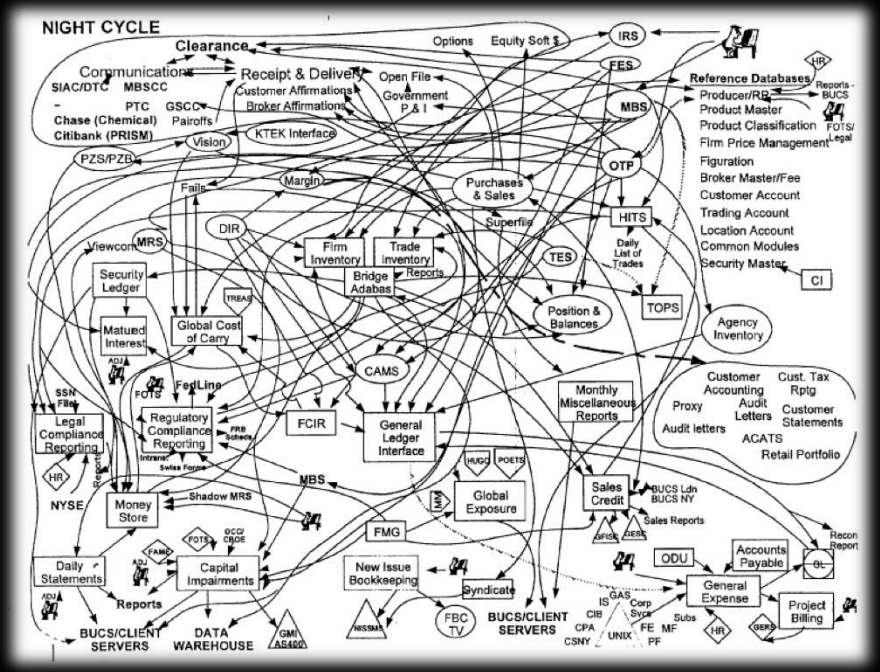
The Life Cycle of a Modeling Project: Estimating Acute HIV Infectivity



DAIDD

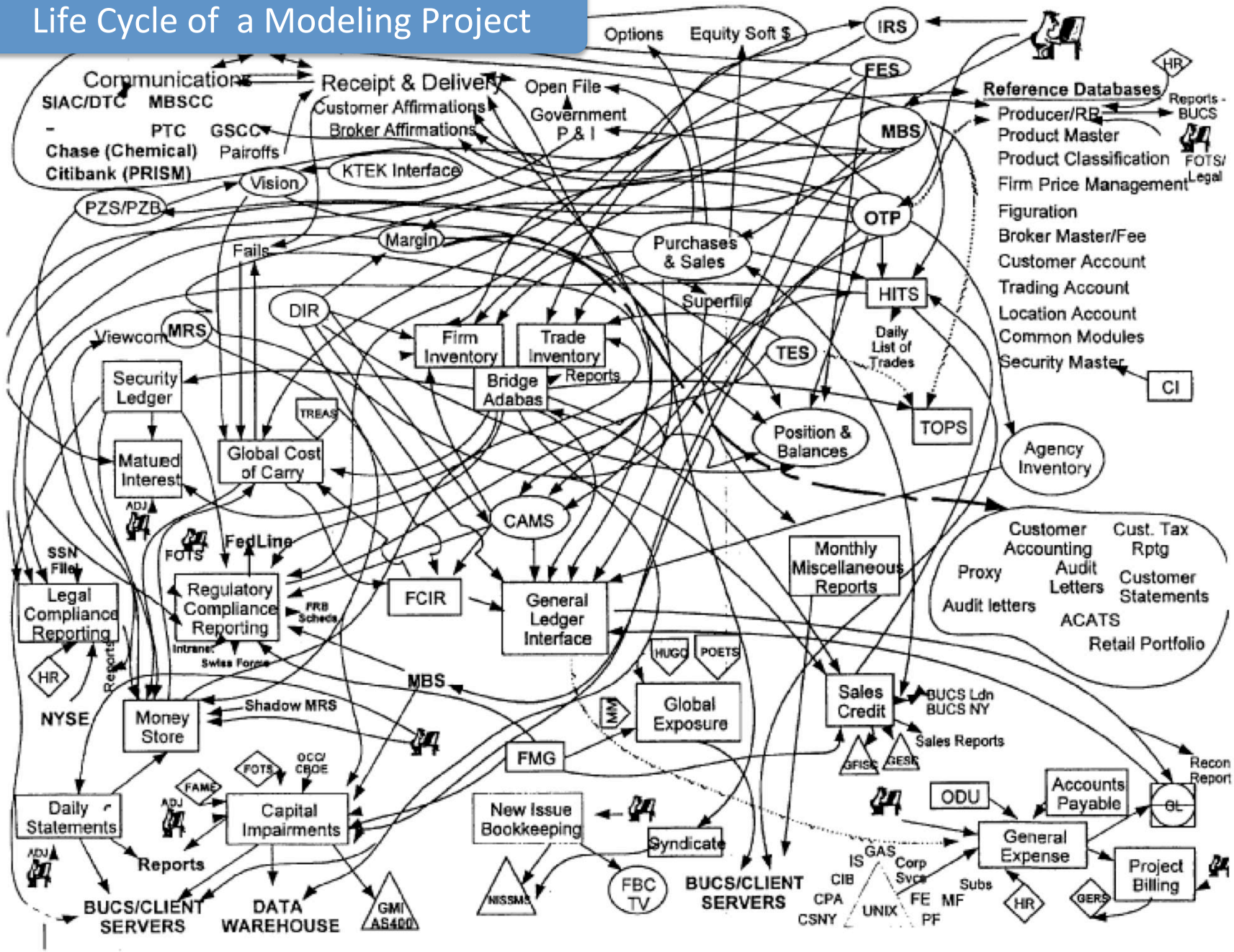
December 14, 2015

Steve Bellan, PhD, MPH

Center for Computational Biology and Bioinformatics

University of Texas at Austin

Life Cycle of a Modeling Project



Units of Science

- Publications
- Policy Reports
- Dissertations
- Presentations

Why publish?

- Communication
- Career
- Peer Review

How do modeling projects differ?

- Not always necessary collect empirical data
- Rely more heavily on literature reviews

Development of Study Concept

- What is your question?
- Why is it interesting?
- Who is interested?
- Can it be narrowed down to a question about specific quantitative relationships?

Review of Literature & Available Data

- Who has tried to answer this before and how did they do it?
  - Empirical studies
  - Modeling studies (perhaps different pathogen)
- What are these studies short-comings?
- Find useful parameter estimates or data sets

Construction of Modeling Framework

- What drawbacks of previous studies can I mitigate (if applicable)

- What modeling elements are necessary for my question?
  - Stochasticity, time step size, compartmental structure, complexity of contact modeling

Writing the Model & Producing Output

- What are the 1-3 graphical outputs that will display the answer(s) to my question?
- Coding & debugging & commenting
- Simulation to verify methods & debug
- Write your methods at this stage!

Model Validation & Robustness

- Sensitivity analyses
- Model validation

  Out-of-sample prediction

  Outputs match patterns that weren't inputs

- Comparison to alternative models

Choose the Journal

- Journal scope statement (on their website)
- Audience
- How mathematical will your article be?
- Text, figure, table limits

Write-Up of Results, Intro/Discussion

- State assumptions clearly
- Critique your own work

PLOS | MEDICINE

RESEARCH ARTICLE

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

Steve E. Bellan[1*], Jonathan Dushoff[2], Alison P. Galvani[3,4], Lauren Ancel Meyers[5,6]

PLOS Medicine | DOI:10.1371/journal.pmed.1001801 March 17, 2015

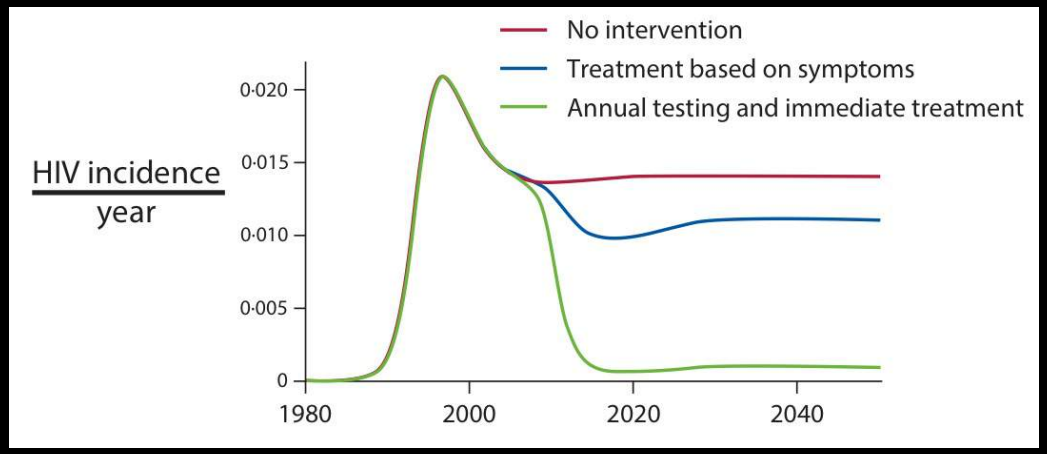
Lauren Meyers
UT Austin

Jonathan Dushoff
McMaster University

Alison Galvani
Yale University

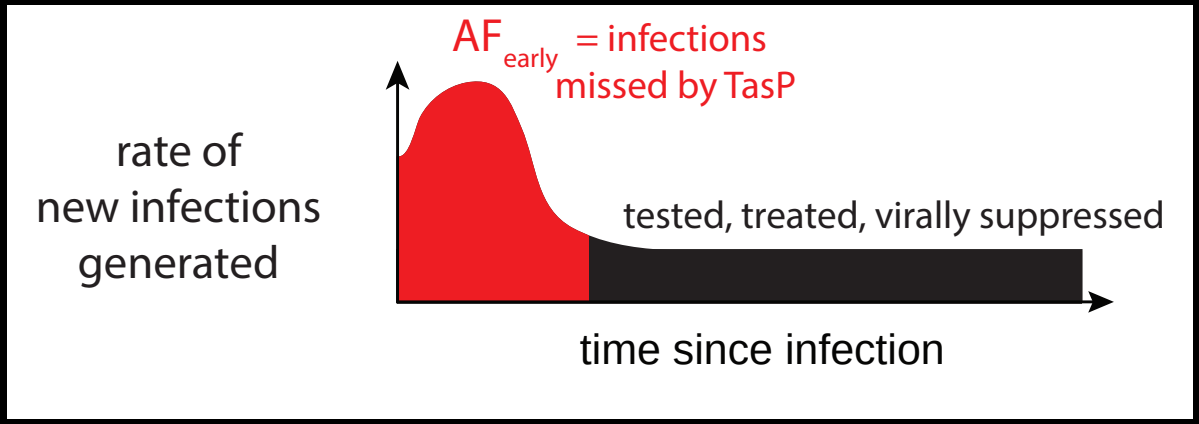
Treatment as Prevention (TasP)

Treatment reduces infectiousness 96%



Cohen et al. (2011). *NEJM*
Granich et al. (2009). *Lancet*.

Early transmission is unblockable by TasP



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

Acute HIV-1 Infection

Myron S. Cohen, M.D., George M. Shaw, M.D., Ph.D.,
Andrew J. McMichael, M.B., B.Ch., Ph.D., and Barton F. Haynes, M.D.

The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study

Kimberly A Powers, Azra C Ghani, William C Miller, Irving F Hoffman, Audrey E Pettifor, Gift Kamanga, Francis E A Martinson, Myron S Cohen

Lancet

OPEN ACCESS Freely available online

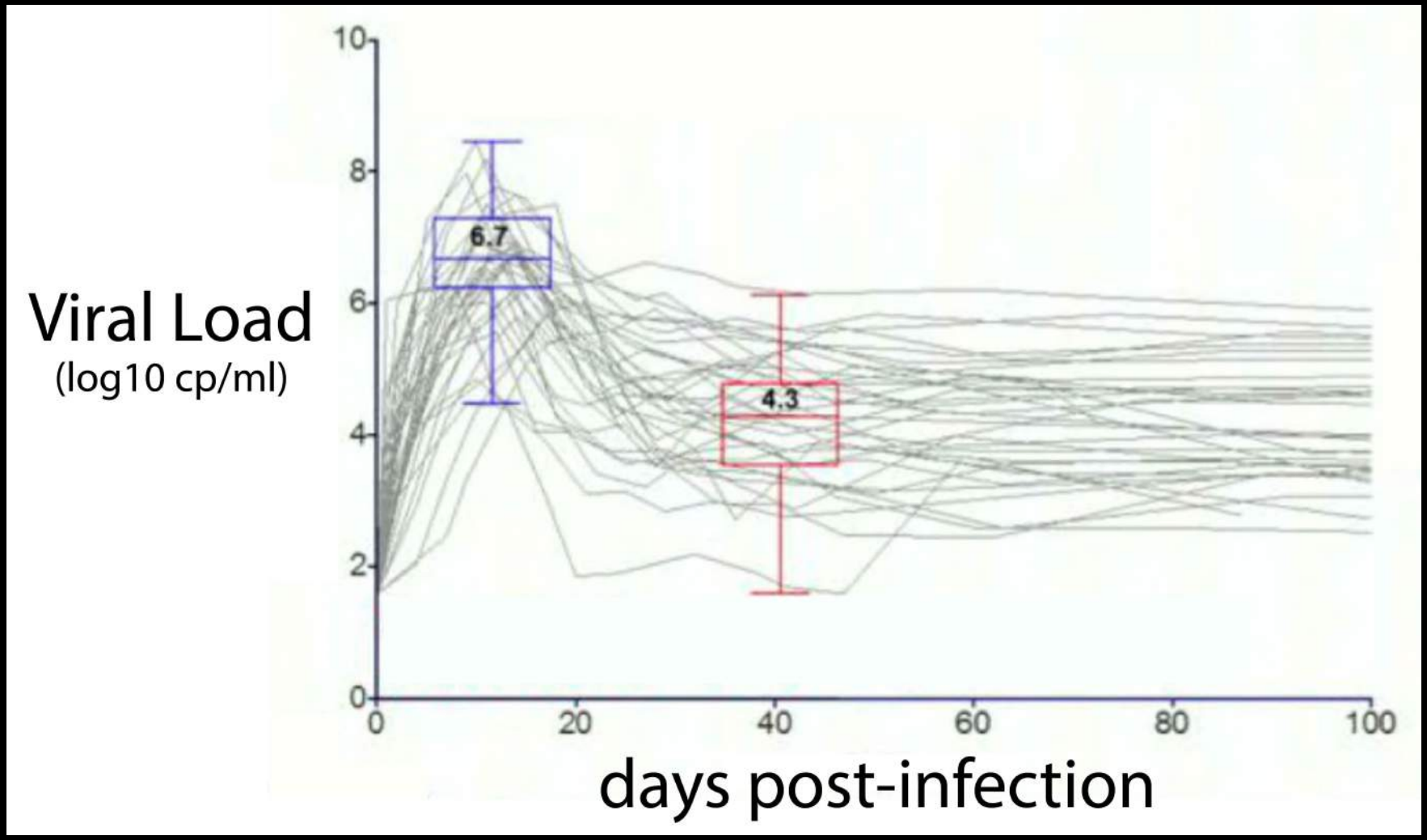
PLoS MEDICINE

Review

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

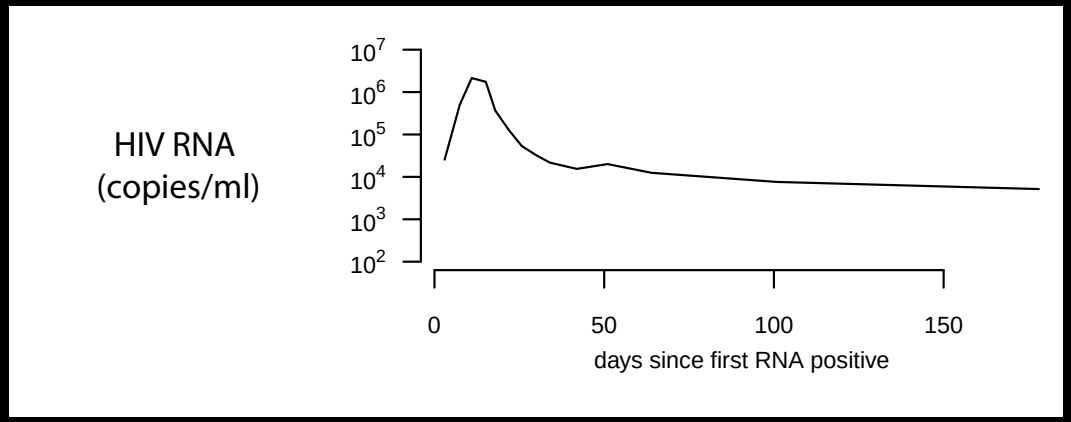
Myron S. Cohen[1,2,3¶], Christopher Dye[4¶], Christophe Fraser[5¶*], William C. Miller[2,3¶], Kimberly A. Powers[2,3¶*], Brian G. Williams[6¶*]

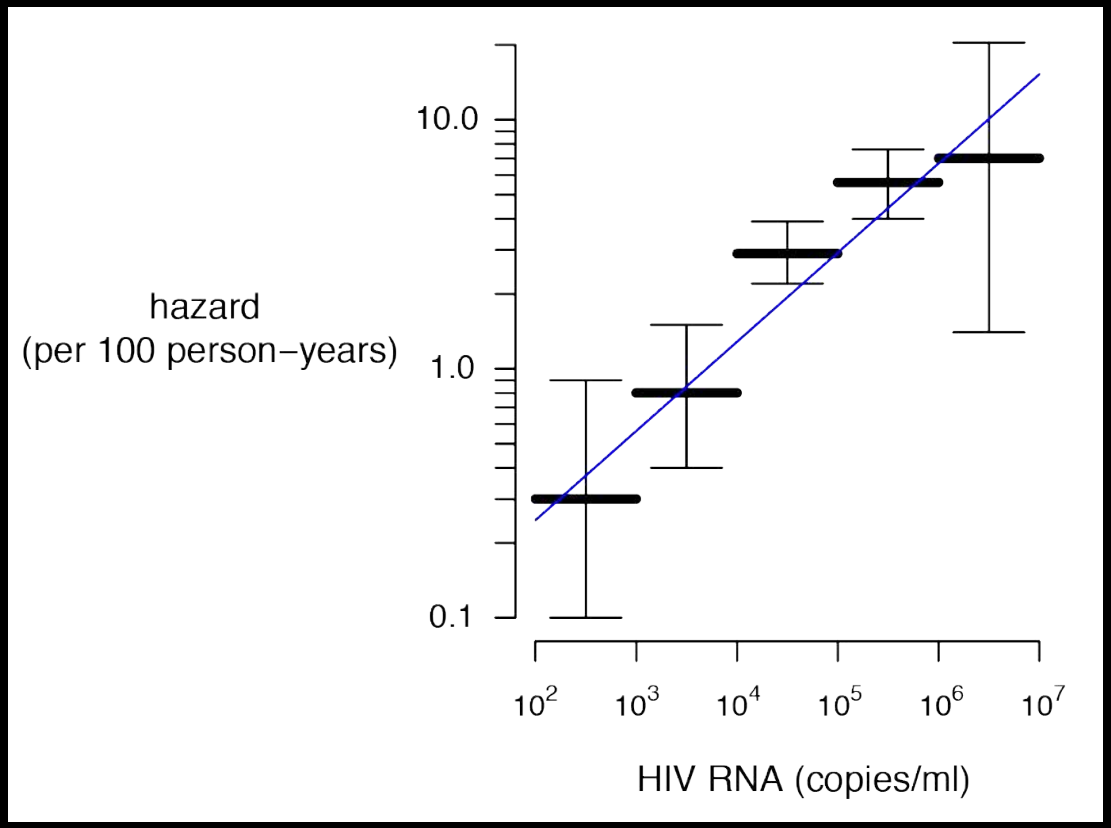
Let’s take the average viral load trajectory



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

Early Transmission

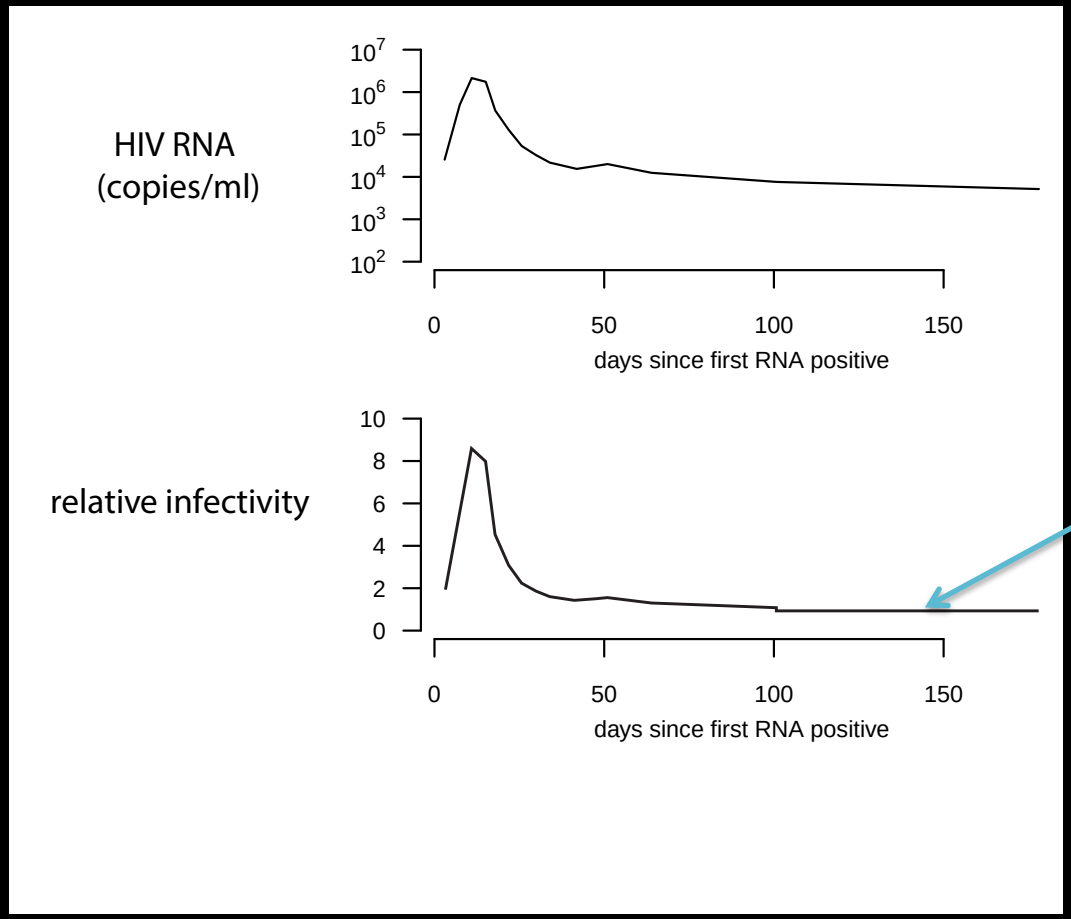




2.5-fold increase in infectivity

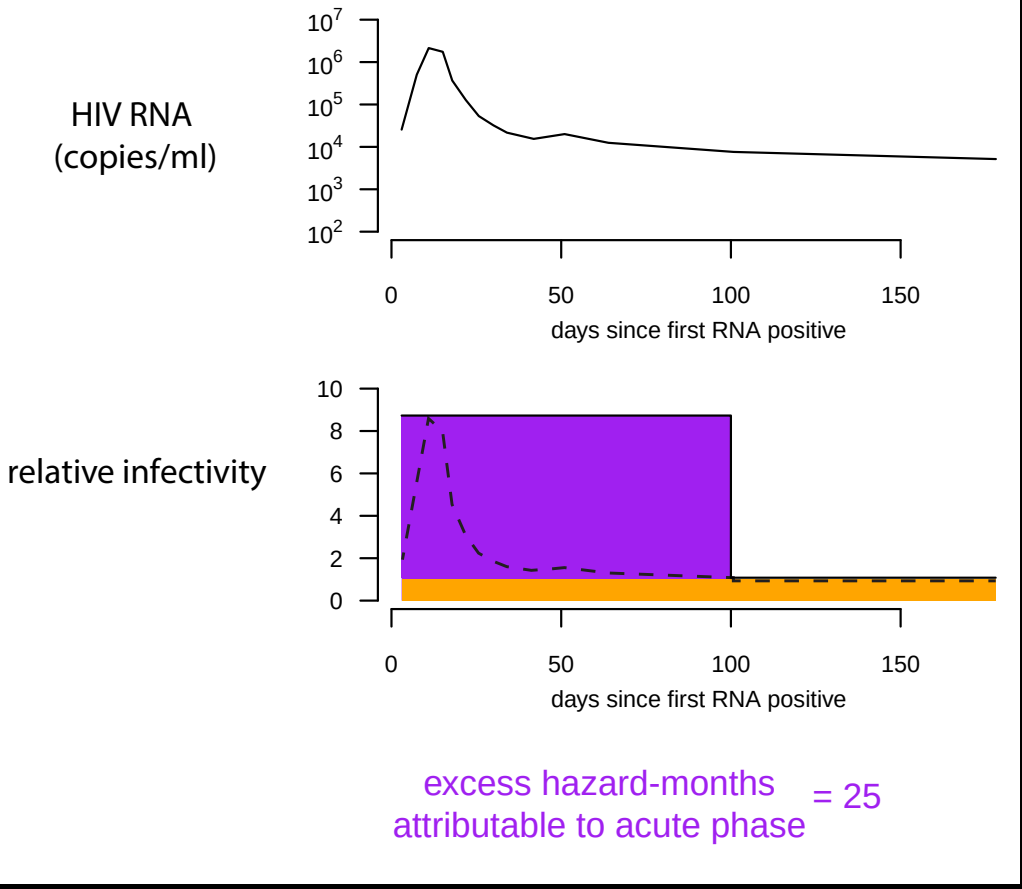
10-fold increase in viral load

Early Transmission



HIV not efficiently transmitted:
~1/300 risk per heterosexual sex act during chronic phase

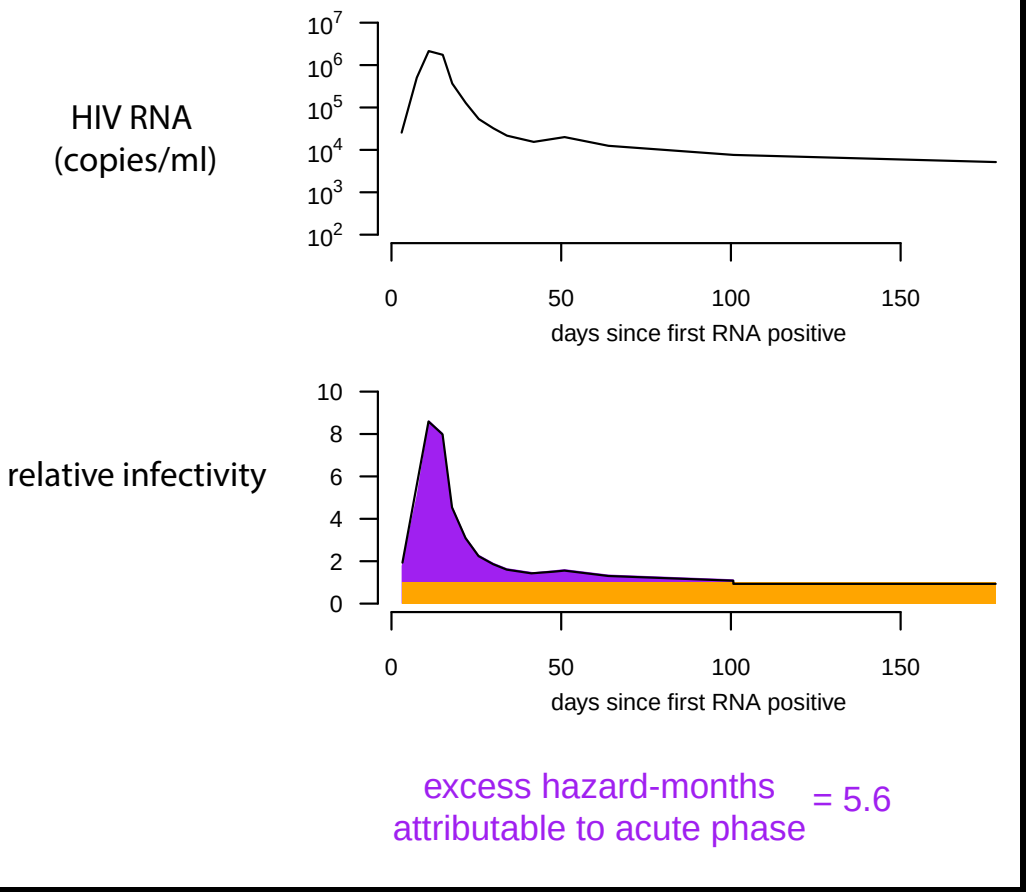
Early Transmission



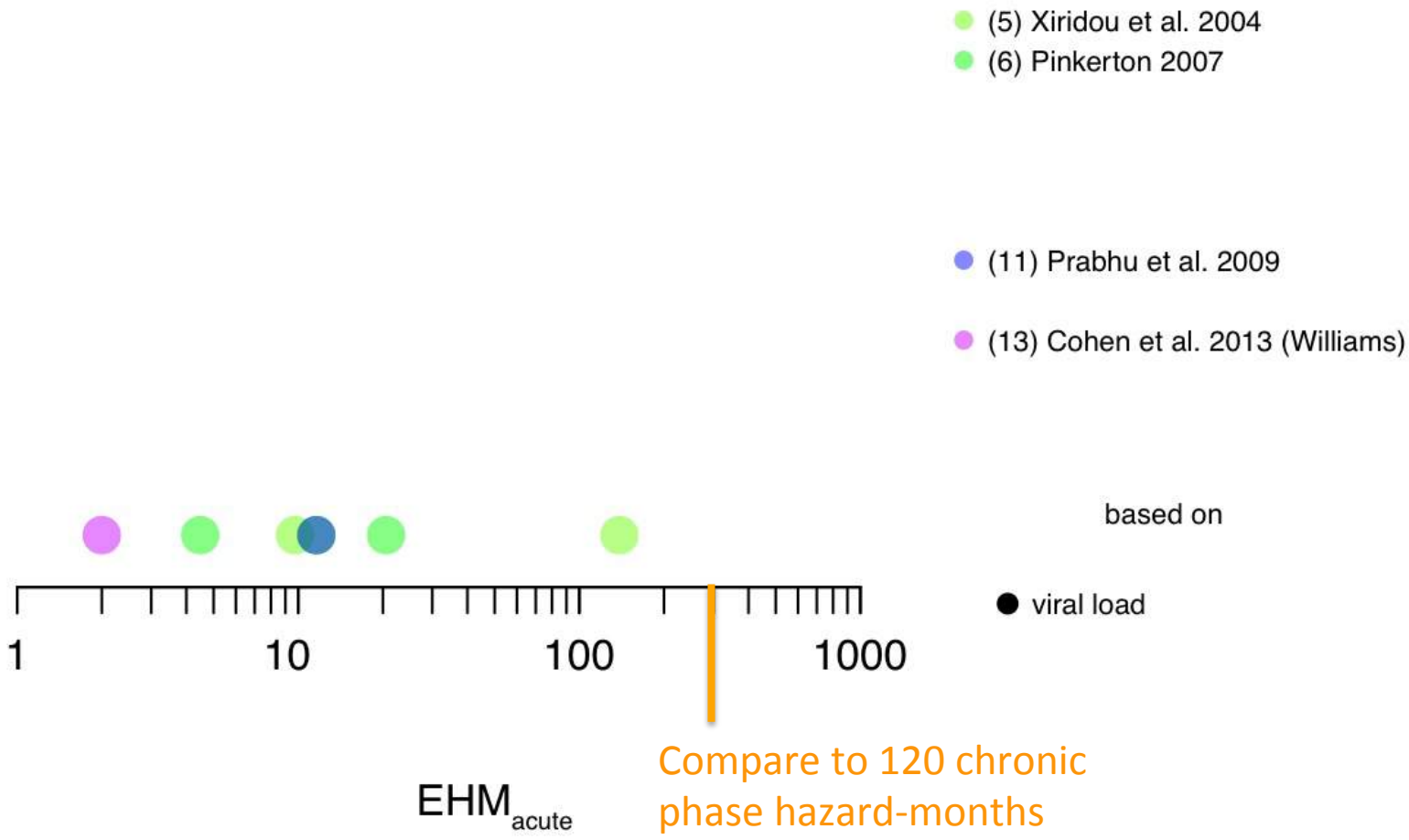
9x as infectious for 3 months

Compare EHM_{acute} to 120 months of total infection

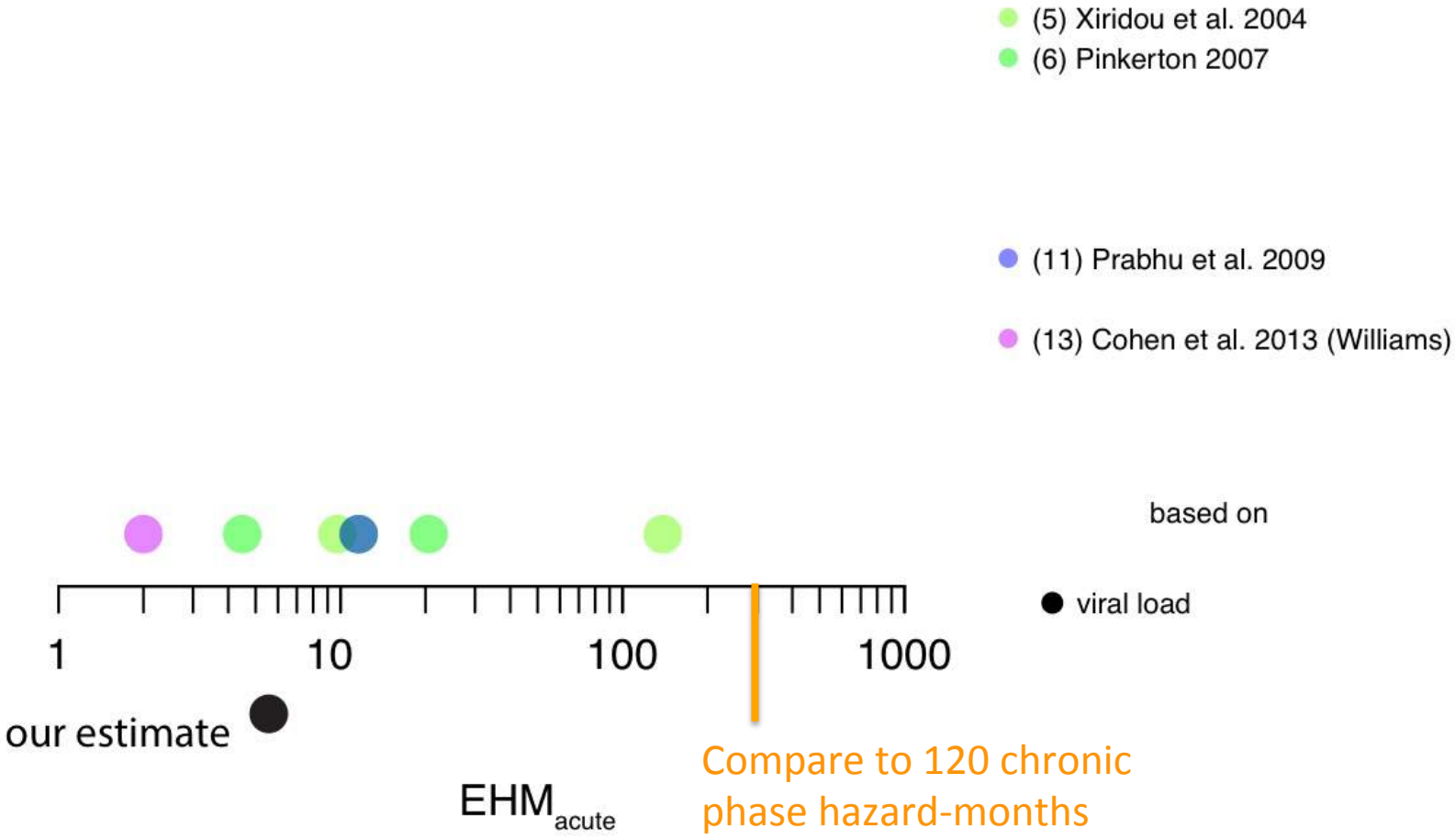
Early Transmission



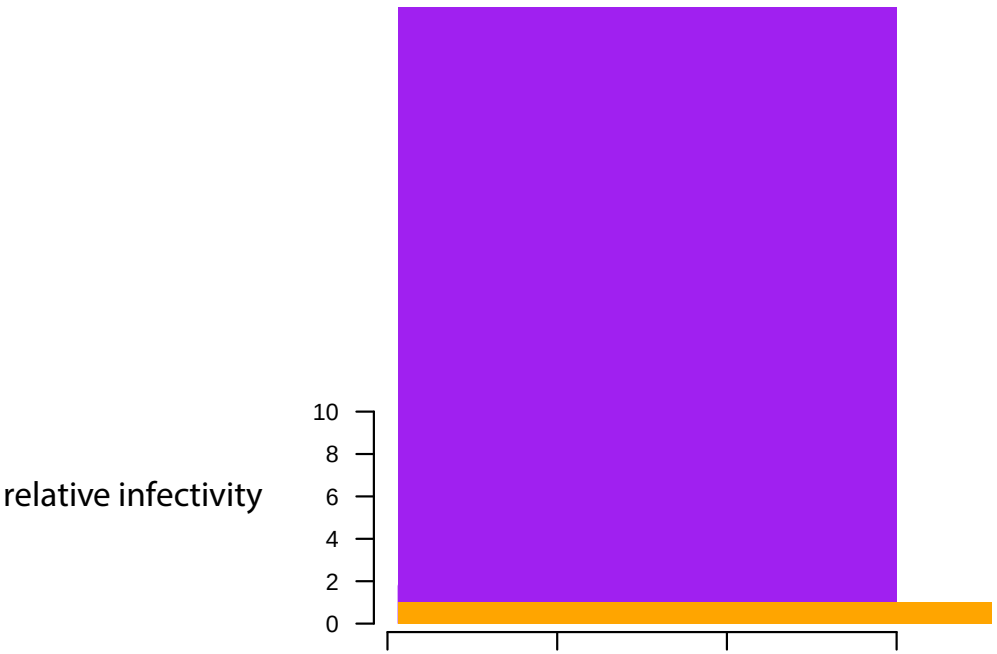
Variation in EHM_{acute} Estimates



Variation in EHM_{acute} Estimates



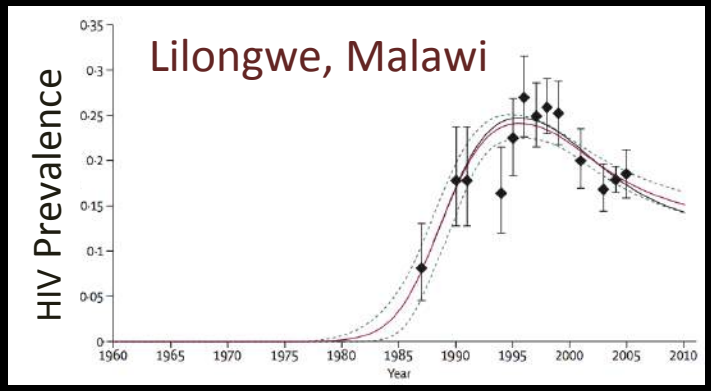
Early Transmission



EHM_{acute} = 100-500

Fast early epidemic growth:

evidence for high acute infectivity???

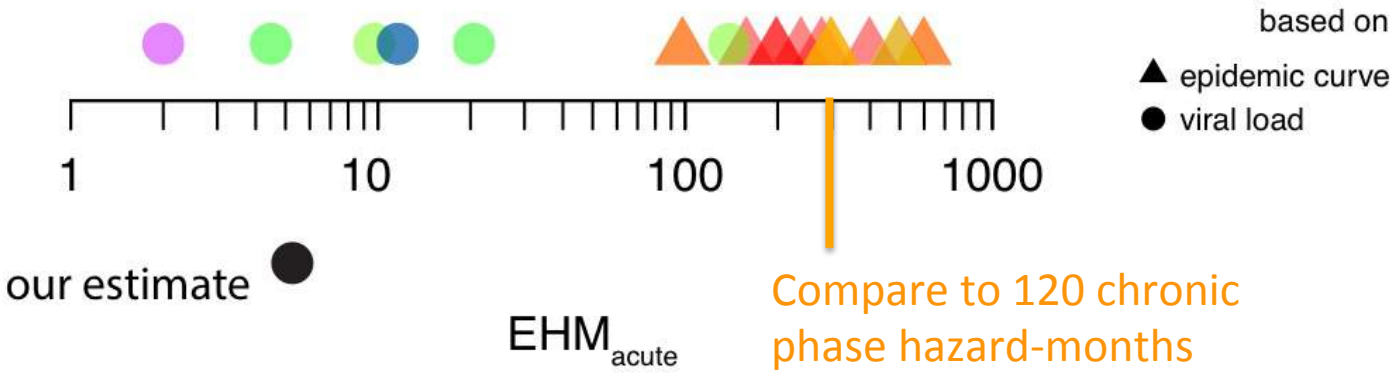


Powers et al. (2011). *Lancet*.

Variation in EHM_{acute} Estimates

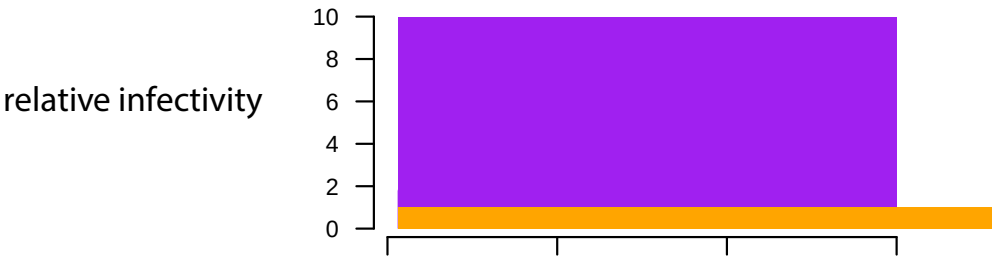
Believe estimates based on viral loads or on epidemic growth???

- (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)



Compare to 120 chronic phase hazard-months

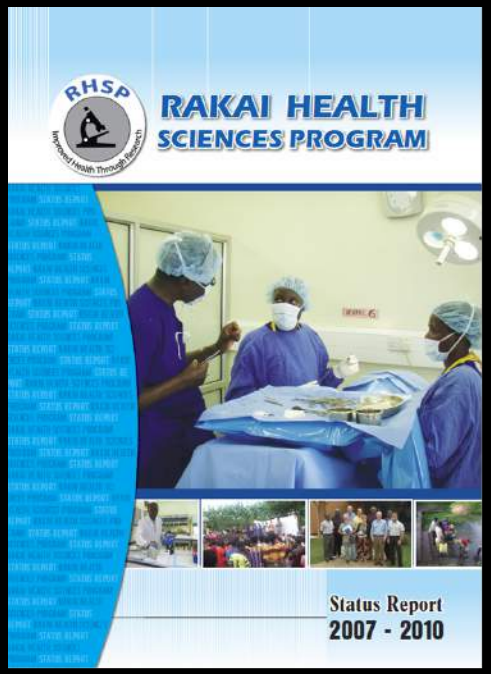
Early Transmission



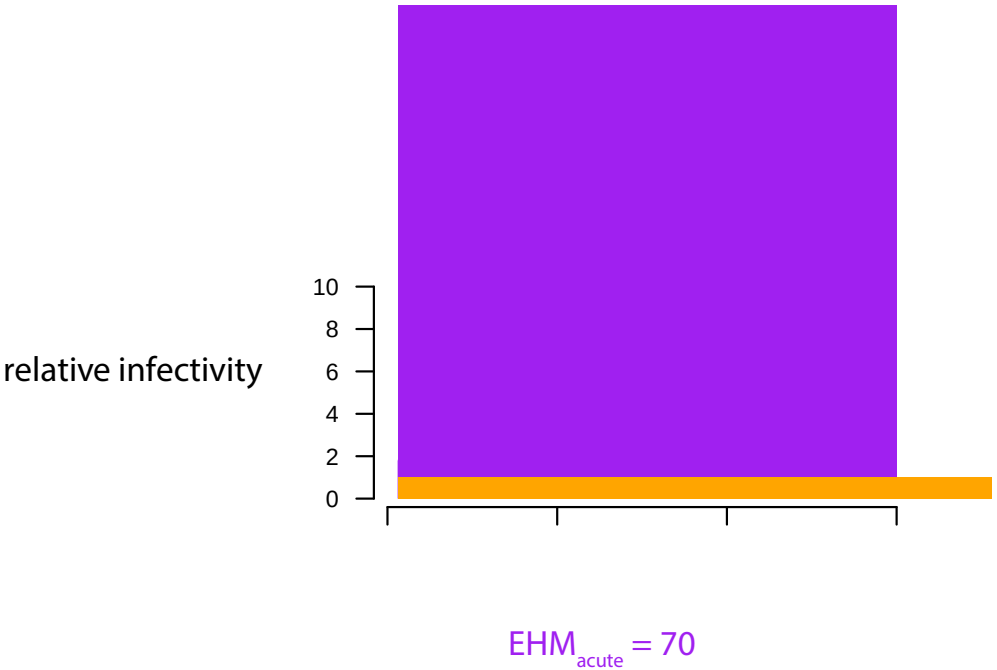
$EHM_{acute} = 30$

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

DIRECTLY MEASURED ONCE!



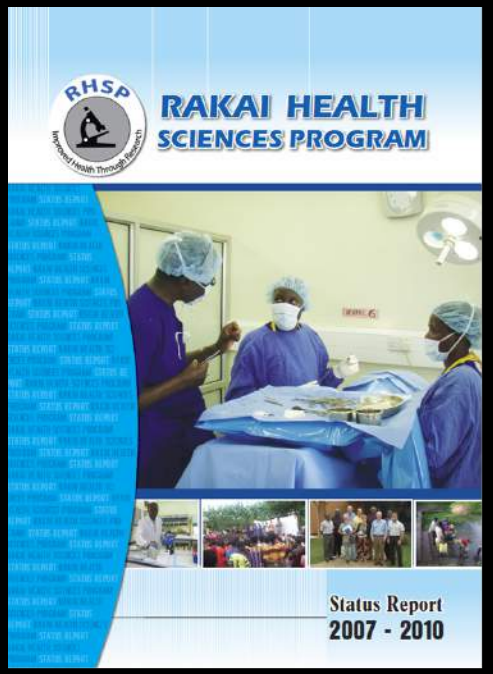
Early Transmission



$EHM_{acute} = 70$

DIRECTLY MEASURED ONCE!

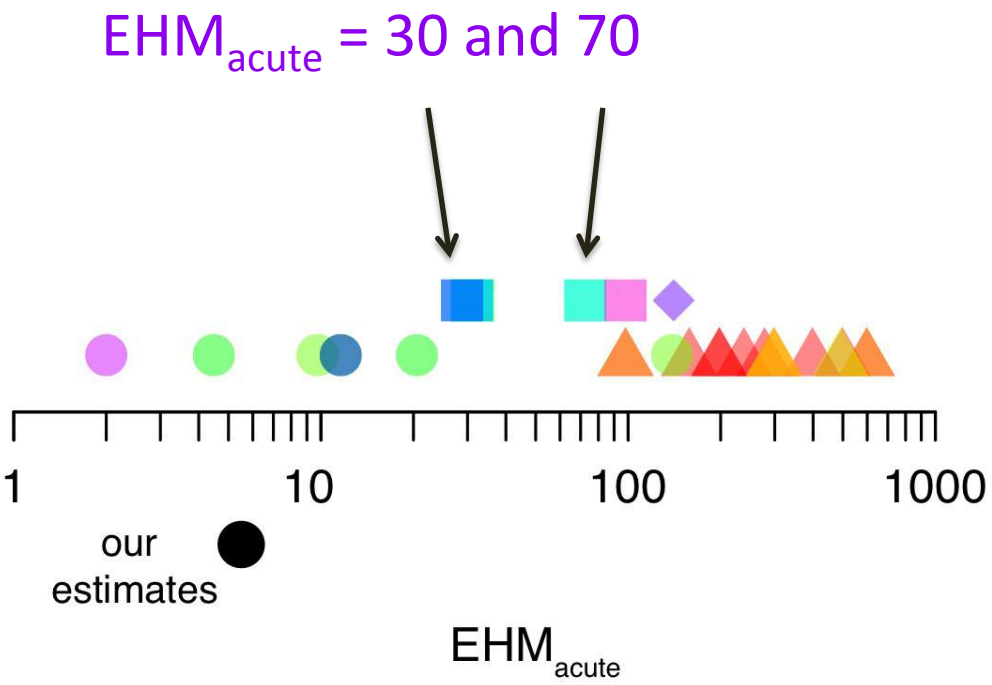
But analyzed many times.



Hollingsworth et al. (2008).
Journal of Infectious Disease.

Variation in EHM_{acute} Estimates

Directly measured once by the
Rakai Community Cohort Study, Uganda



(1) Jacquez et al. 1994
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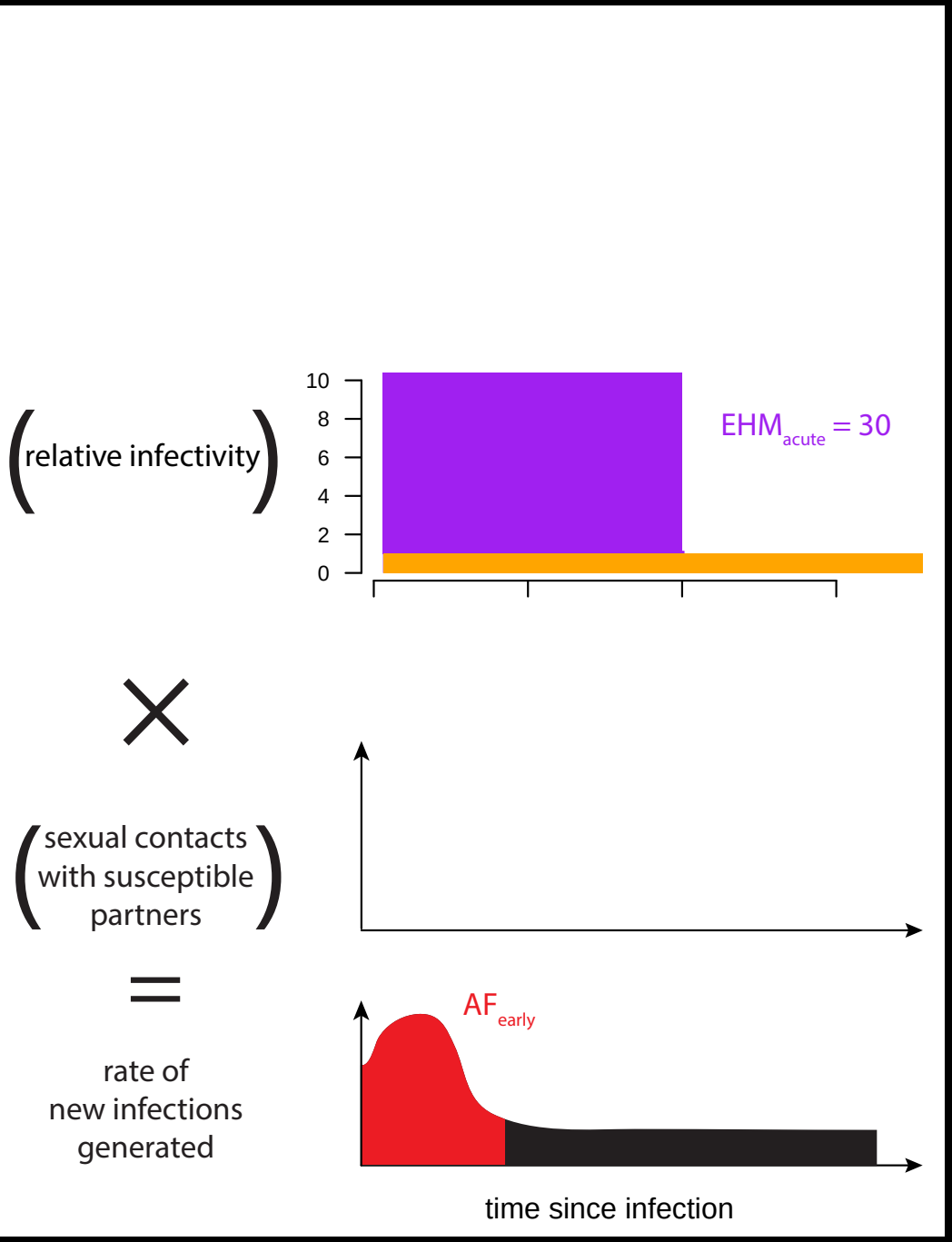
(8) Hollingsworth et al. 2008
(9) Abu–Raddad et al. 2008
(10) Salomon & Hogan 2008
(11) Prabhu et al. 2009
(12) Powers et al. 2011
(13) Cohen et al. 2013 (Williams)
(14) Romero–Severson et al. 2013
(15) Rasmussen et al. 2014

based on
epidemic curve
viral load
Rakai
Rakai & epidemic curve

Early Transmission

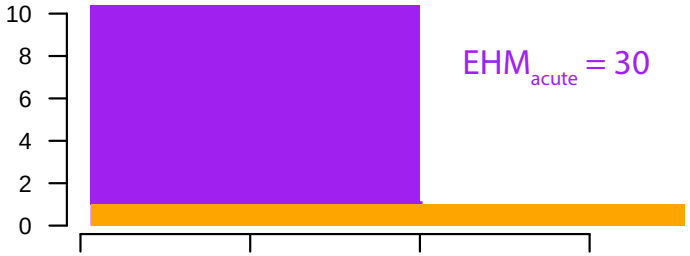
Infectivity only matters
during sex
with susceptible partners



Early Transmission

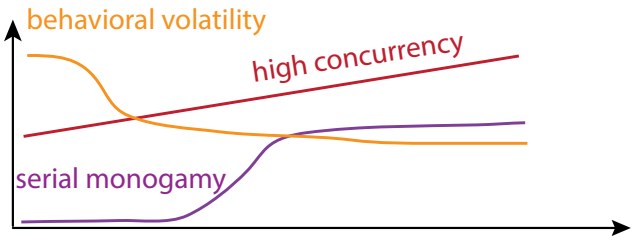
Infectivity only matters
during sex
with susceptible partners

(relative infectivity)



×

(sexual contacts with susceptible partners)

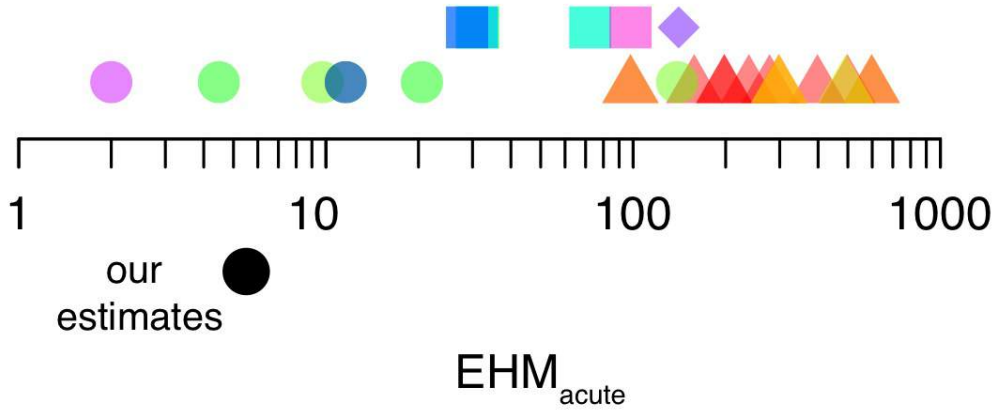


=

rate of
new infections
generated

time since infection

Variation in EHM_{acute} Estimates



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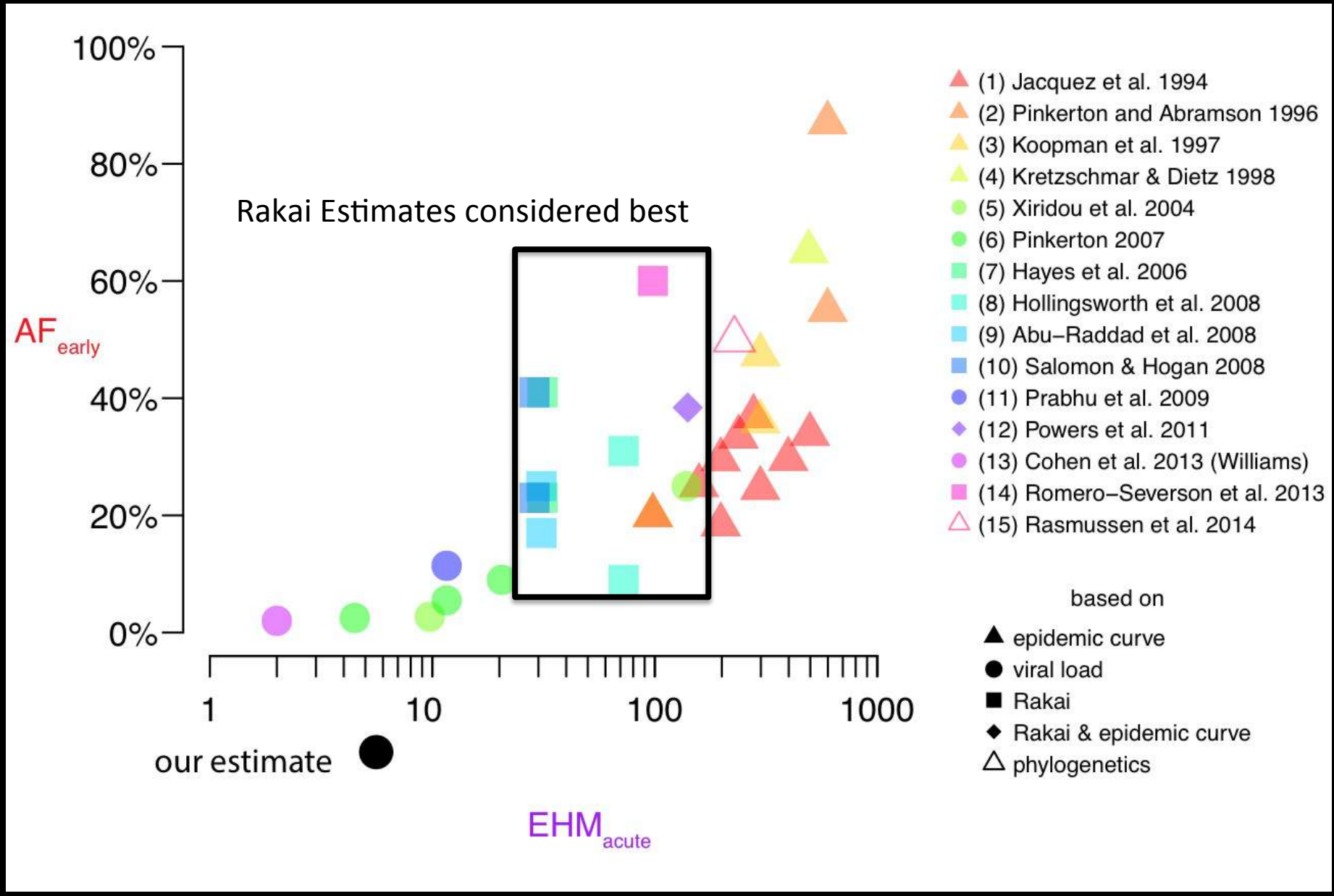
- (15) Rasmussen et al. 2014

based on

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

Variation in AF_{early} Estimates



Conclusion

We found these Rakai estimates are substantially upwards-biased.

Identified biases by simulating transmission & study design.

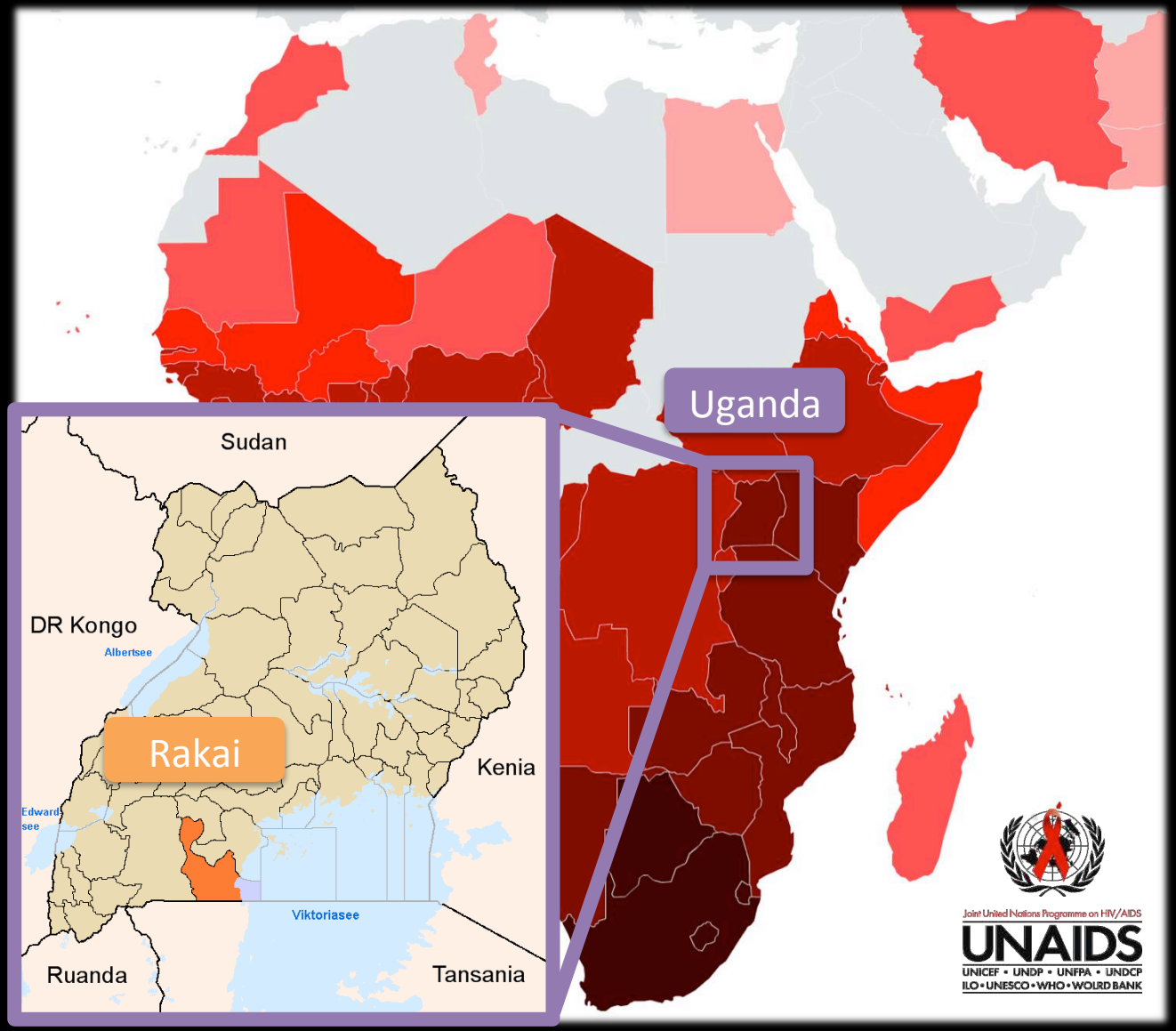
in silico analysis

Direct Measurement of Acute Infectivity

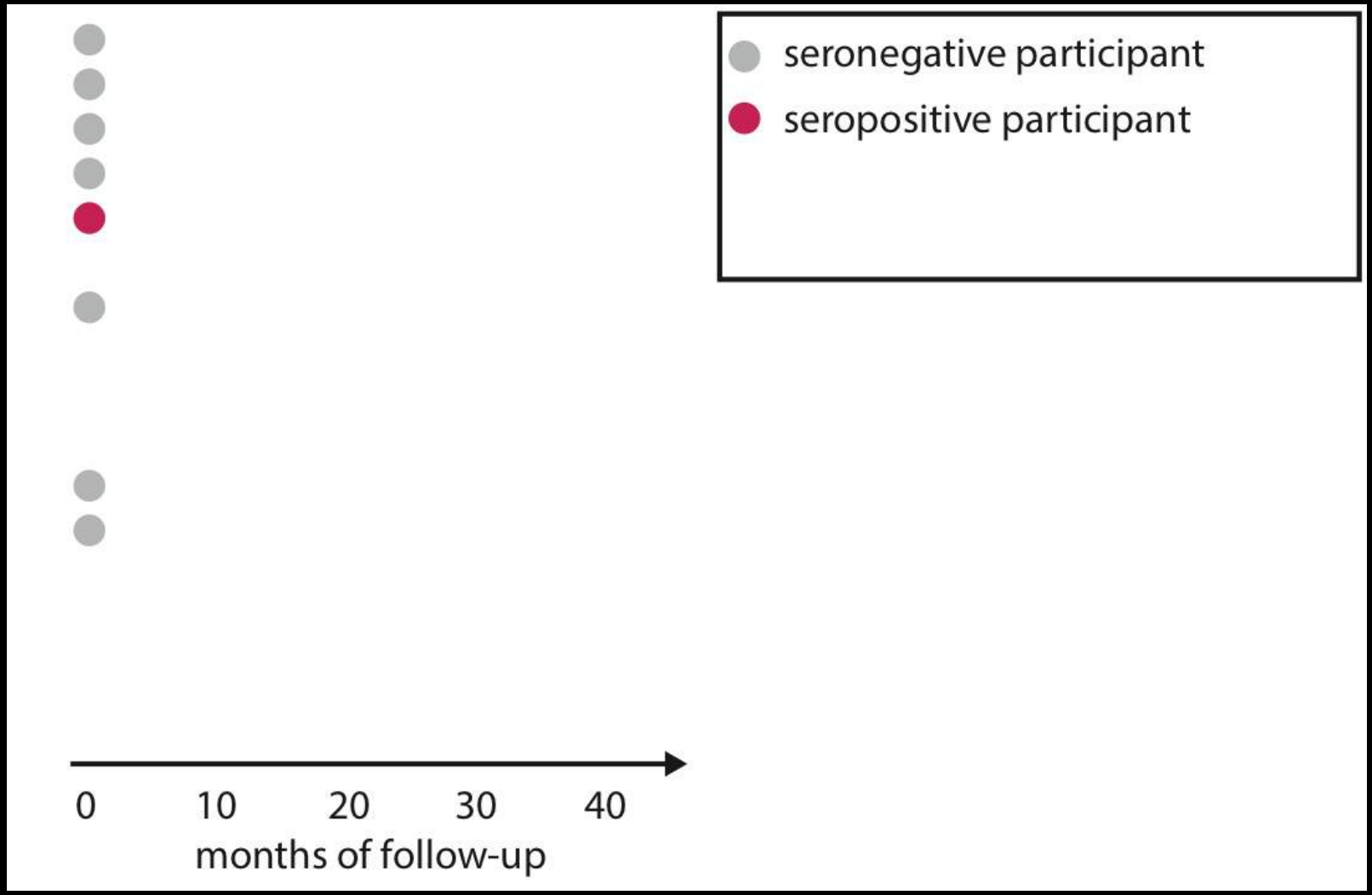
- Identify recently infected individuals
- Observe rate at which they infect sexual partners
    - Must be switching between partners
    - Moral imperative to intervene

Very challenging!

Rakai Community Cohort Study



Rakai *Retrospective Couples* Cohort



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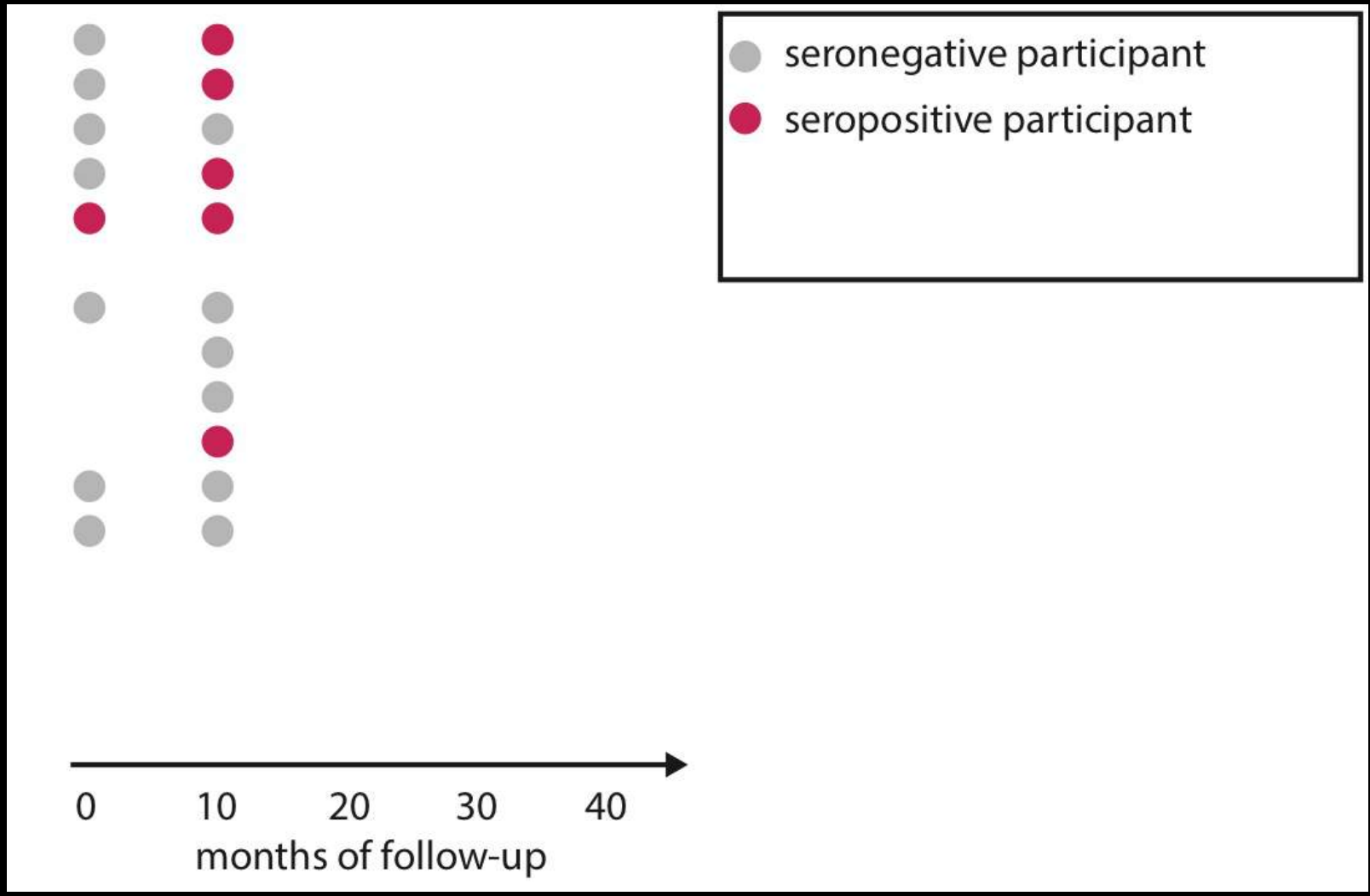

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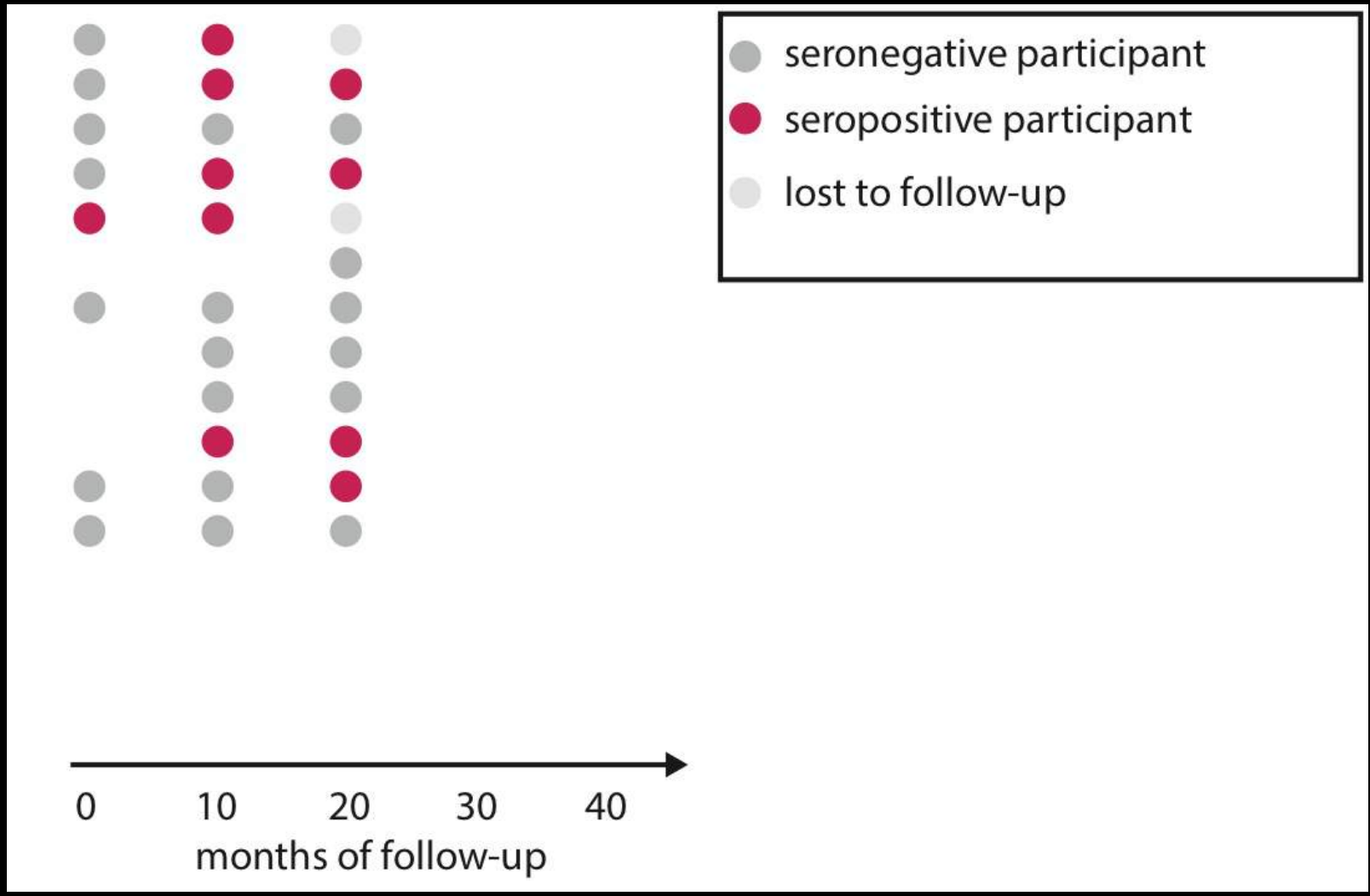

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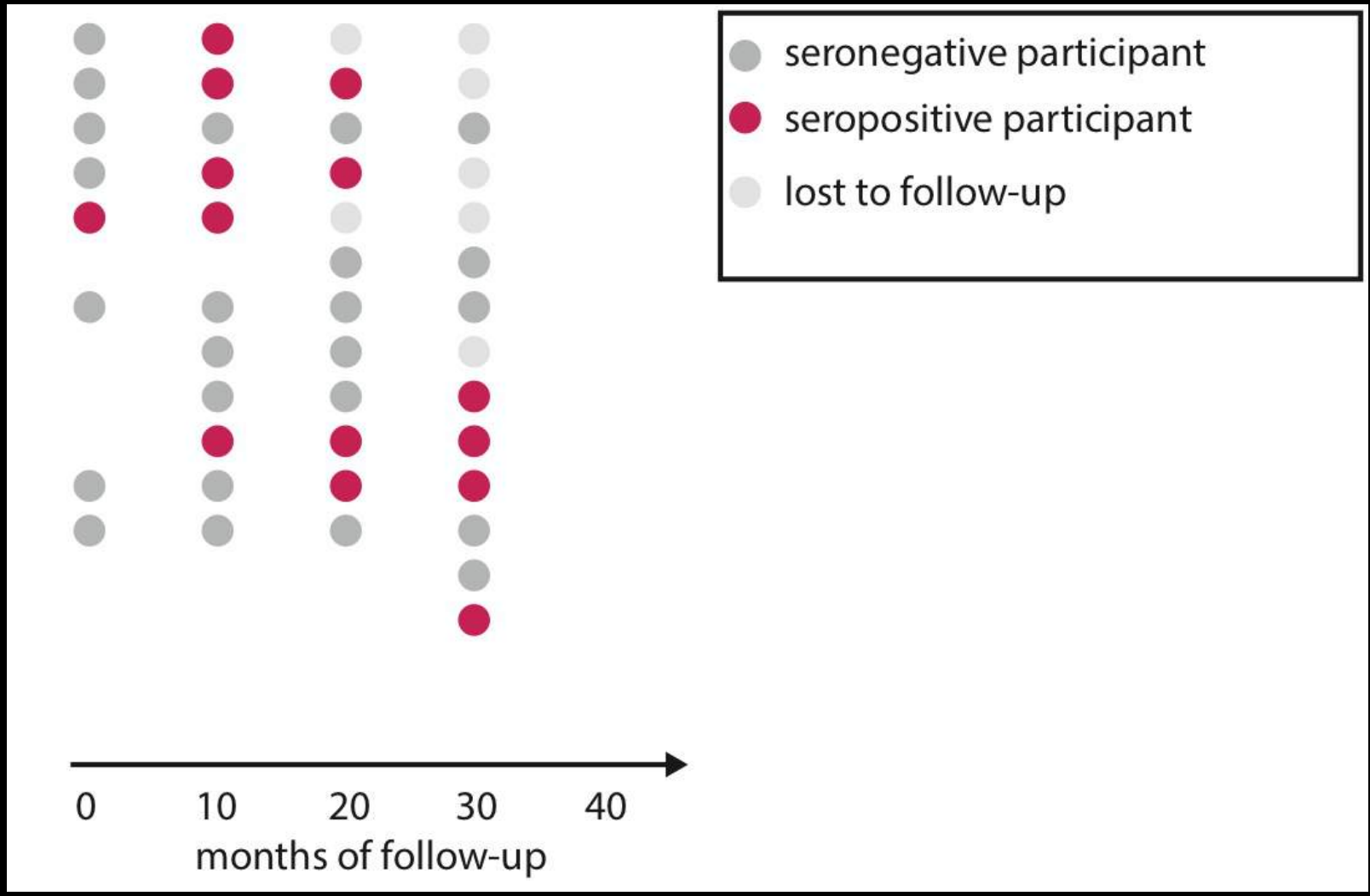

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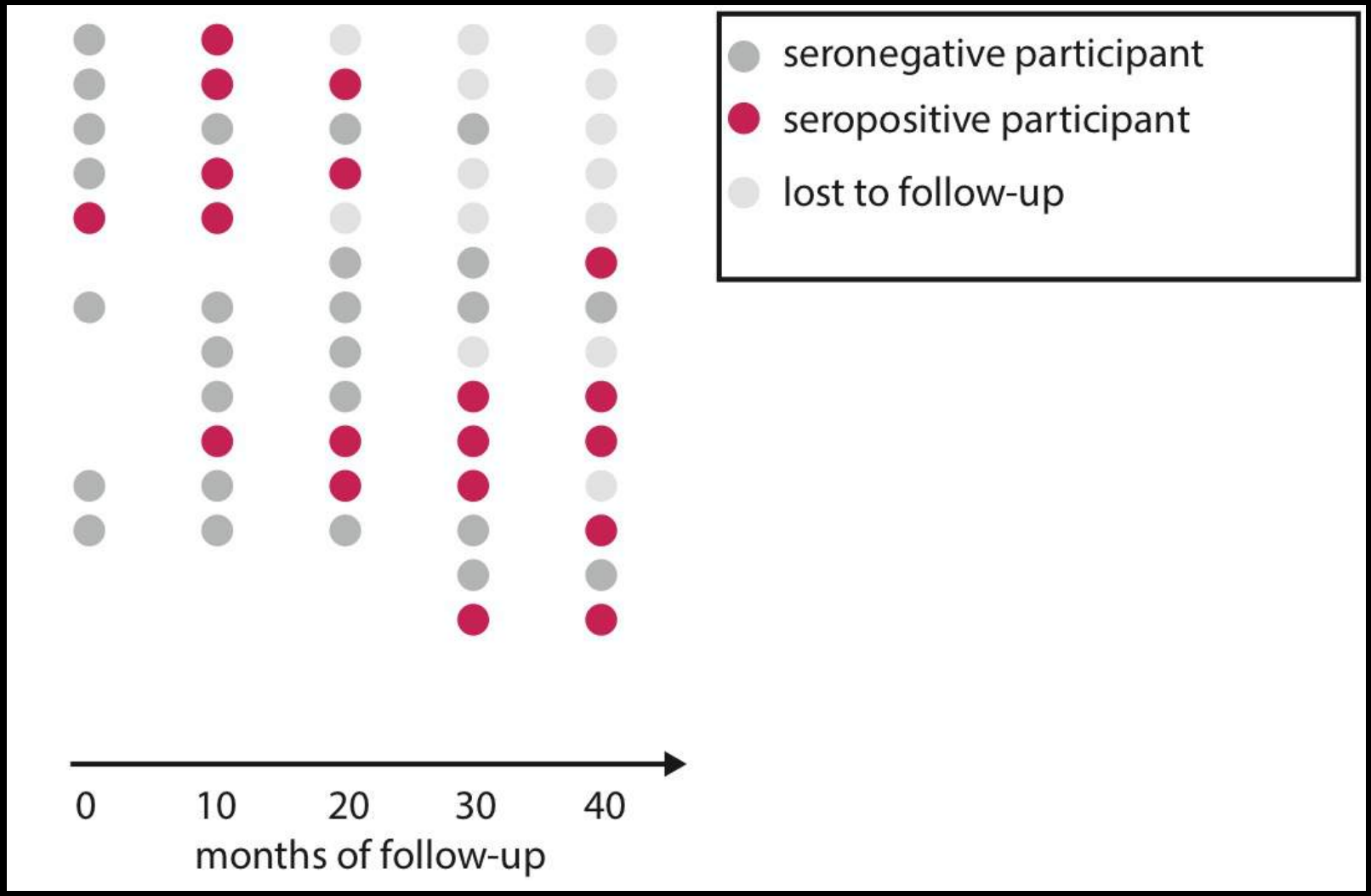

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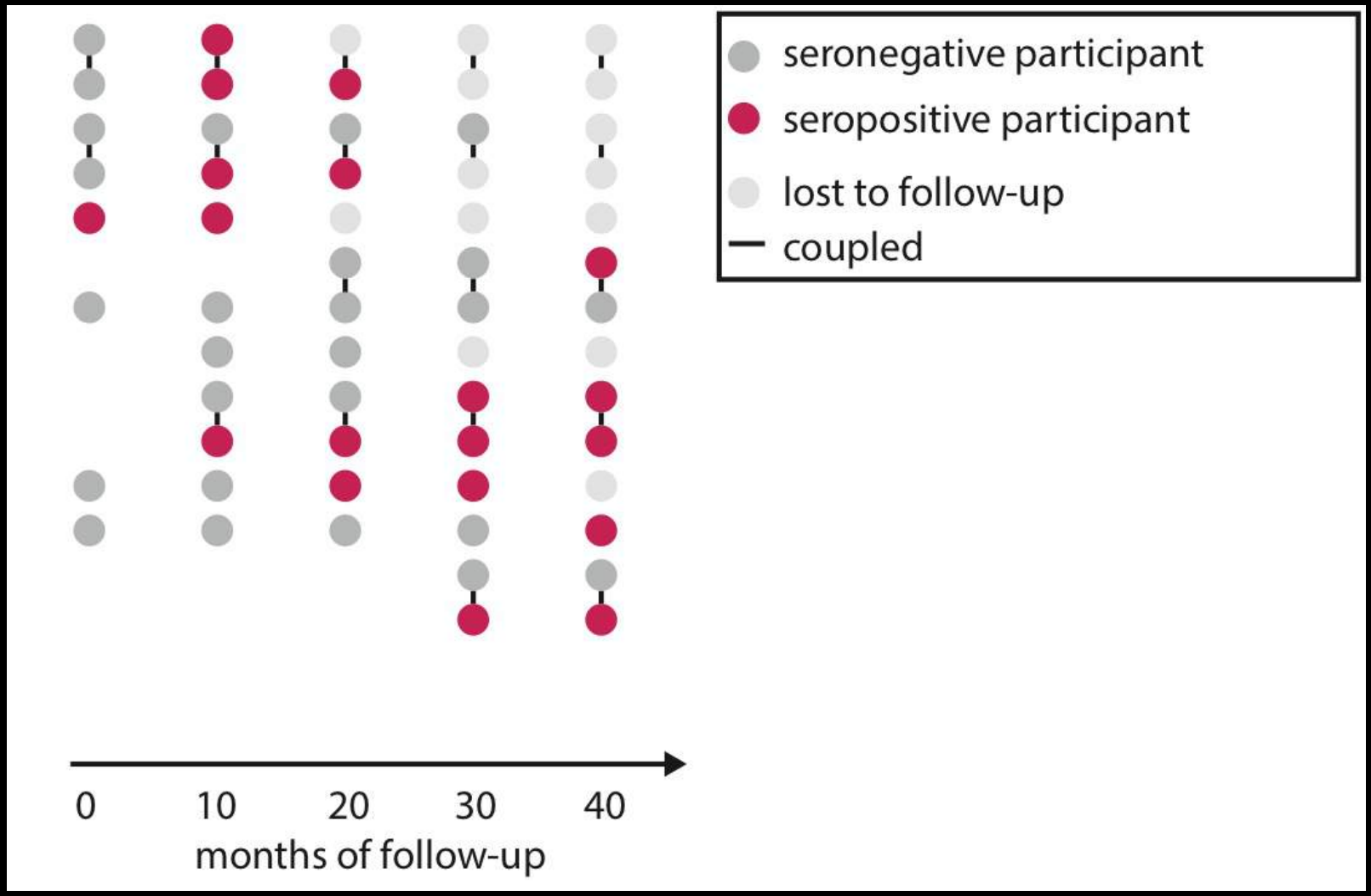

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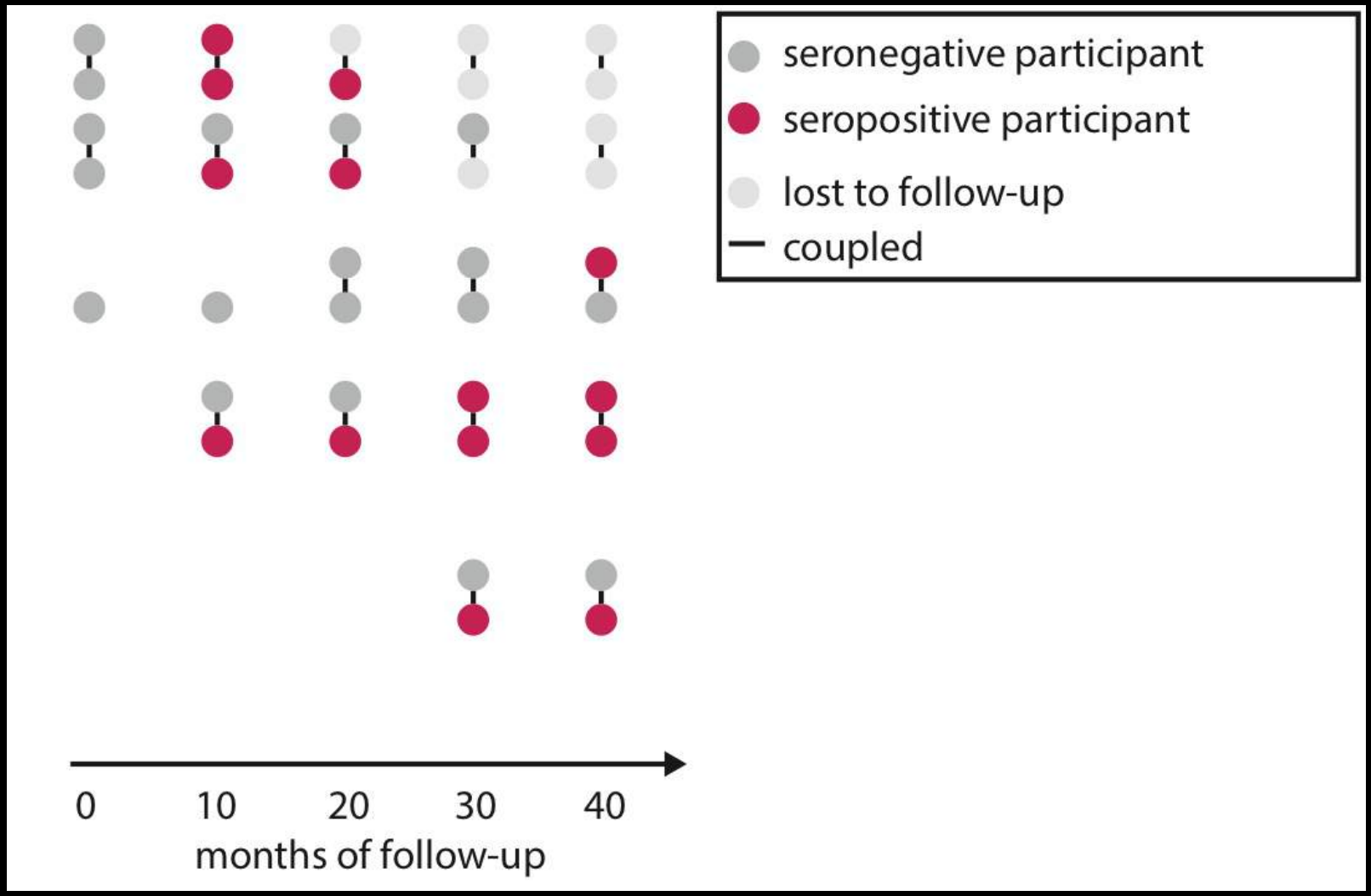
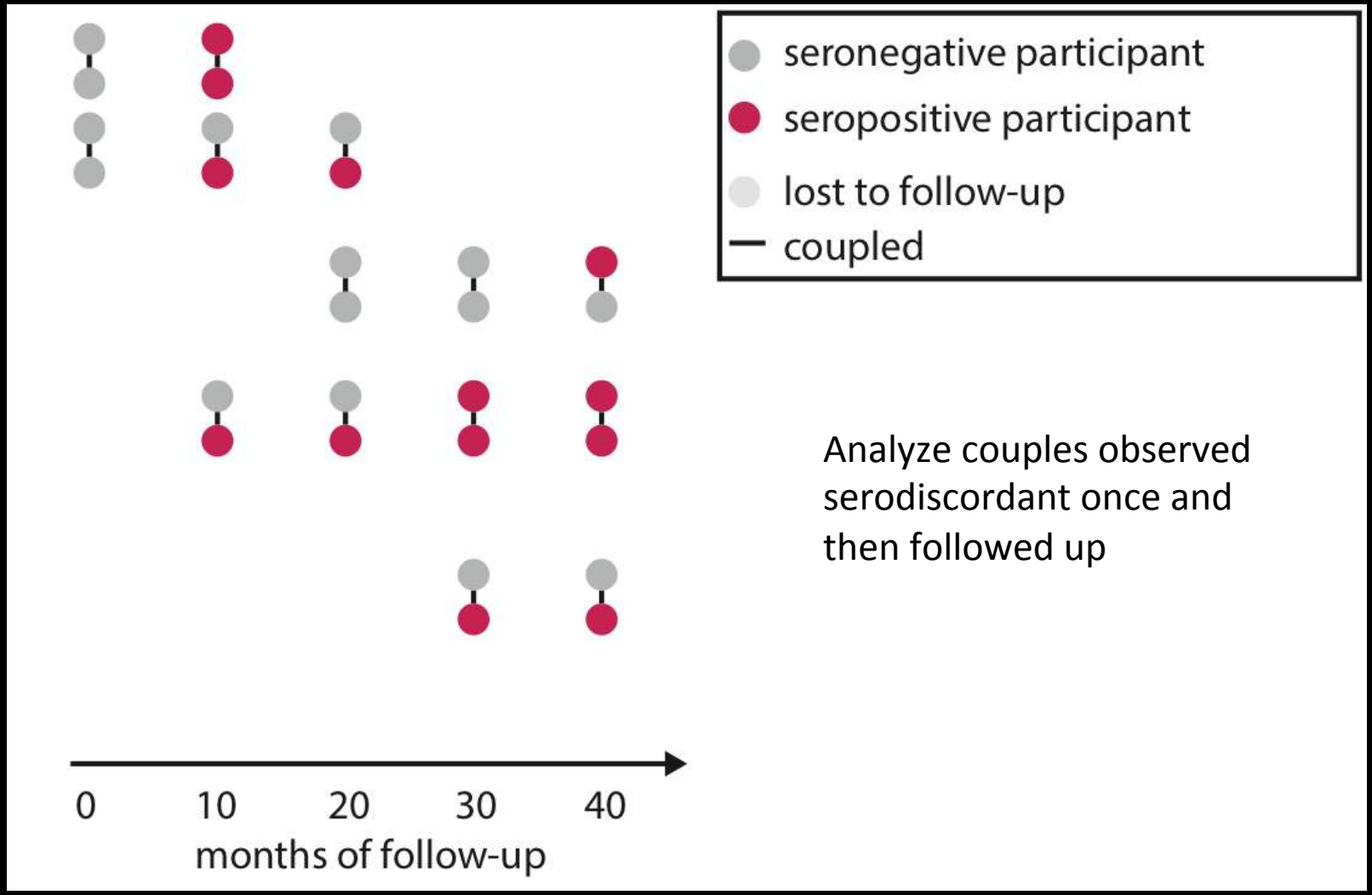
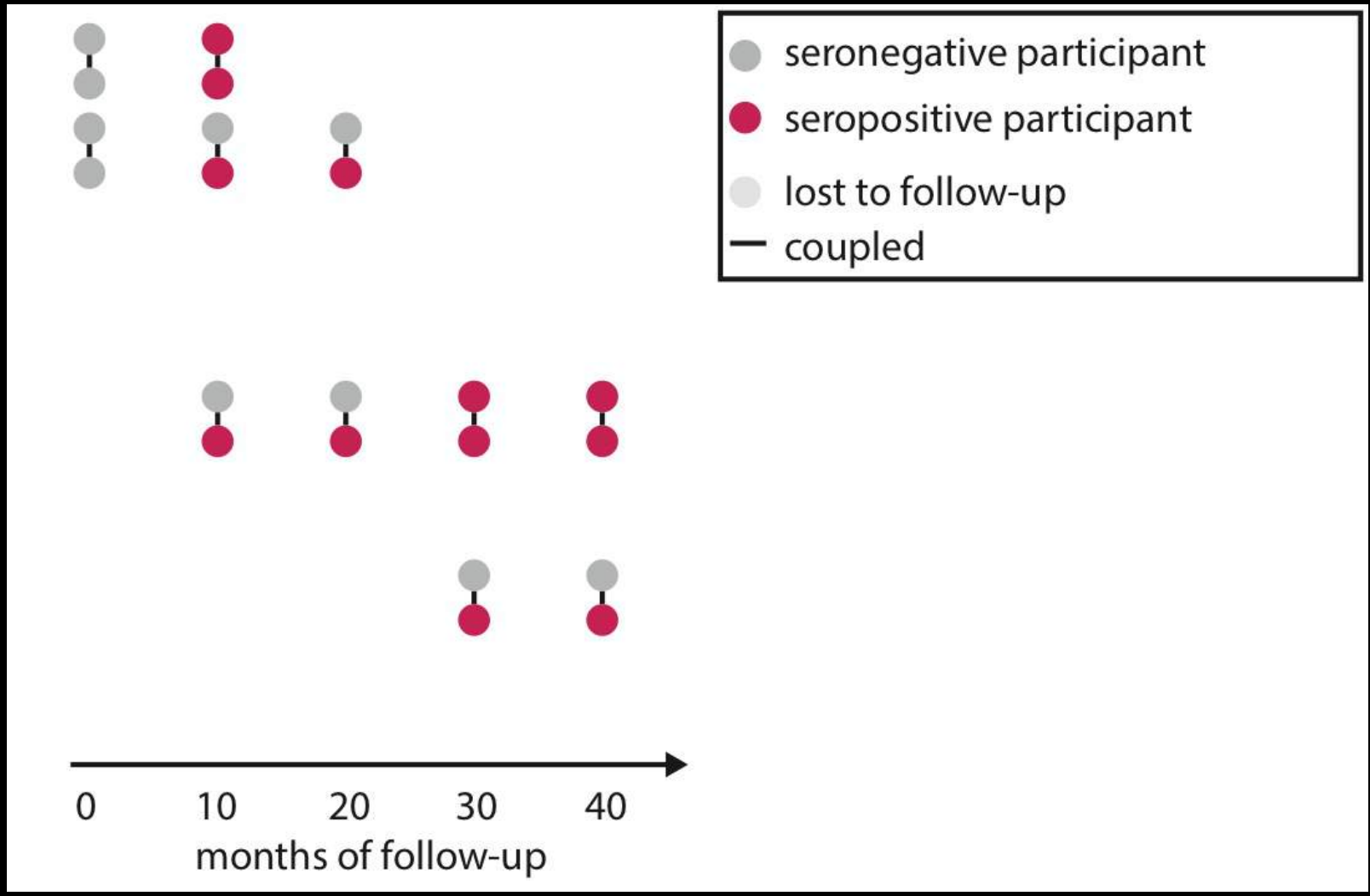


Rakai *Retrospective Couples* Cohort

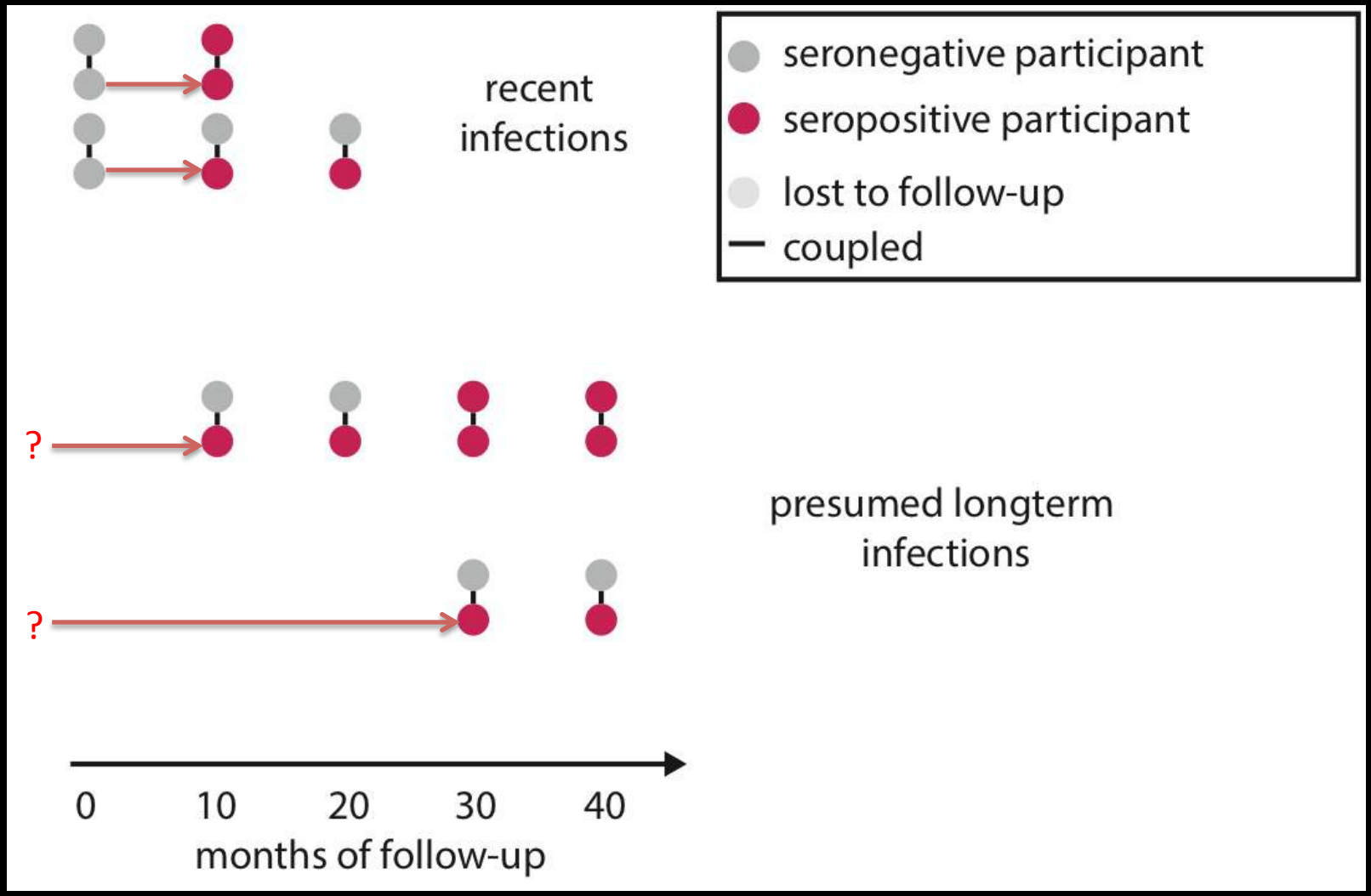


Analyze couples observed serodiscordant once and then followed up

Rakai *Retrospective Couples* Cohort



Rakai *Retrospective Couples* Cohort



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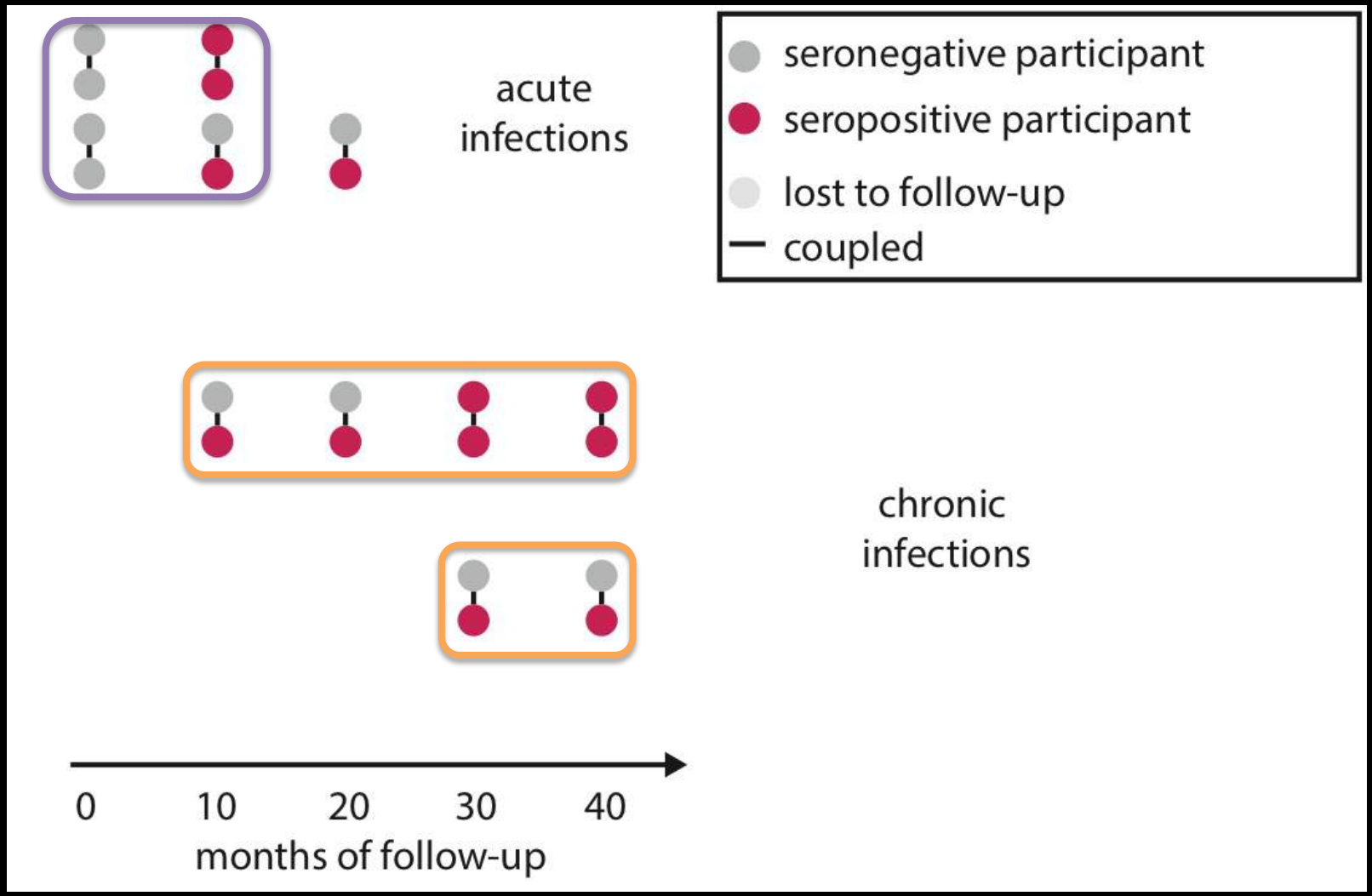

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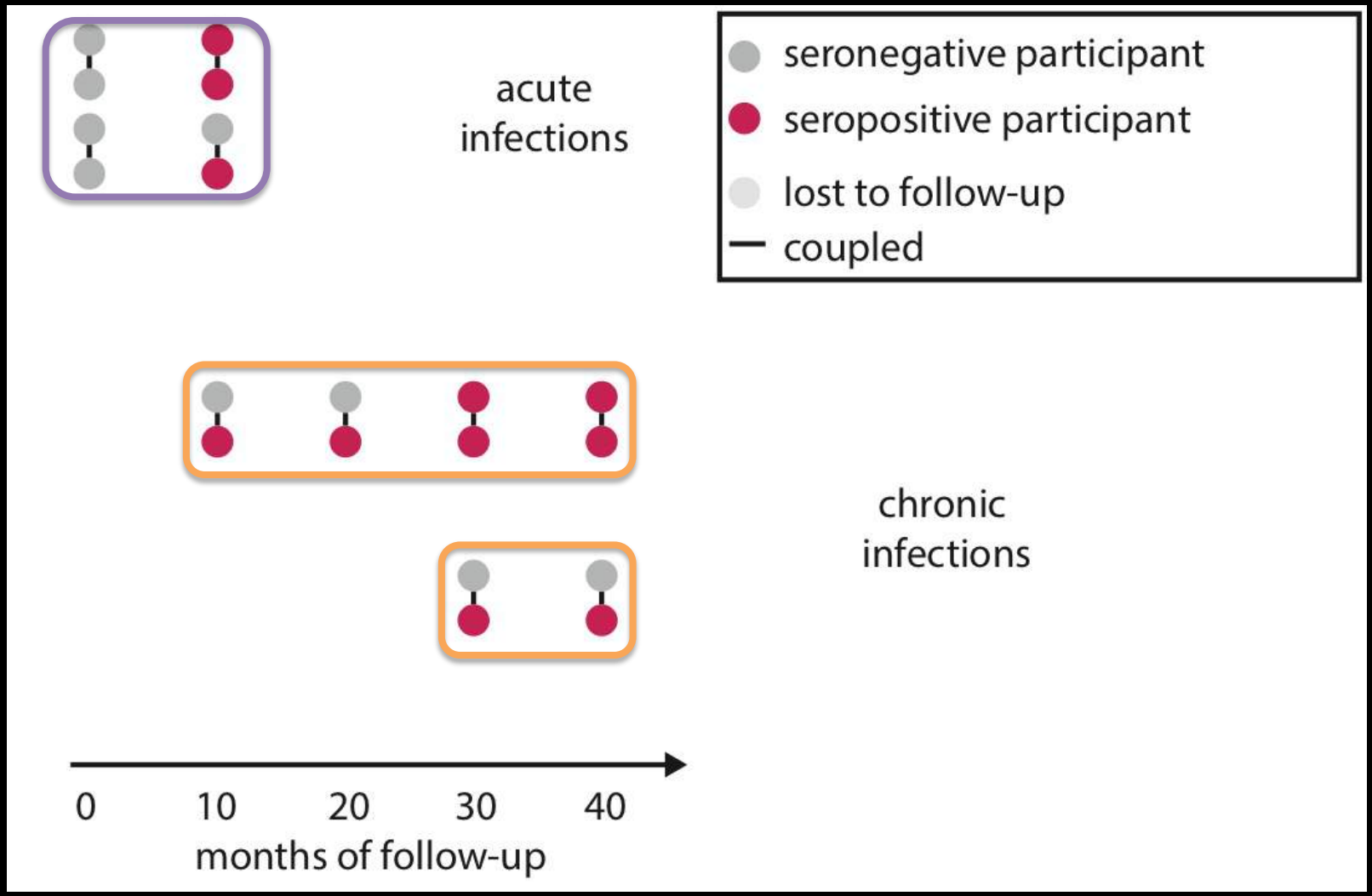

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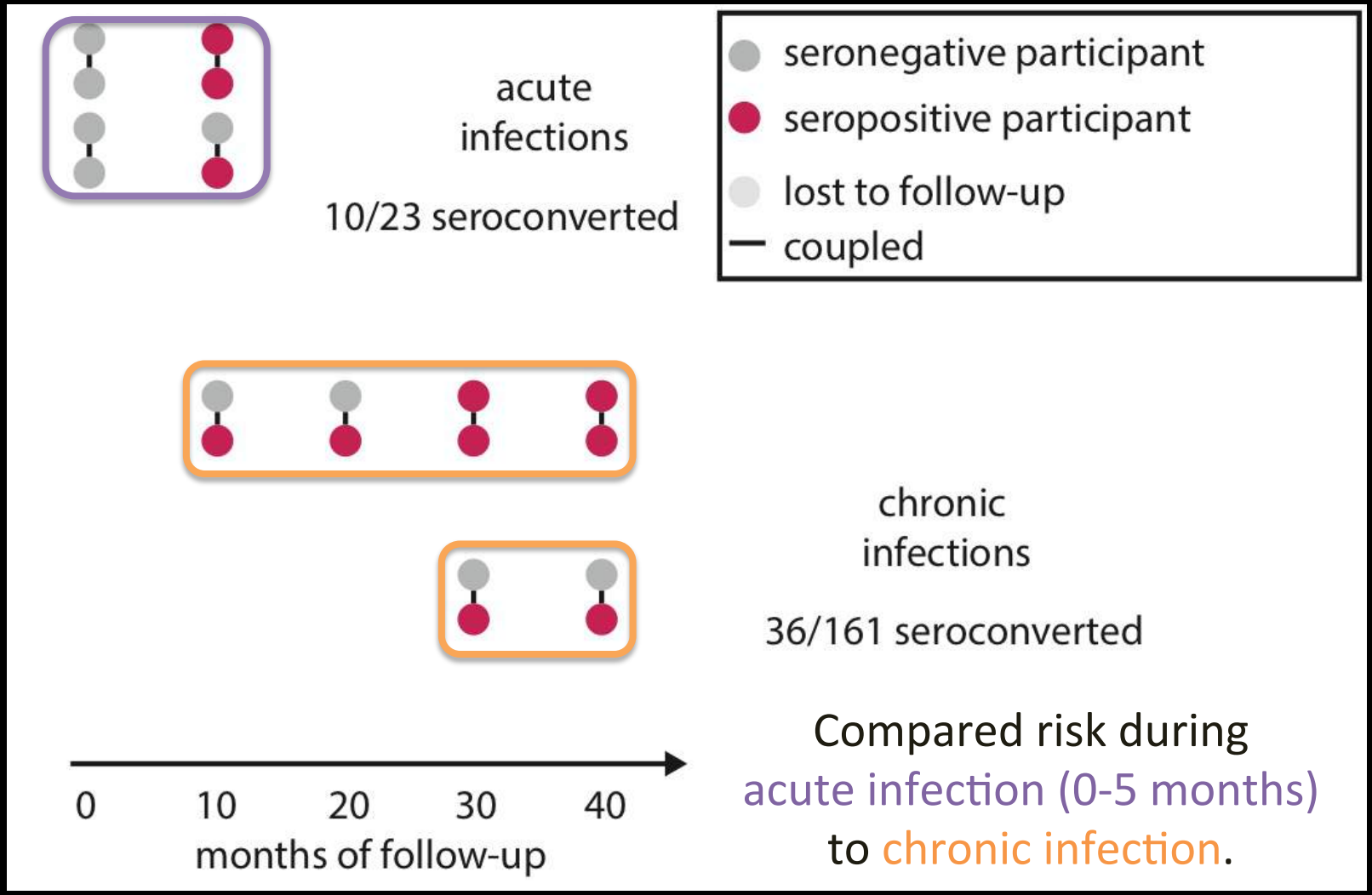
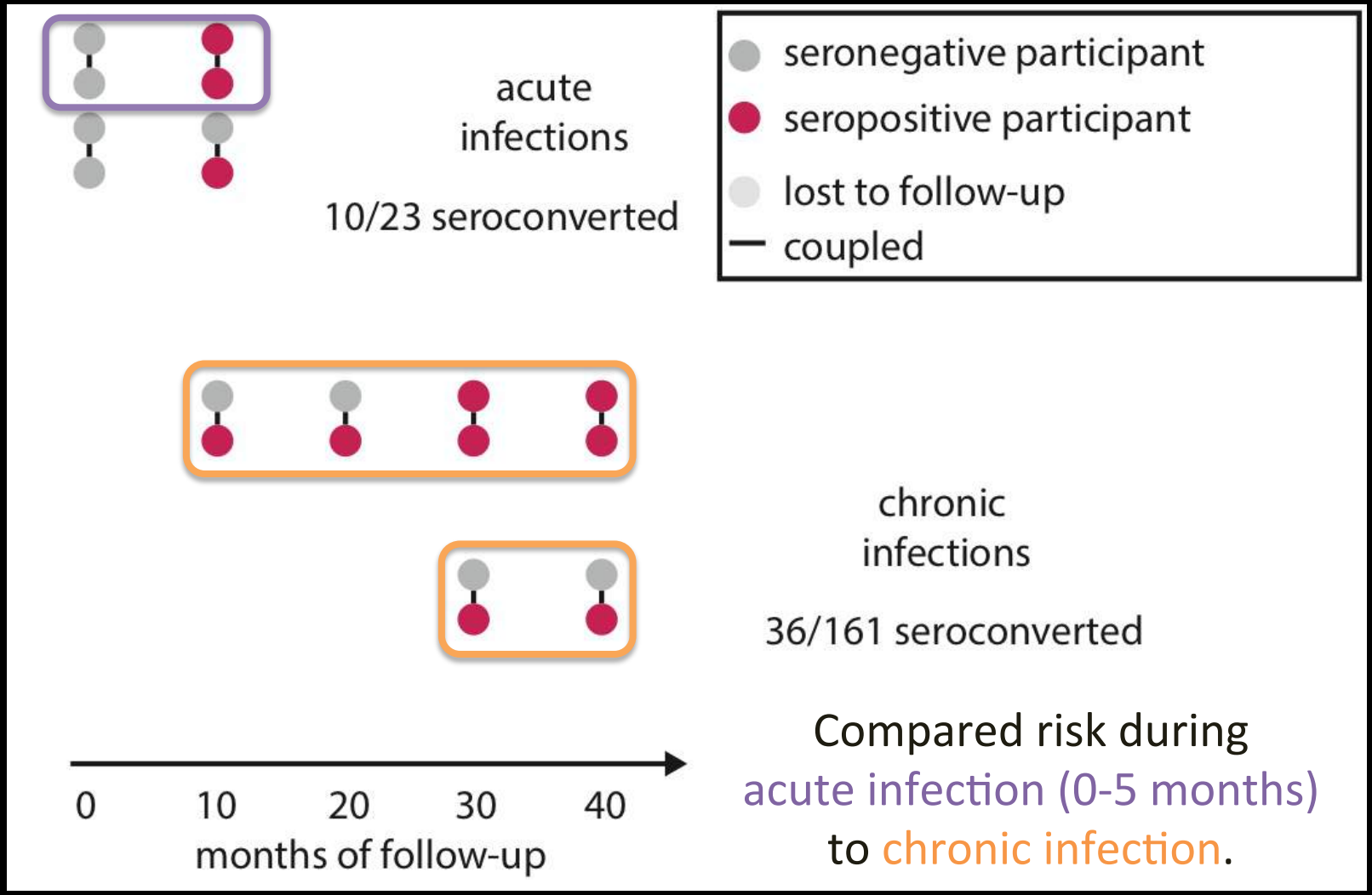


Rakai *Retrospective Couples* Cohort

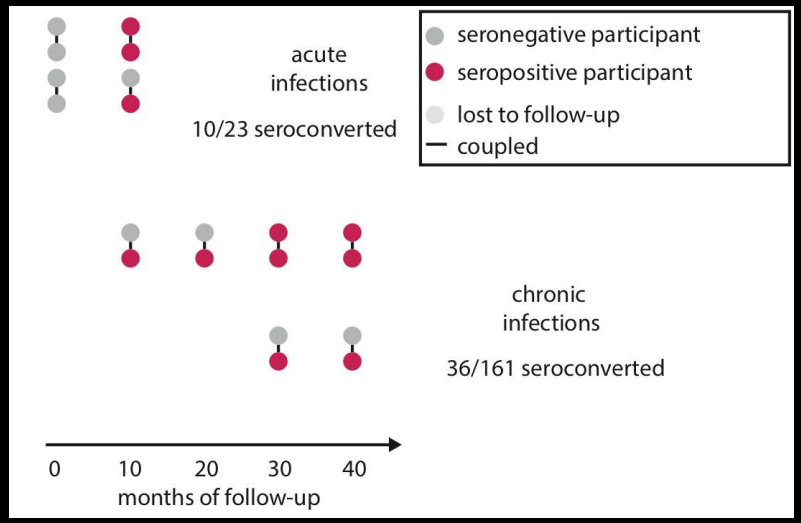
Suggestive of HIGH acute infectivity



Rakai *Retrospective Couples* Cohort

7x as infectious for first 5 month

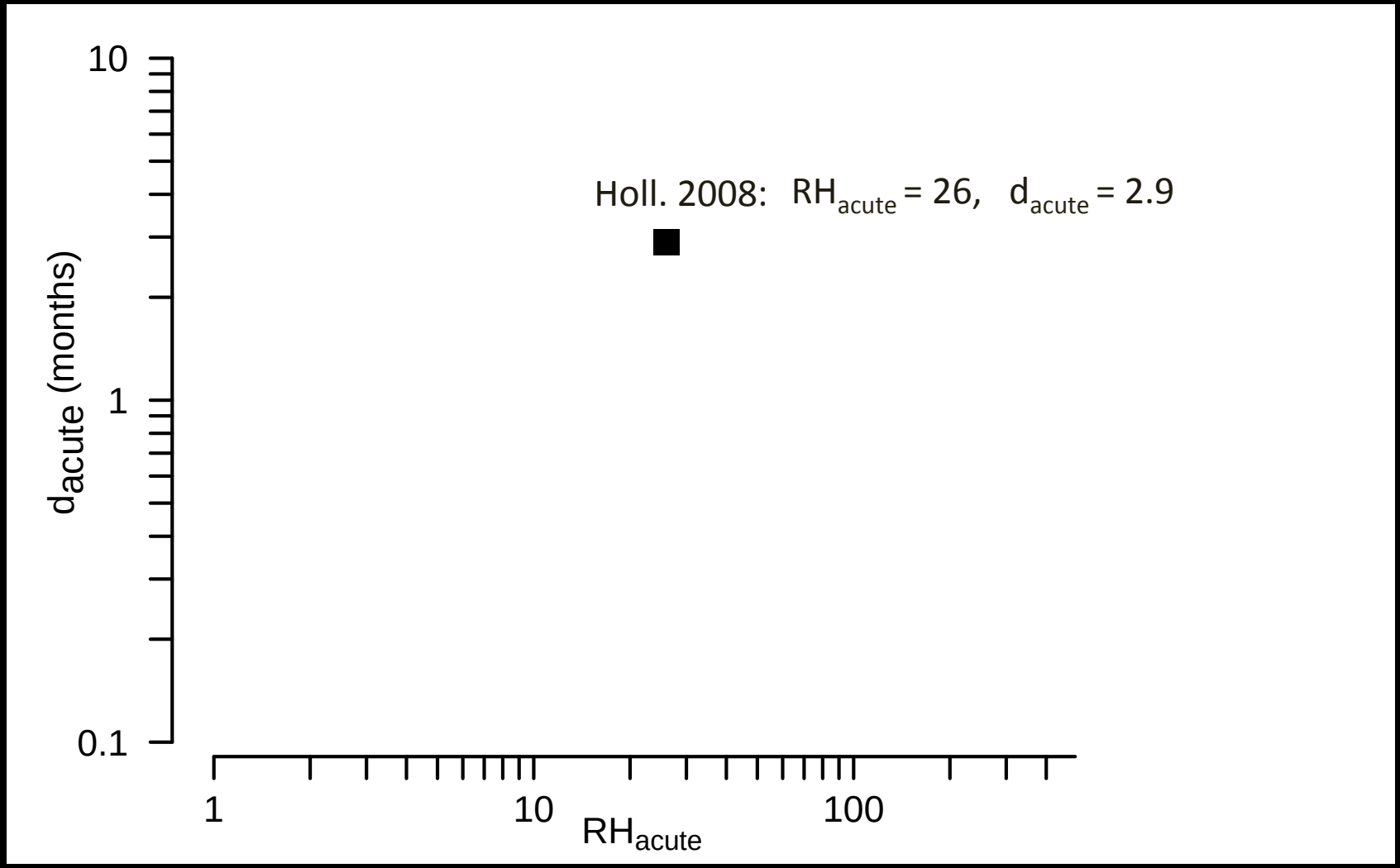
$EHM_{acute} = 30$



Comparing Results

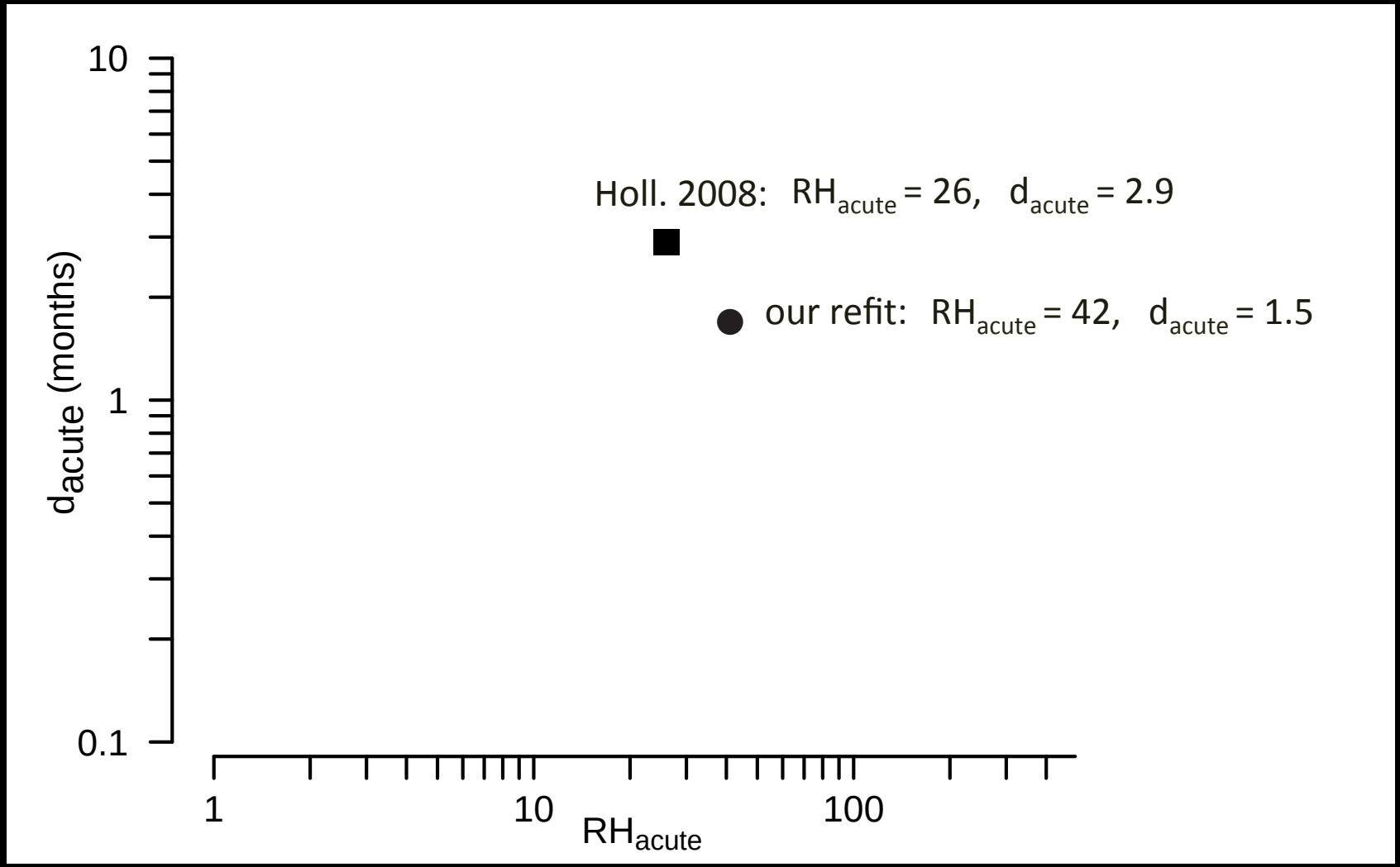
Study	RH_{acute}	d_{acute} (months)
Wawer et al. (2005)	7.25 (3.05 – 17.3)	5
Hollingsworth et al. (2008)	26	2.9 (1.23-6)

Collinearity in Fitted Parameters



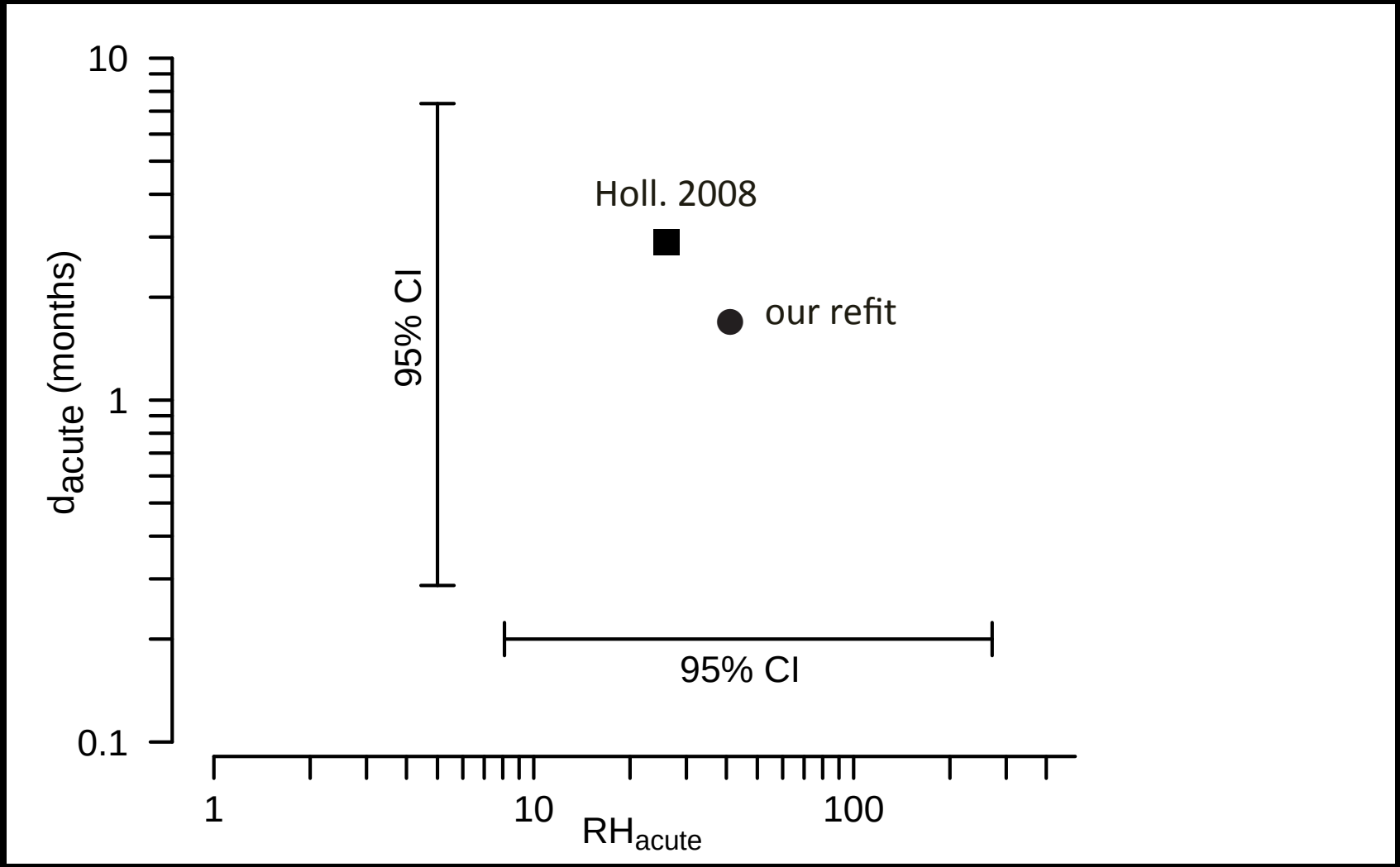
Revisit original data & method.

Collinearity in Fitted Parameters



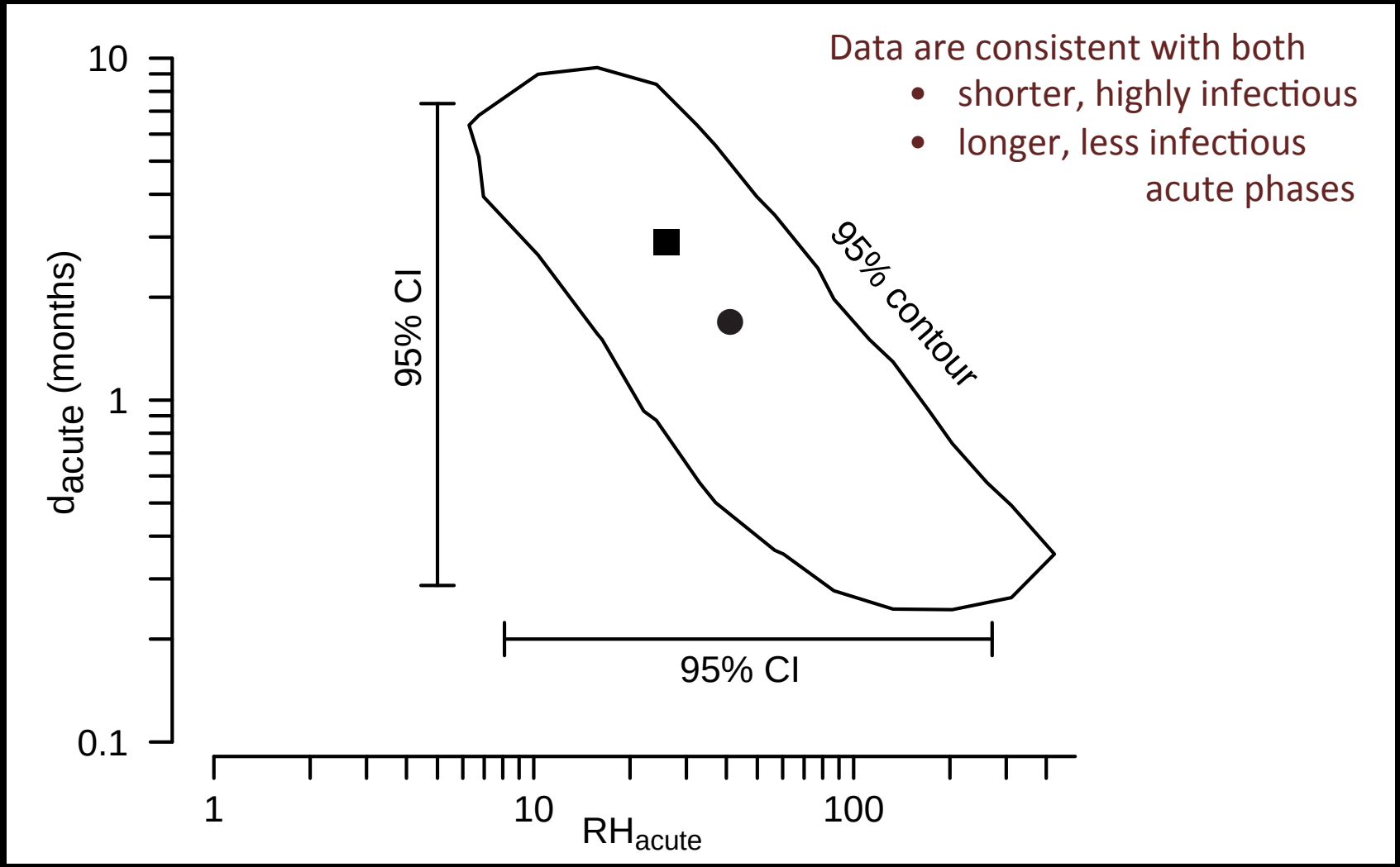
Refit the same model using Bayesian MCMC

Collinearity in Fitted Parameters



Refit the same model using Bayesian MCMC

Collinearity in Fitted Parameters



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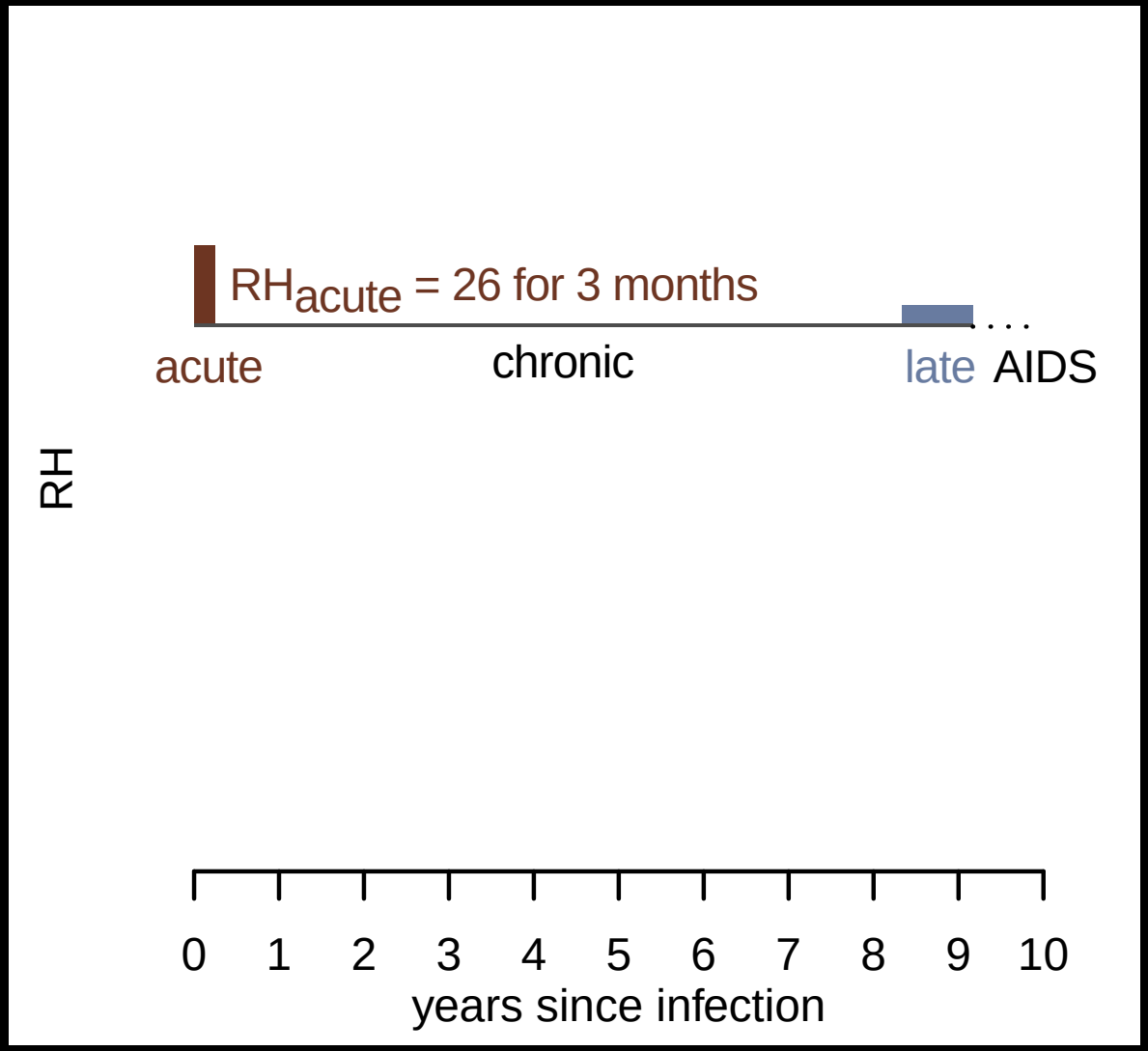


What is actually Identifiable?

Excess Hazard-Months due to acute phase

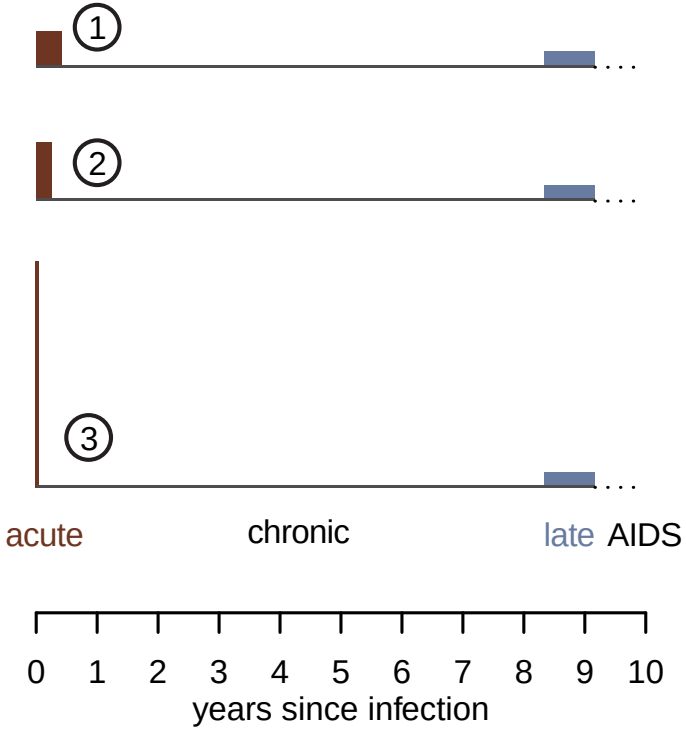
$EHM_{acute} = (RH_{acute}-1)d_{acute}$

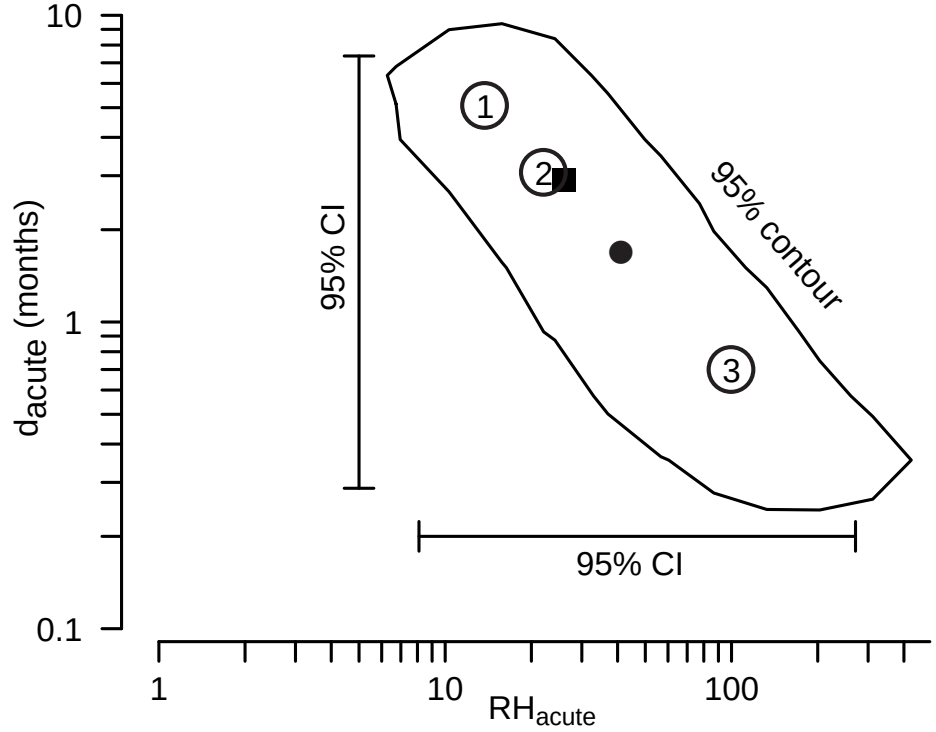
$EHM_{acute} = 25*3 = 75$

$EHM_{acute} = 15*5 = 75$

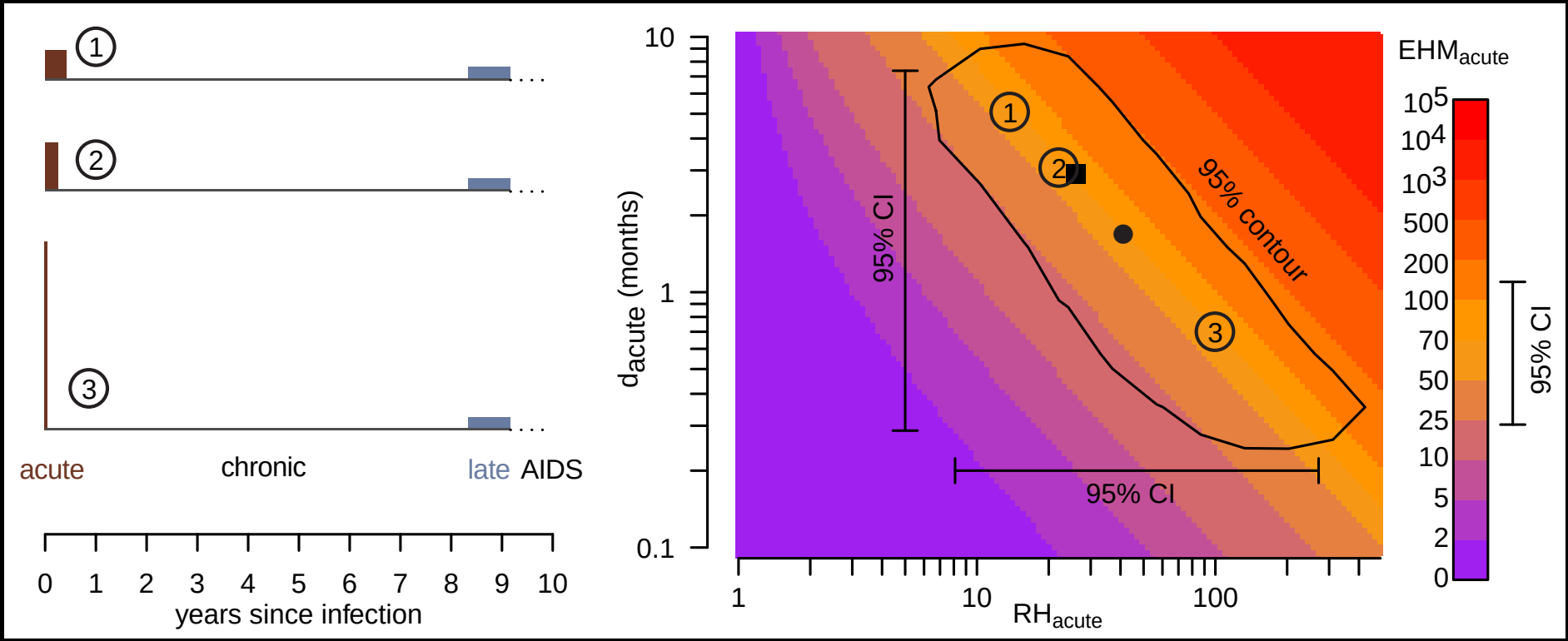
$EHM_{acute} = 100*3/4 = 75$

Excess Hazard Months (EHM_{acute})





Excess Hazard Months (EHM_{acute})



RH_{acute} and d_{acute} are not identifiable from 10-month interval cohorts

We should focus on EHM_{acute}

Comparing Results

Study	RH_{acute}	d_{acute} (months)	EHM_{acute}
Wawer et al. (2005)	7.25 (3.05 – 17.3)	5	~30
Hollingsworth et al. (2008)	26	2.9 (1.23-6)	~70

Why re-analyze these data?

Comparing Results

Adjusted for	RH_{acute}	d_{acute} (months)	EHM_{acute}
Coital Acts, GUD, Age	7.25 (3.05 – 17.3)	5	~30
—	26	2.9 (1.23-6)	~70

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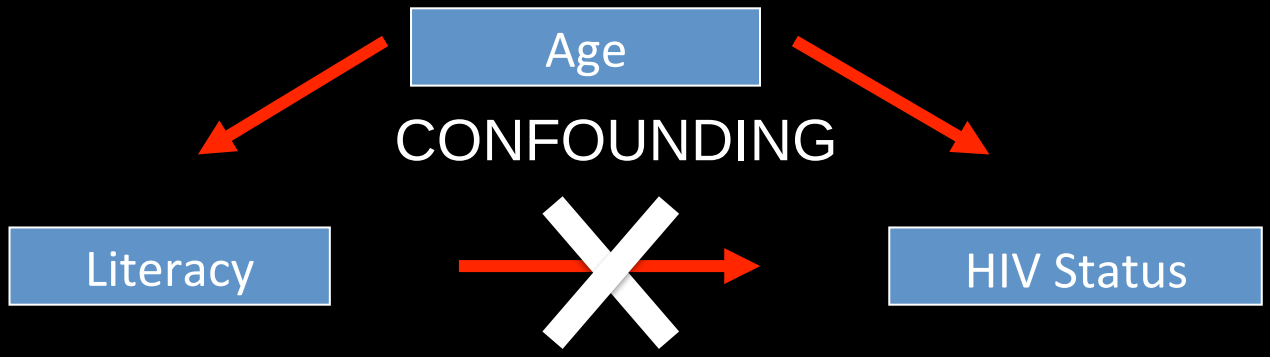

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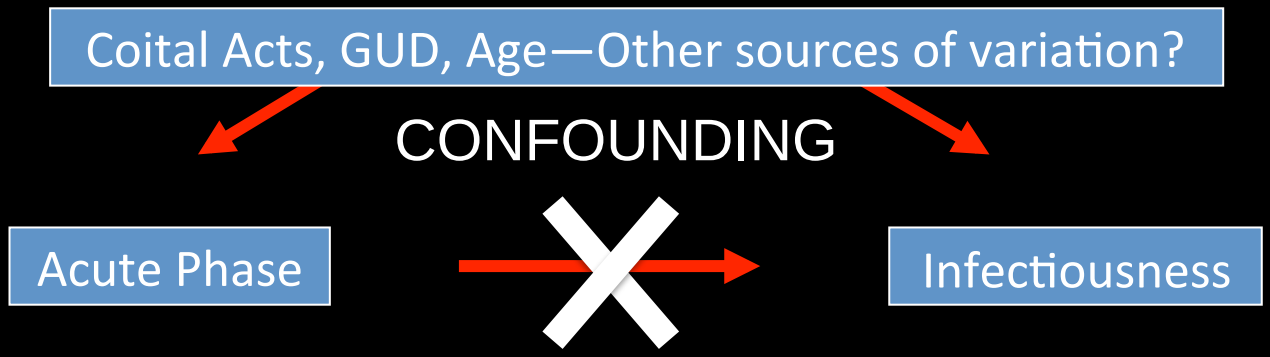


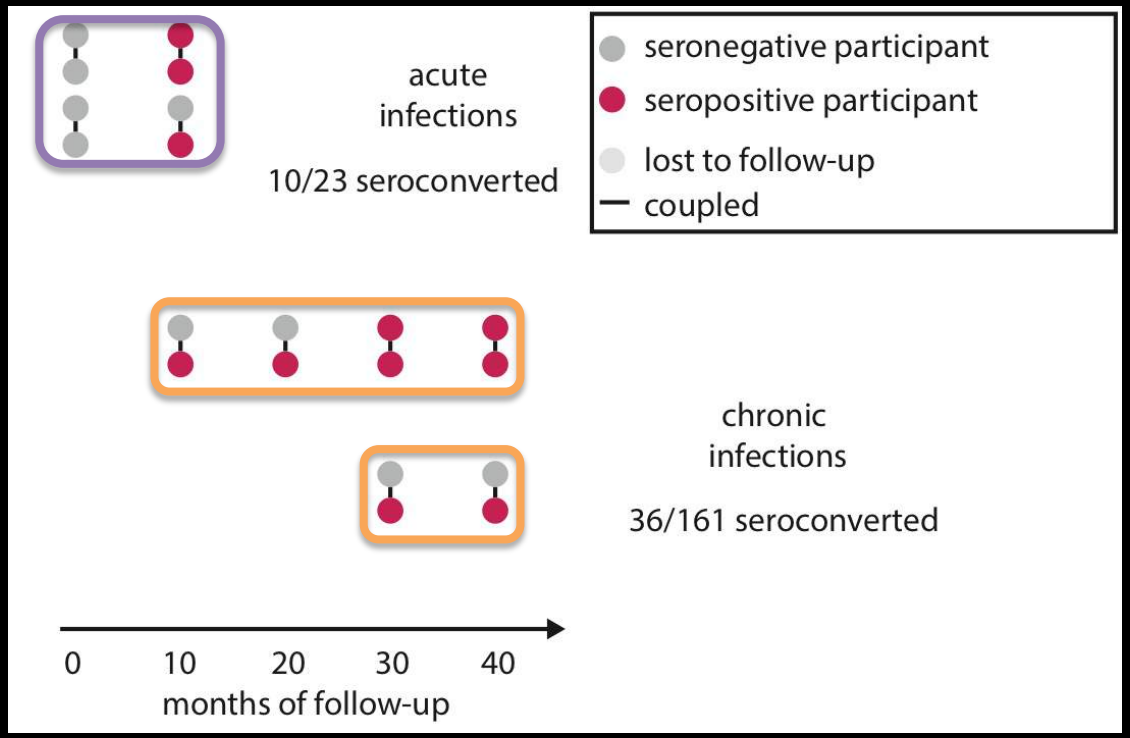
Heterogeneity in Transmission Rates

- Host genetics
- Circumcision
- Viral load
- Viral genotype
- Coital Rate
- Intercourse type (anal, dry, vaginal)
- Condom usage
- STIs
- Coinfections
- Nutrition

Bias 1: Unmodeled Heterogeneity

"Naïve" Couples.
Some are high risk

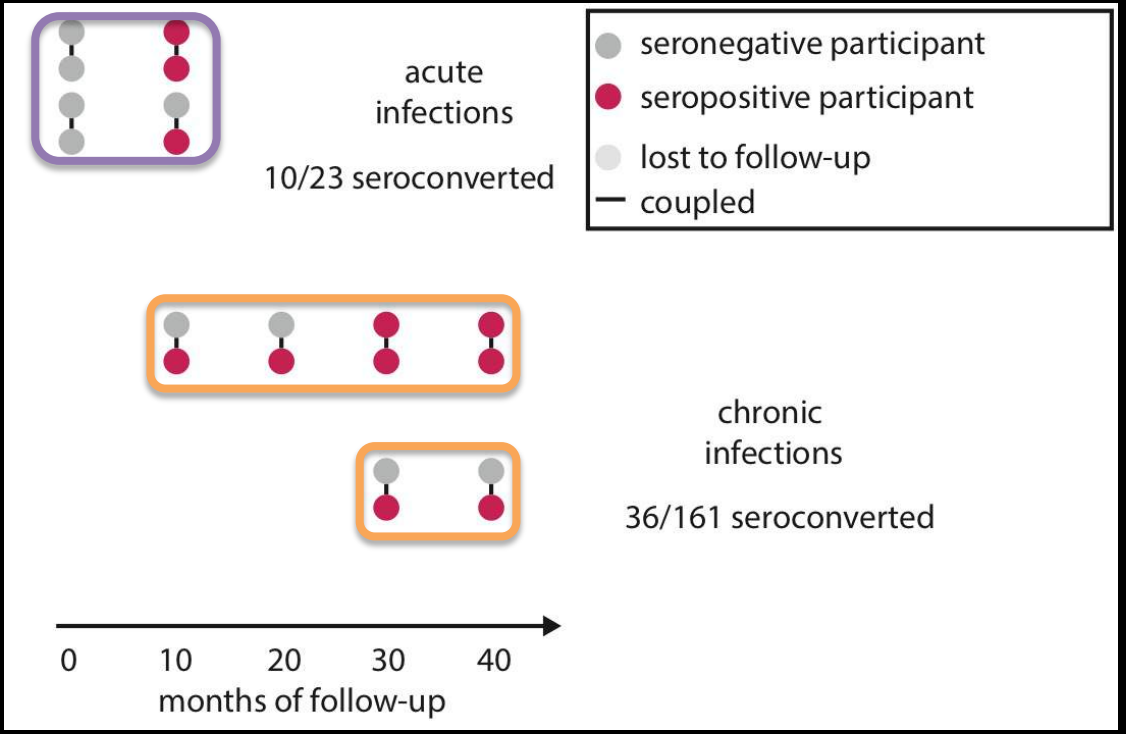
Persistently serodiscordant.
Selected to be low risk

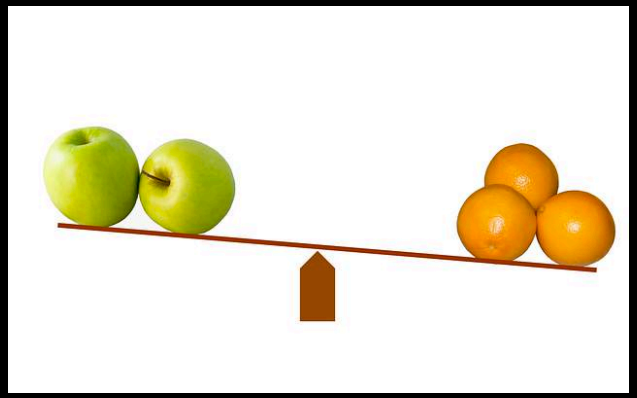


Bias 1: Unmodeled Heterogeneity

Average risk
acutely infected partners

Low risk
chronically infected partners

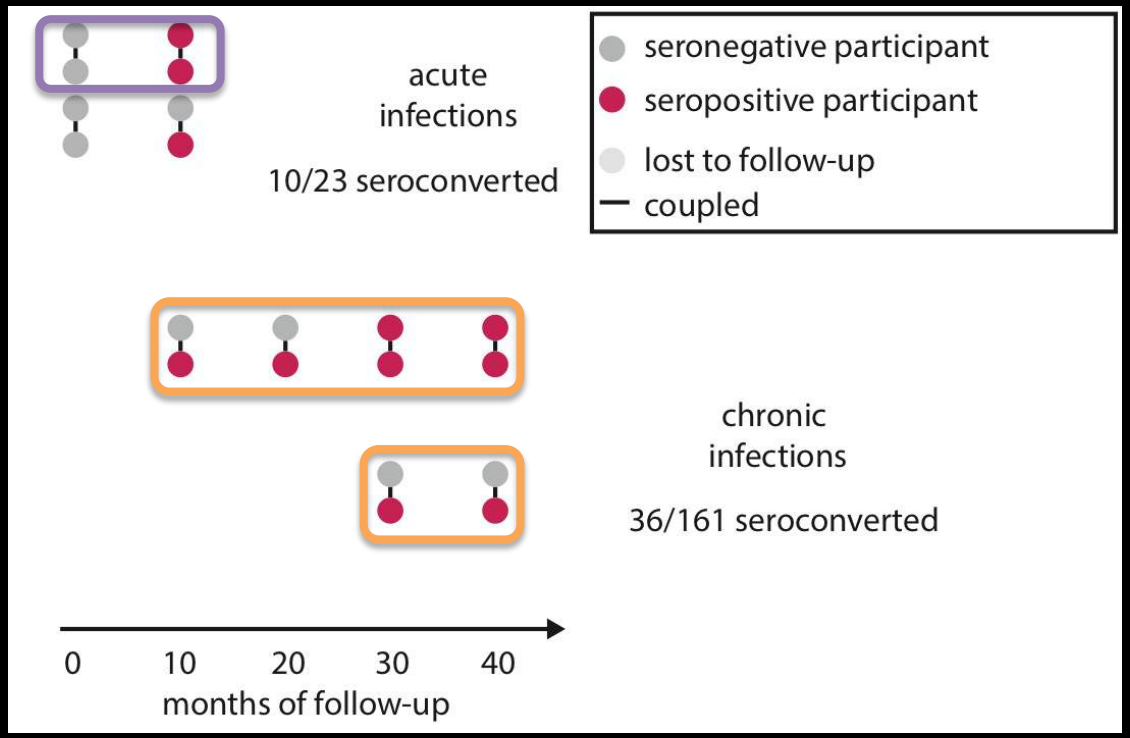




Unmodeled heterogeneity might bias EHM_{acute} upwards

Bias 2: Inclusion Criteria

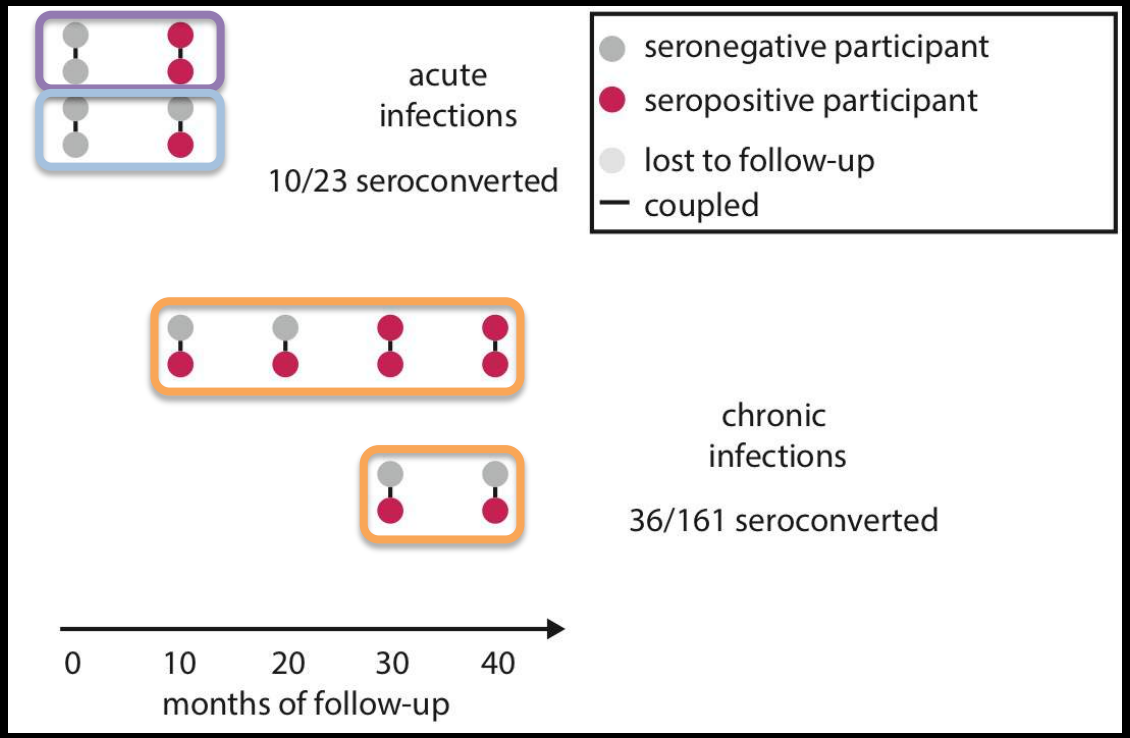
HIGH acute infectivity



Bias 2: Inclusion Criteria

HIGH acute infectivity

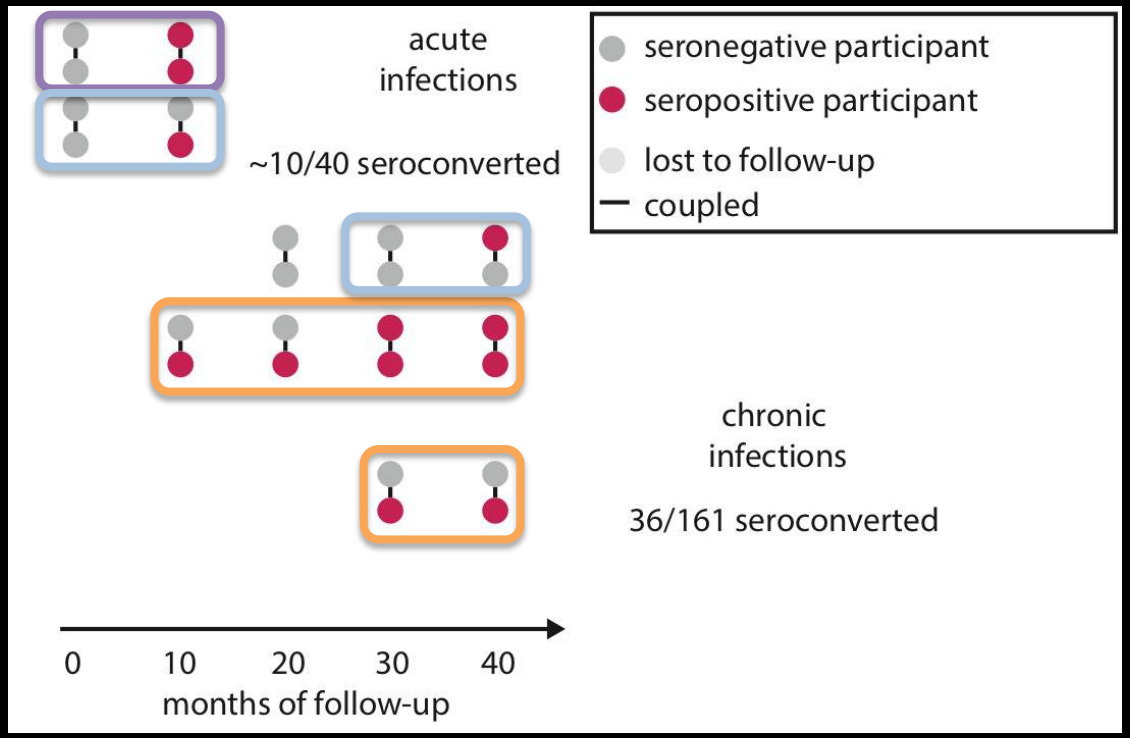
LOW acute infectivity



Bias 2: Inclusion Criteria

HIGH acute infectivity

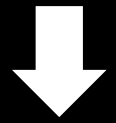
LOW acute infectivity



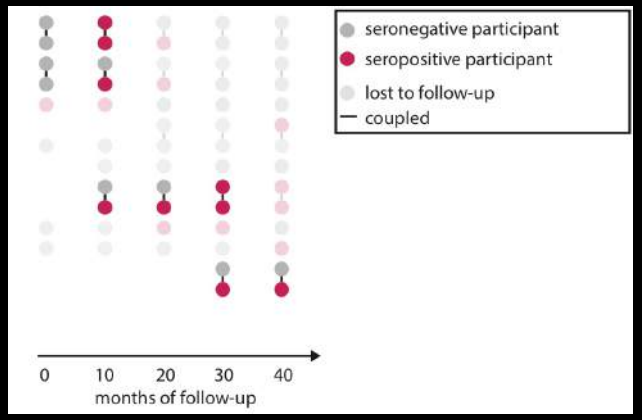
Accidentally excluded
~17 couples suggestive of low infectivity

Simulating Rakai Transmission & Observation

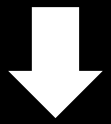
Input EHM_{acute}



1. Simulate transmission
2. Replicate Rakai study design

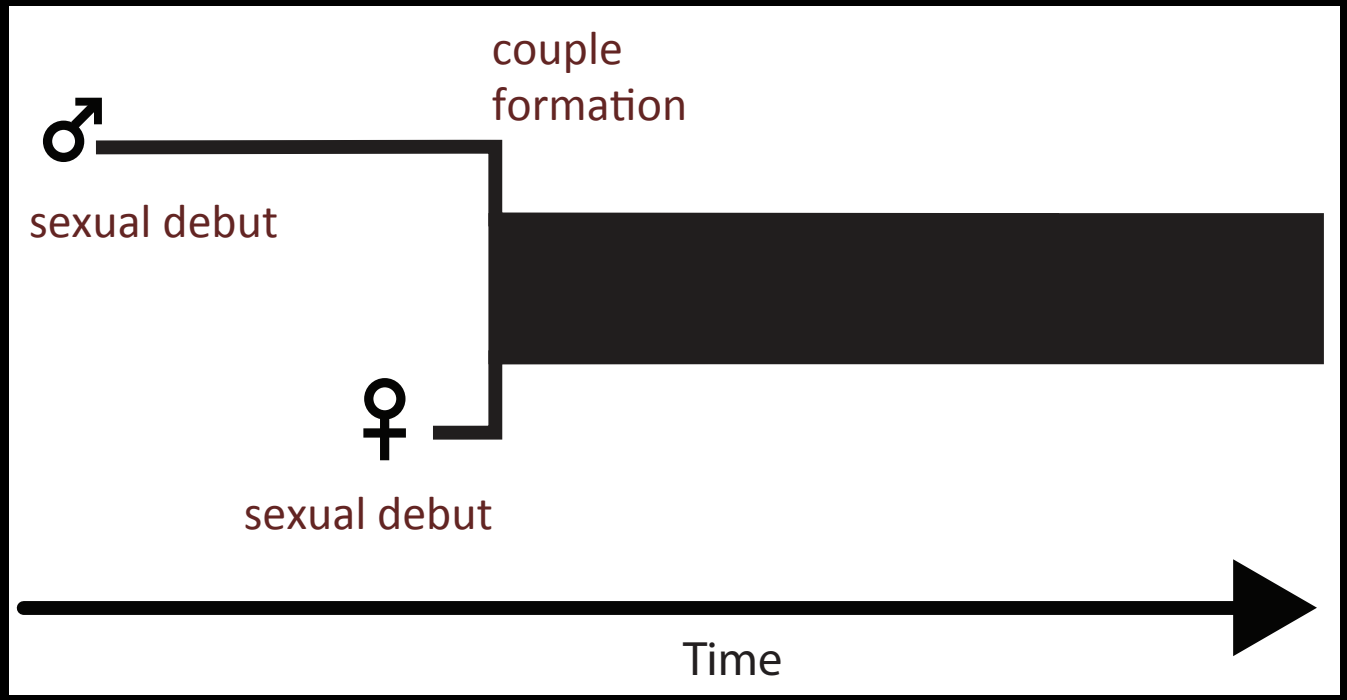


3. Apply published analyses to simulated data.



Estimated EHM_{acute}

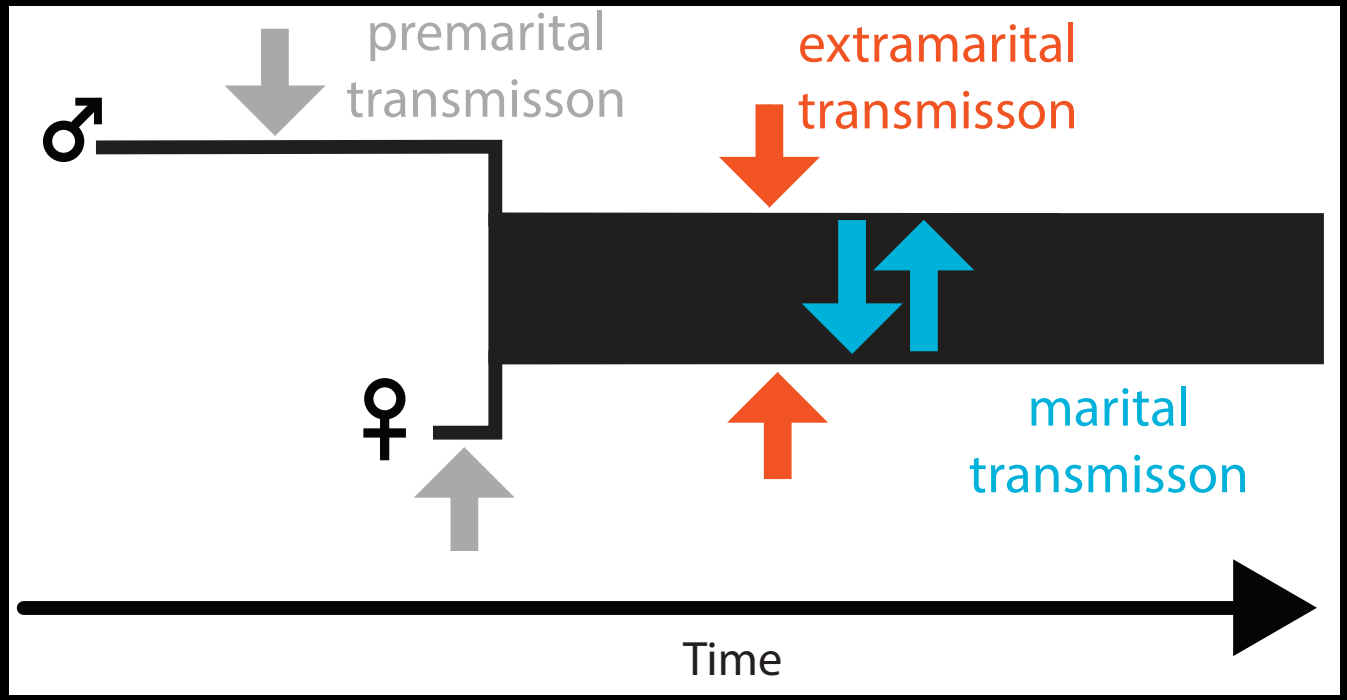
Couple Transmission Model



example relationship history

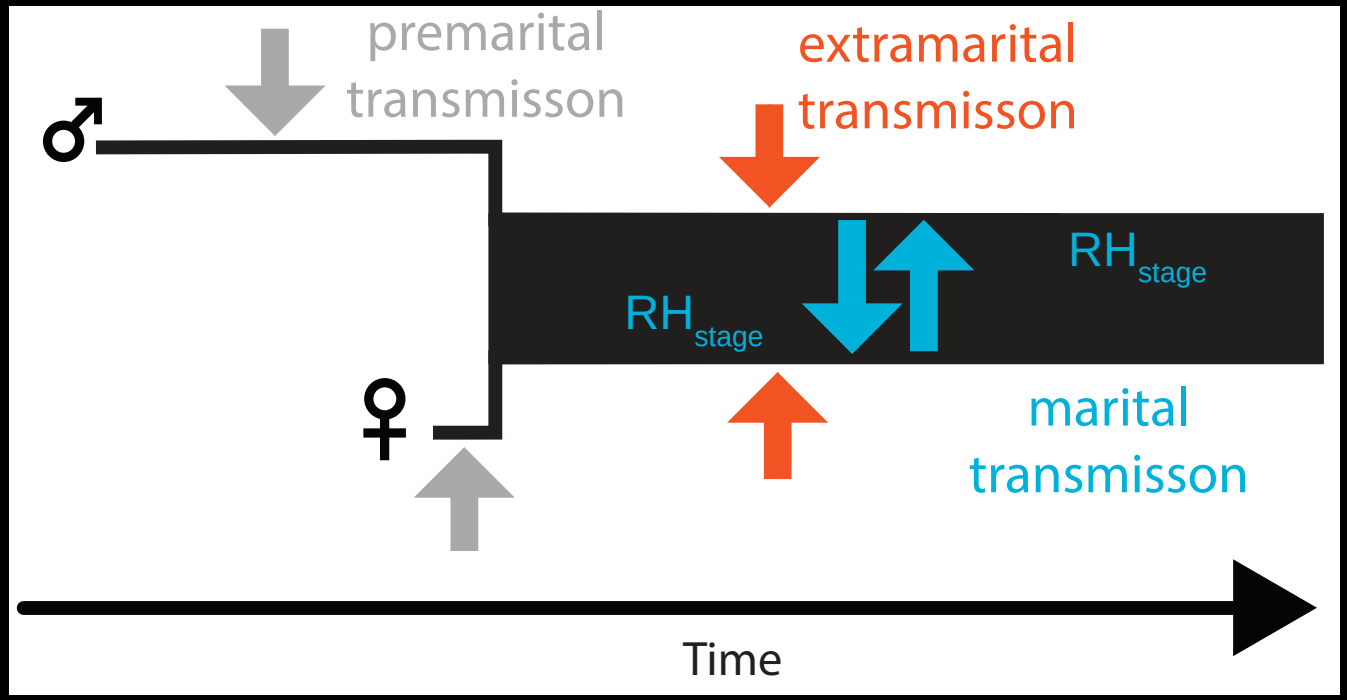
Bellan et al. (2013). *Lancet*.

Couple Transmission Model



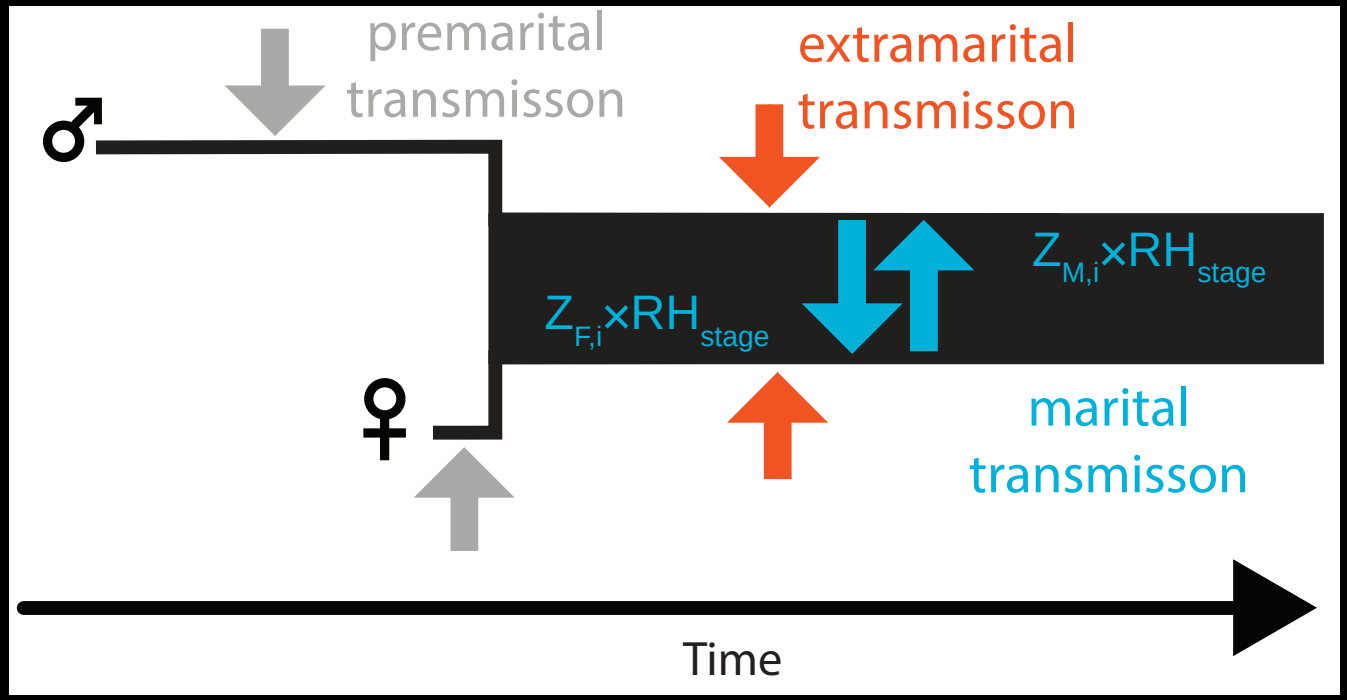
Bellan et al. (2013). *Lancet*.

Couple Transmission Model

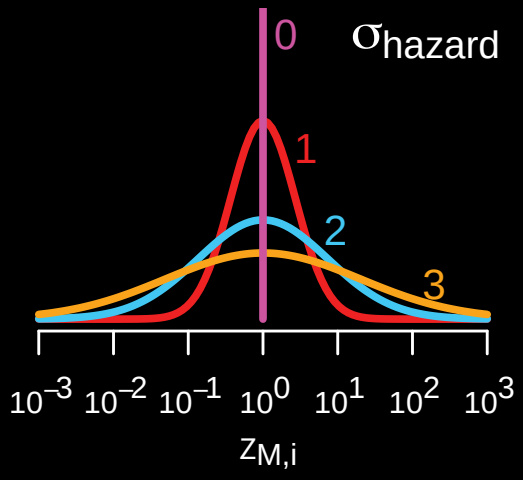


relative hazard (RH) varies by HIV stage

Couple Transmission Model

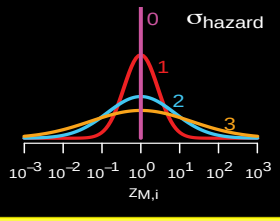


Heterogeneity



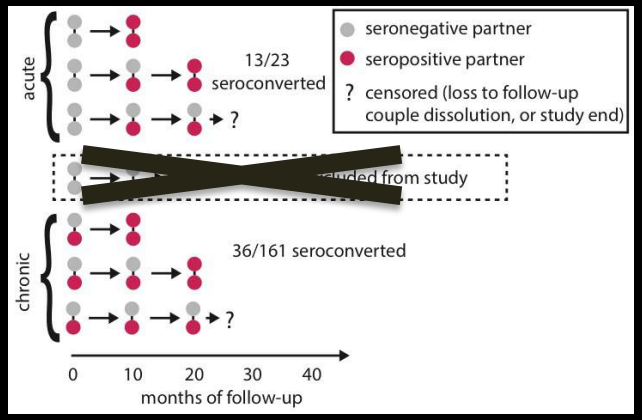
Simulating Rakai Transmission & Observation

Inputs



1. Simulate transmission in couples cohort ← process-centric
2. Replicate Rakai study design

data-centric →



3. Apply published analyses to simulated data.

Estimated EHM_{acute}

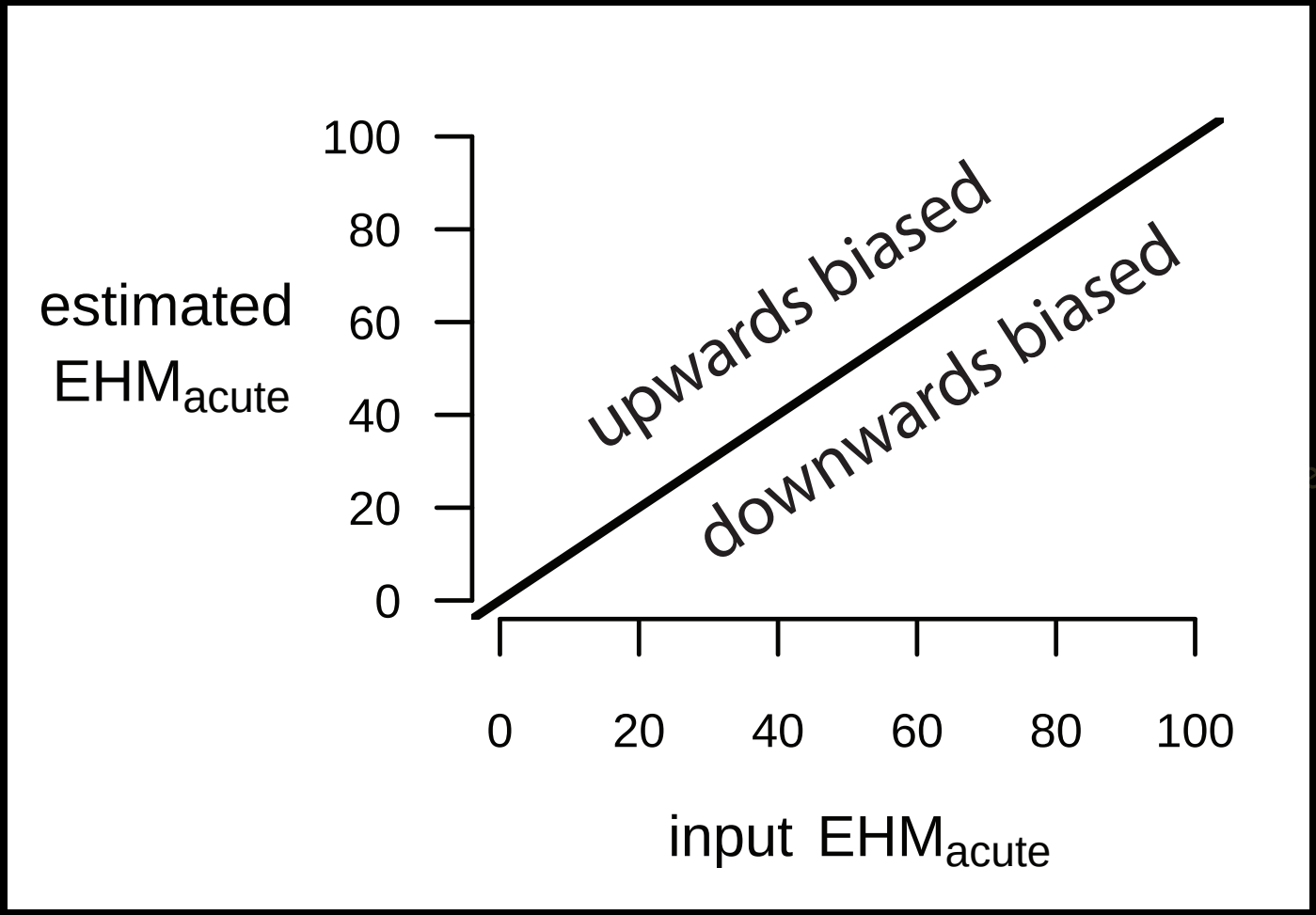
Simulating Rakai Transmission & Observation

Bias Analysis

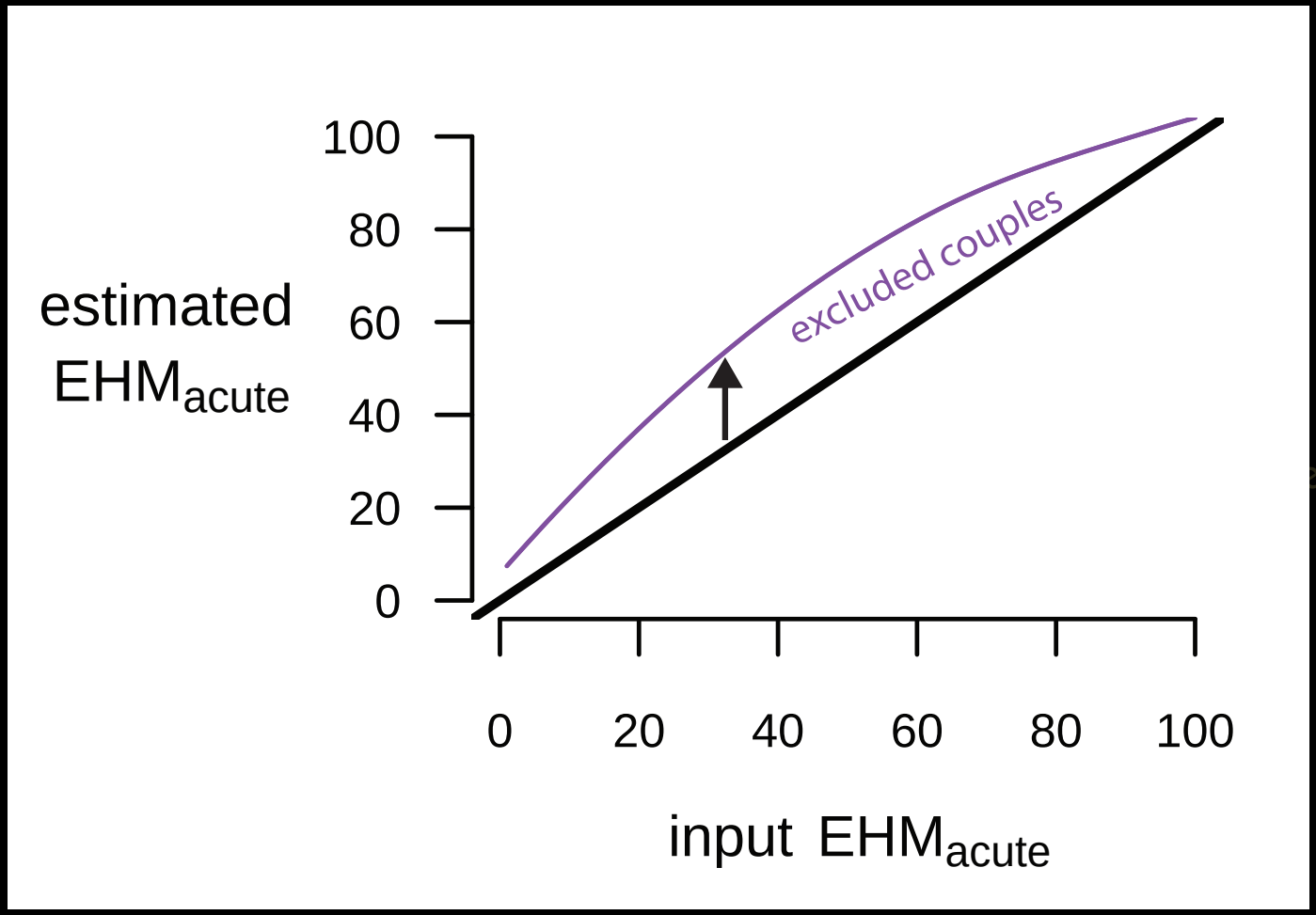
Estimates = Input Parameters ?

If not, what drives bias?

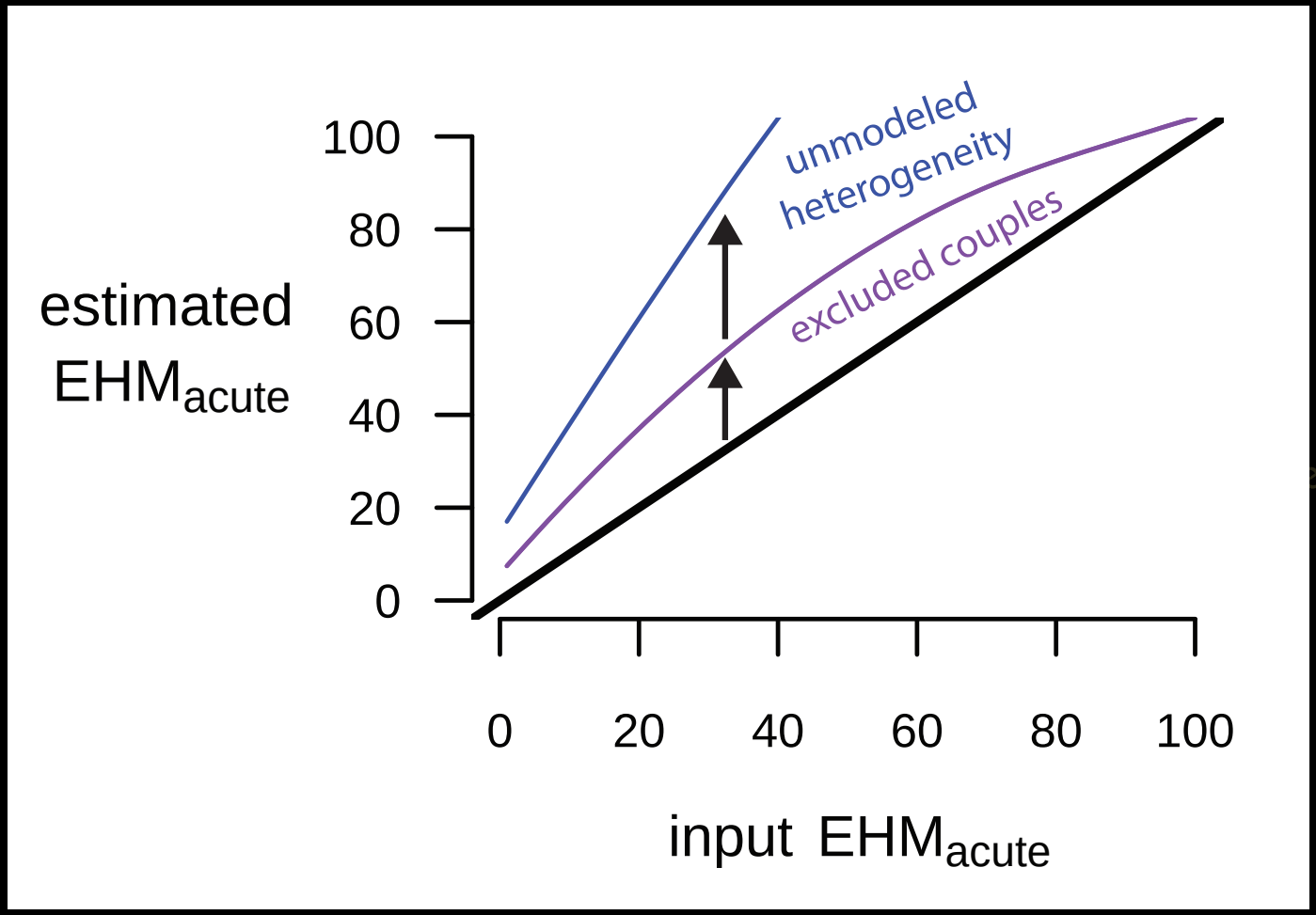
Bias Analysis



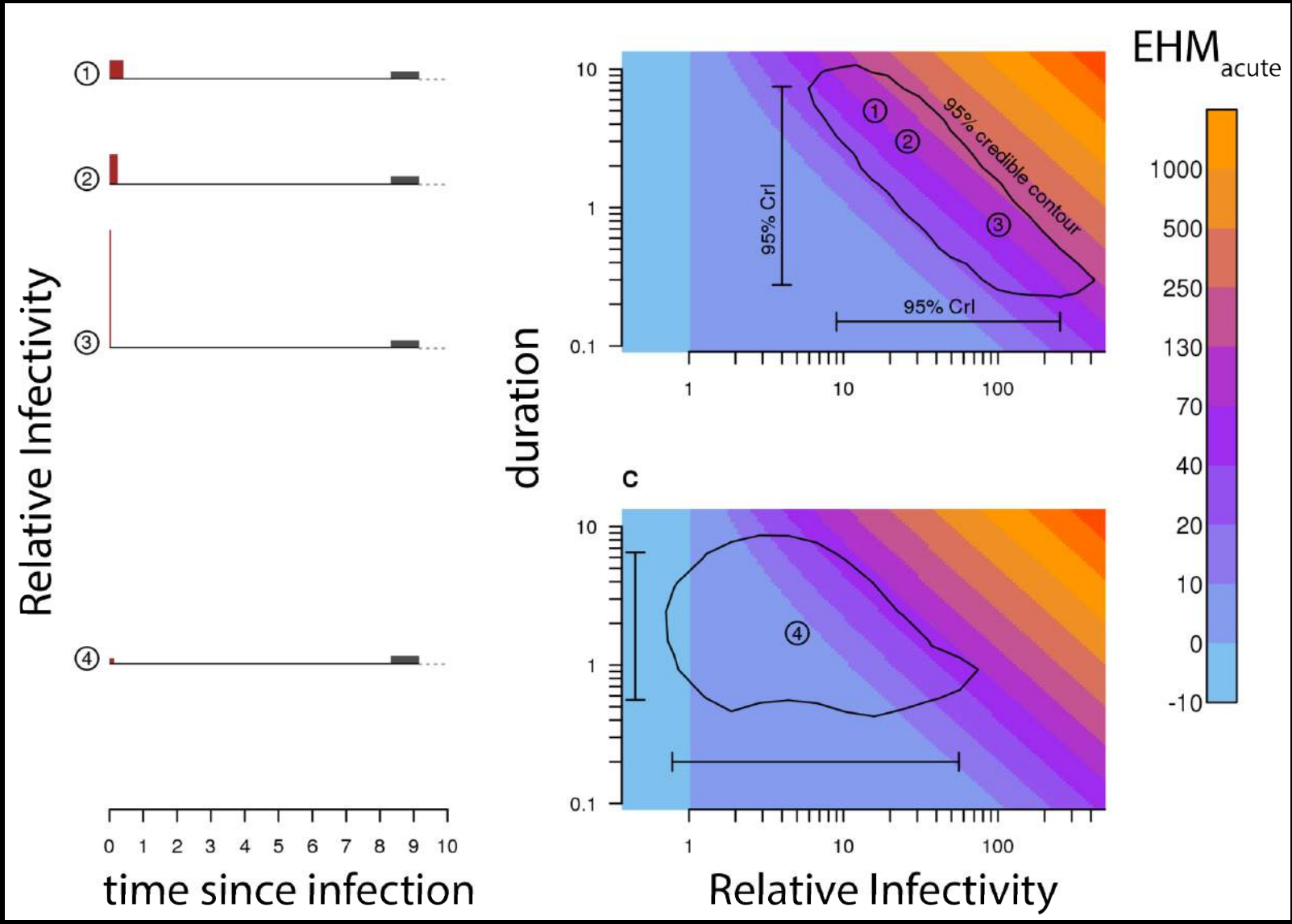
Bias Analysis



Bias Analysis



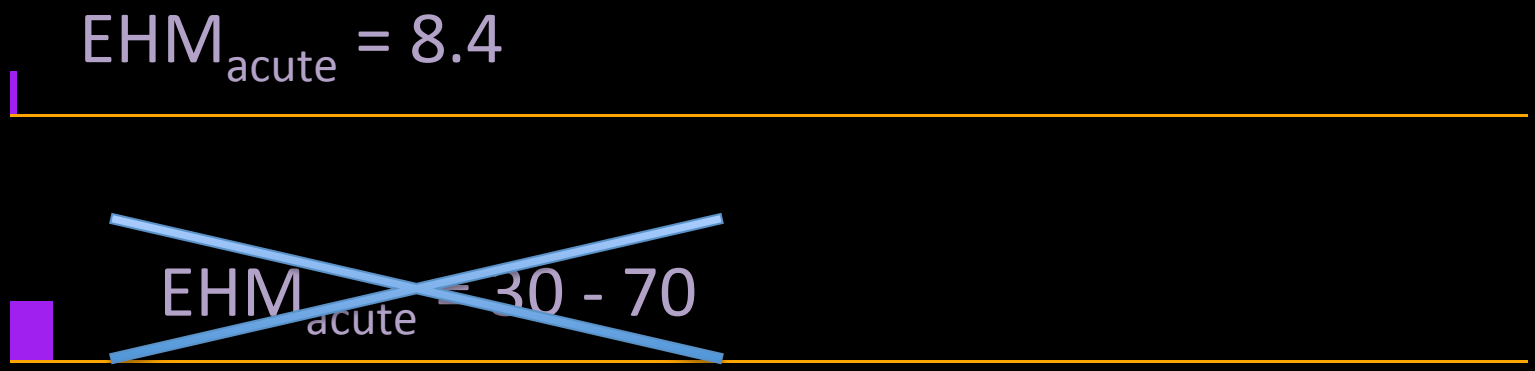
Bias-Adjusted Estimates



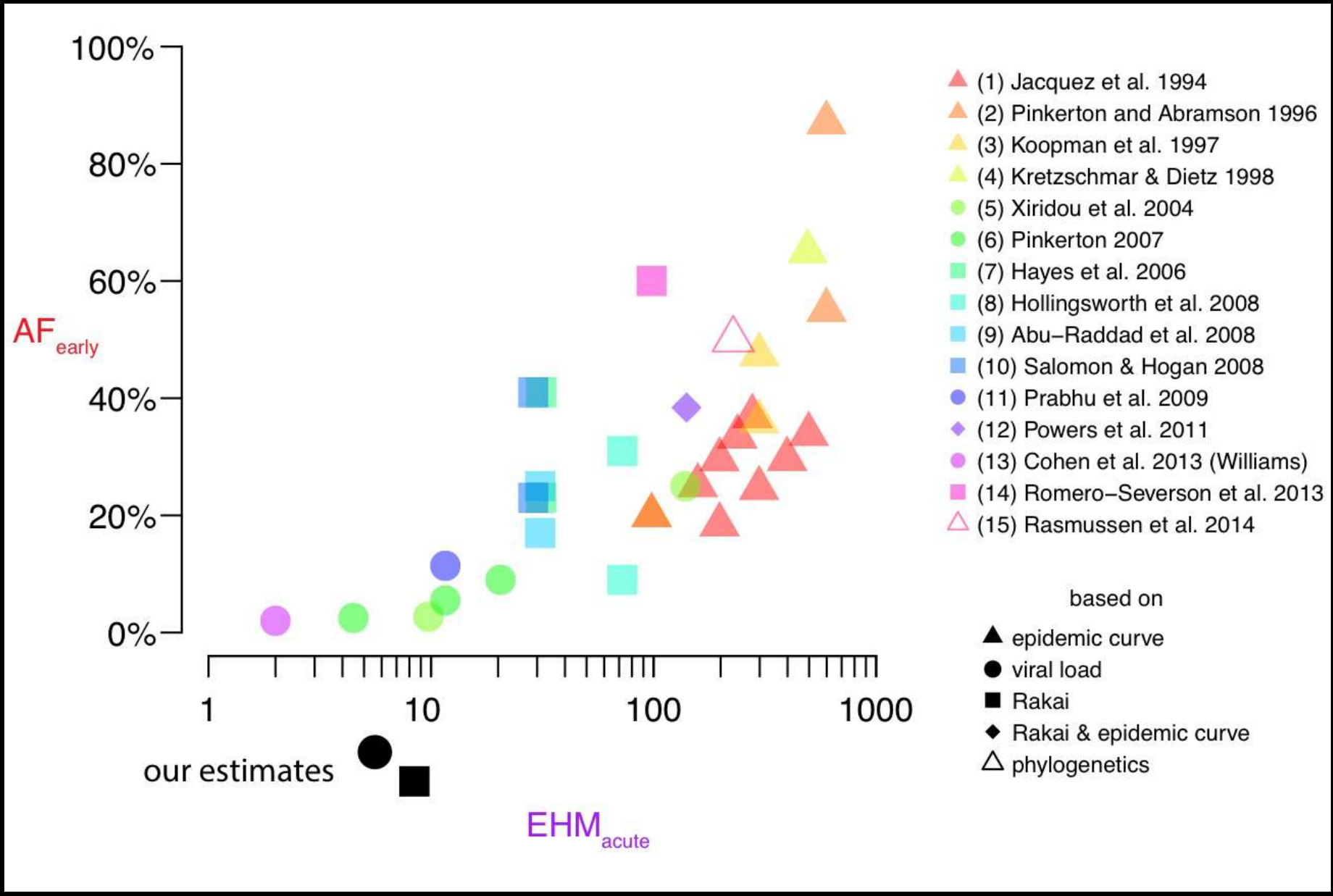
Bias-Adjusted Estimates

Estimation

What inputs consistent with Rakai data?



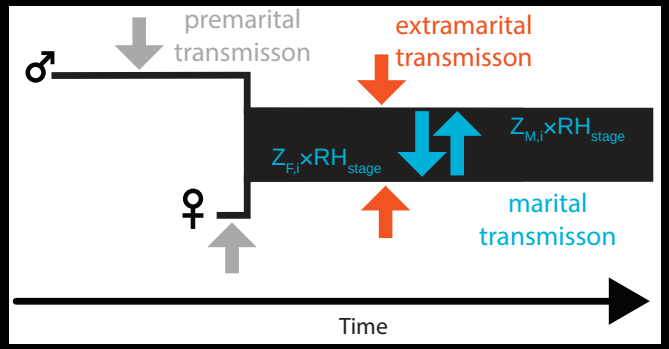
Variation in AF_{early} Estimates



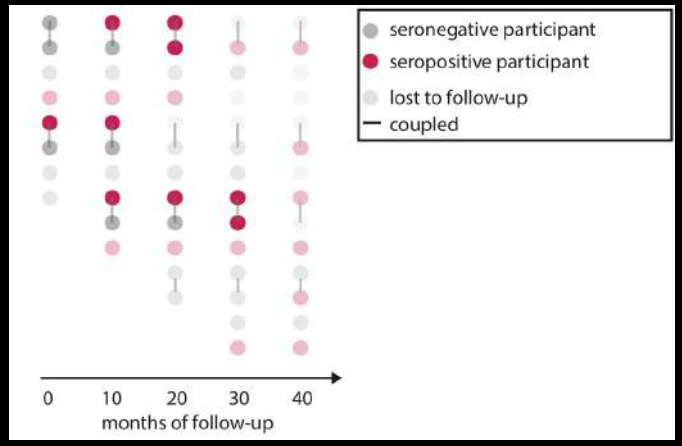
Conclusions

- Acute infectivity substantially overestimated
- Early transmission less likely to undermine Treatment as Prevention

process-centric



data-centric



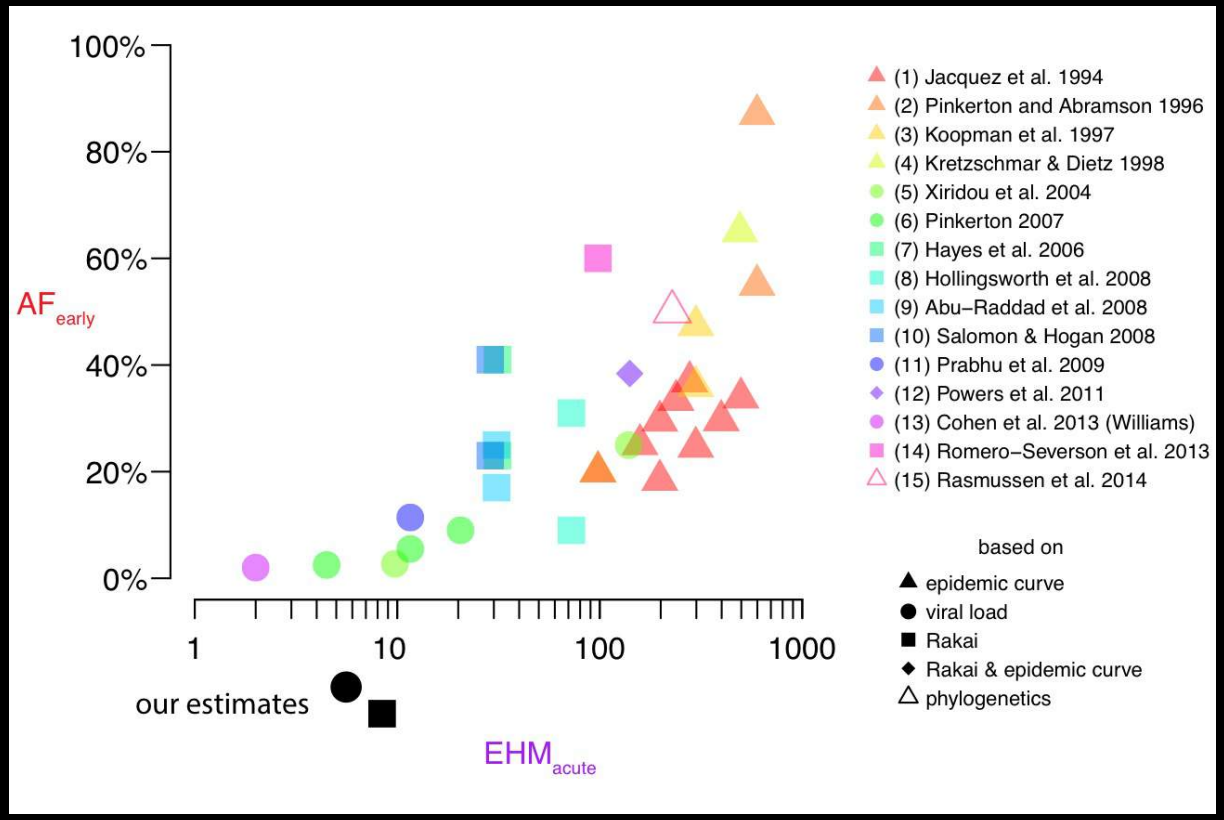
Bellan et al. 2015. *PLOS Medicine*.

Why publish?

- Communication (advance science & policy)
- Career
- Peer Review

How do modeling projects differ?

- Do not always collect empirical data
- Rely more heavily on literature



Development of Study Concept

- What is your question?

  How infectious is acute phase of HIV?

- Why is it interesting?

  Affects effectiveness of TasP

- Who is interested?

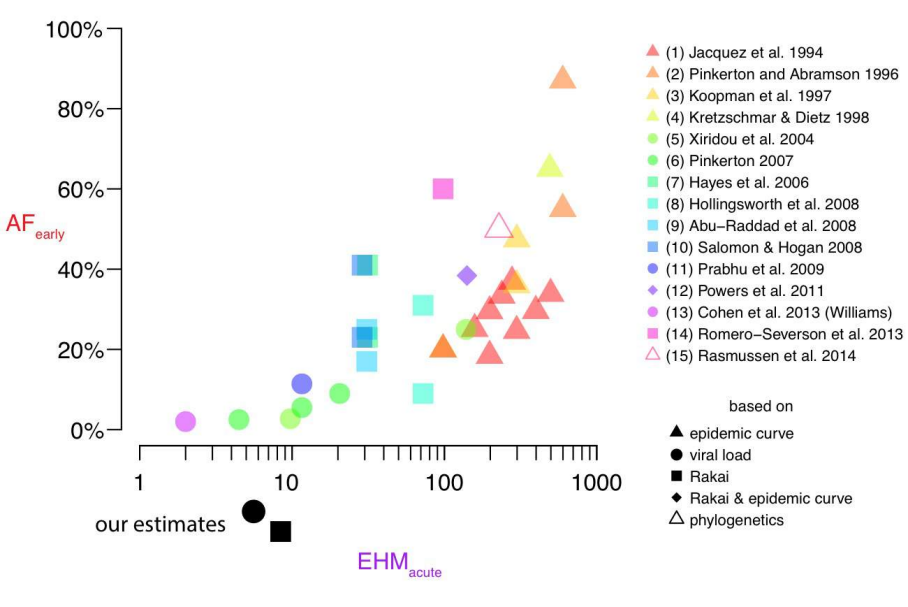
  HIV epidemiologists, policy makers

- Can it be narrowed down to a question about specific quantitative relationships?

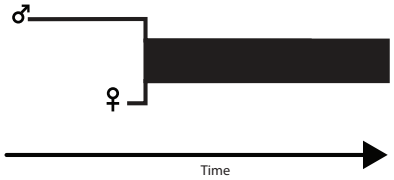
  EHM_{acute} estimated from available data

Review of Literature & Available Data

- Who has tried to answer this before and how did they do it?
- What are these studies short-comings?
- Find useful parameter estimates or data sets



The DHS Program
Demographic and Health Surveys



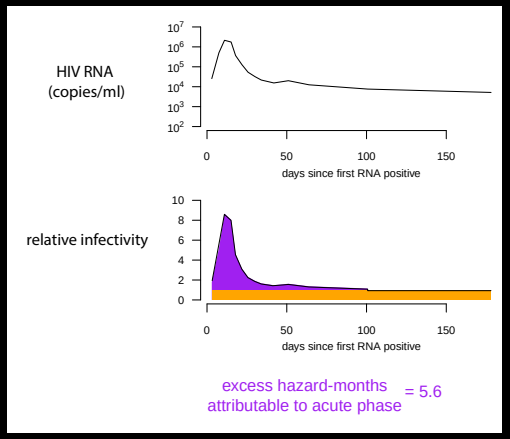
Construction of Modeling Framework

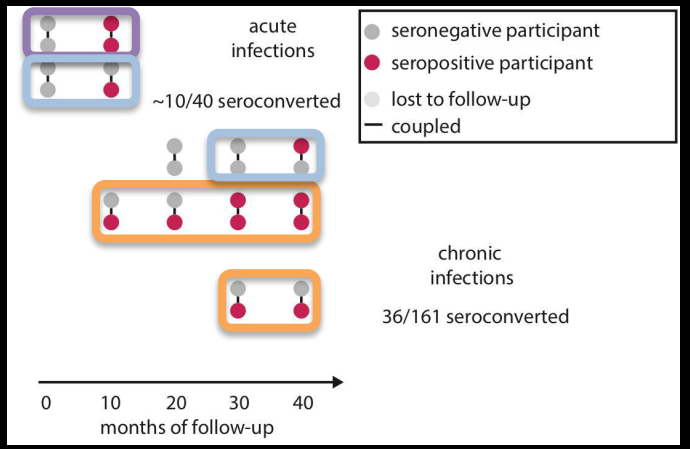
- Drawbacks of previous studies to mitigate
  - EHM_{acute}
  - heterogeneity/study design
  - simulation for validation

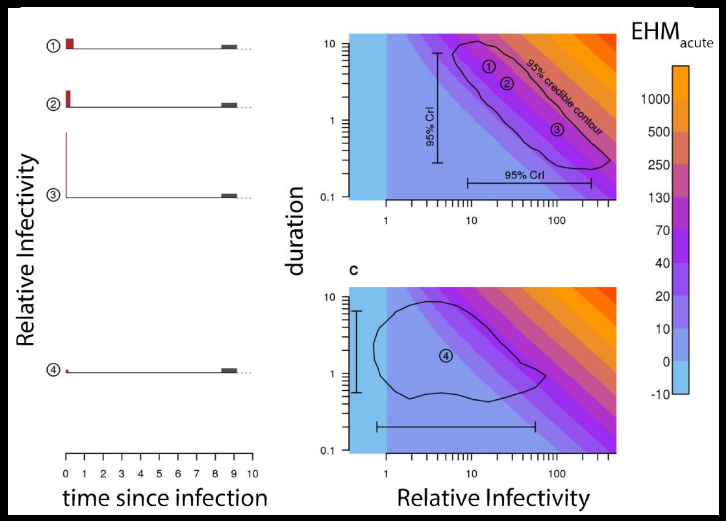
- modeling elements necessary for question
  - couple-centric
  - stochastic
  - monthly time step
  - heterogeneity, study design, variable infectivity

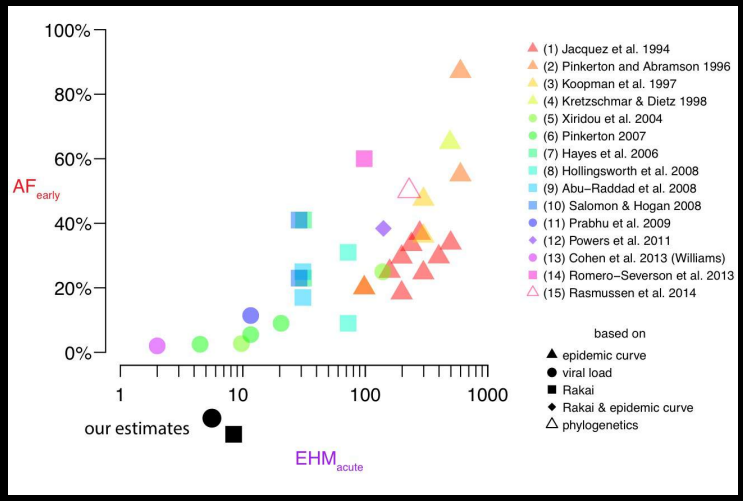
Writing the Model & Producing Output

- What are the 1-3 graphical outputs that will display the answer(s) to my question?









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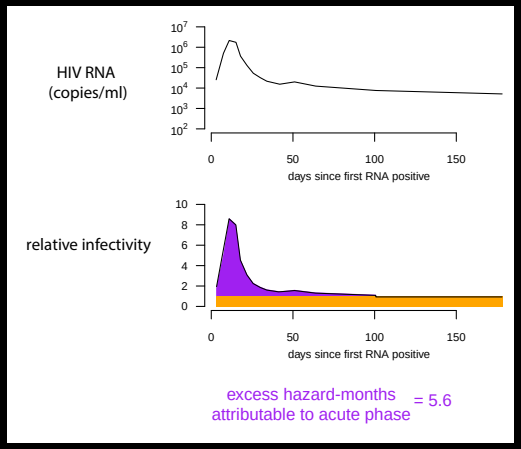

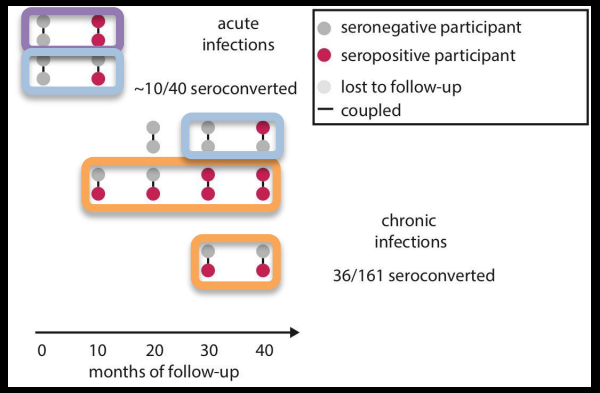

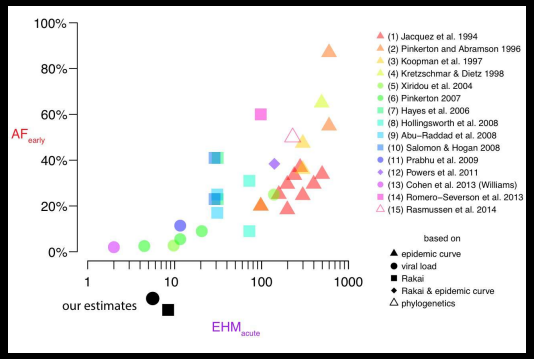

- Coding & debugging & commenting
- Simulation to verify methods & debug
- Write your methods at this stage!

Model Validation & Robustness

- Sensitivity/Elasticity analyses
- Model Validation (out-of-sample predictions)
- Comparison to alternative models

Choose the Journal

- Journal scope statement (on their website)

  "general interest on biomedical, environmental, social and political determinants of health… emphasizes work that advances clinical practice, health policy or pathophysiological understanding to benefit health"

- Audience

  epidemiologists, clinicians, policymakers, modelers

- How mathematical will your article be?

  slightly, most math in appendix (23 pgs, 9 figures, data)

- Text, figure, table limits

Write-Up of Results, Intro/Discussion

- State assumptions clearly

S5 Table. Assumptions made by previous analyses of the Rakai retrospective cohort that are relaxed in our re-analysis.

Study	Assumption	Bias in EHM_{acute}	Correction
Wawer et al. 2005	All infections and deaths occur exactly at the midpoint of the cohort interval in which they were observed.	Slight downward	We relax this assumption (as does Hollingsworth et al.) by including a latent (unobserved) variable for infection time.
Wawer et al. 2005 Hollingsworth et al. 2008	Incident, prevalent and late couples are *different types* of couples and real couples do *not* switch between these categories.	Slight downward	We relax this assumption by modeling in such a way that each of these categories simply represents that the cohort study only *observed* each couple in one of their disease phase categories.
Wawer et al. 2005 Hollingsworth et al. 2008	Couples were sampled in an unbiased manner.	Substantial upward	In reality, couples providing strong evidence for lower acute phase infectivity were more likely to be excluded from the Rakai cohort based on exclusion criteria of couples lost to follow-up. We relaxed this assumption by explicitly including the study inclusion criteria in our model.
Wawer et al. 2005 Hollingsworth et al. 2008	Transmission rates into couples and between serodiscordant partners are the same (i.e. homogenous) for all couples.	Substantial upward	We relaxed this assumption by allowing each individual to have a risk deviate that affects their risk of acquiring HIV; risk deviates were sampled from lognormal distributions with standard deviations estimated by fitting our couples transmission model to the data.

Submission

- Cover letter:

  If journal isn't mathematical,
  state clearly why approach is appropriate!

Revisions

- Expect reviewers to question assumptions
  - Helps you choose additional sensitivity analyses
- Expect some reviewers to not understand methods
  - Helps improve clarity

Revisions

Please also keep in mind the general medical audience of PLOS Medicine; the paper needs to be understandable by individuals who are not expert modellers in the field.

We have made several changes to the manuscript to make it more understandable to the general reader:

- We have moved the technical explanation of the couples transmission model to the appendix, and only highlight the two main points necessary to understand our results: (1) changing hazard by disease stage, (2) heterogeneity in risk between couples.
- Replaced the technical description of the simulation model with a schematic diagram in Figure 3.

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- Replaced the technical description of the simulation model with a schematic diagram in Figure 3.

Revisions

"We believe that the reviewer misinterpreted our XXXX because we were not clear enough. We have clarified this by XXXX."

Acknowledgements

- Juliet Pulliam, Meyers Lab
- International Clinics on Infectious Disease Dynamics and Data (ICI3D)

MIDAS
Models of Infectious Disease Agent Study
Funded by the National Institutes of Health

NATIONAL INSTITUTES OF HEALTH

U.S. DEPARTMENT OF HOMELAND SECURITY

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

FOGARTY

NSF

SACEMA
DST/NRF Centre of Excellence in Epidemiological Modelling and Analysis

NSERC CRSNG

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).