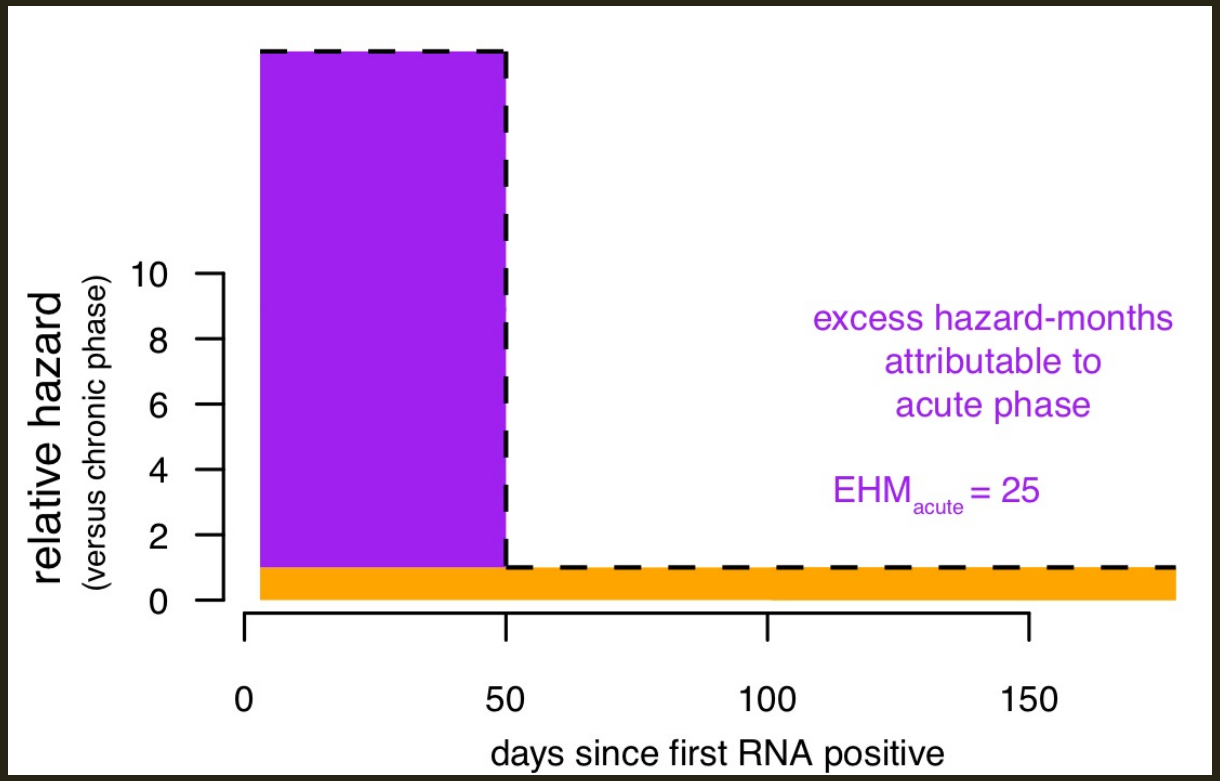

comparable across
different
acute phase durations

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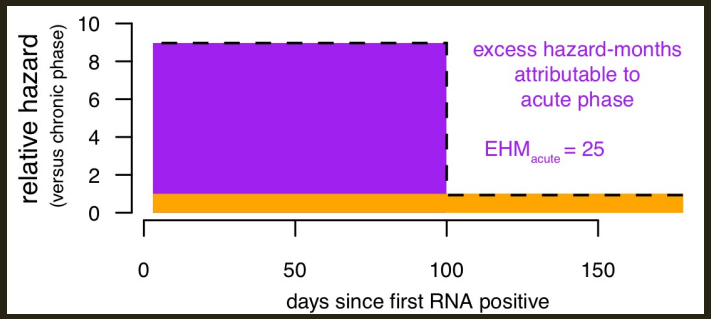
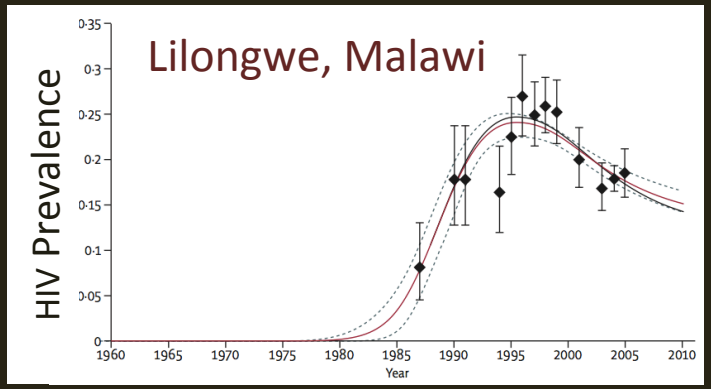
Estimating EHM_{acute} Indirectly

- Viral load trajectories

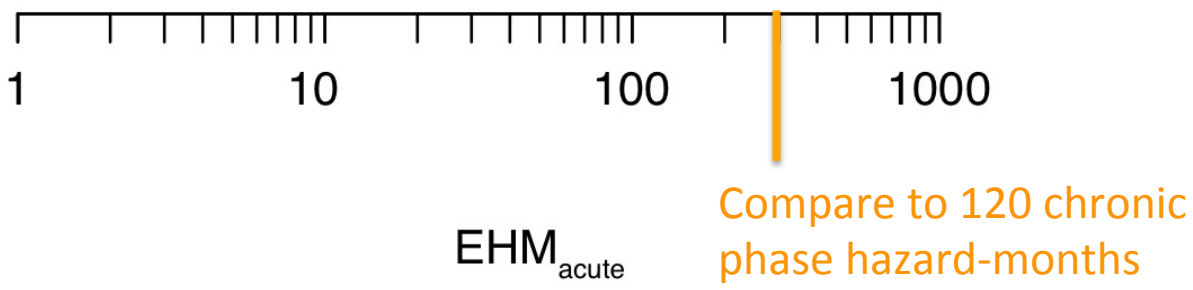


- Fast epidemic growth explainable by
  - early transmission



Powers et al. (2011). *Lancet*.

Variation in EHM_{acute} Estimates



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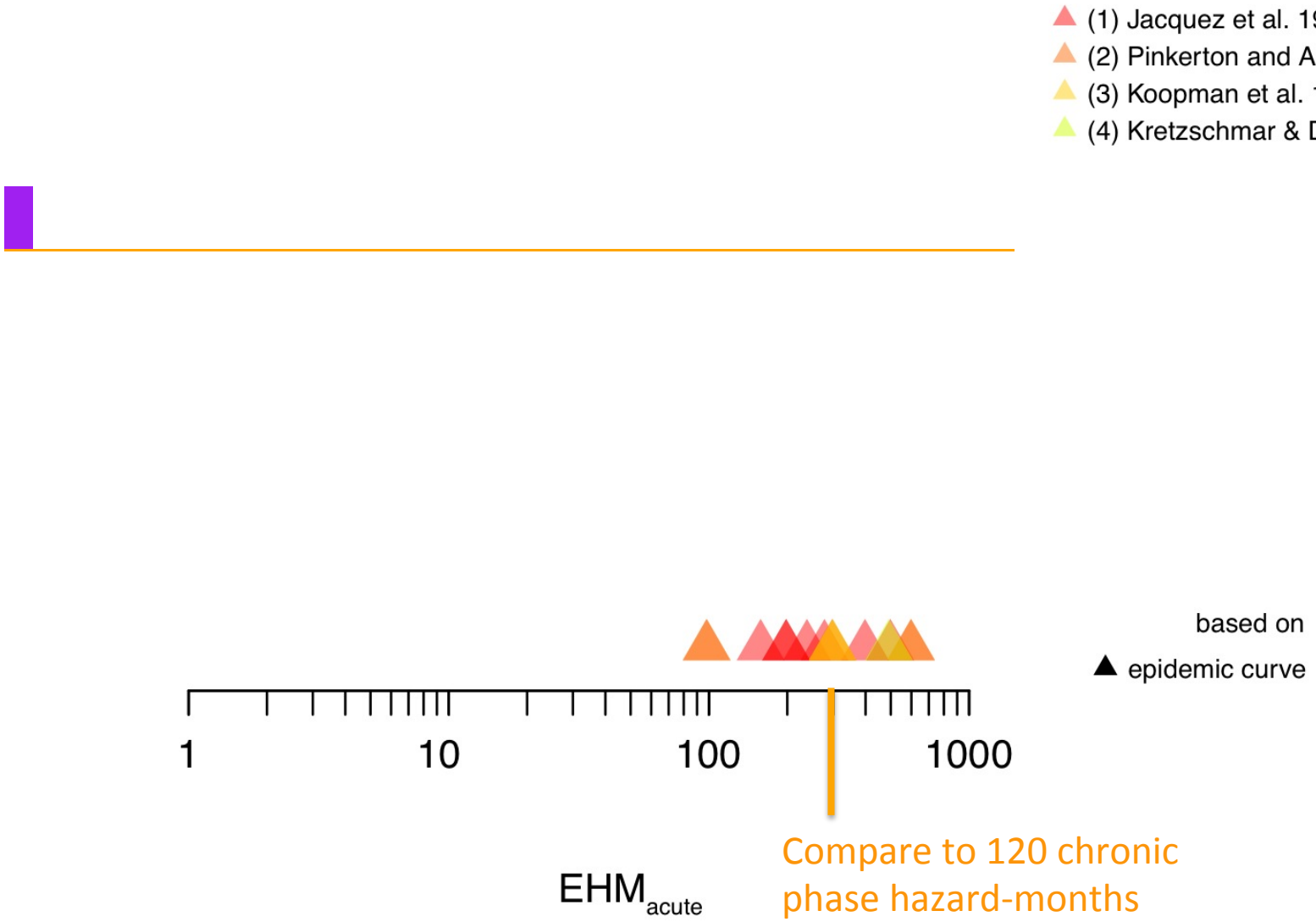

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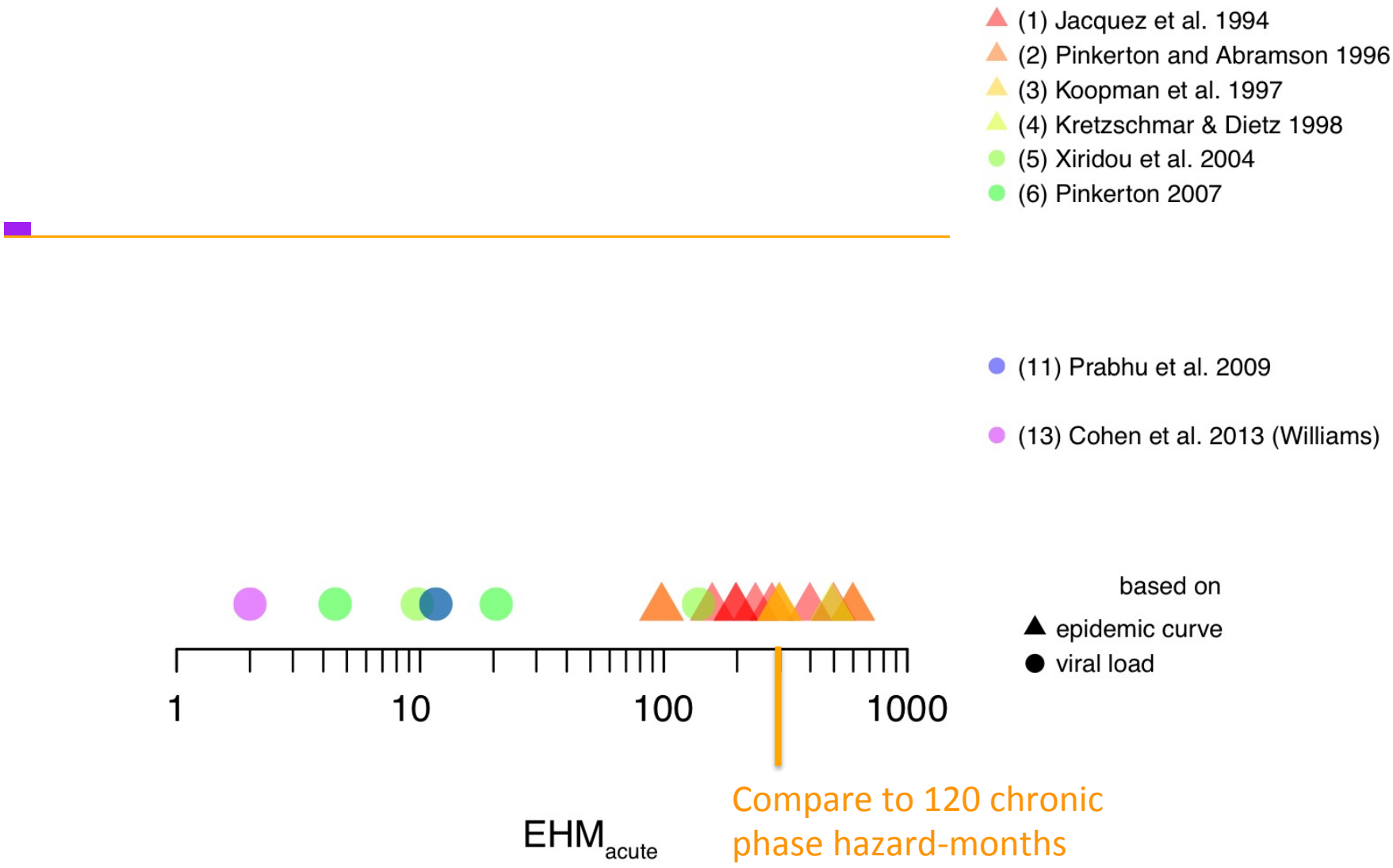


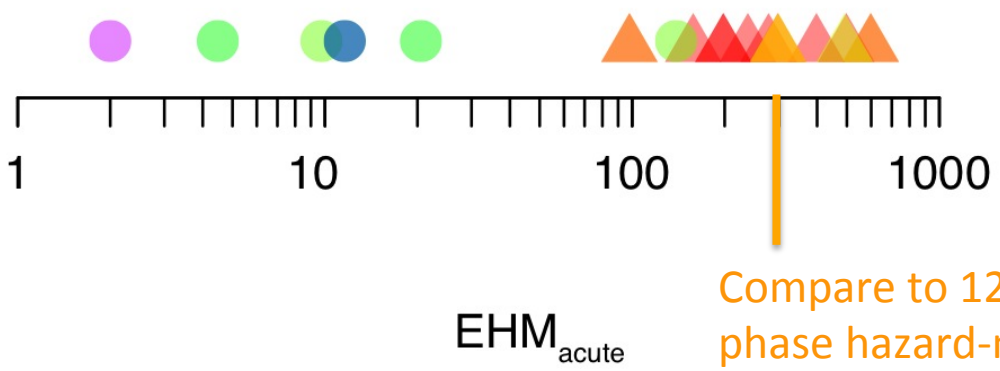
Variation in EHM_{acute} Estimates

Directly measured once by the
Rakai Community Cohort Study, Uganda

- (1) Jacquez et al. 1994
- (2) Pinkerton and Abramson 1996
- (3) Koopman et al. 1997
- (4) Kretzschmar & Dietz 1998
- (5) Xiridou et al. 2004
- (6) Pinkerton 2007

- (11) Prabhu et al. 2009

- (13) Cohen et al. 2013 (Williams)



based on
- epidemic curve
- viral load

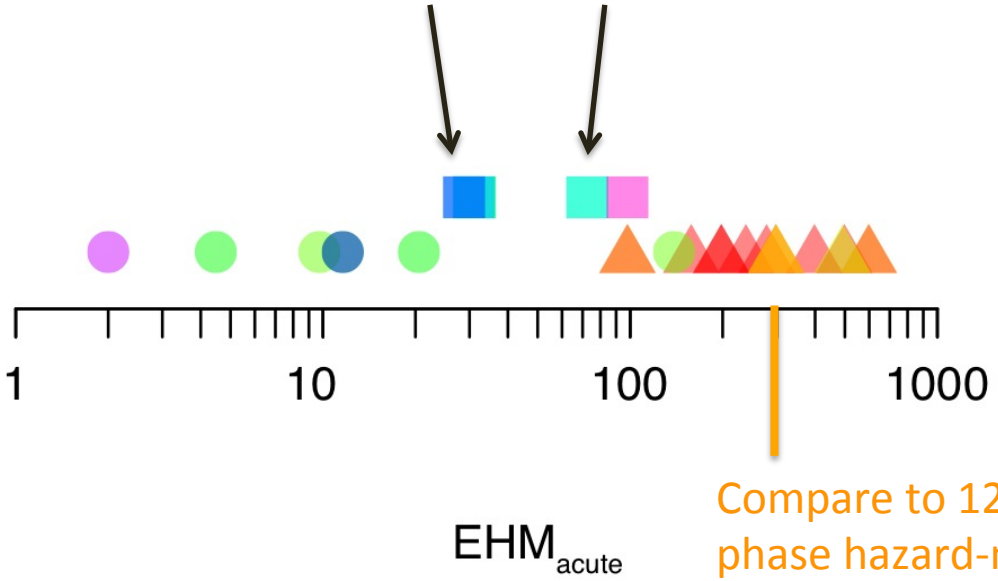
Compare to 120 chronic phase hazard-months

Variation in EHM_{acute} Estimates

Directly measured once by the
Rakai Community Cohort Study, Uganda

Most commonly cited estimates

EHM_{acute} = 35 and 71



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(14) Romero–Severson et al. 2013

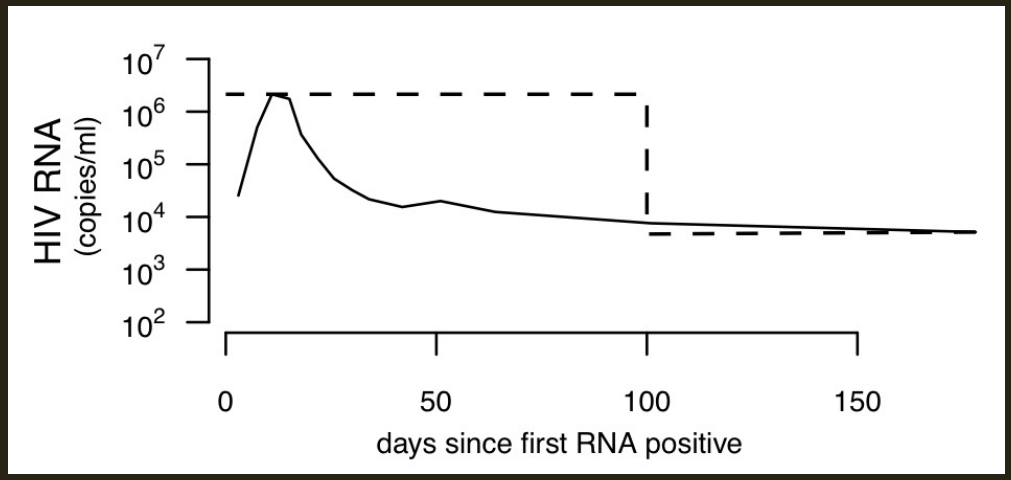
based on
epidemic curve
viral load
Rakai

Compare to 120 chronic phase hazard-months

Why reevaluate EHM_{acute} estimates?

- Viral Load

  Continuous trajectory
  instead of discrete phases



- Rakai Retrospective Cohort Study

  Biases due to (1) unmodeled heterogeneity
  (2) study design

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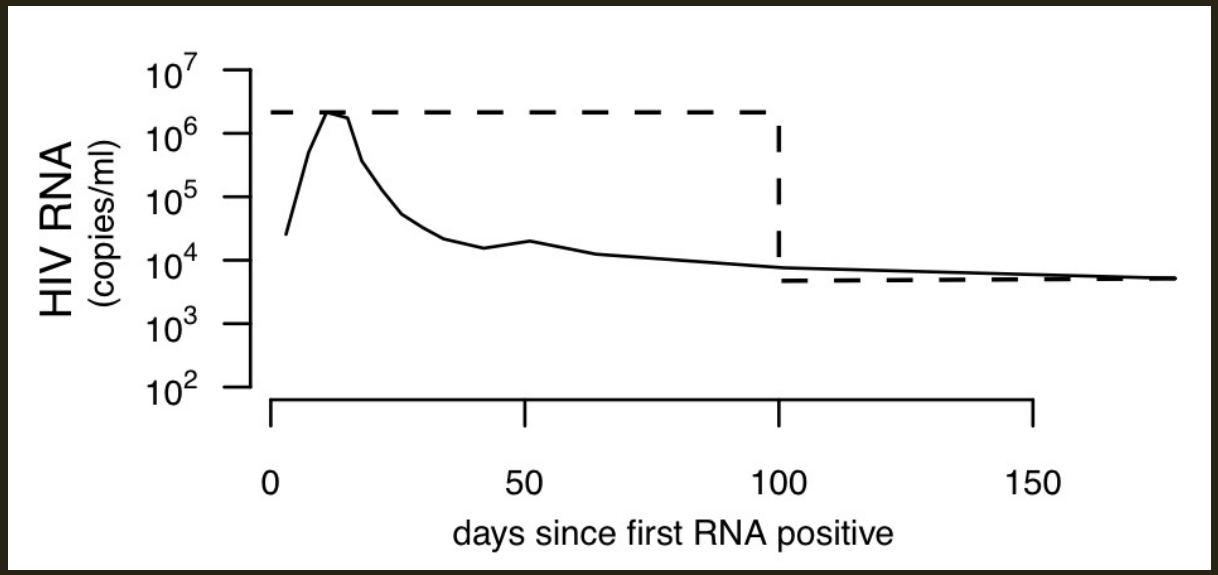
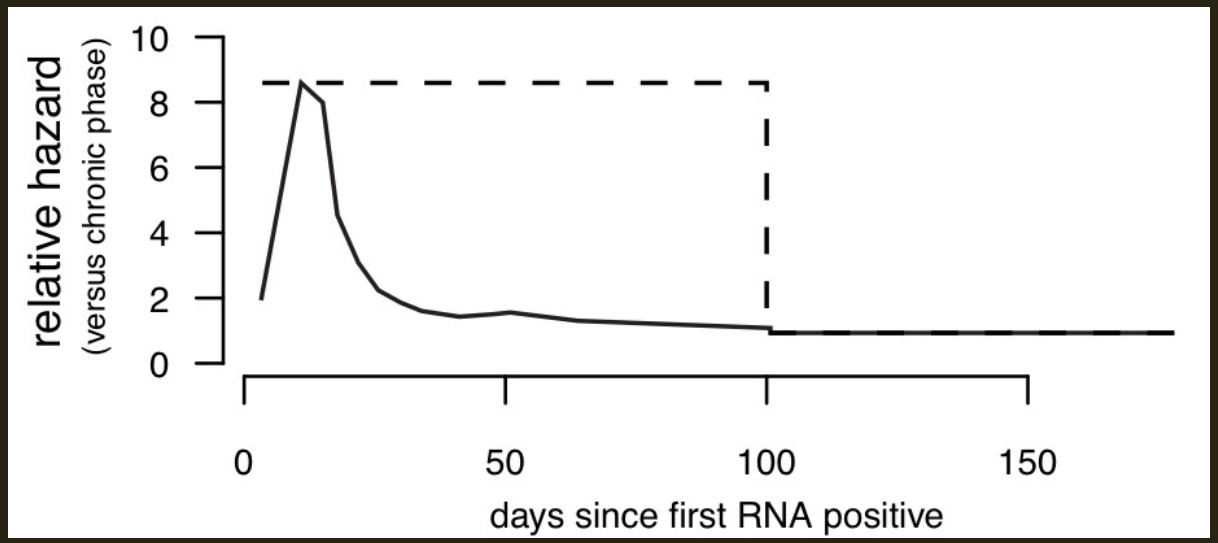
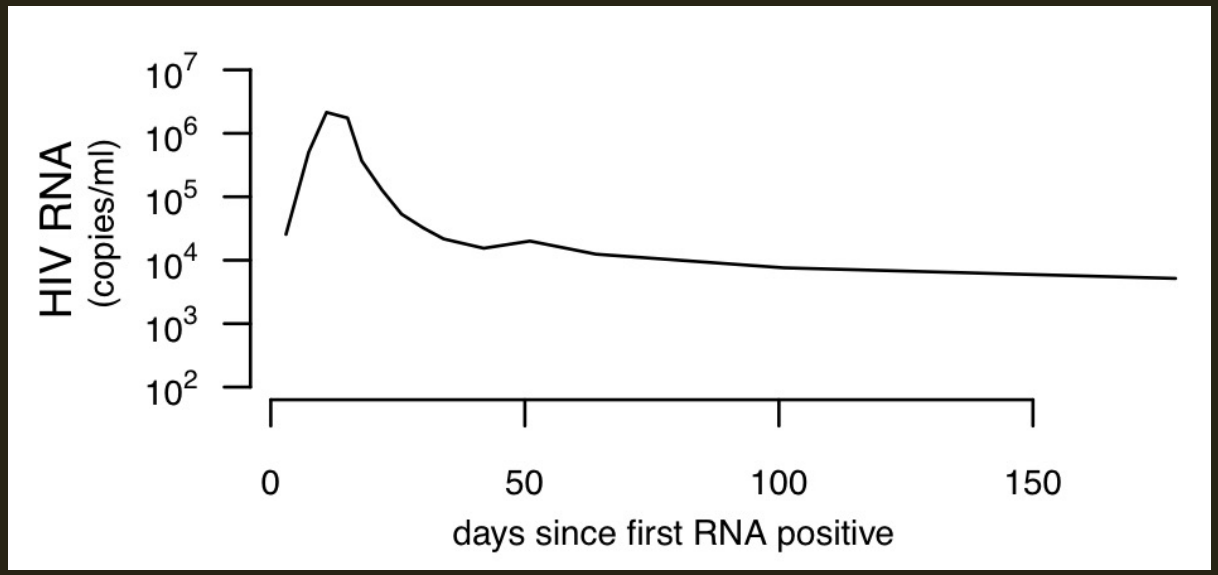
Determining a biological infectivity profile

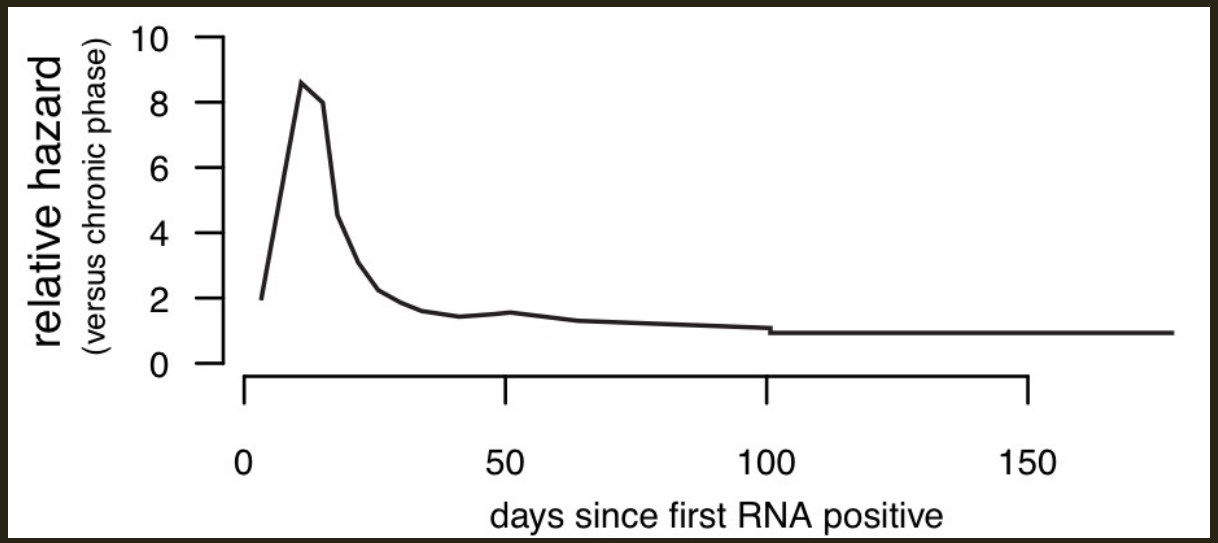


continuous trajectory to avoid overestimation

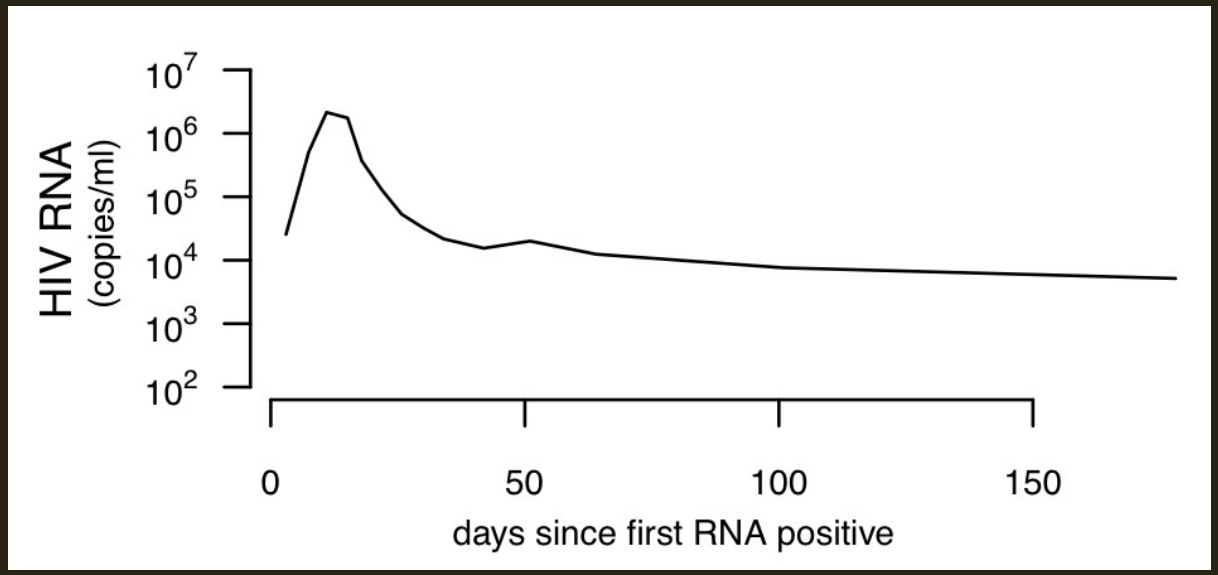


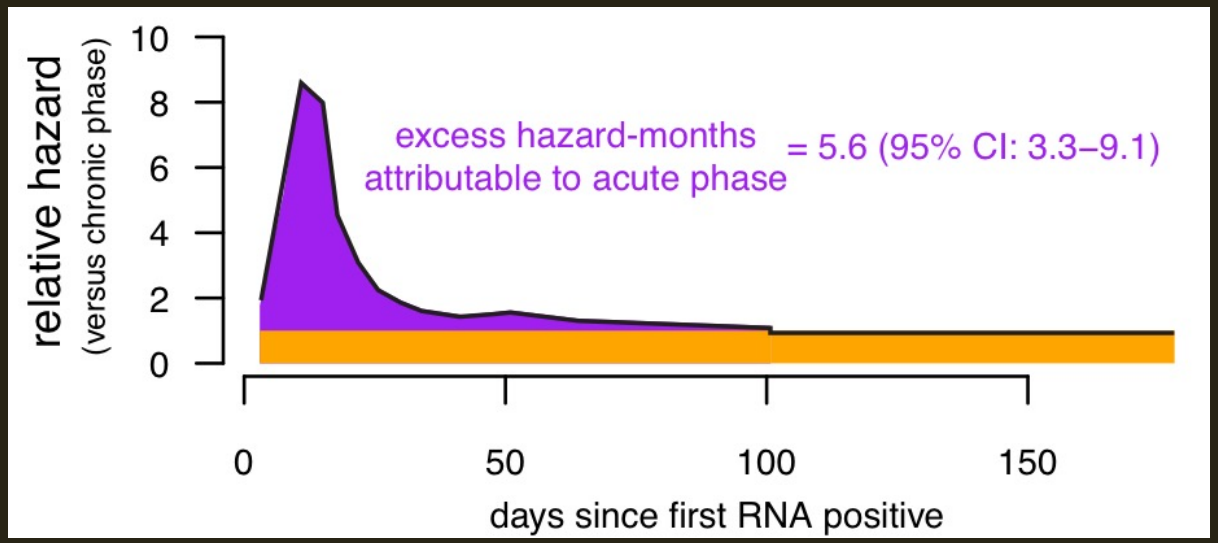
Determining a biological infectivity profile



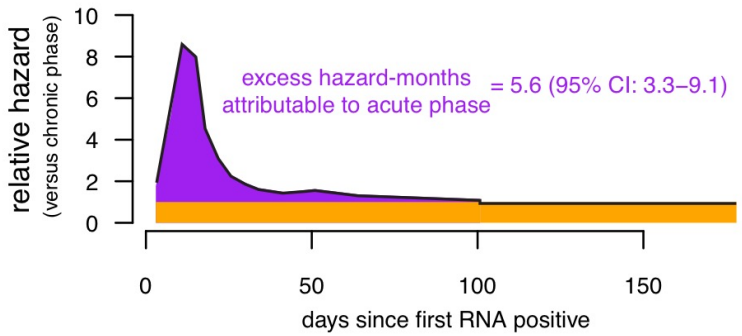


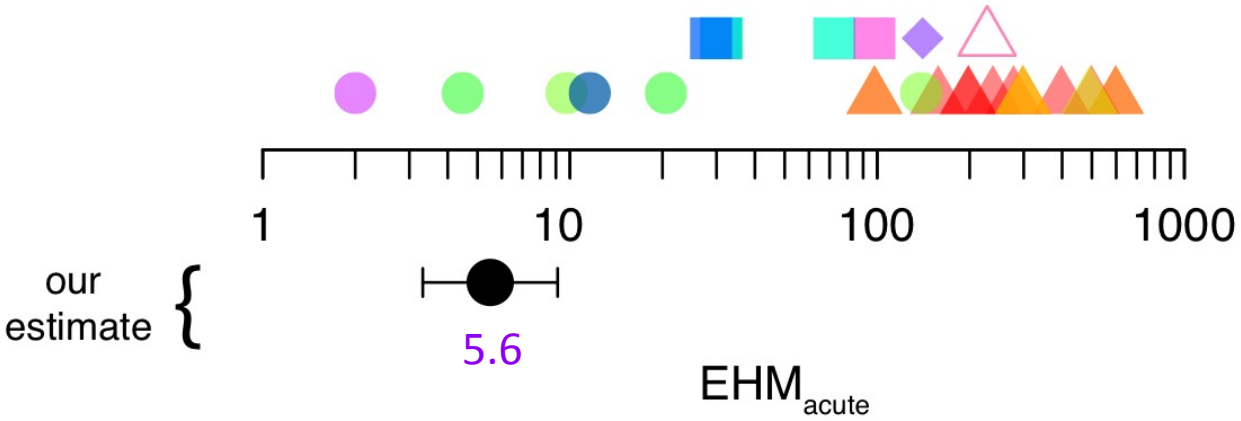
Determining a biological infectivity profile





Variation in EHM_{acute} Estimates





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- (15) Rasmussen et al. 2014

based on

- epidemic curve
- viral load
- Rakai
- Rakai & epidemic curve
- phylogenetics

Outline

1. Relevance: Treatment as Prevention (TasP)
2. Measuring excess infectivity with EHM_{acute}
3. Literature review of past estimates
4. Re-estimation of EHM_{acute} from viral load
5. Re-estimation of EHM_{acute} from the Rakai cohort

Direct Measurement of Acute Infectivity

- Identify recently infected individuals
- Observe rate at which they infect sexual partners
    - Must be switching between partners
    - Moral imperative to intervene

Very challenging and only done once!

The Rakai Retrospective Cohort Study

In a prospective population cohort study 1994-1999

retrospectively identified

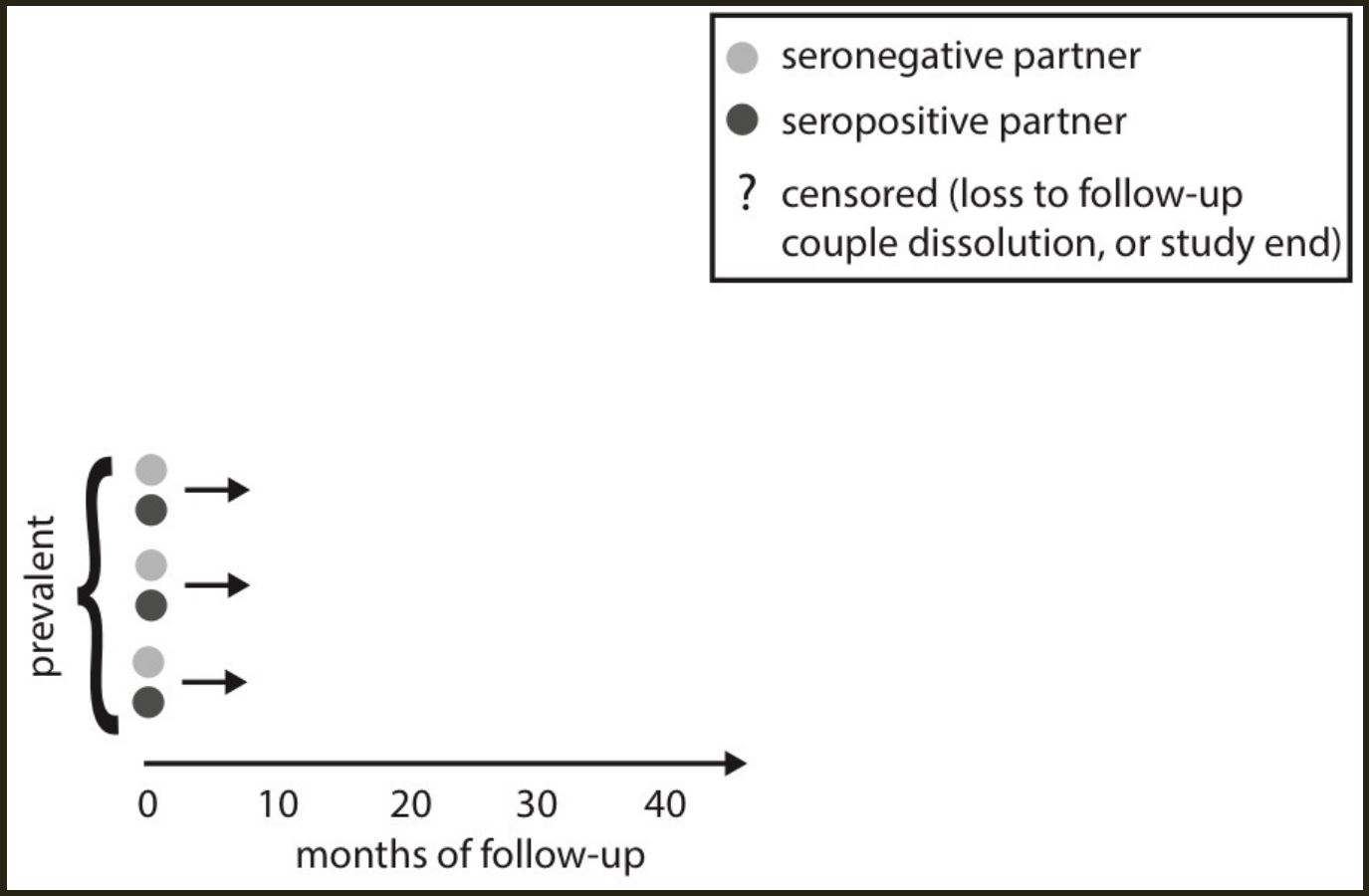
235 stable couples observed serodiscordant at least once

Do individuals infect their partners at
different rates
early vs. later in infection?

Wawer et al. (2005). *Journal of Infectious Disease*.

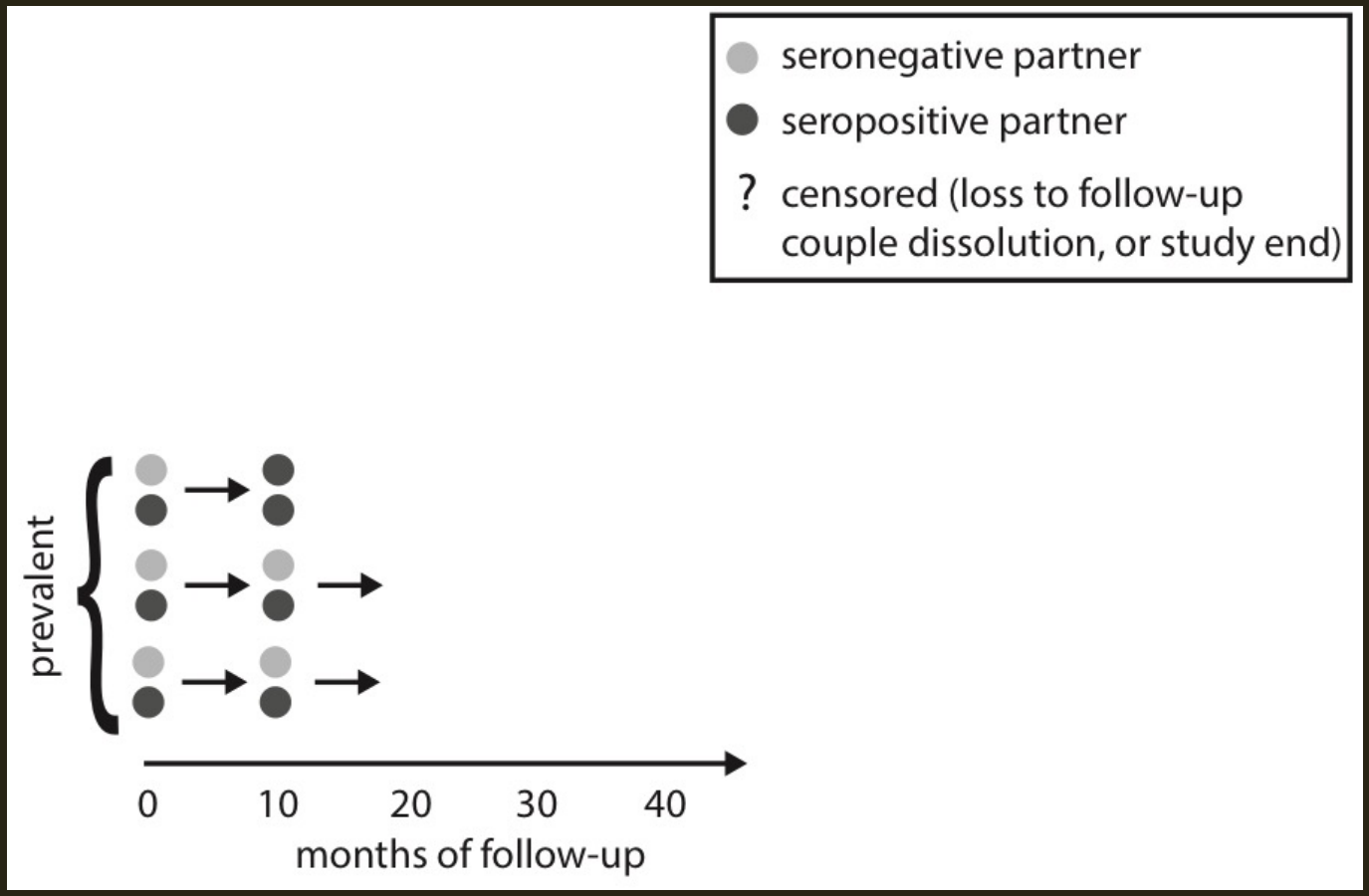
The Rakai Retrospective Cohort Study

chronic



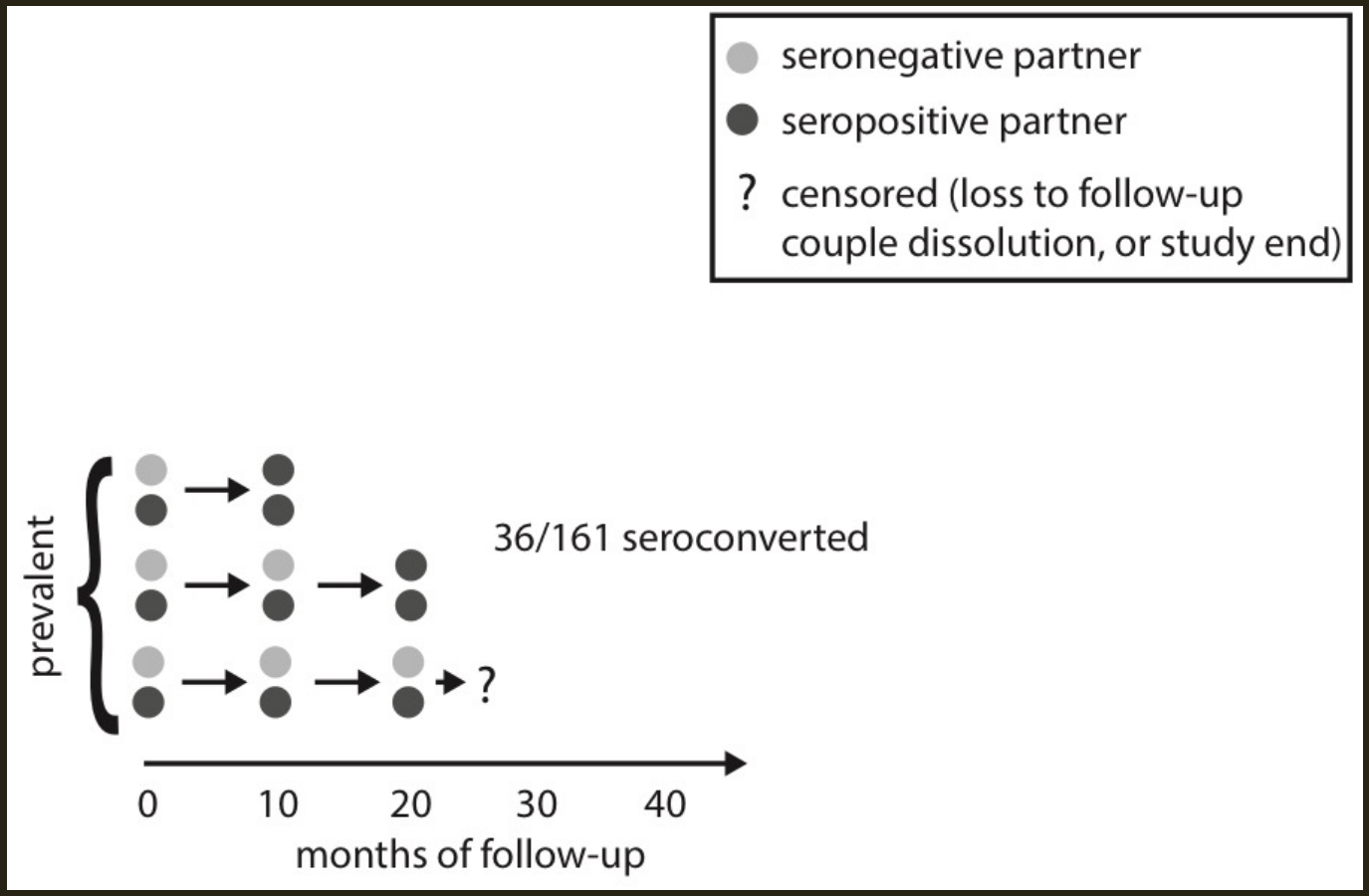
The Rakai Retrospective Cohort Study

chronic



The Rakai Retrospective Cohort Study

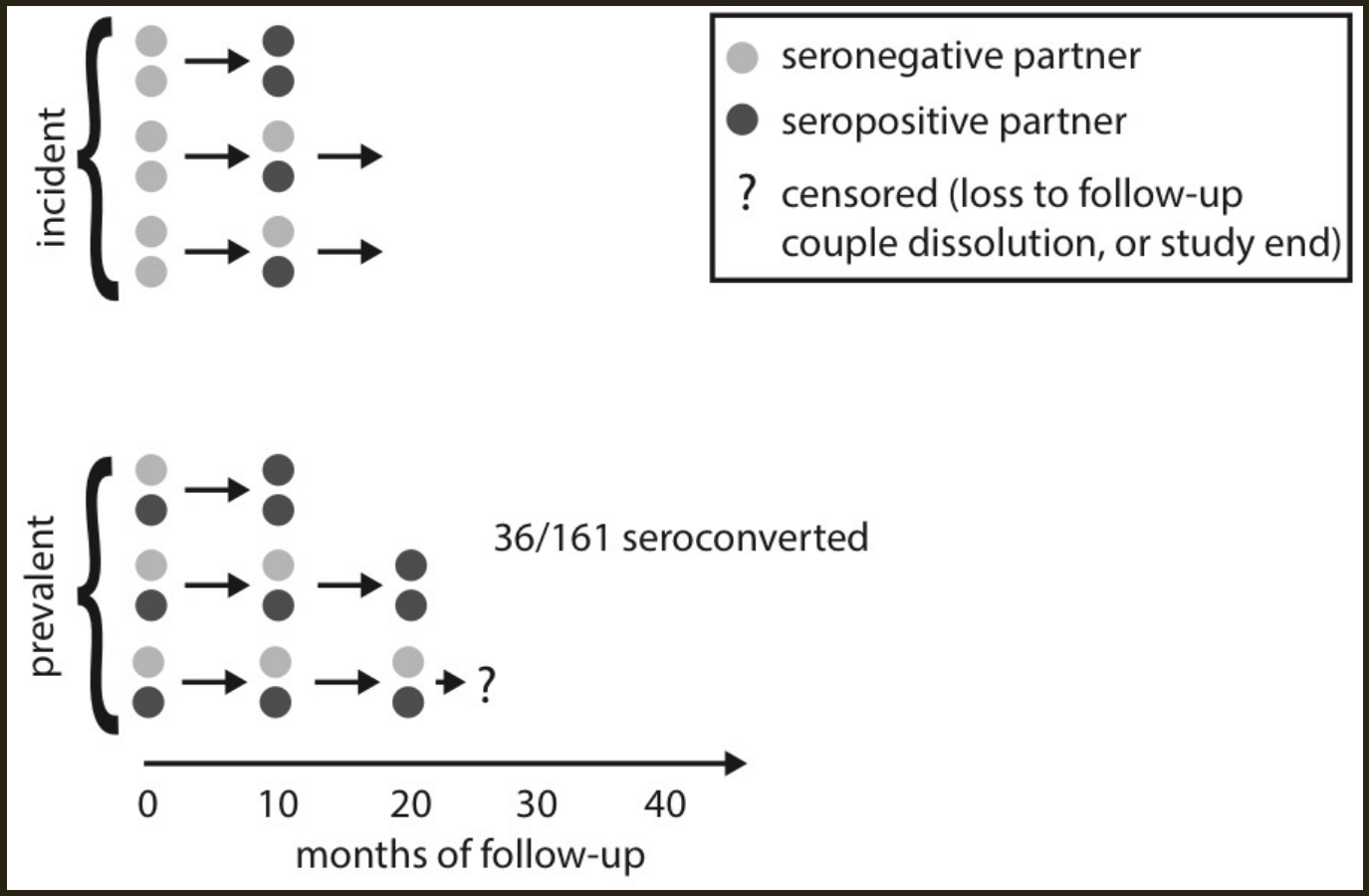
chronic



The Rakai Retrospective Cohort Study

acute

chronic

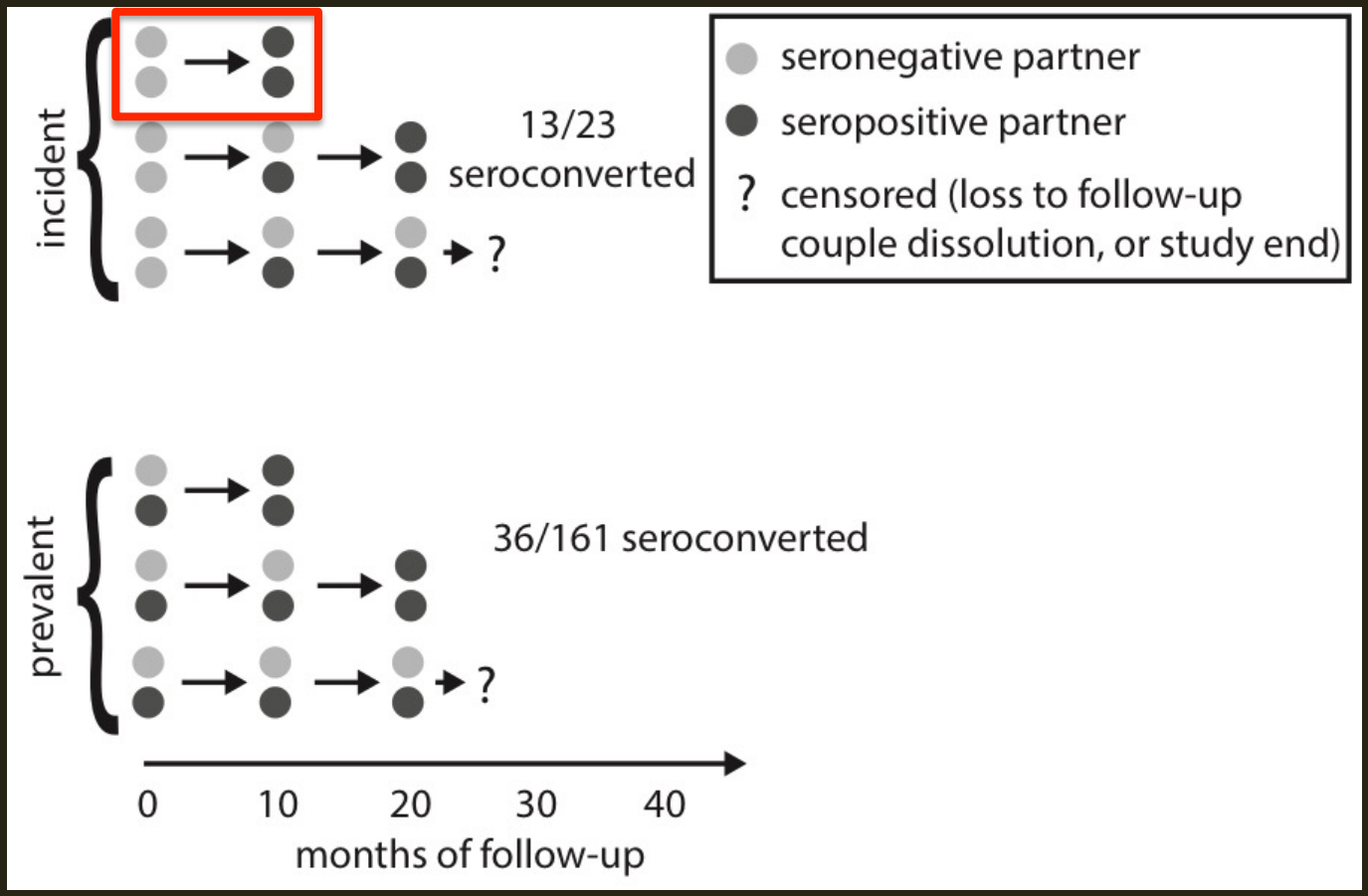


The Rakai Retrospective Cohort Study

Suggestive of HIGH acute infectivity

acute

chronic

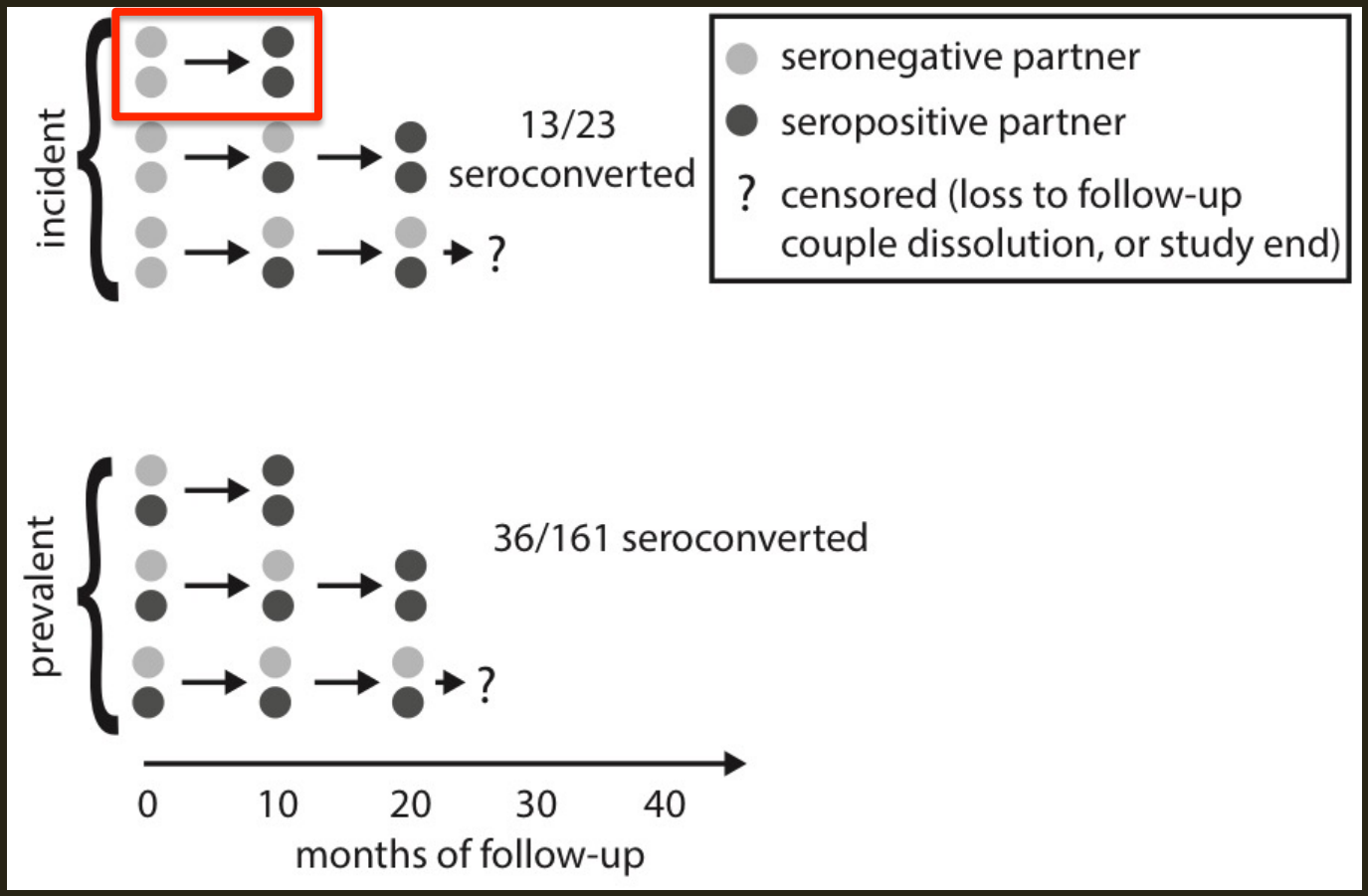


The Rakai Retrospective Cohort Study

Suggestive of HIGH acute infectivity

acute

chronic



EHM_{acute} = 35 to 71 depending on analysis

The Rakai Retrospective Cohort Study

Concluded acute infectivity >>> expected based on viral load

EHM_{acute} = 35 to 71 depending on analysis

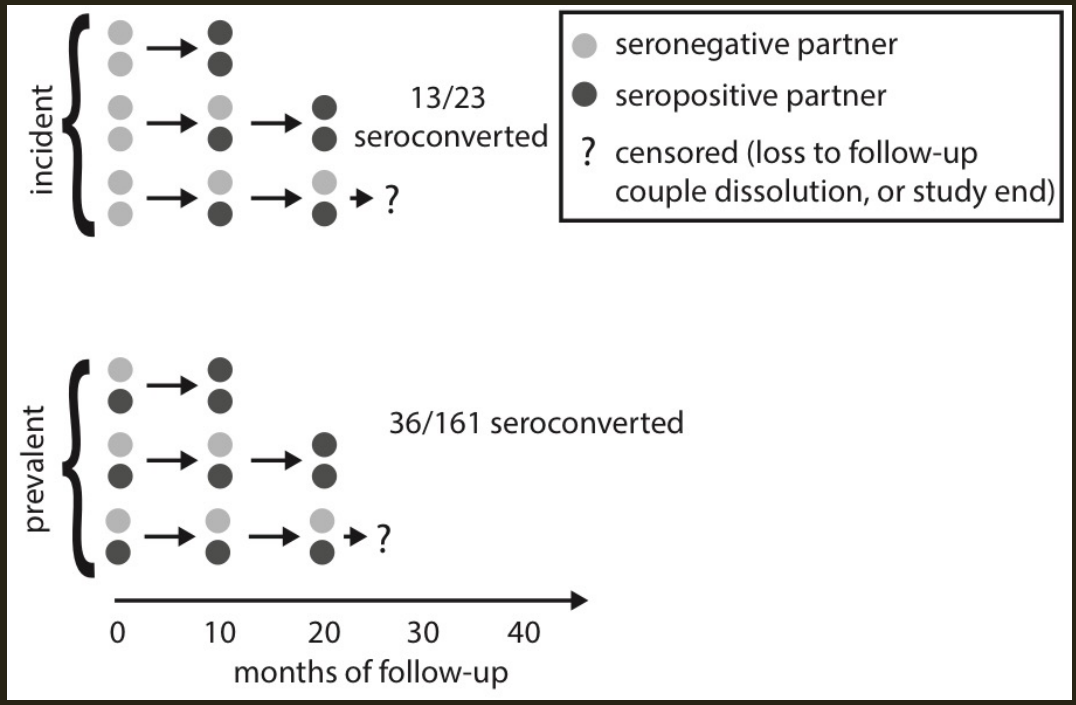
Heterogeneity in Transmission Rates

- Host genetics (e.g. CCR5)
- Circumcision
- Viral load of infected partner
- Viral genotype of infected partner
- Coital Rate
- Intercourse type (anal, dry, vaginal)
- Condom usage
- STIs
- Coinfections
- Nutrition

Bias 1: Unmodeled Heterogeneity

"Naïve" Couples.
Some are high risk

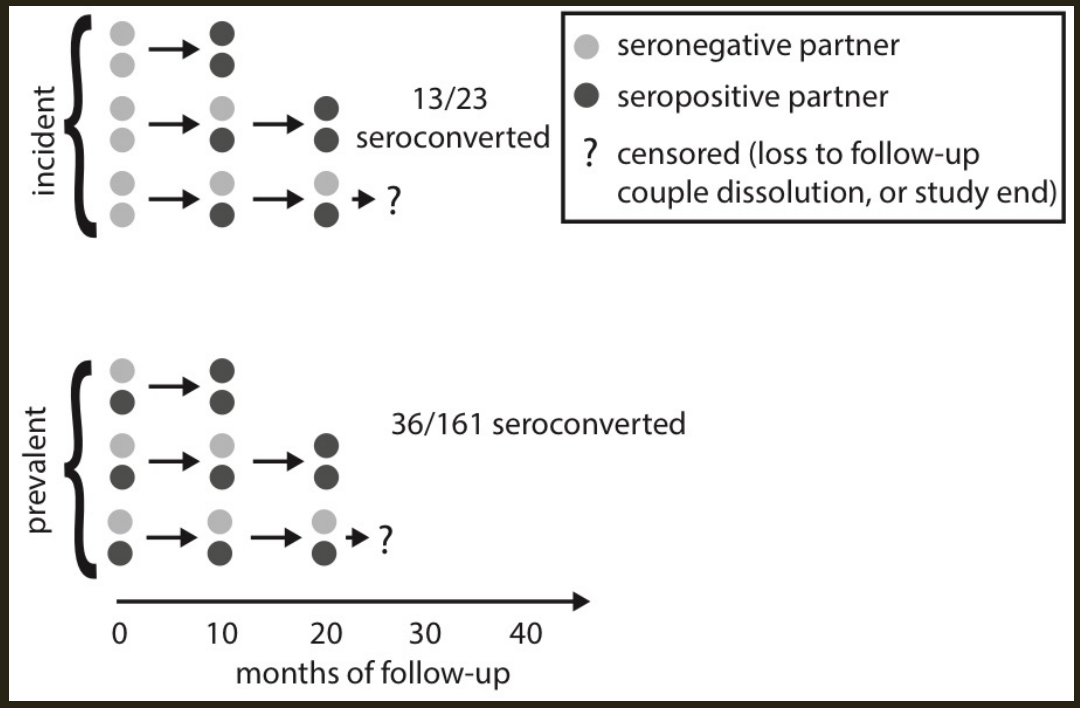
Persistently serodiscordant.
Selected to be low risk

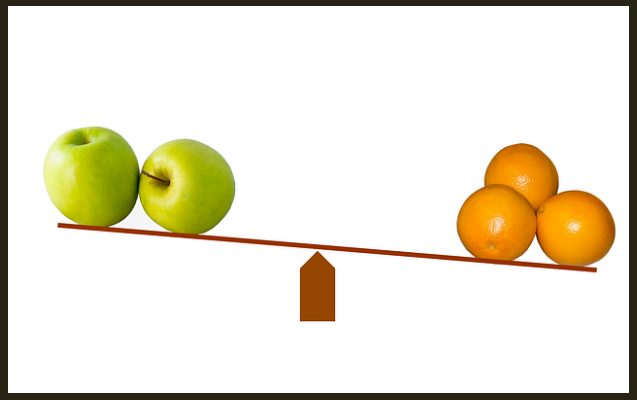


Bias 1: Unmodeled Heterogeneity

Average risk
acutely infected partners

Low risk
chronically infected partners

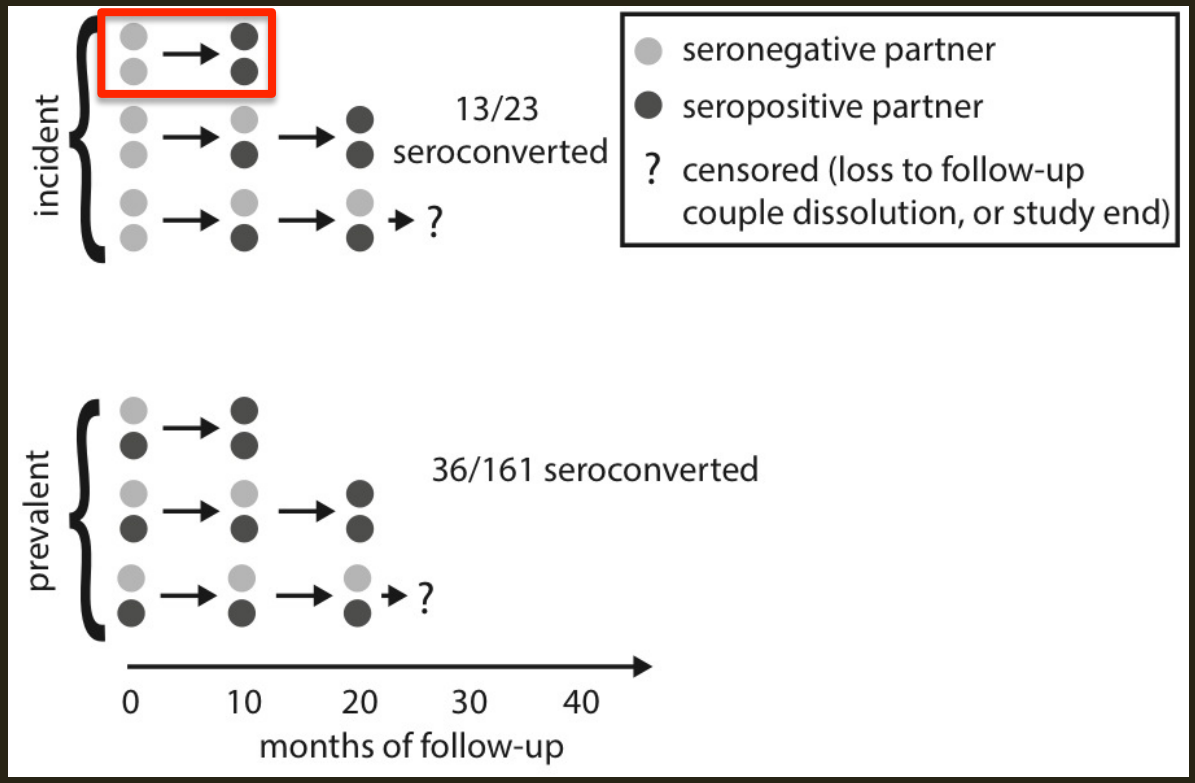




Unmodeled heterogeneity might bias EHM_{acute} upwards

Bias 2: Inclusion Criteria

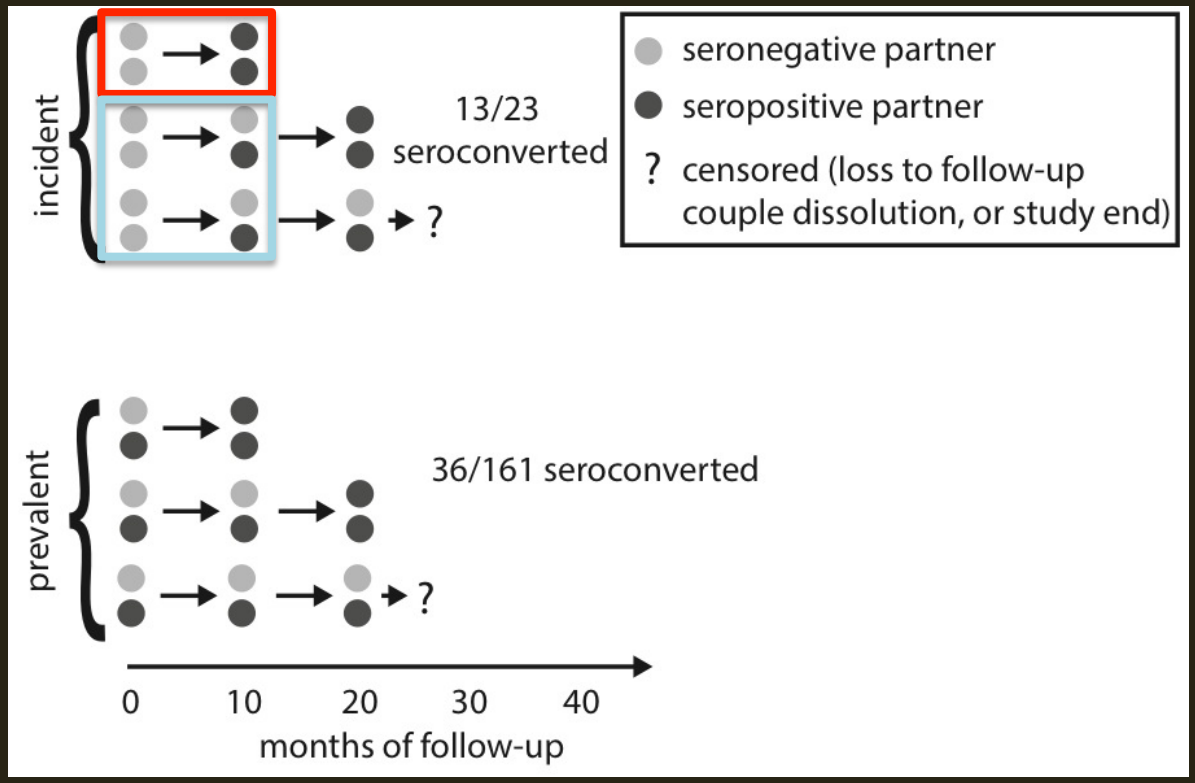
HIGH acute infectivity



Bias 2: Inclusion Criteria

HIGH acute infectivity

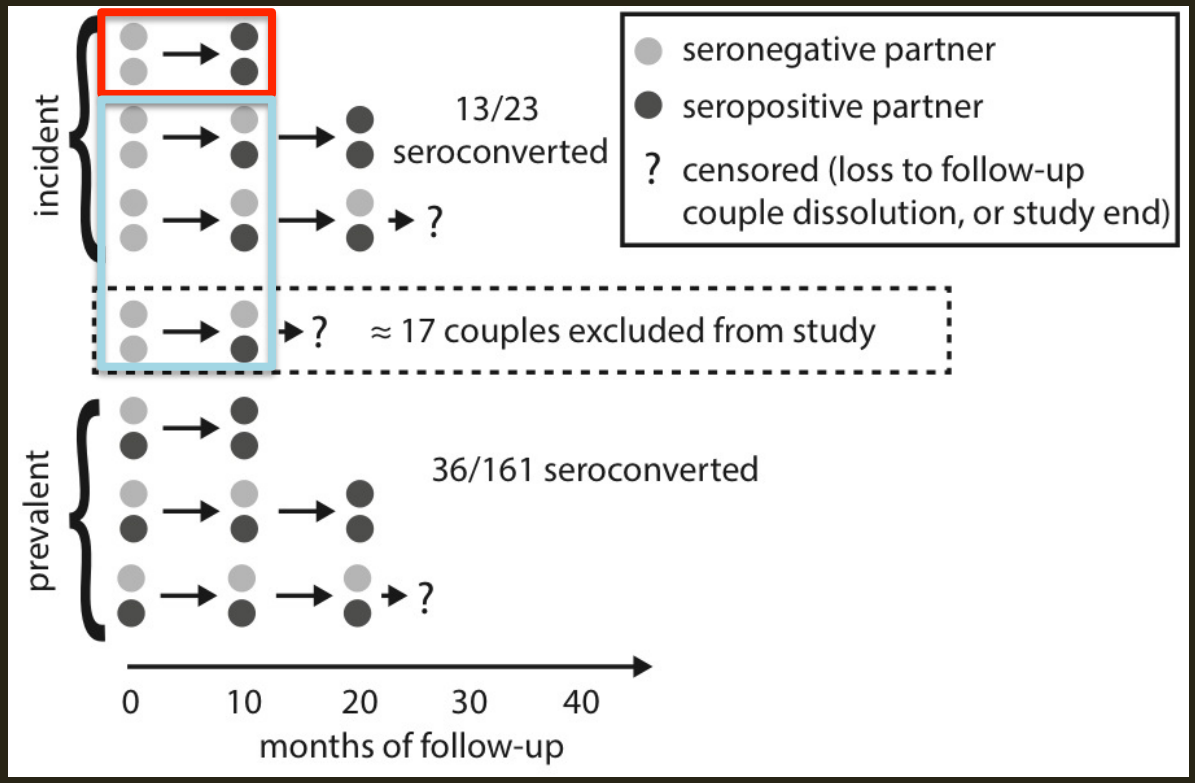
LOW acute infectivity



Bias 2: Inclusion Criteria

HIGH acute infectivity

LOW acute infectivity

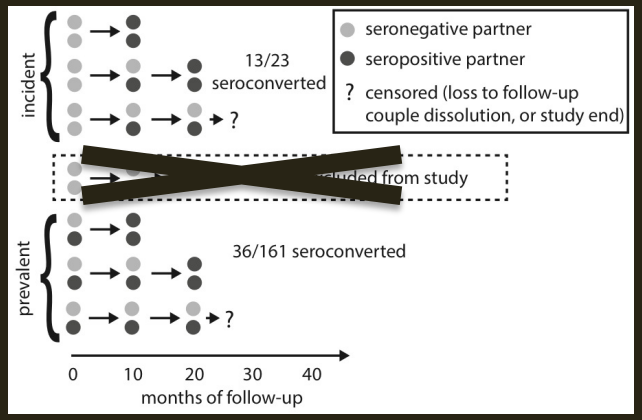


Accidentally excluded couples suggestive of low infectivity

Simulating Rakai Transmission & Observation

Input EHM_{acute}

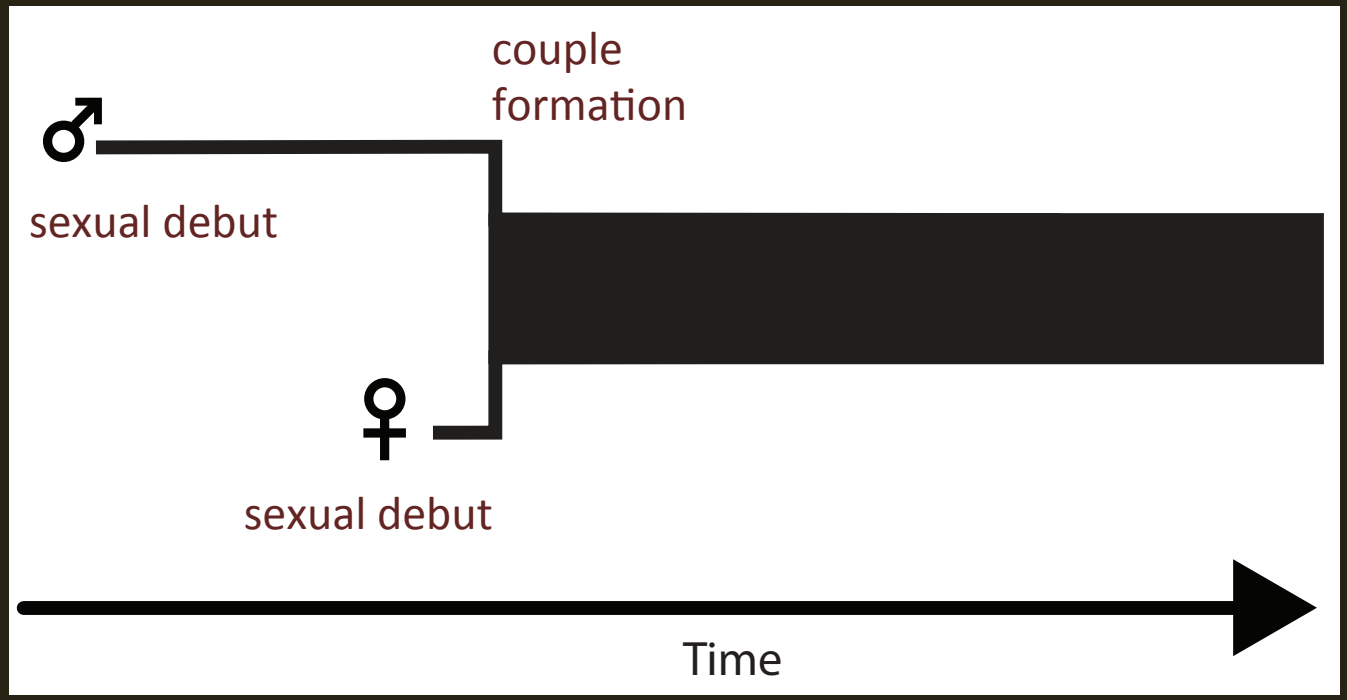
1. Simulate transmission in couples cohort
2. Replicate Rakai study design



3. Apply published analyses to simulated data.

Estimated EHM_{acute}

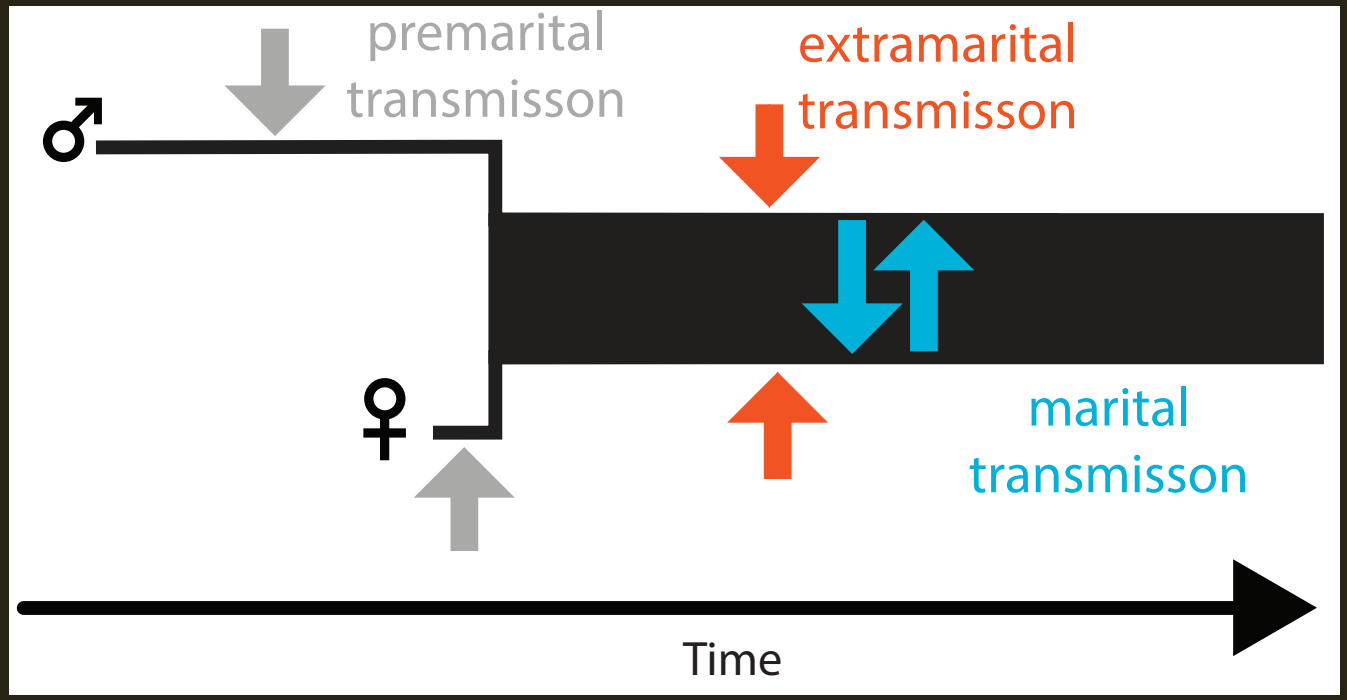
Couple Transmission Model



example relationship history

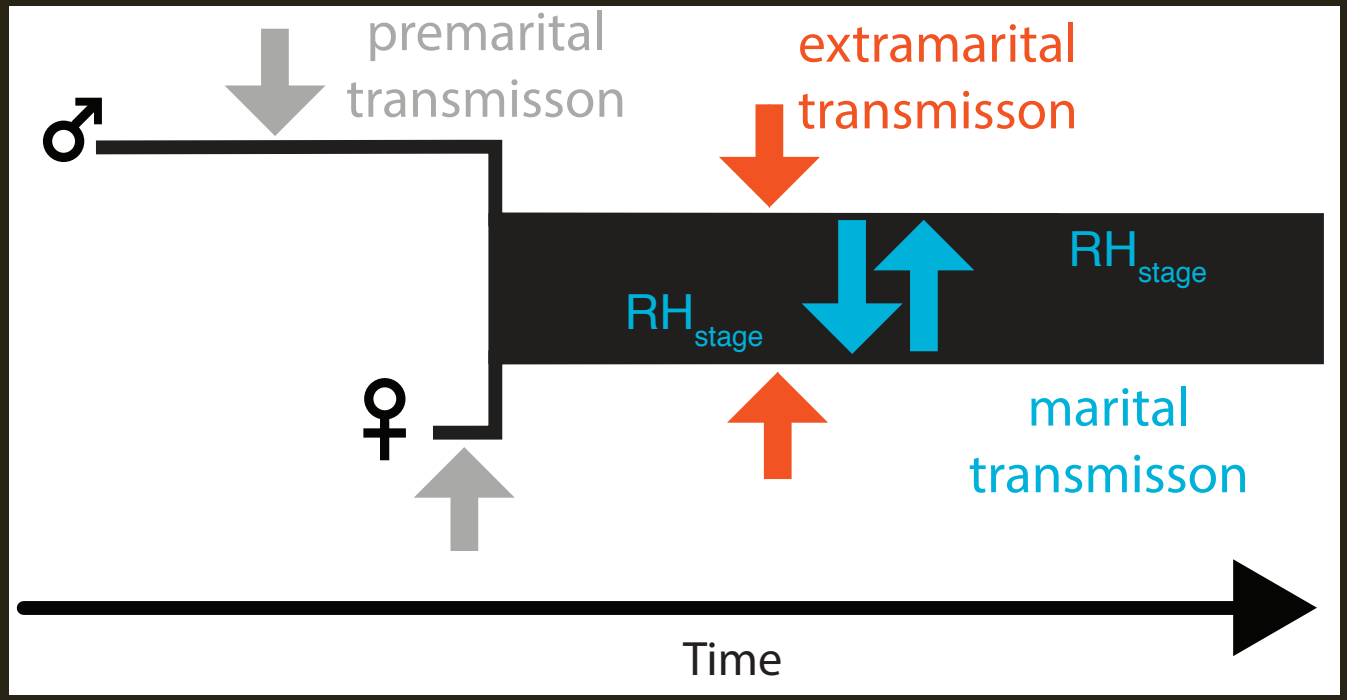
Bellan et al. (2013). *Lancet*.

Couple Transmission Model



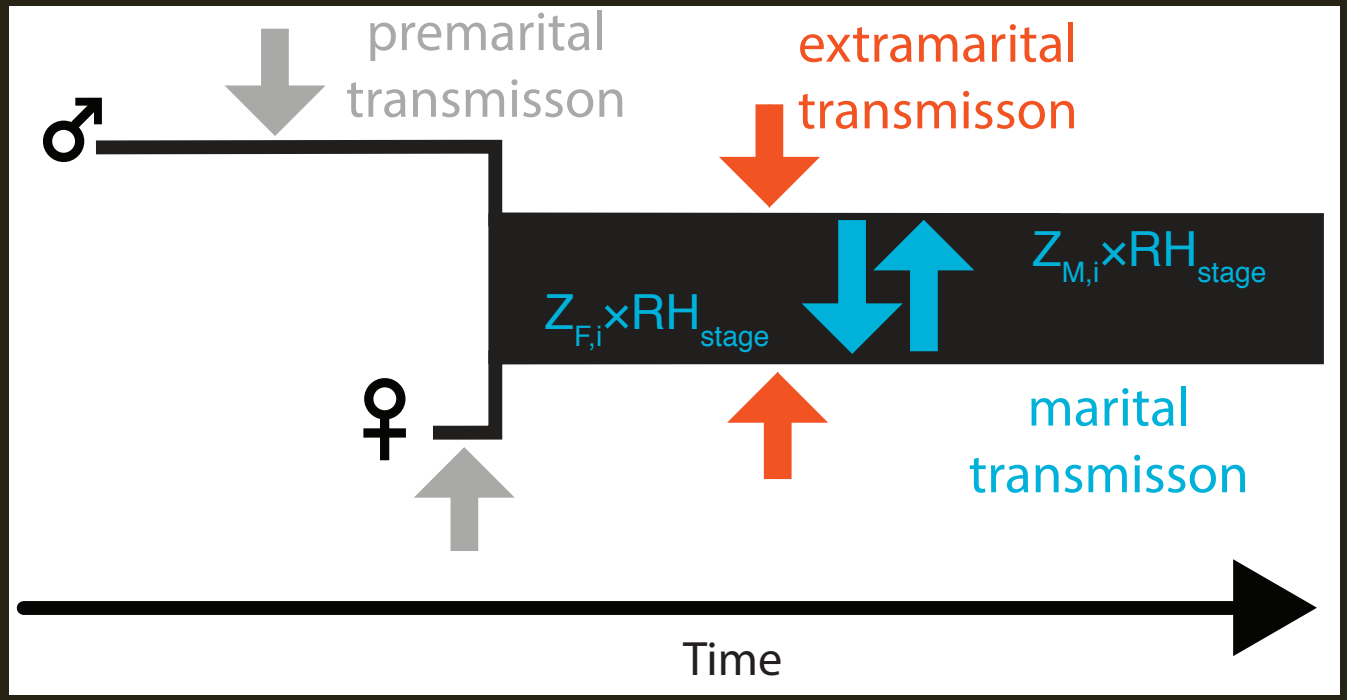
Bellan et al. (2013). *Lancet*.

Couple Transmission Model



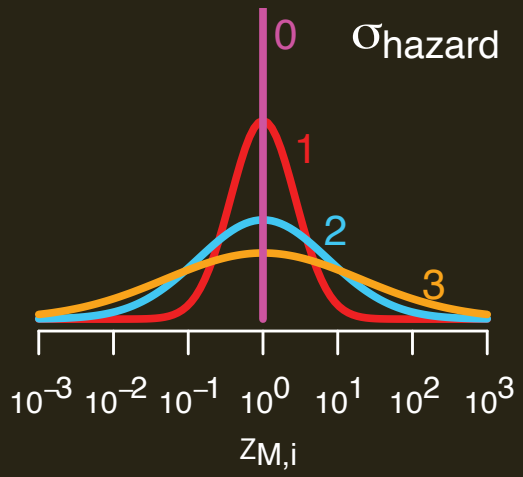
stage-dependent transmission

Couple Transmission Model



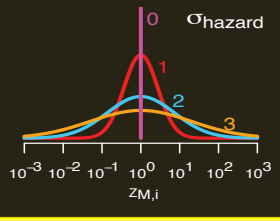
Heterogeneity

$$Z_{M,i} \sim \text{logNormal}(1, \sigma_{\text{hazard}})$$

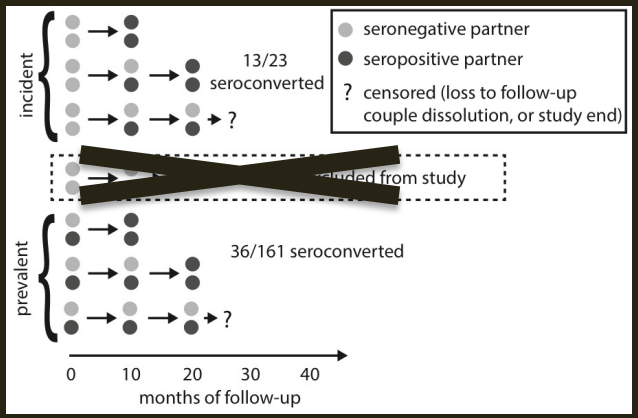


Simulating Rakai Transmission & Observation

Inputs



1. Simulate transmission in couples cohort
2. Replicate Rakai study design



3. Apply published analyses to simulated data.

Estimated EHM_{acute}

Simulating Rakai Transmission & Observation

Bias Analysis

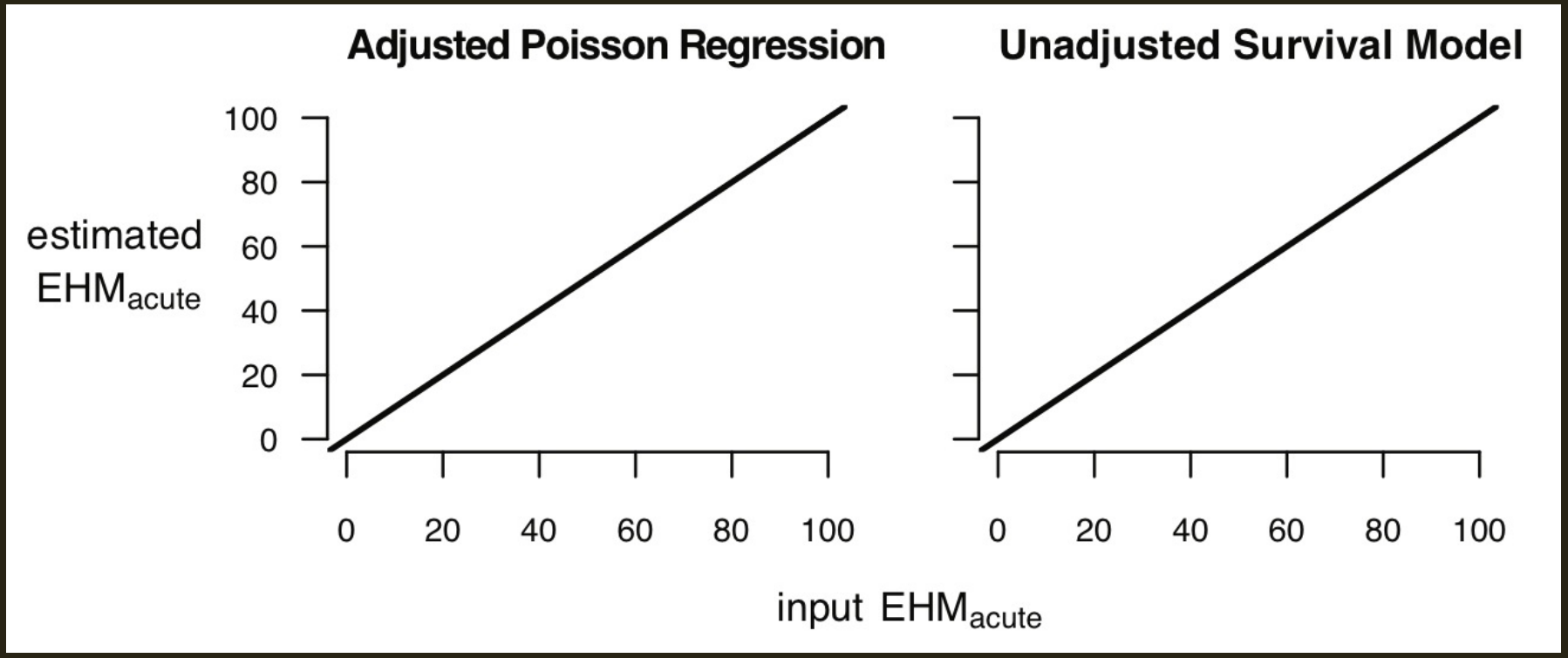
Estimates = Input Parameters ?

If not, what drives bias?

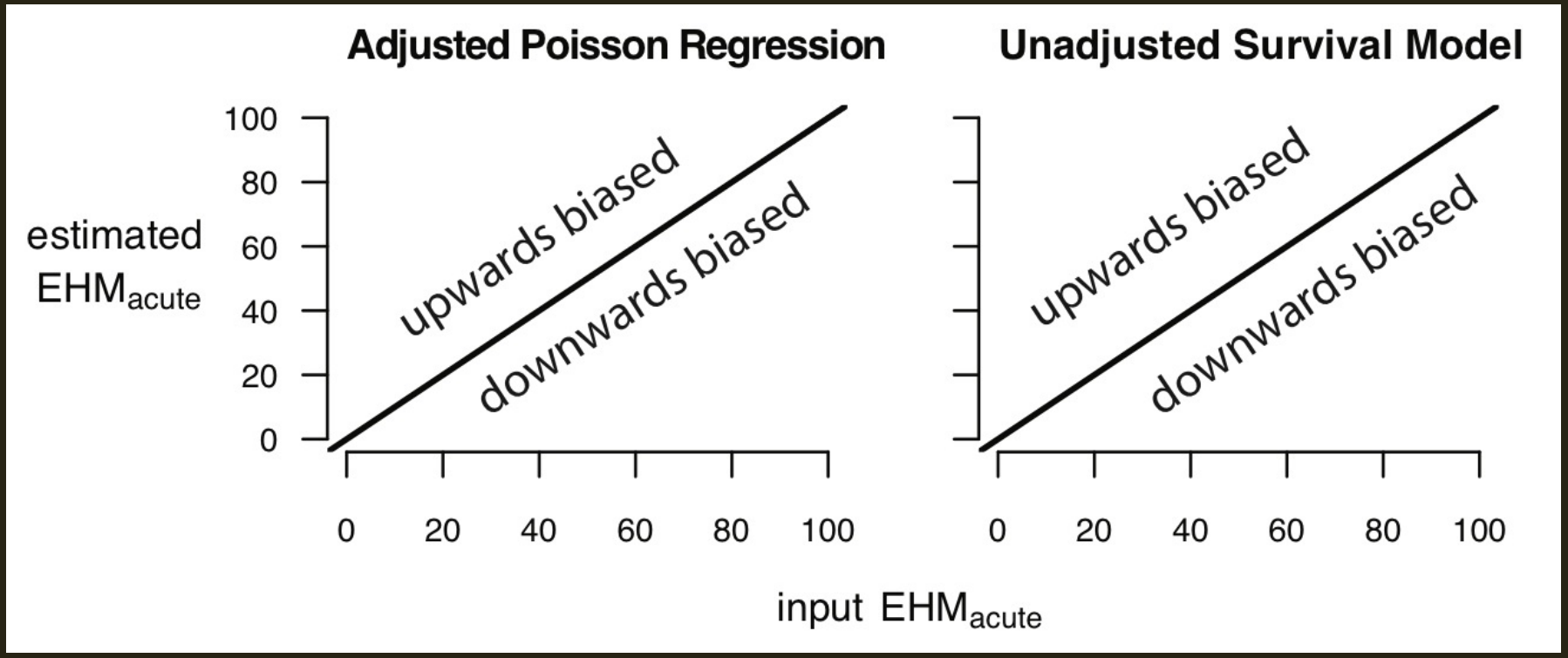
Estimation with ABC-SMC

What inputs generate data like the actual Rakai data?

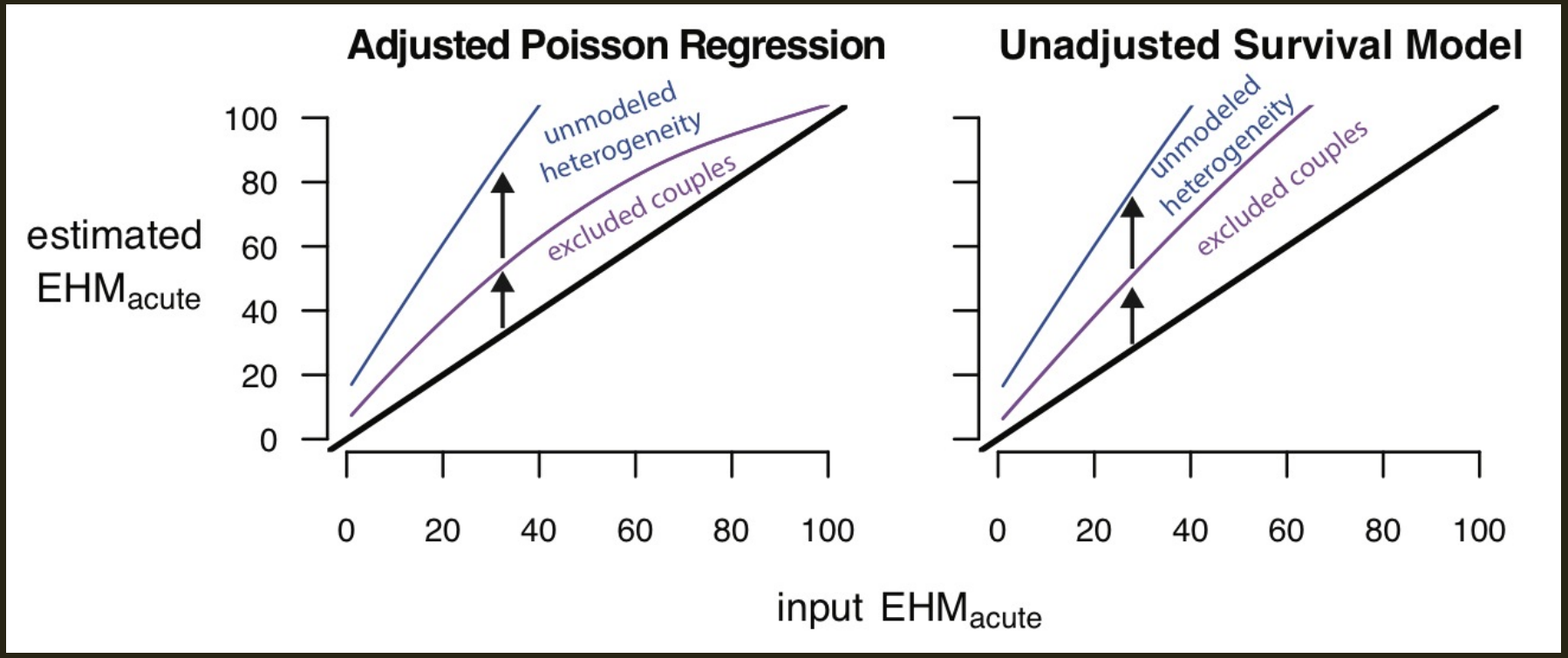
Bias Analysis



Bias Analysis



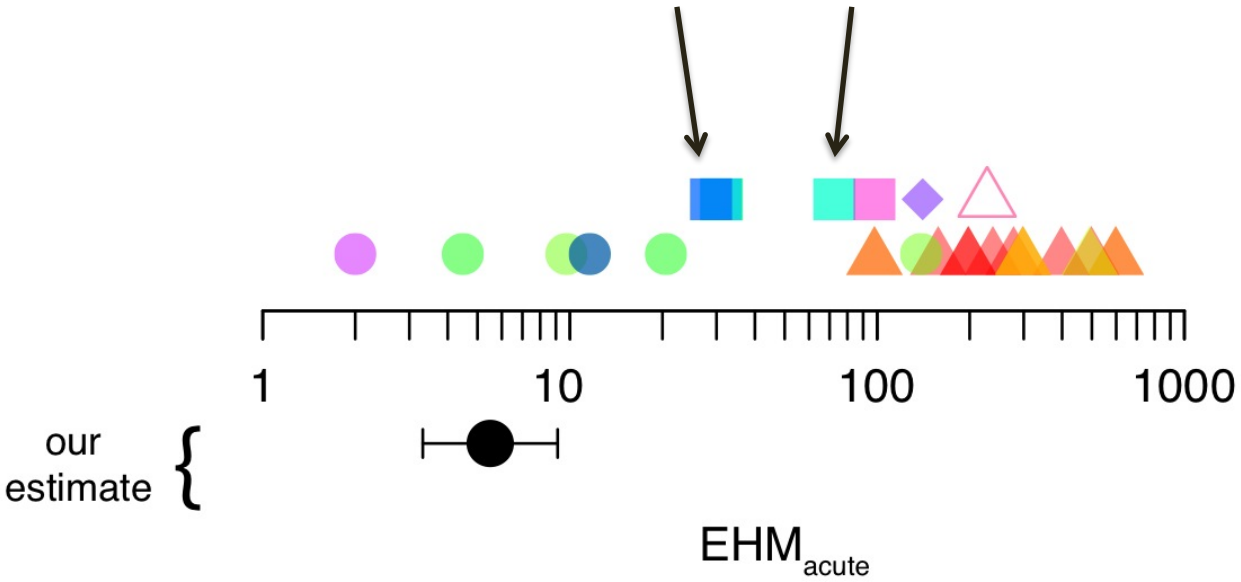
Bias Analysis



Variation in EHM_{acute} Estimates

Most commonly cited estimates

EHM_{acute} = 35 and 71



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based on
epidemic curve
viral load
Rakai
Rakai & epidemic curve
phylogenetics

Variation in EHM_{acute} Estimates

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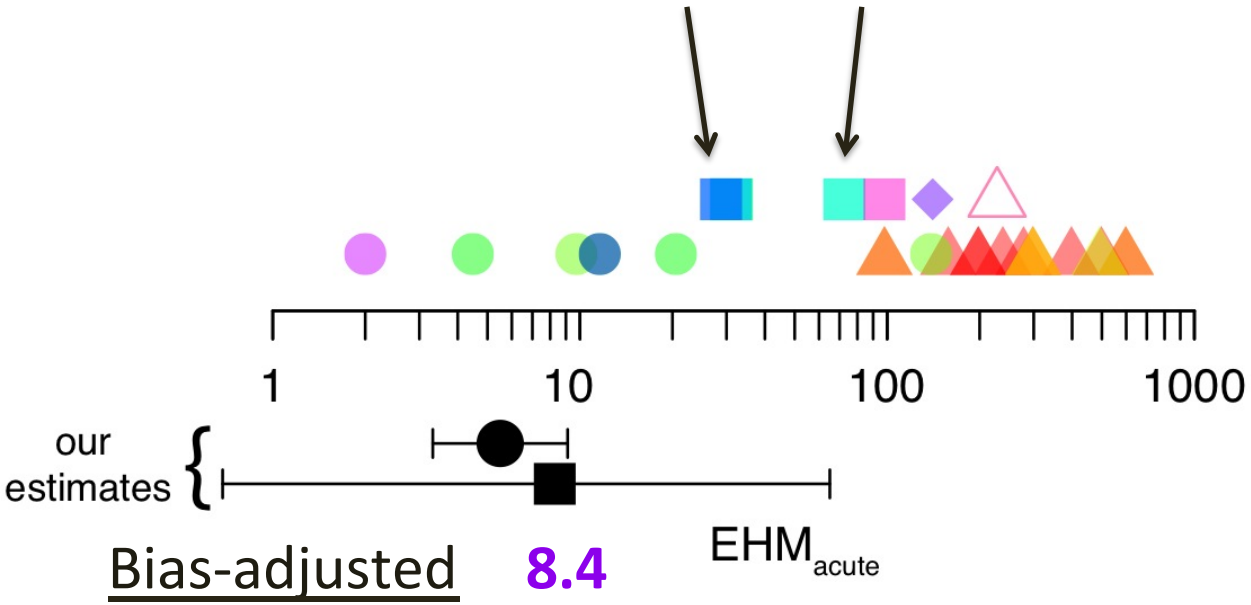

Bias-adjusted **8.4**

- (1) Jacquez et al. 1994
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- (4) Kretzschmar & Dietz 1998
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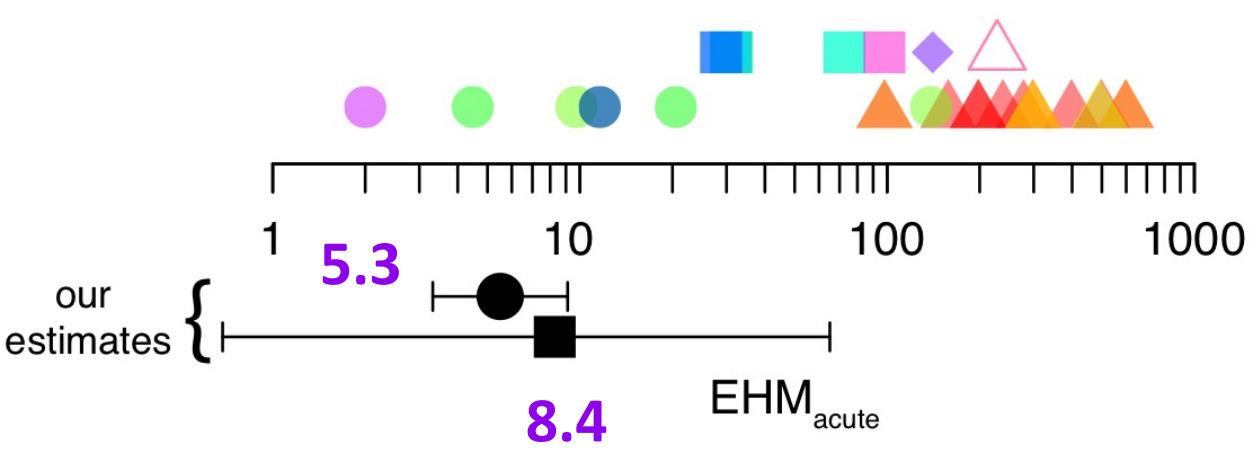
based on

- epidemic curve
- viral load
- Rakai
- Rakai & epidemic curve
- phylogenetics

Variation in EHM_{acute} Estimates

Viral load & Rakai estimates reconciled by adjusting for biases.



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based on

- epidemic curve
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- Rakai & epidemic curve
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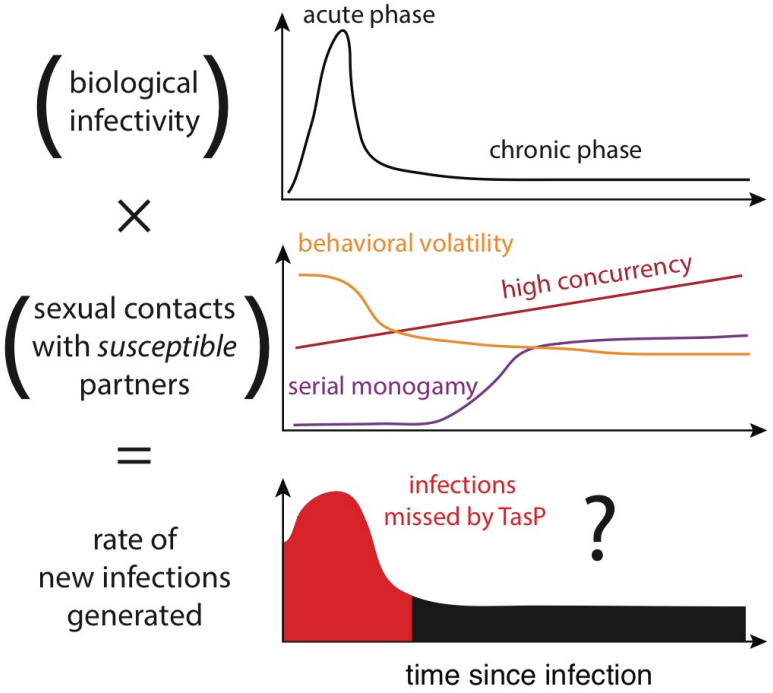
Early proportion of transmission AF_{early}?



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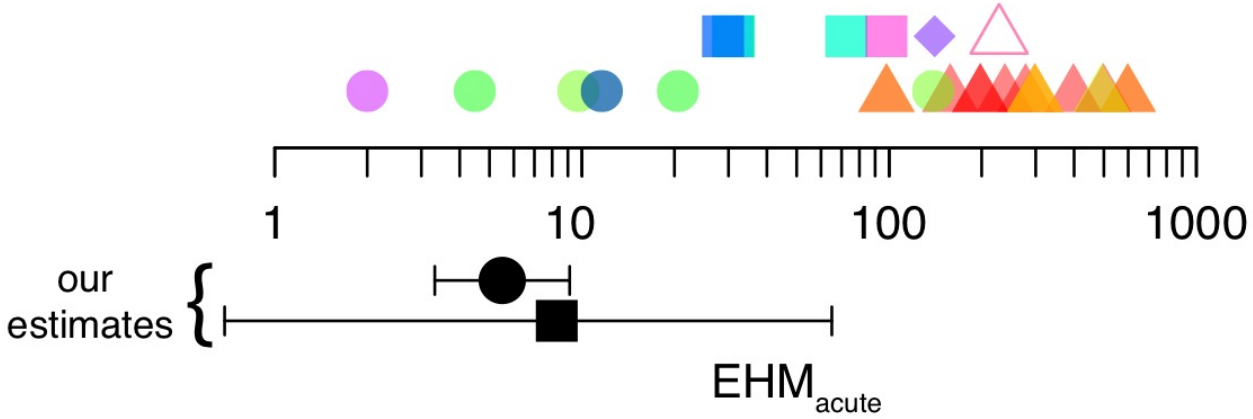
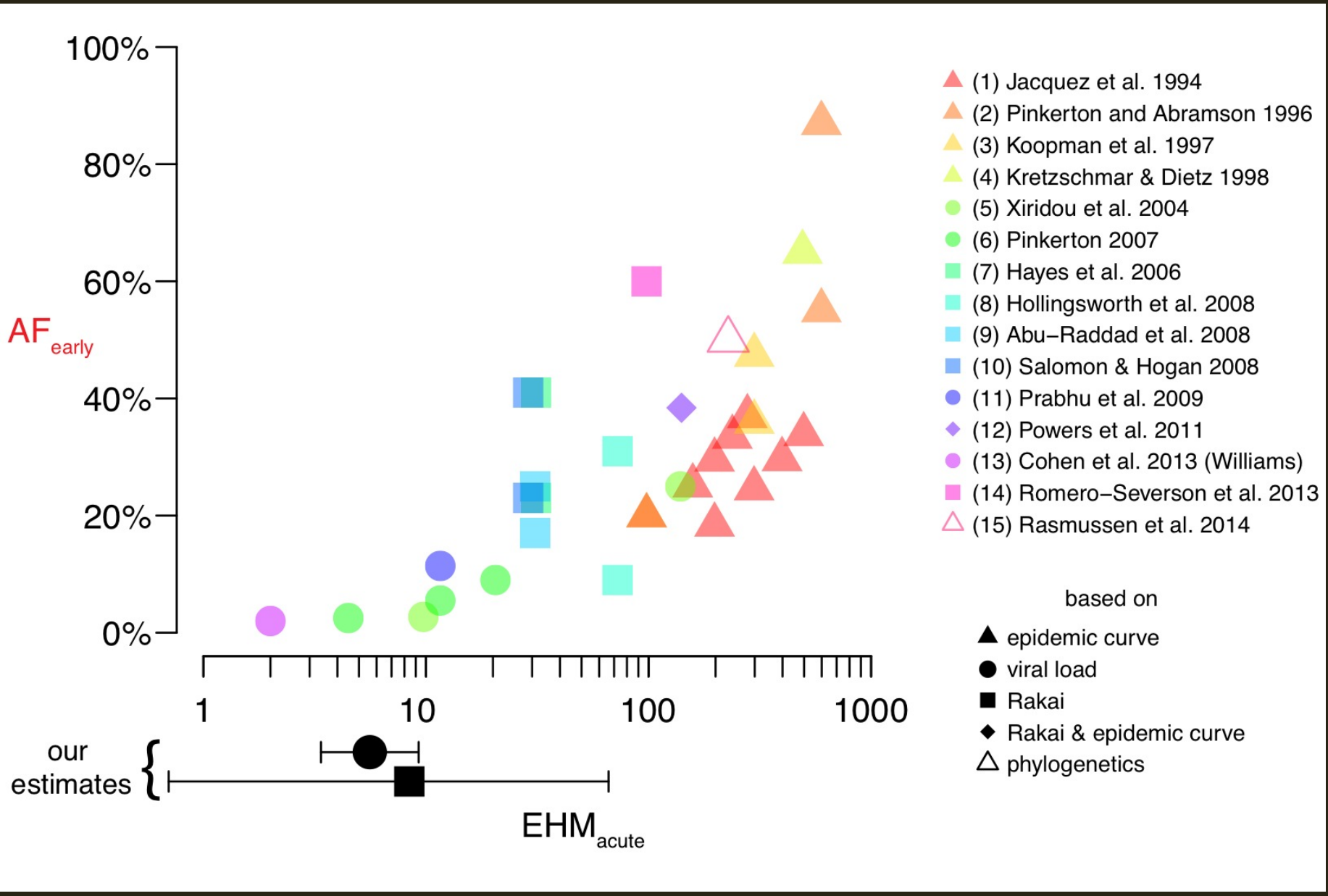


What about AF_{early}?



Conclusions

- Acute infectivity *not* significantly greater than expected by viral load-infectivity relationship

- Both EHM_{acute} estimates <<< previous estimates

- Role of early transmission likely overestimated
- Acute HIV less likely to undermine TasP

Simulation of study design & observation to identify biases

Statistical power and validity of Ebola vaccine trials in Sierra Leone: a simulation study of trial design and analysis

Steven E Bellan, Juliet R C Pulliam, Carl A B Pearson, David Champredon, Spencer J Fox, Laura Skrip, Alison P Galvani, Manoj Gambhir, Ben A Lopman, Travis C Porco, Lauren Ancel Meyers, Jonathan Dushoff

Published online April 15, 2015 http://dx.doi.org/10.1016/S1473-3099(15)70139-8

THE LANCET Infectious Diseases

- Simulation of transmission and study design/analysis
- Arose from GA Tech Modeling Conference in Jan 2015
- In collaboration with CDC (Lopman, Gambhir, Vaccine Team)
- Ethical & statistical merits of Stepped Wedge vs RCT
- EVD incidence declining & spatiotemporally variable

Acknowledgements

- Meyers Lab
- Kate Grabowski, Justin Lessler, Ron Gray, Brian Williams, Jim Hughes
- Mike Daniels, Juliet Pulliam, Molly Davies
- International Clinics on Infectious Disease Dynamics and Data (ICI3D)

Funders

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- NSF-NIH EID (1134964) and NSF RAPID to JRC Pulliam
- South African Centre for Epidemiological Modelling and Analysis (SACEMA)

Title: Reassessment of HIV-1 Acute Phase Infectivity

Attribution:

Bellan SE, Dushoff J, Galvani AP, Meyers LA (2015) Reassessment of HIV-1 Acute Phase Infectivity: Accounting for Heterogeneity and Study Design with Simulated Cohorts. PLOS Med: 1–28. doi:10.1086/429411.

Code: https://github.com/sbellan61/AcuteRetroSim

For further information or slides in Microsoft Powerpoint please contact Steve Bellan (steve.bellan@gmail.com).