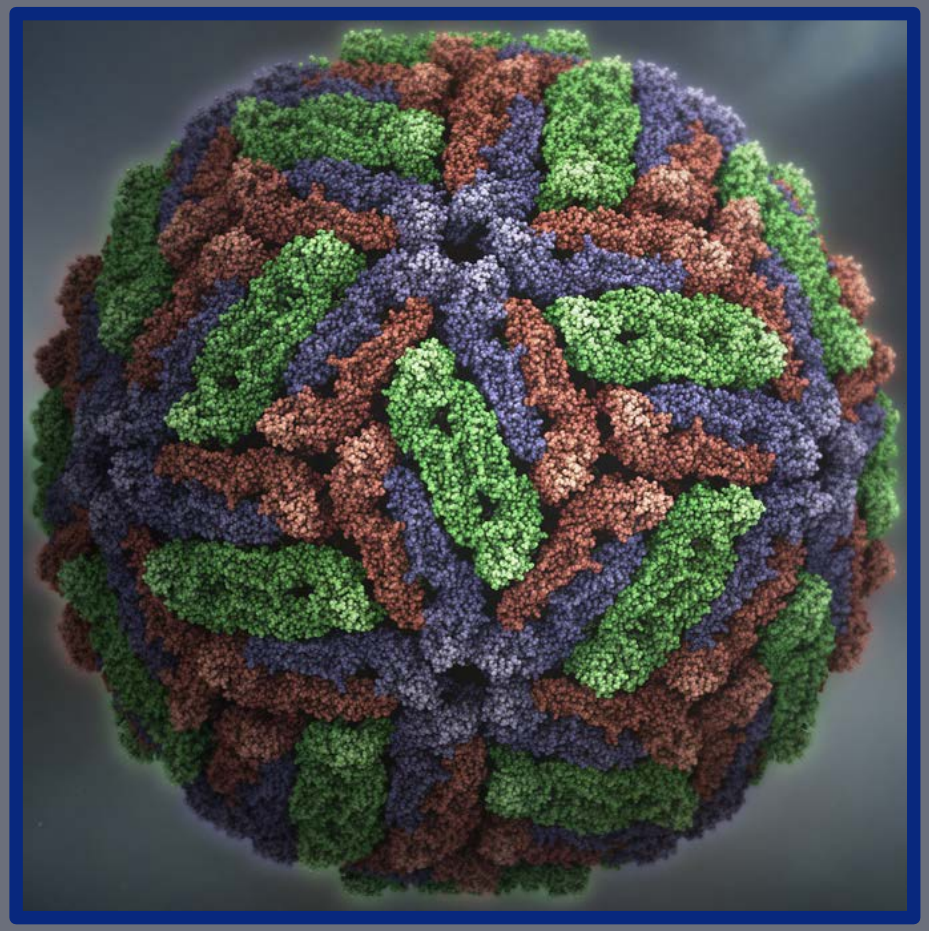
Estimating serotype-specific dengue virus force of infection and temporary cross immunity using longitudinal serological data

Bobby Reiner
Assistant Professor
Epidemiology & Biostatistics
Indiana University School of Public Health



Dengue virus

Dengue virus (DENV) is a mosquito-borne viral infection caused by any of four related, but antigenically distinct virus serotypes (DENV-1, -2, -3, and -4)

Dengue virus

The primary vector of DENV is *Aedes aegypti* (the yellow-fever mosquito). *Aedes albopictus* (the tiger mosquito) is another, less competent, vector.

Dengue virus

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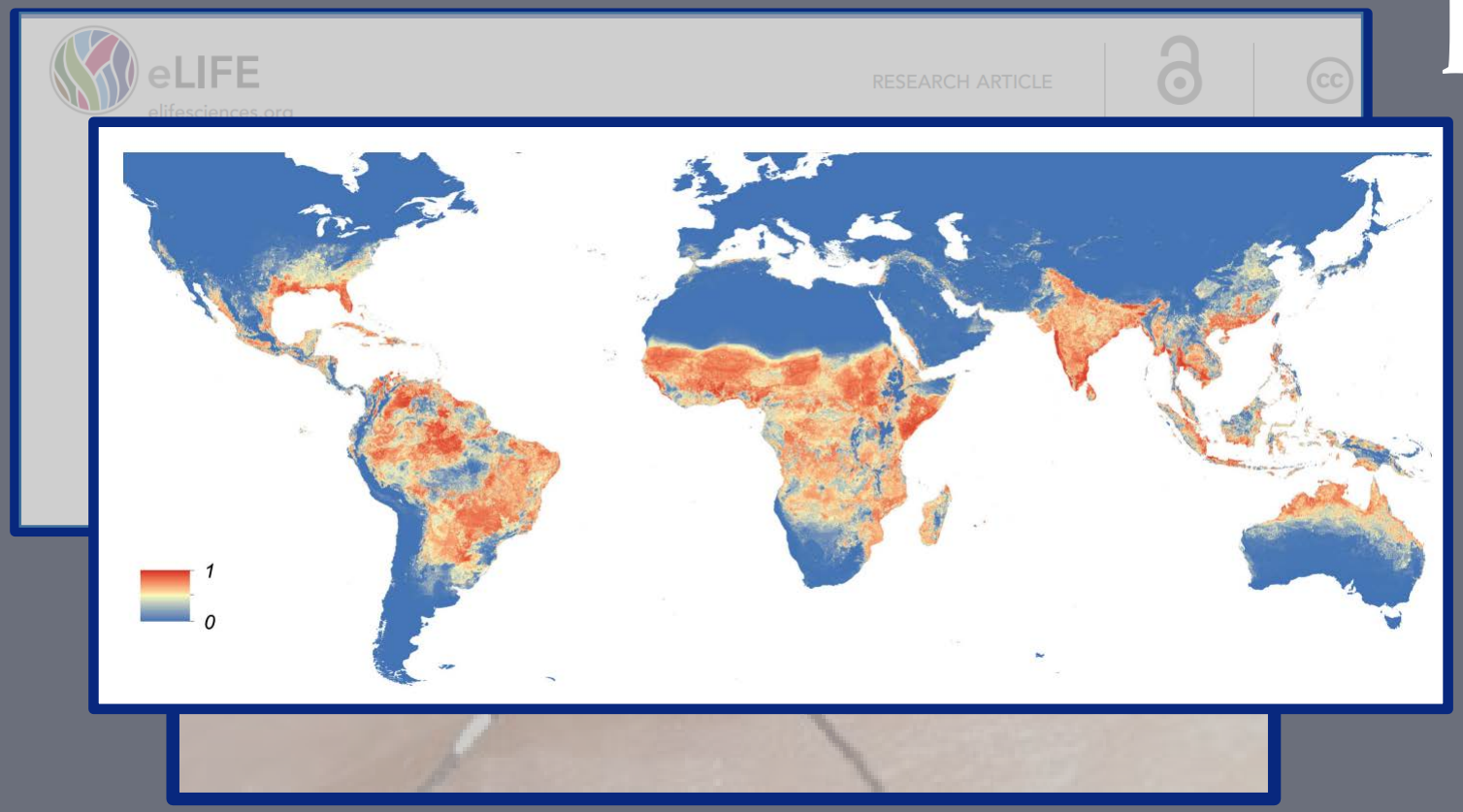
Crucially, *Ae. aegypti* has a limited dispersal distance (<100m)

Dengue virus

Recent work has shown that the range of these mosquitoes has grown in the past 40 years.



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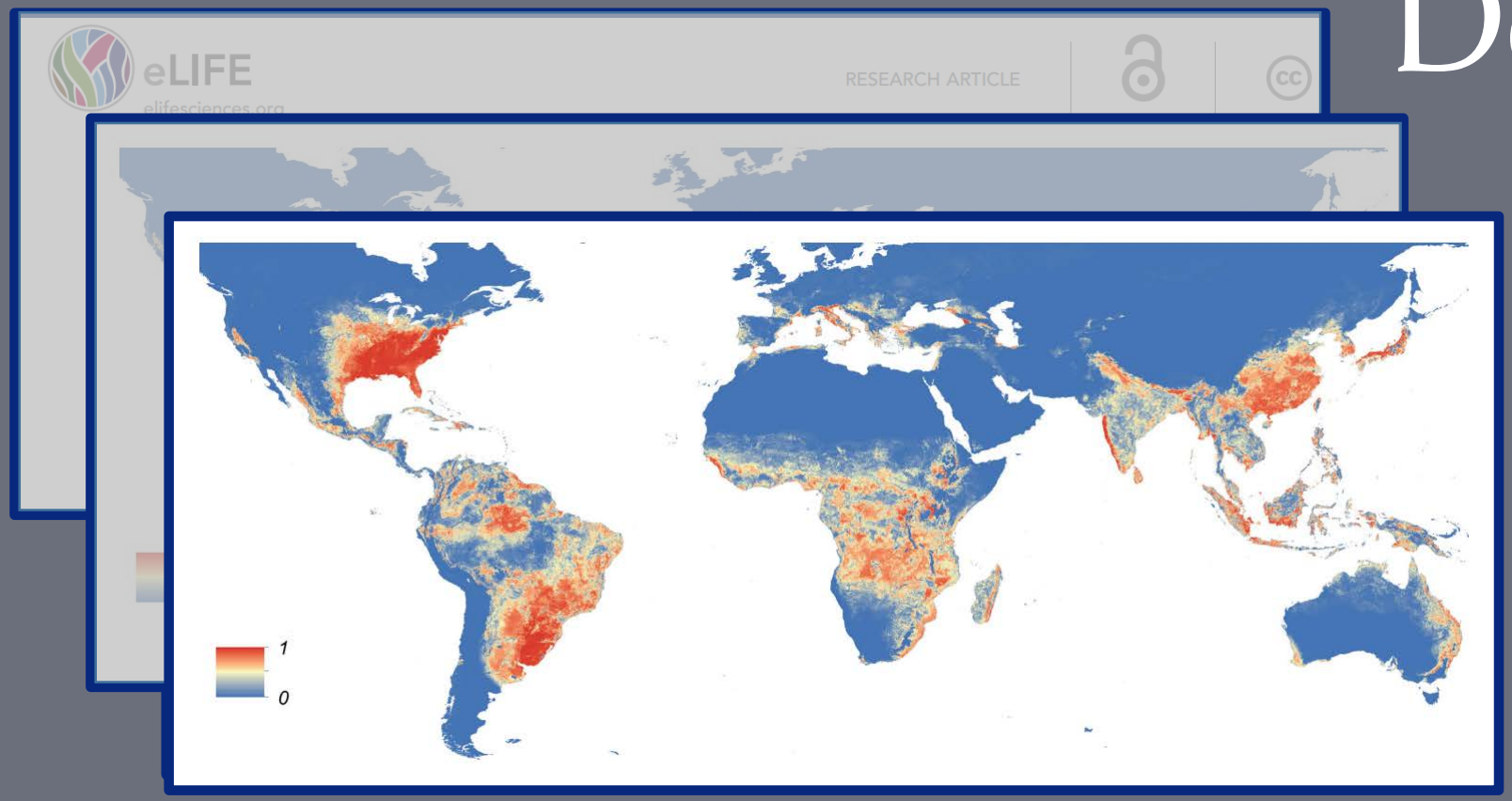

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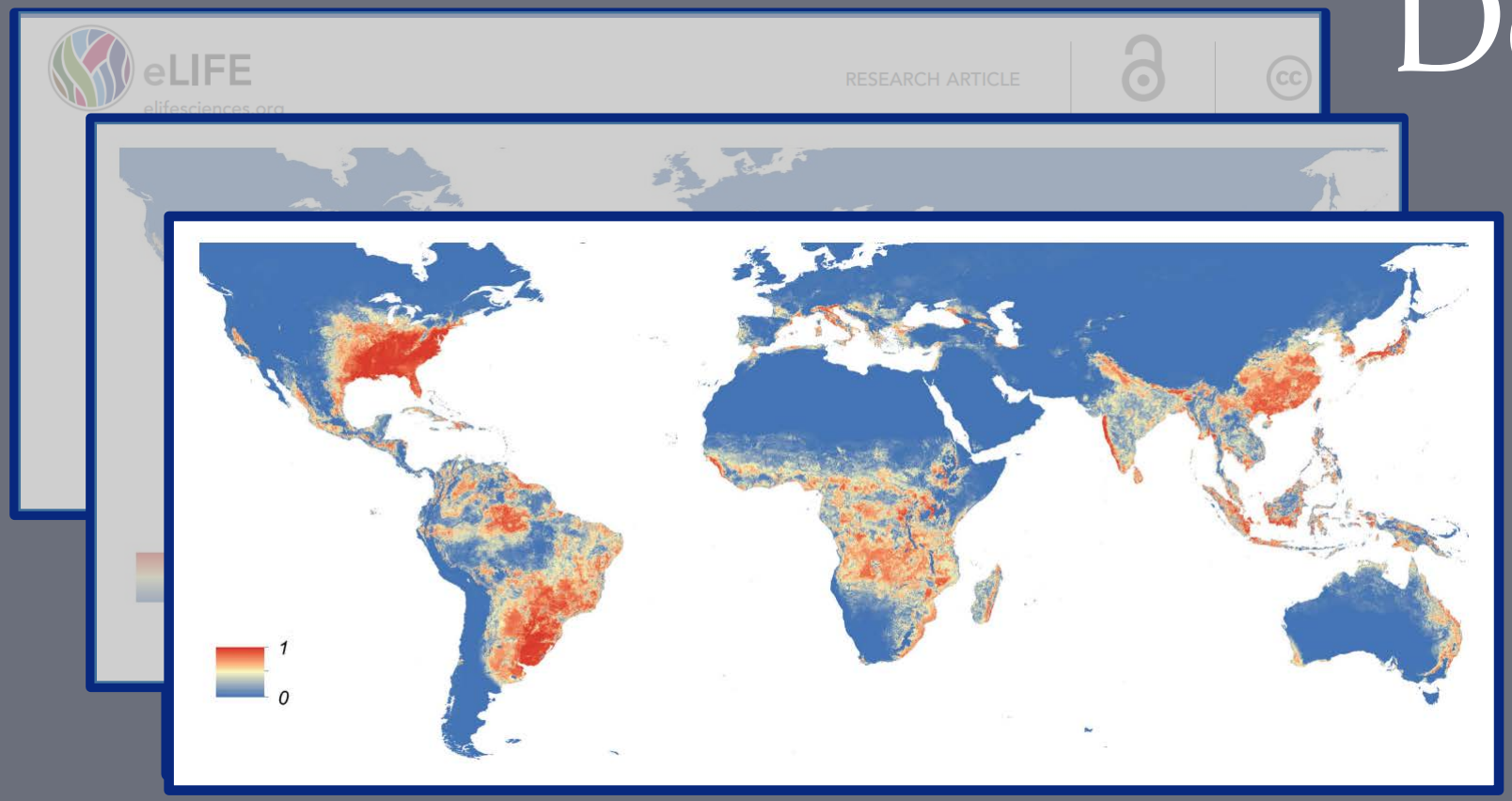
Dengue virus



Recent work has shown that the range of these mosquitoes has grown in the past 40 years.

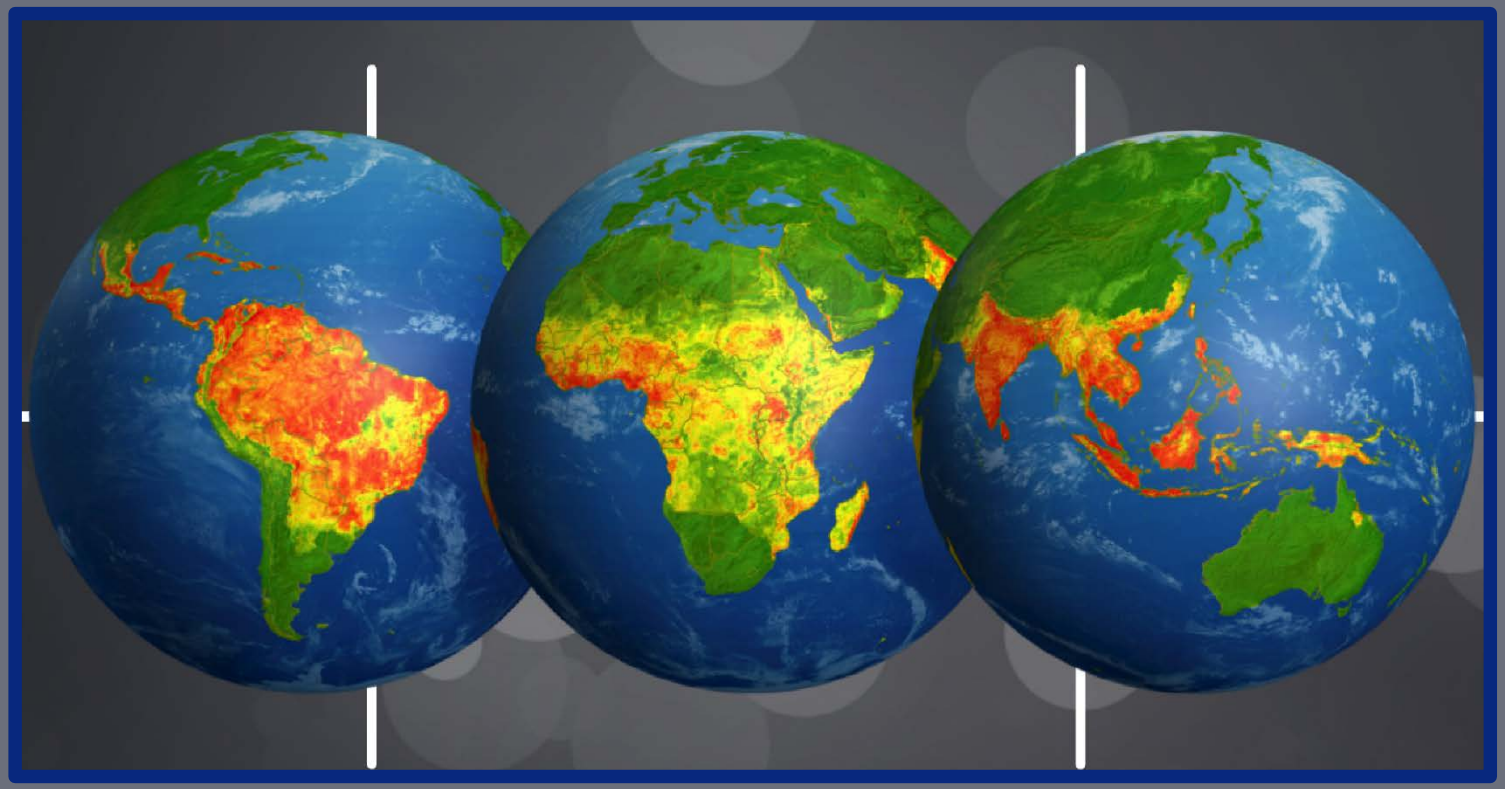
These mosquitoes are also vectors for chikungunya virus and Zika virus

LETTER

doi:10.1038/nature12060

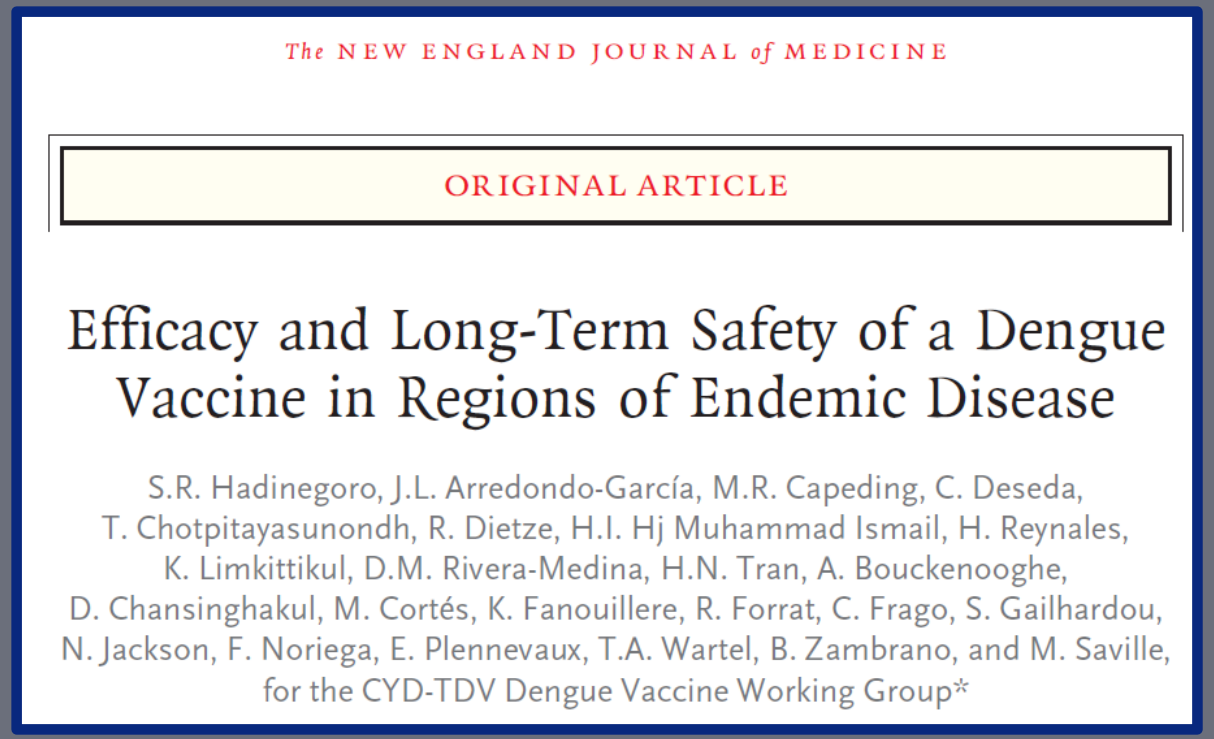
The global distribution and burden of dengue

Samir Bhatt[1], Peter W. Gething[1], Oliver J. Brady[1,2], Jane P. Messina[1], Andrew W. Farlow[1], Catherine L. Moyes[1], John M. Drake[1,3], John S. Brownstein[4], Anne G. Hoen[5], Osman Sankoh[6,7,8], Monica F. Myers[1], Dylan B. George[9], Thomas Jaenisch[10], G. R. William Wint[1,11], Cameron P. Simmons[12,13], Thomas W. Scott[9,14], Jeremy J. Farrar[12,13,15] & Simon I. Hay[1,9]



Dengue virus

Not surprisingly (based on the increased range of the vectors) the burden of DENV has also increased to include half the world's population with an estimated 50-100 million infections and 20,000 deaths yearly



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease

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Dengue virus

Over the past decades, there has been increased interest (and development) in vaccines for DENV.

Dengue virus

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for the CYD-TDV Dengue Vaccine

B Participants under 9 Yr of Age

Serotype in Trial CYD14	Vaccine Group	Control Group	Vaccine Efficacy (95% CI)
	no. of cases/total no.		
All serotypes	196/3532	173/1768	44.6 (31.6 to 55.0)
Serotype 1	80/3532	74/1768	46.6 (25.7 to 61.5)
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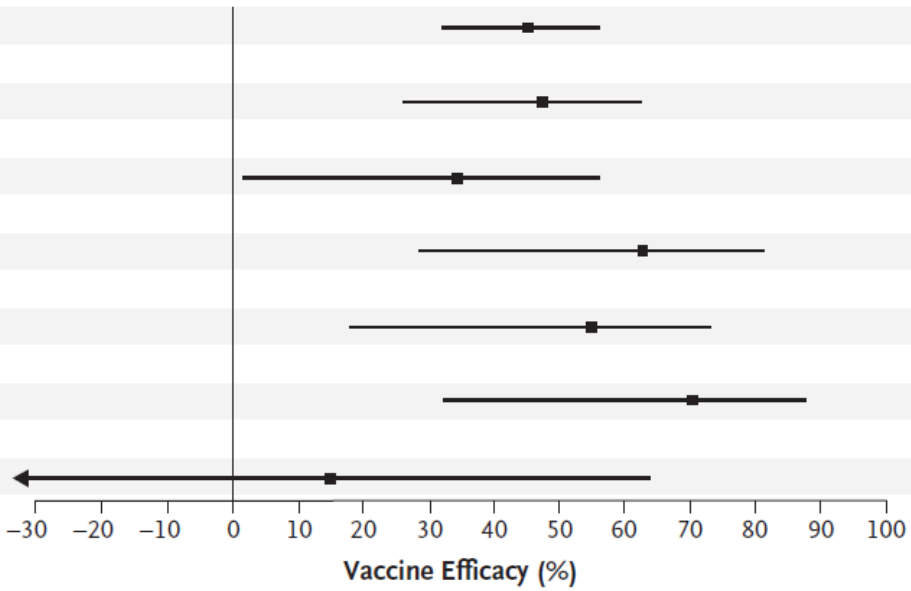

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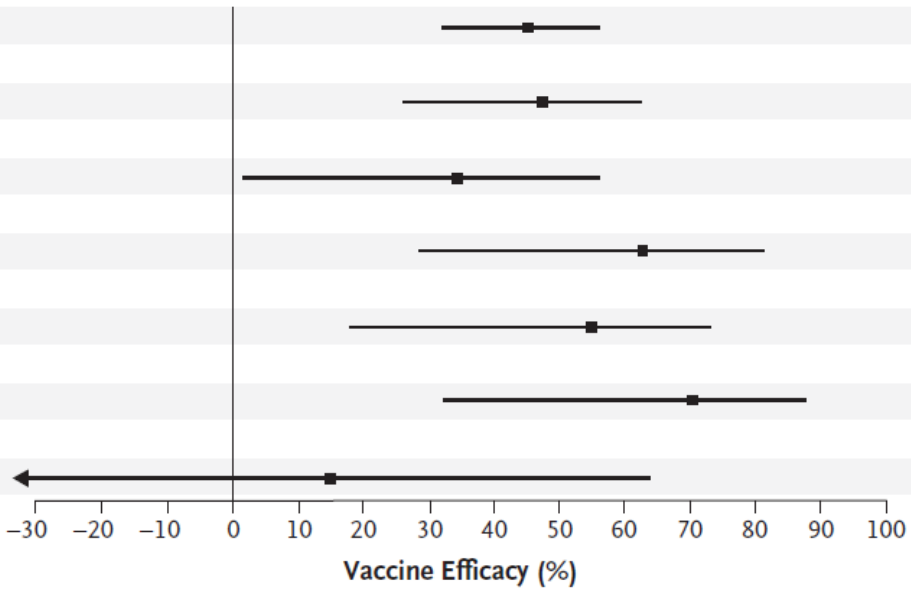

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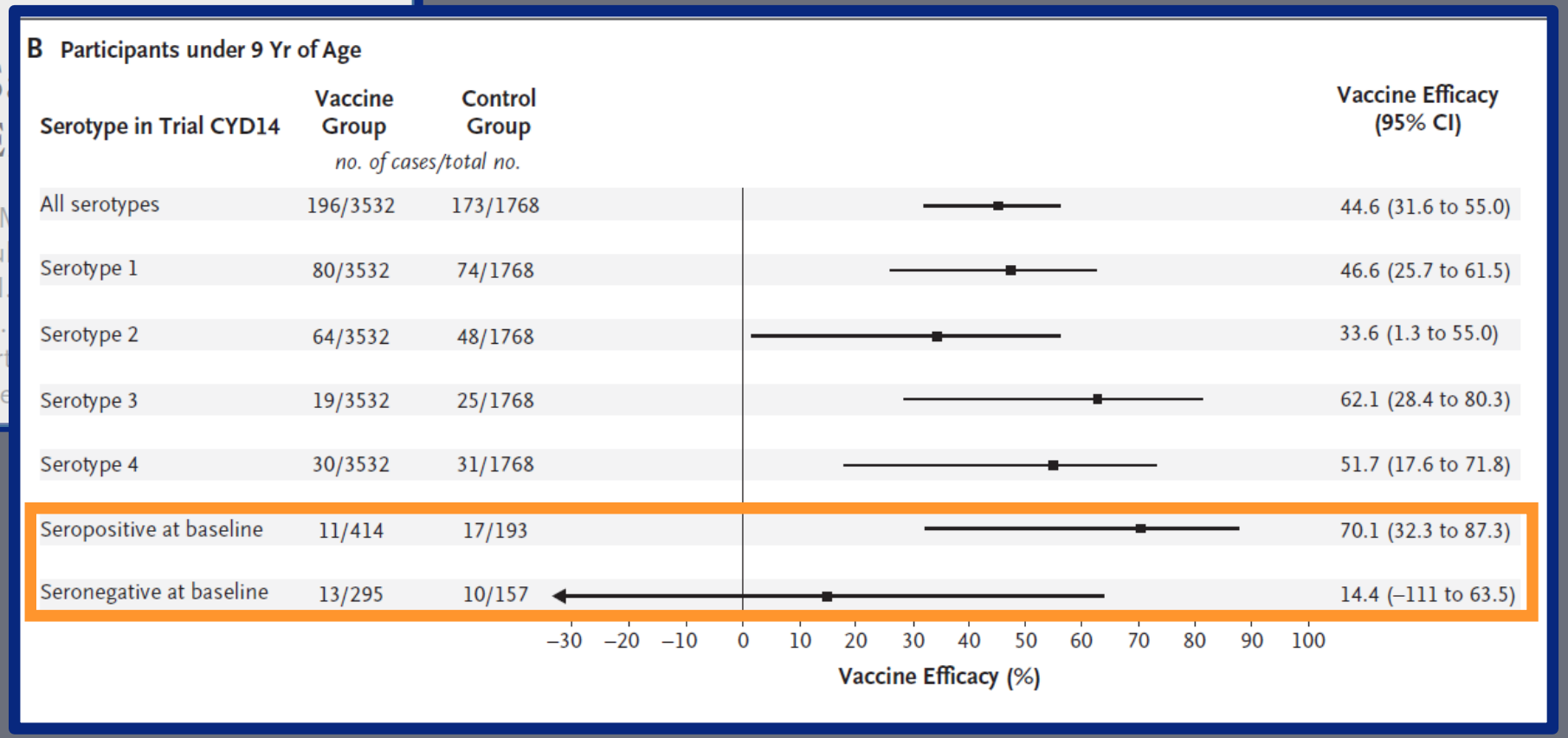

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Performance has been sub-optimal

Ecology of DENV

INTERFACE

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Research

Cite this article: Kraemer MUG, Perkins TA, Cummings DAT, Zakar R, Hay SI, Smith DL, Reiner Jr RC. 2015 Big city, small world: density, contact rates, and transmission of dengue across Pakistan. *J. R. Soc. Interface* **12**: 20150468.
http://dx.doi.org/10.1098/rsif.2015.0468

Big city, small world: density, contact rates, and transmission of dengue across Pakistan

M. U. G. Kraemer[1], T. A. Perkins[2,3], D. A. T. Cummings[4], R. Zakar[5], S. I. Hay[3,6,7], D. L. Smith[1,3,8] and R. C. Reiner Jr[3,9]

[1]Department of Zoology, University of Oxford, Oxford OX1 3PS, UK
[2]Department of Biological Sciences and Eck Institute for Global Health, University of Notre Dame, Notre Dame, IN 46556, USA
[3]Fogarty International Center, National Institutes of Health, Bethesda, MD 20892, USA
[4]Department of Epidemiology, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD 21205, USA
[5]Department of Public Health, University of Punjab, Lahore 54590, Pakistan
[6]Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK
[7]Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA 98121, USA
[8]Sanaria Institute for Global Health and Tropical Medicine, Rockville, MD 20850, USA
[9]Department of Epidemiology and Biostatistics, Indiana University School of Public Health, Bloomington, IN 47405, USA

Ecology of DENV

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Big city, small world: density, contact rates, and transmission of dengue across

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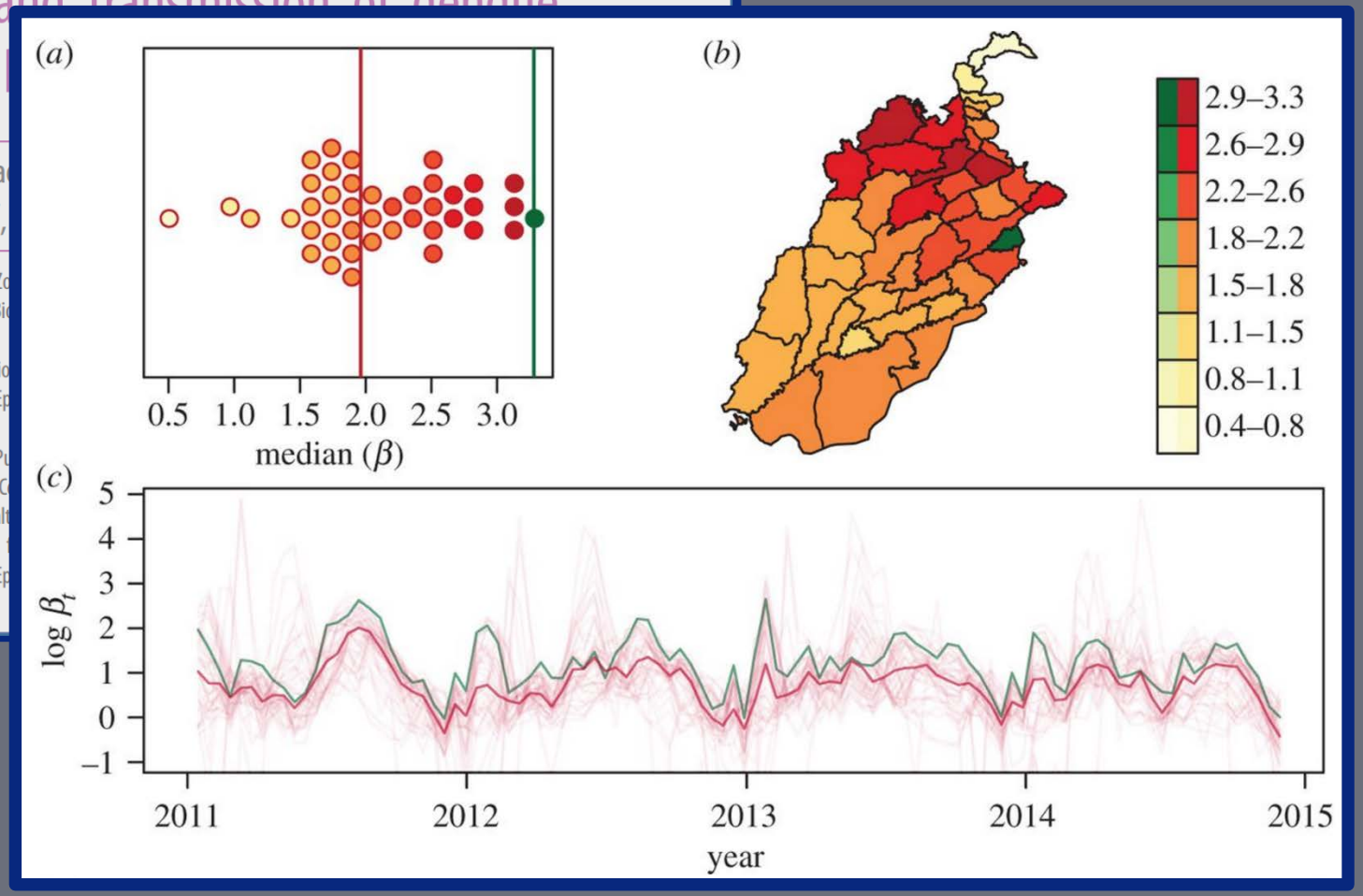

Ecology of DENV

PNAS

House-to-house human movement drives dengue virus transmission

Steven T. Stoddard[a,b,1], Brett M. Forshey[c,d,e], Amy C. Morrison[a,c,d], Valerie A. Paz-Soldan[f], Gonzalo M. Vazquez-Prokopec[b,g], Helvio Astete[c,d], Robert C. Reiner, Jr.[a,b], Stalin Vilcarromero[c,d], John P. Elder[h], Eric S. Halsey[c,d], Tadeusz J. Kochel[c,d,2], Uriel Kitron[b,g], and Thomas W. Scott[a,b]

[a]Department of Entomology, University of California, Davis, CA 95616; [b]Fogarty International Center, National Institutes of Health, Bethesda, MD [c]Virology Department, US Naval Medical Research Unit No. 6, Hospital Centro Medico Naval, Lima, Peru; [d]Virology Department, US Naval Medical Unit No. 6, Clinica Naval de Iquitos, Iquitos, Peru; [e]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, IA 52242; [f]Glob Systems and Development, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA 70112; [g]Department of Environmenta Emory University, Atlanta, GA 30322; and [h]Division of Health Promotion and Behavioral Sciences, Graduate School of Public Health, San Diego St

Ecology of DENV

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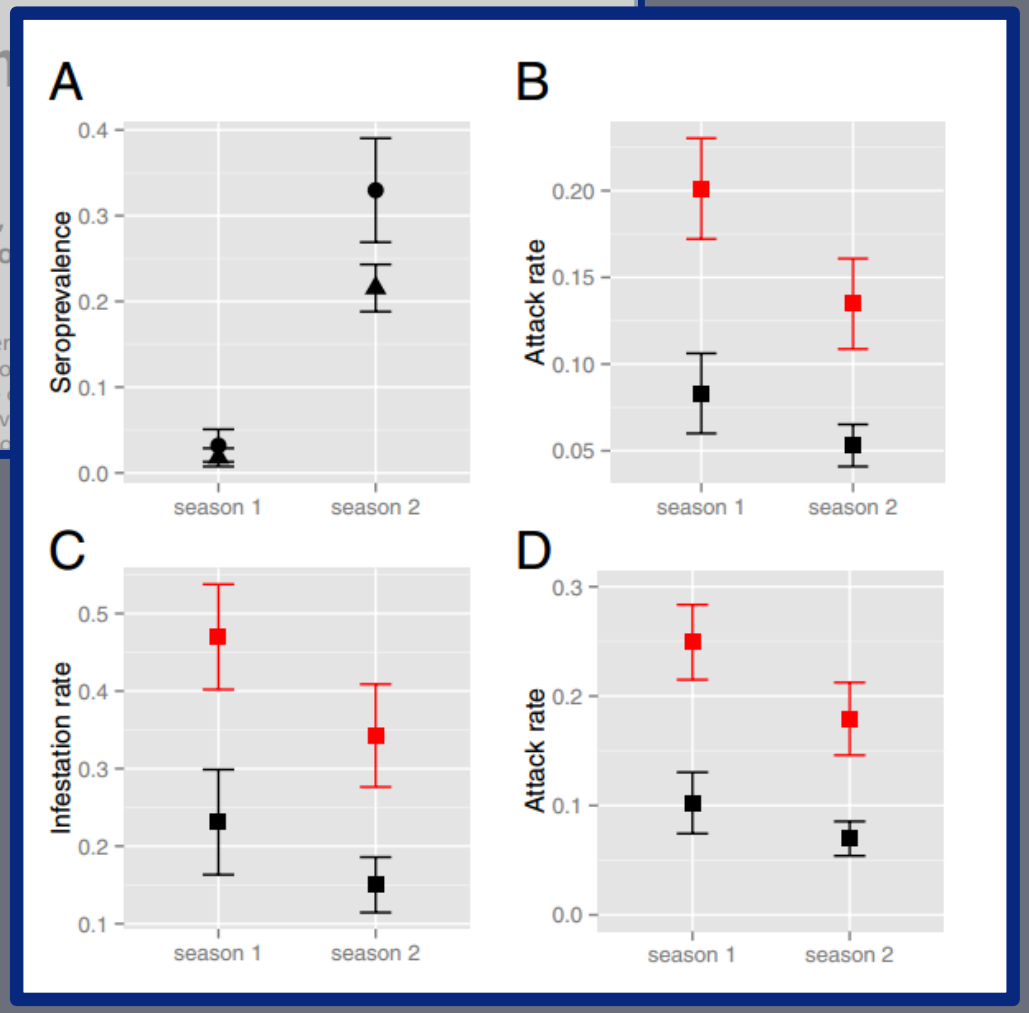

Ecology of DENV

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House-to-house human movement drives dengue vi

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Epidemics

journal homepage: www.elsevier.com/locate/epidemics

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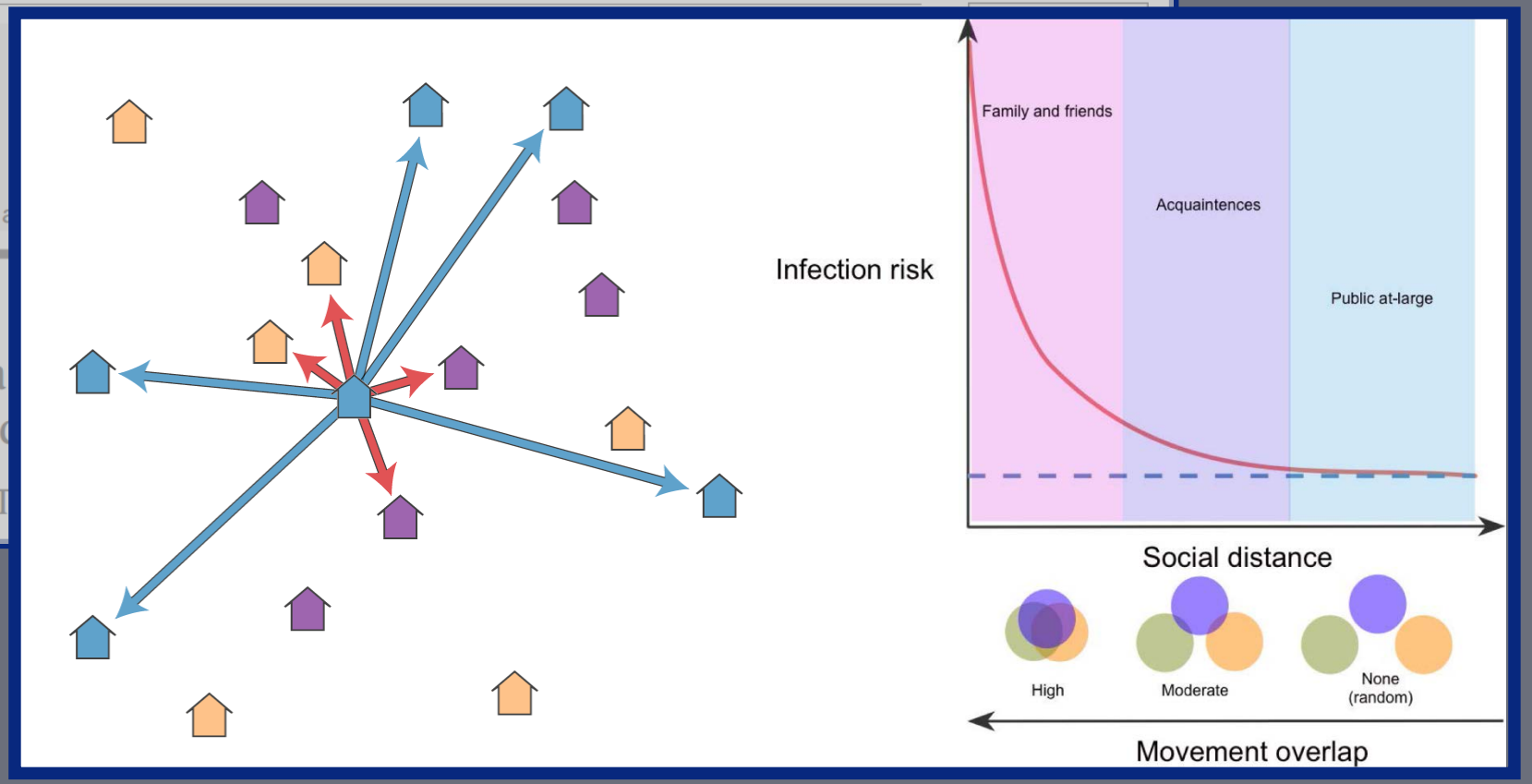
Ecology of DENV



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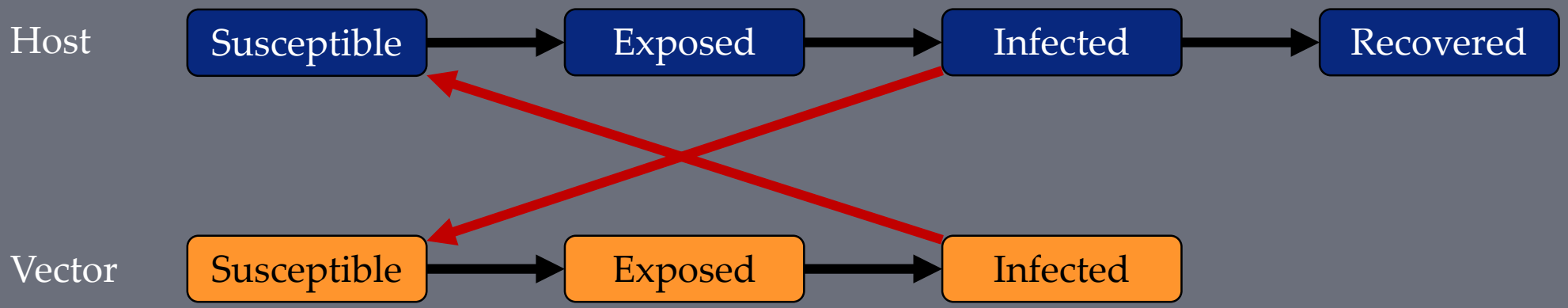

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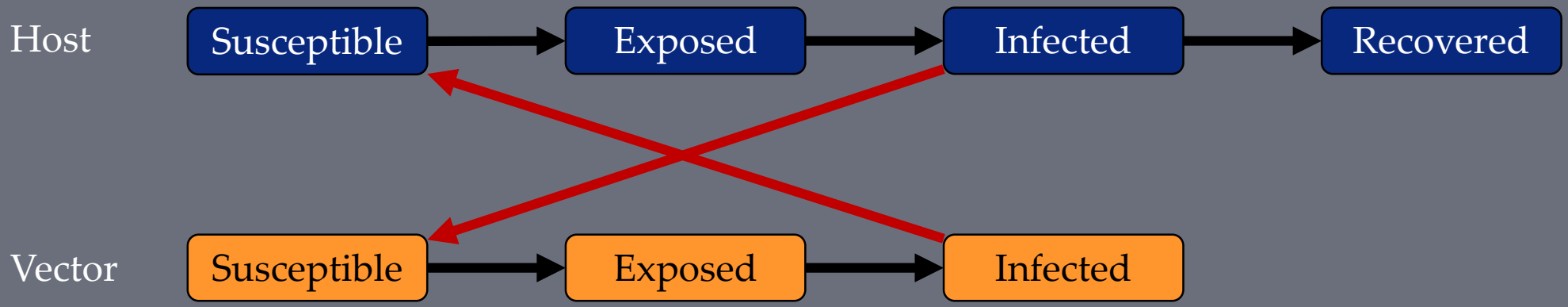

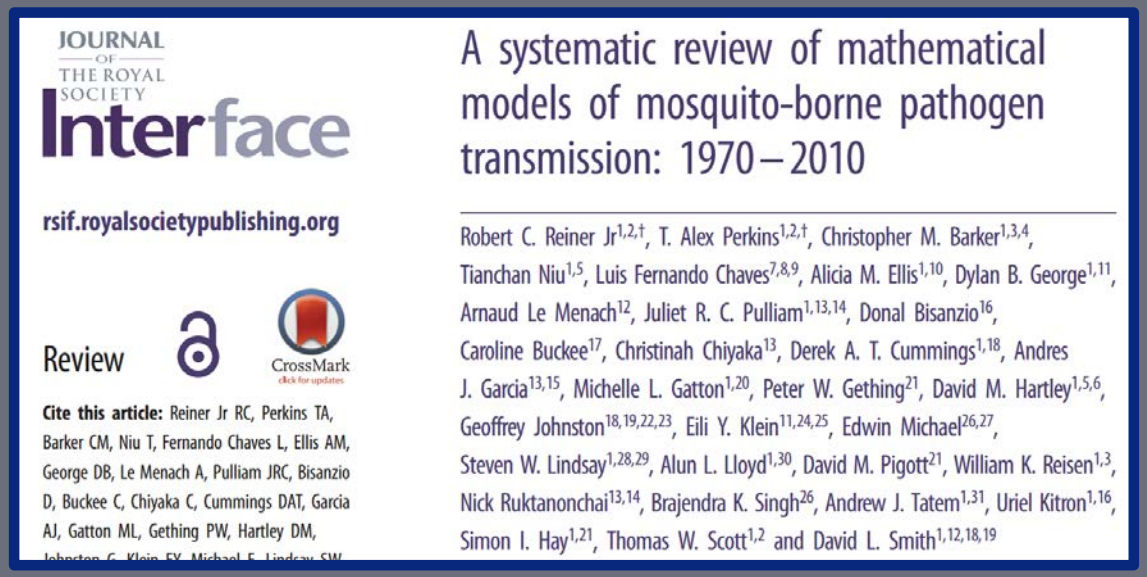

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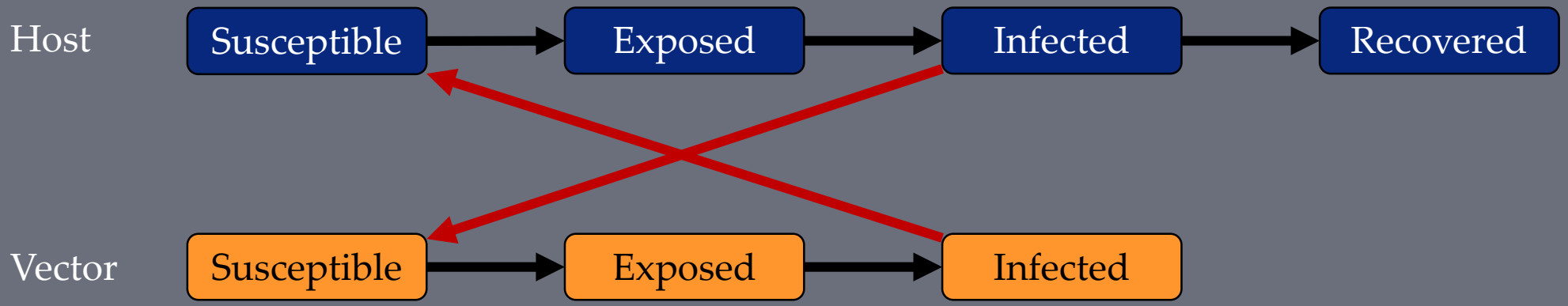

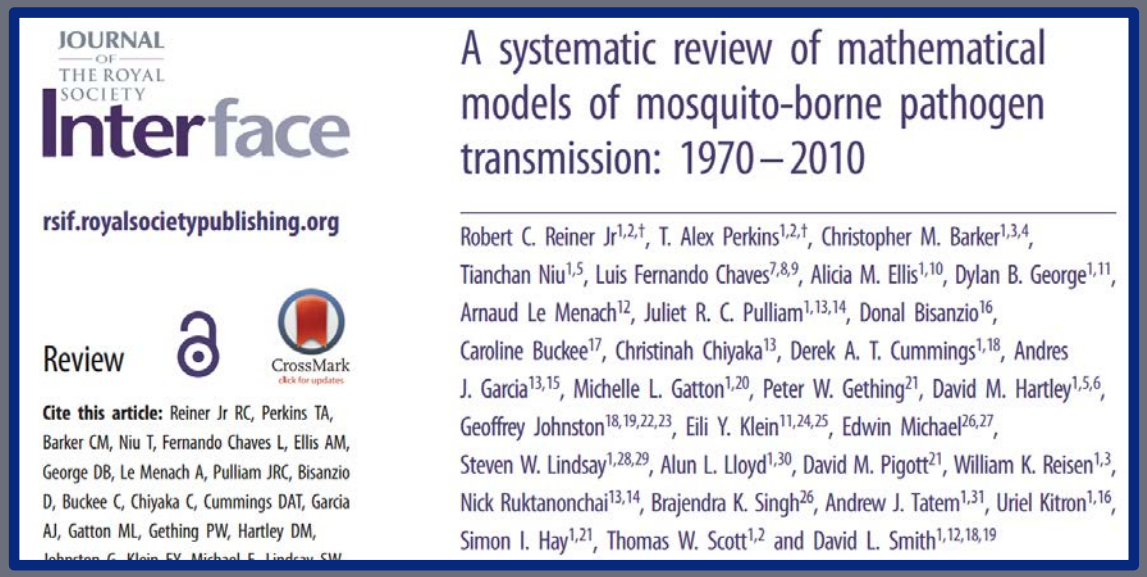
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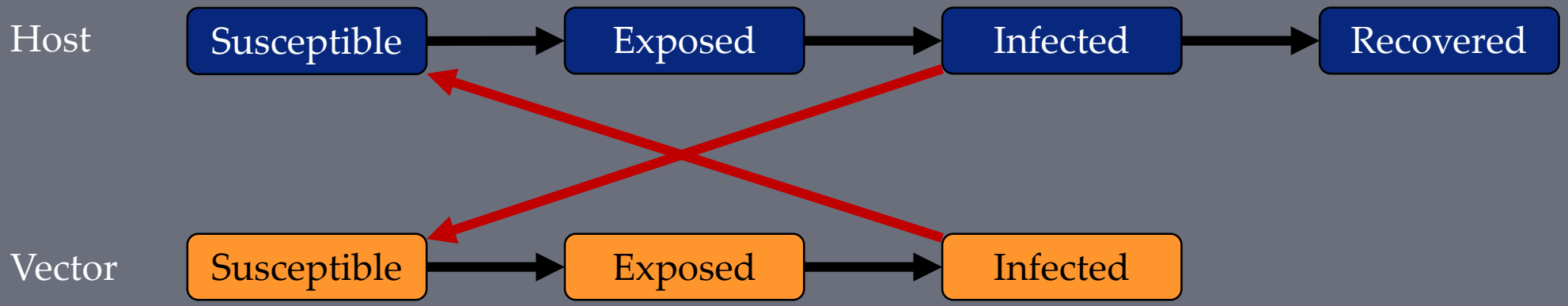

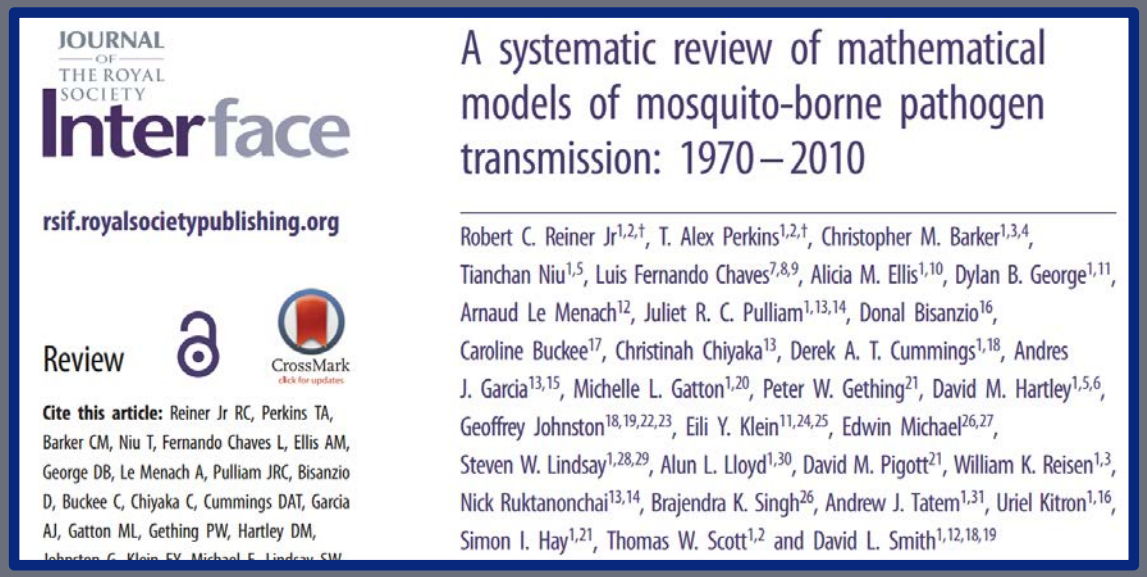
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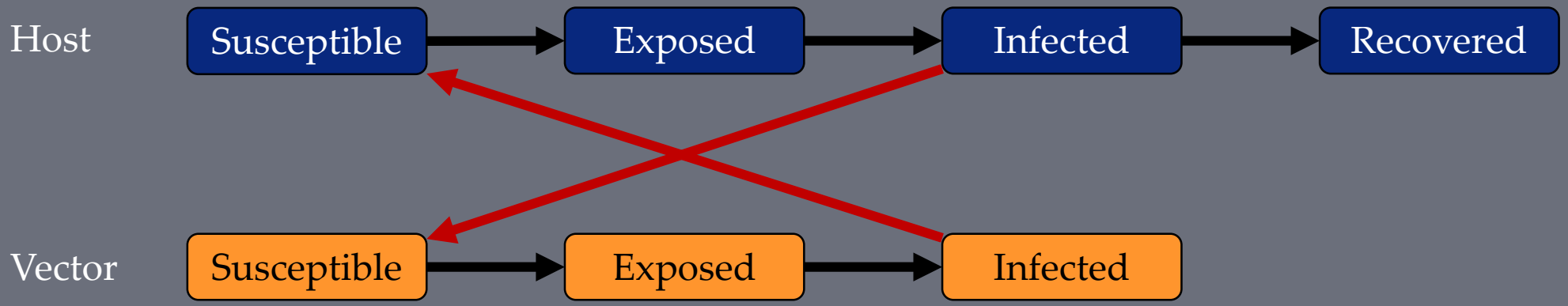
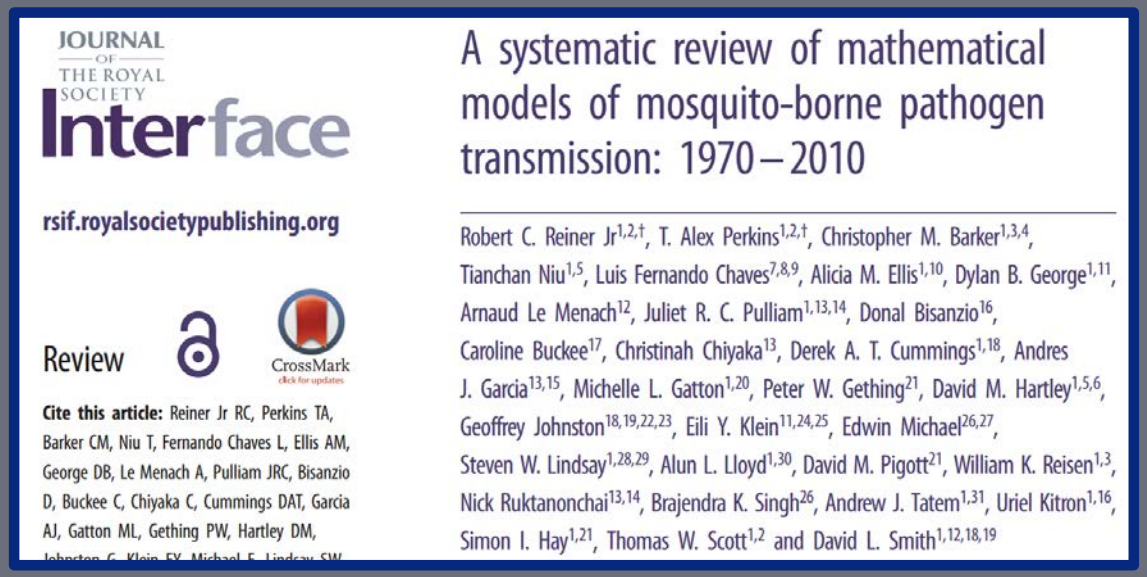
Ecological Complexity

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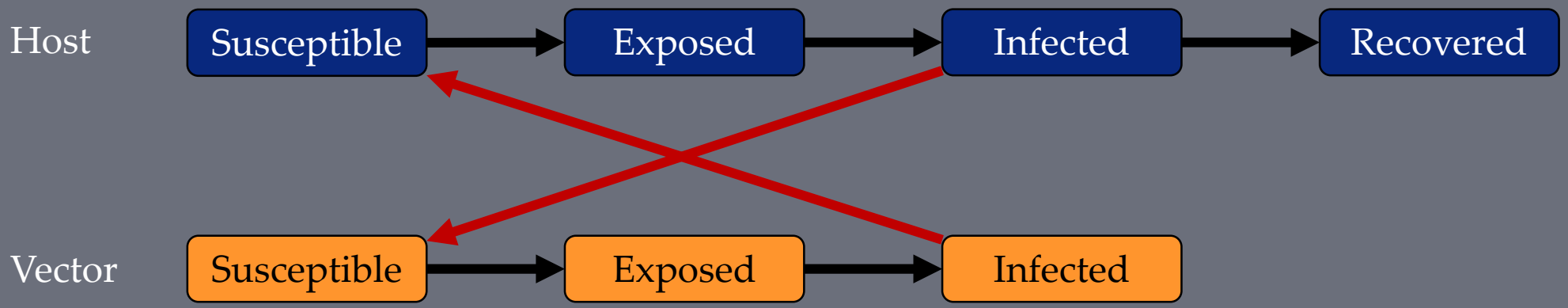
Robert C. Reiner Jr[1,2,†], T. Alex Perkins[1,2,†], Christopher M. Barker[1,3,4], Tianchan Niu[1,5], Luis Fernando Chaves[7,8,9], Alicia M. Ellis[1,10], Dylan B. George[1,11], Arnaud Le Menach[12], Juliet R. C. Pulliam[1,13,14], Donal Bisanzio[16], Caroline Buckee[17], Christinah Chiyaka[13], Derek A. T. Cummings[1,18], Andres J. Garcia[13,15], Michelle L. Gatton[1,20], Peter W. Gething[21], David M. Hartley[1,5,6], Geoffrey Johnston[18,19,22,23], Eili Y. Klein[11,24,25], Edwin Michael[26,27], Steven W. Lindsay[1,28,29], Alun L. Lloyd[1,30], David M. Pigott[21], William K. Reisen[1,3], Nick Ruktanonchai[13,14], Brajendra K. Singh[26], Andrew J. Tatem[1,31], Uriel Kitron[1,16], Simon I. Hay[1,21], Thomas W. Scott[1,2] and David L. Smith[1,12,18,19]

We found that the vast majority of models haven't changed much from the frameworks of the 1950s

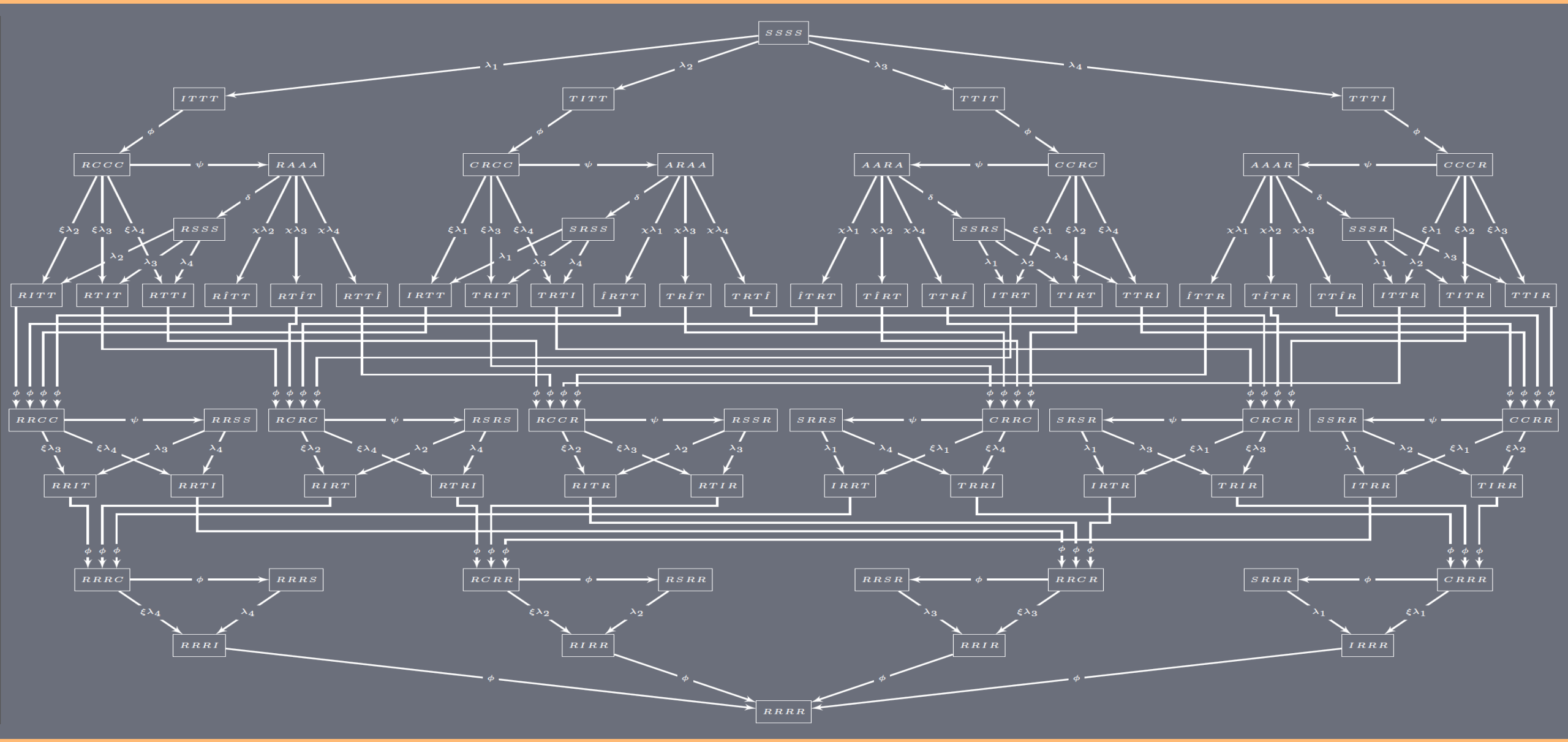
Fewer than 10% incorporated any abiotic temporal variation

Almost every DENV-specific models assumed a single serotype in spite of crucial empirical evidence of complex interactions between serotypes



Given these complexities (and the presence of four distinct serotypes), the above model is inadequate

Ecological Complexity



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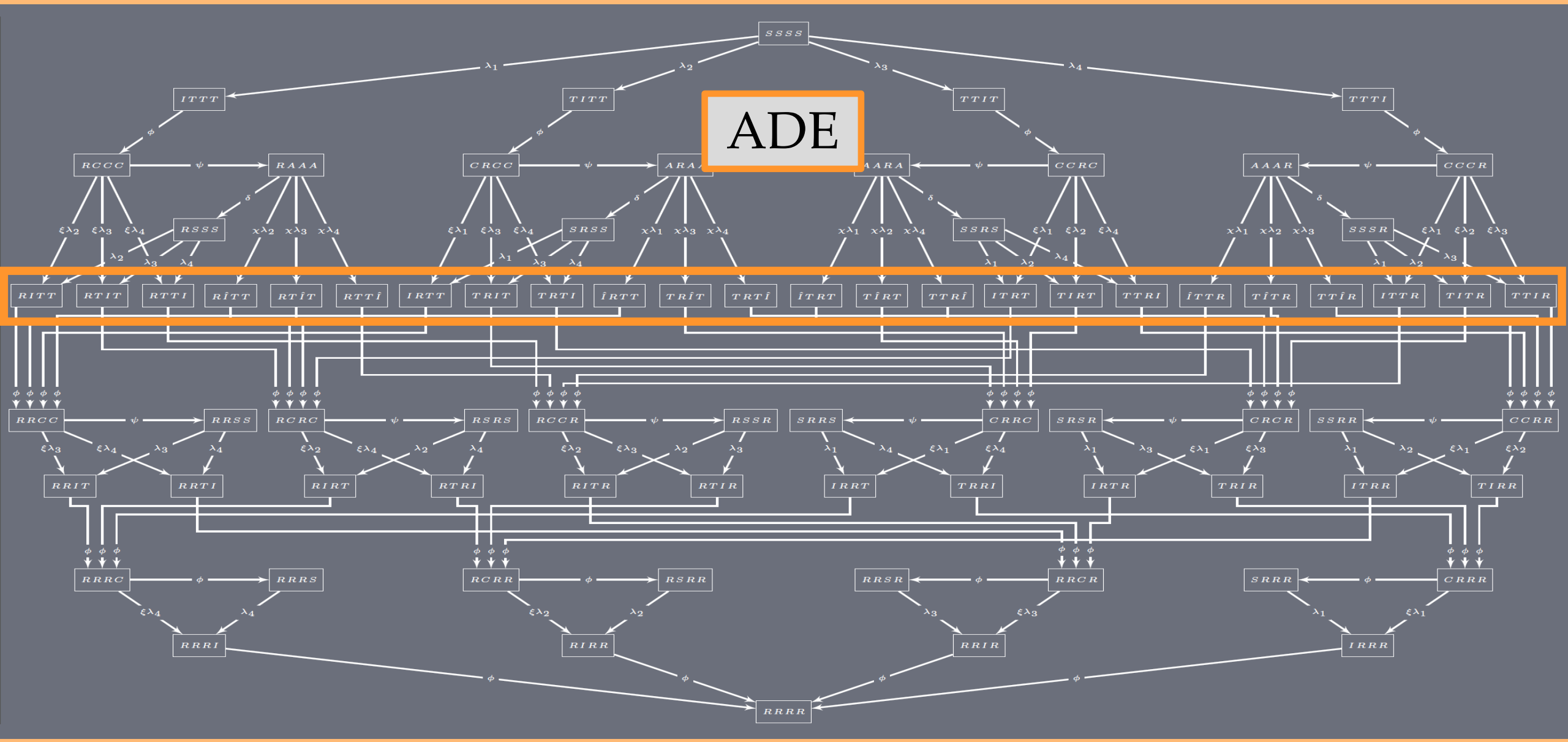

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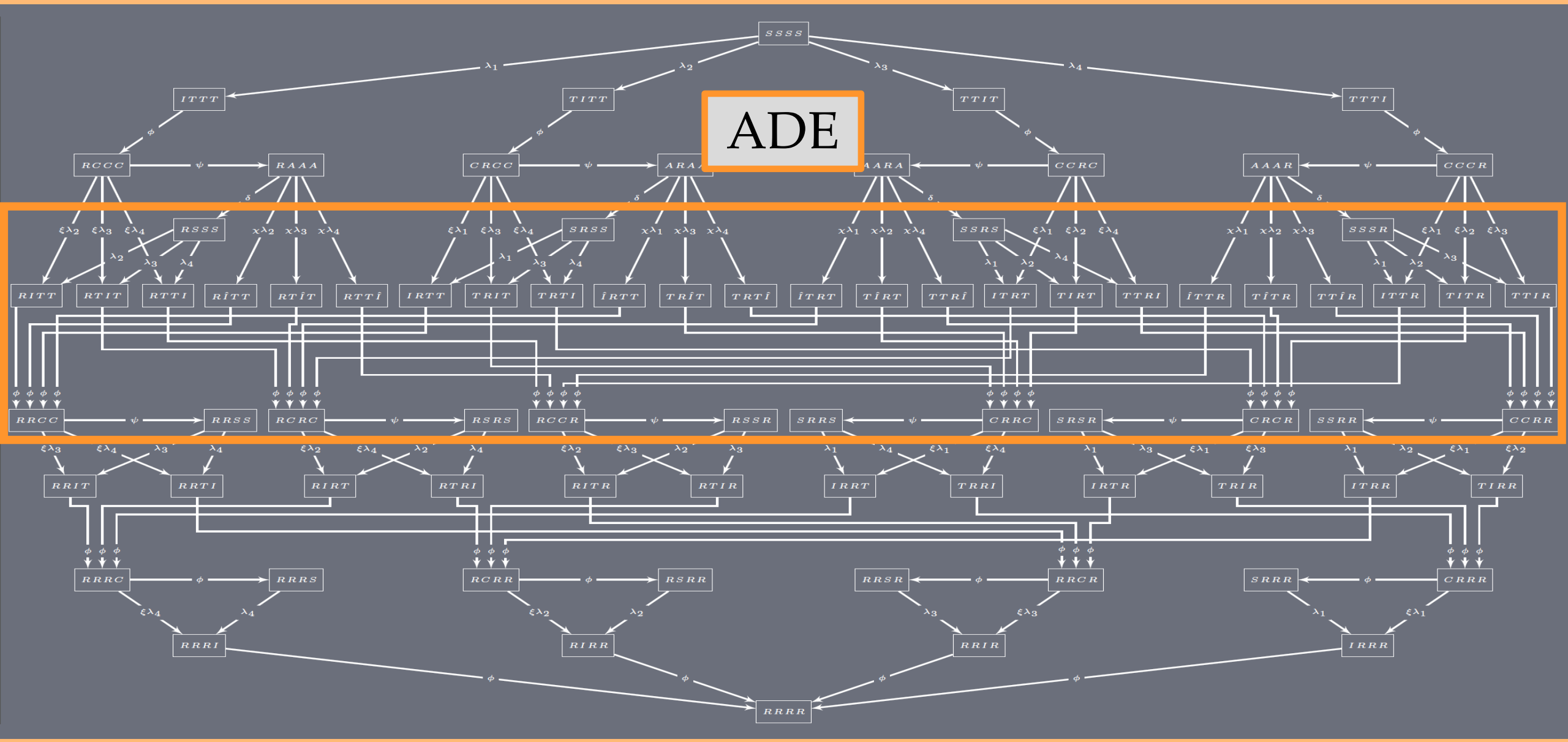

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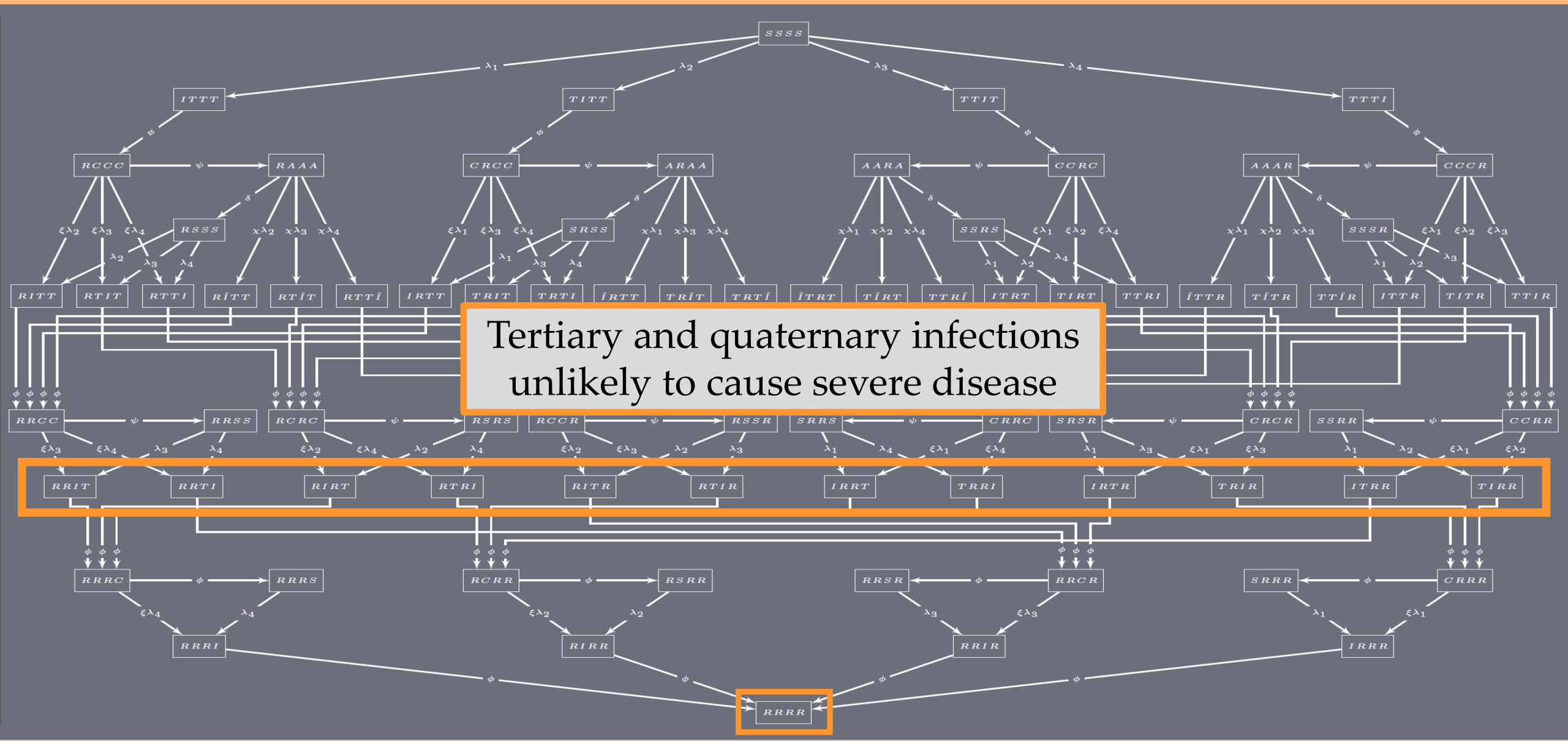

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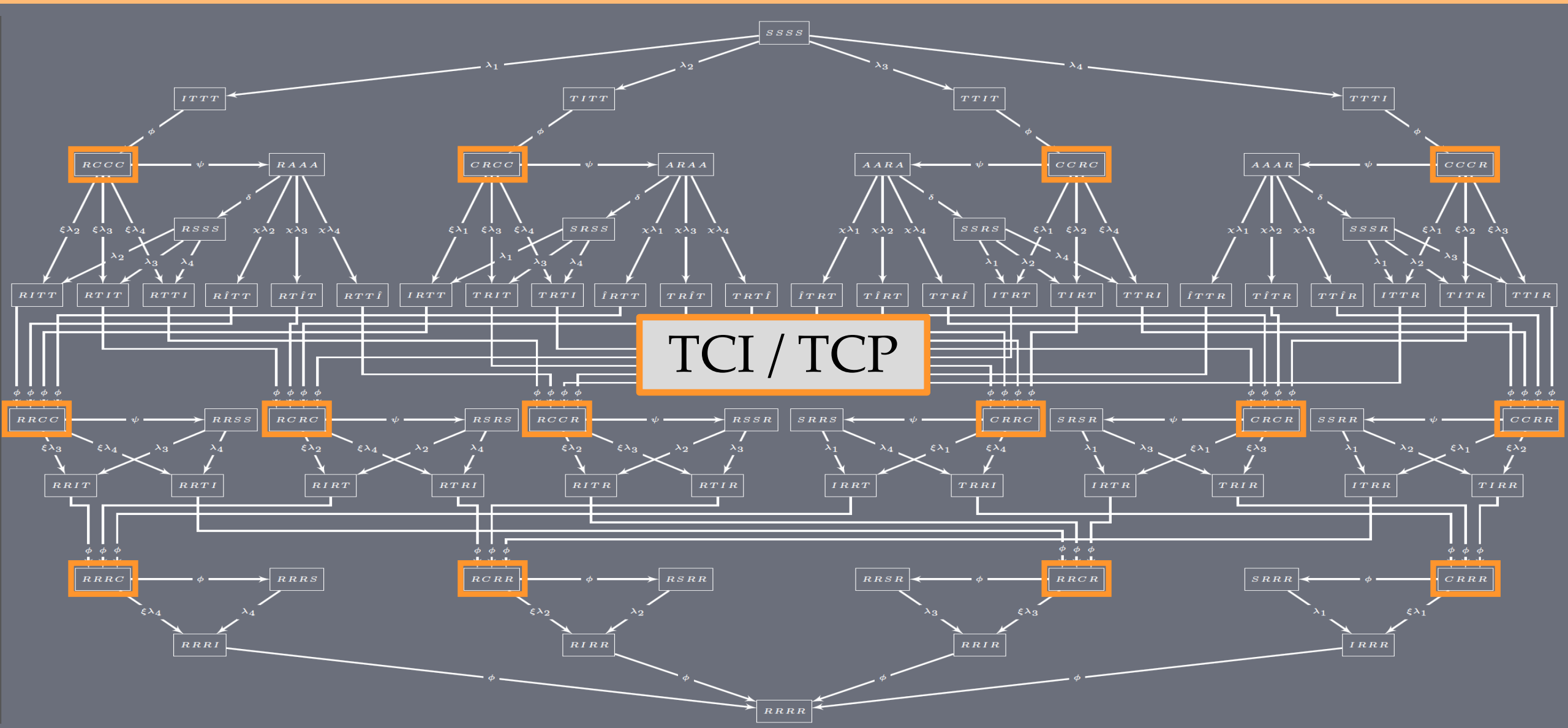

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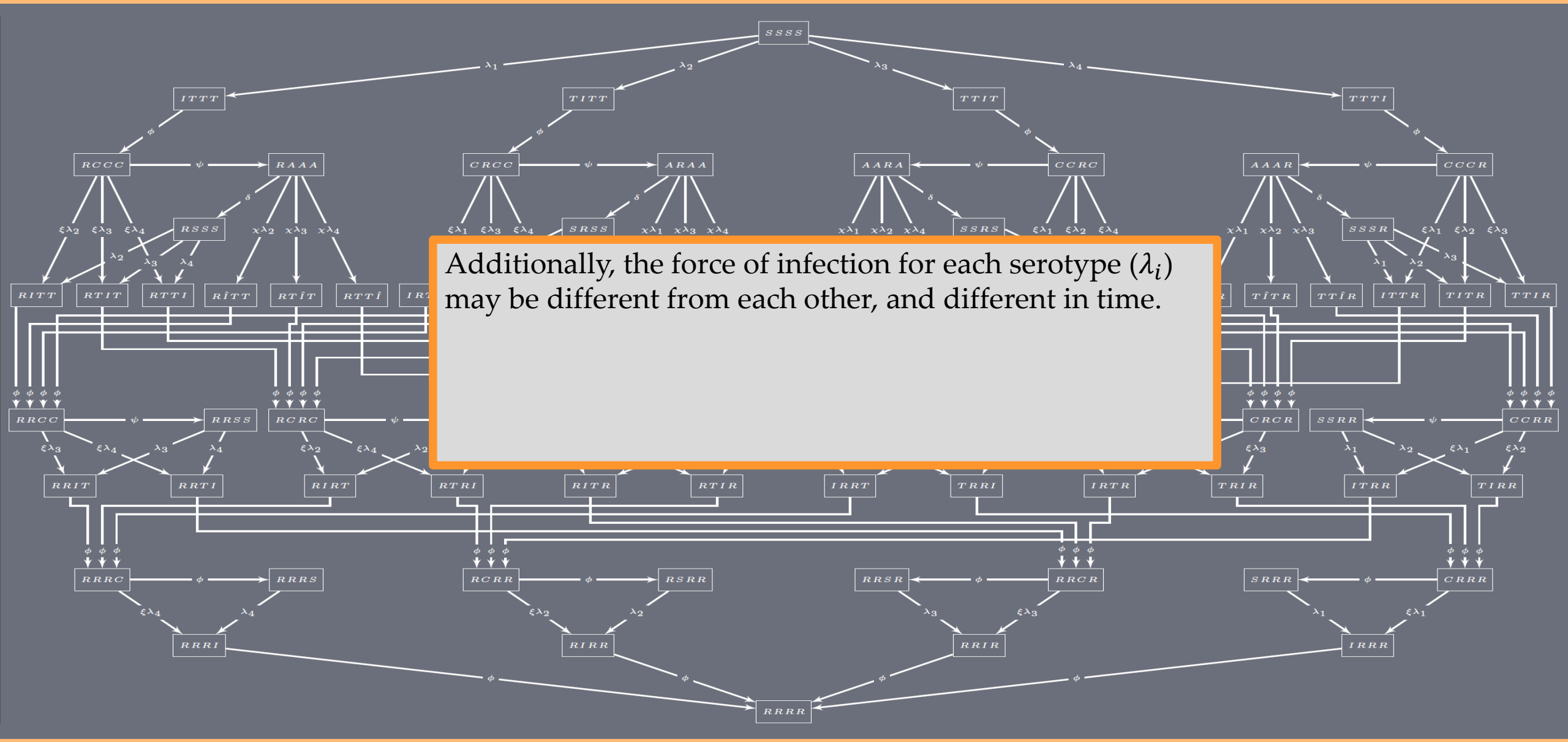
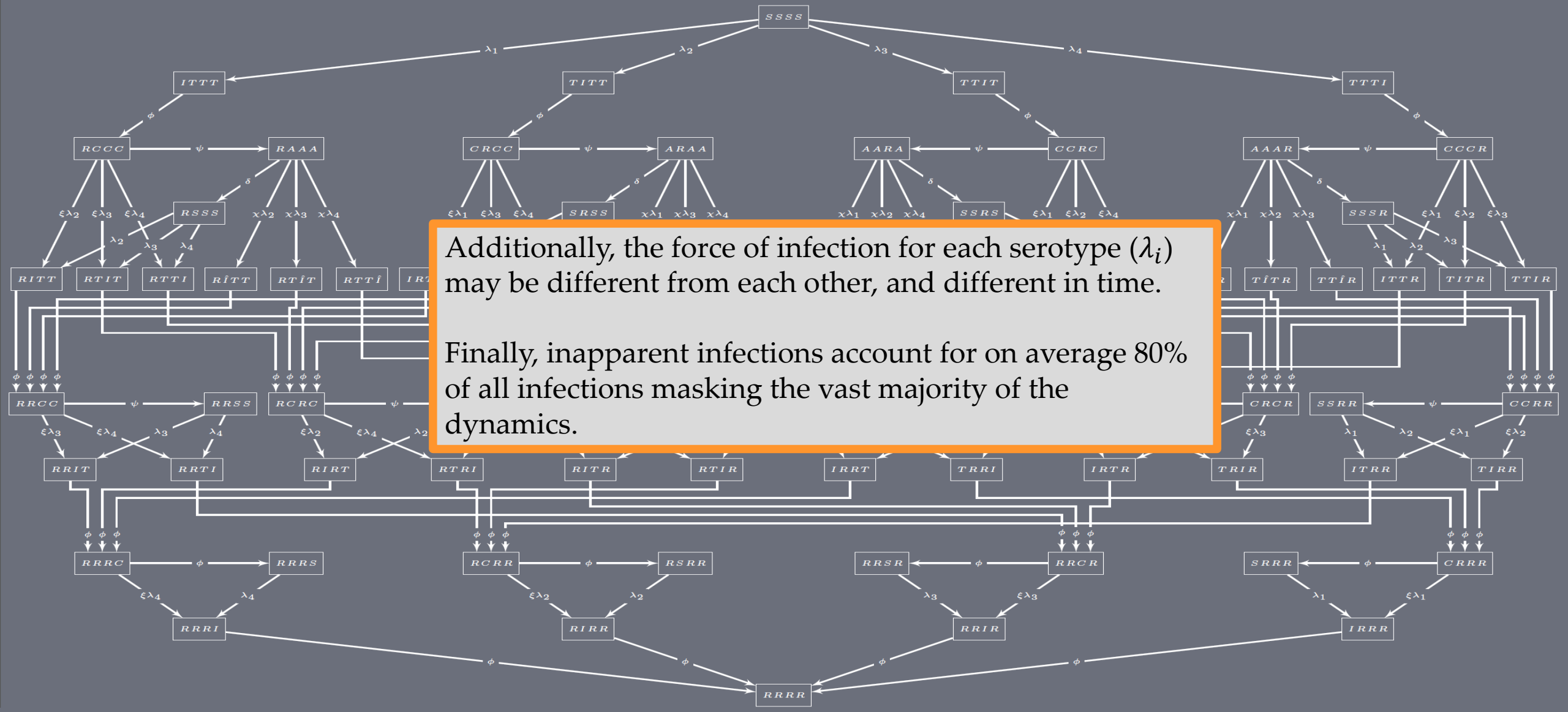


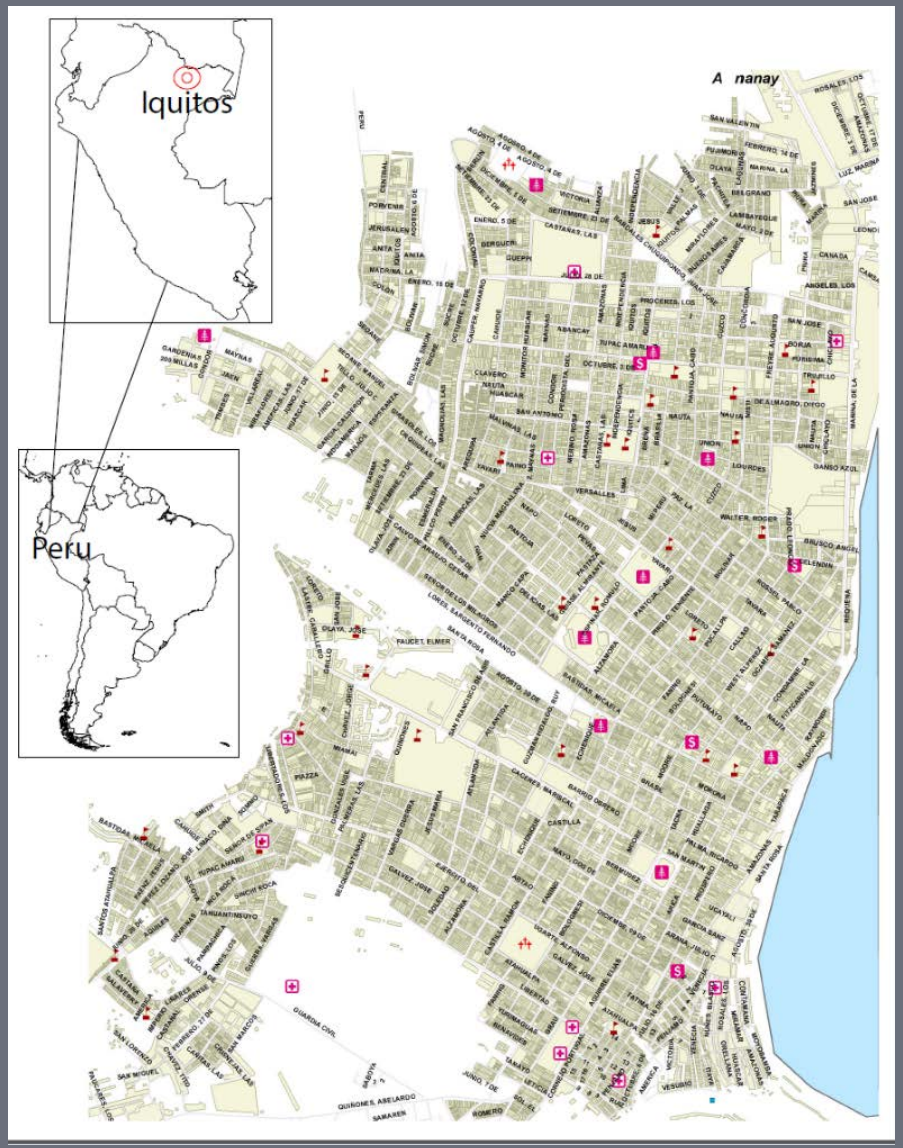
Additionally, the force of infection for each serotype (λ_i) may be different from each other, and different in time.

Ecological Complexity



Additionally, the force of infection for each serotype (λ_i) may be different from each other, and different in time.

Finally, inapparent infections account for on average 80% of all infections masking the vast majority of the dynamics.



Iquitos, Peru

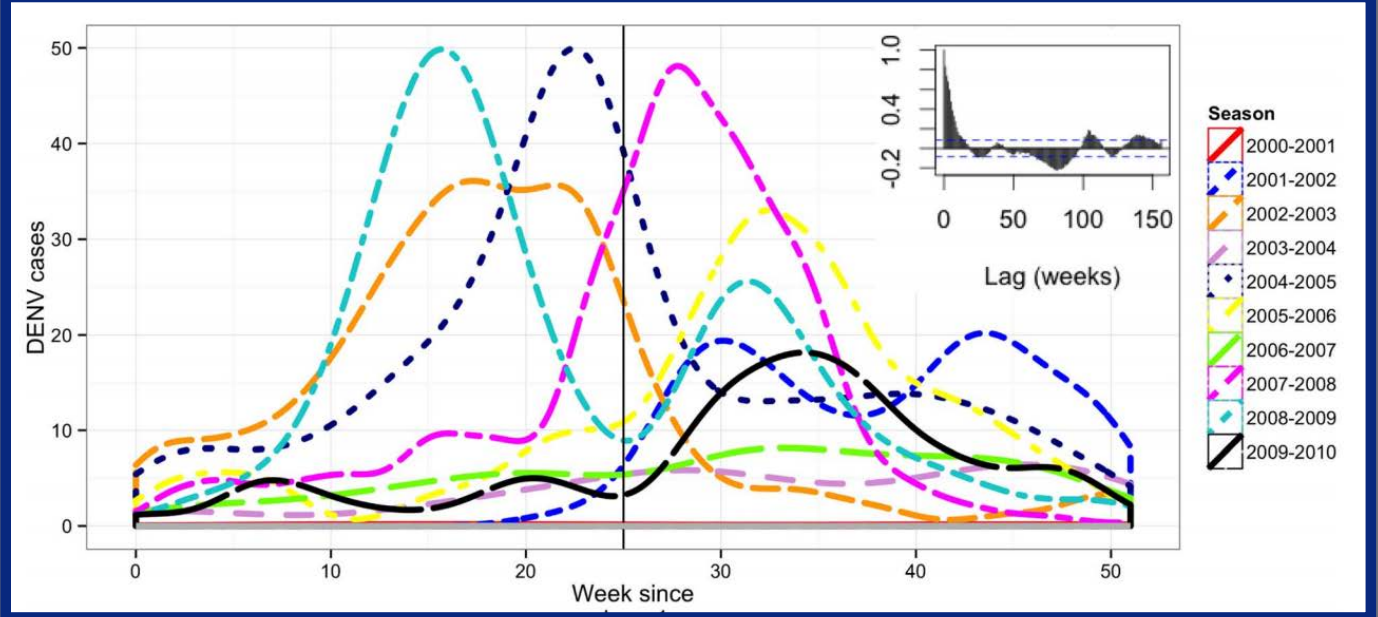
- Iquitos has a population of 400,000. The city, located at the beginning of the Amazon river, is relatively isolated from other large cities.
- DENV-1 was introduced in 1991, DENV-2 in 1995, DENV-3 in 2001 and DENV-4 in 2008-2009.
- The Scott lab at UC Davis began extensive studies of dengue in Iquitos in 1999 and thus were able to collect data during two `virgin-soil' invasions

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

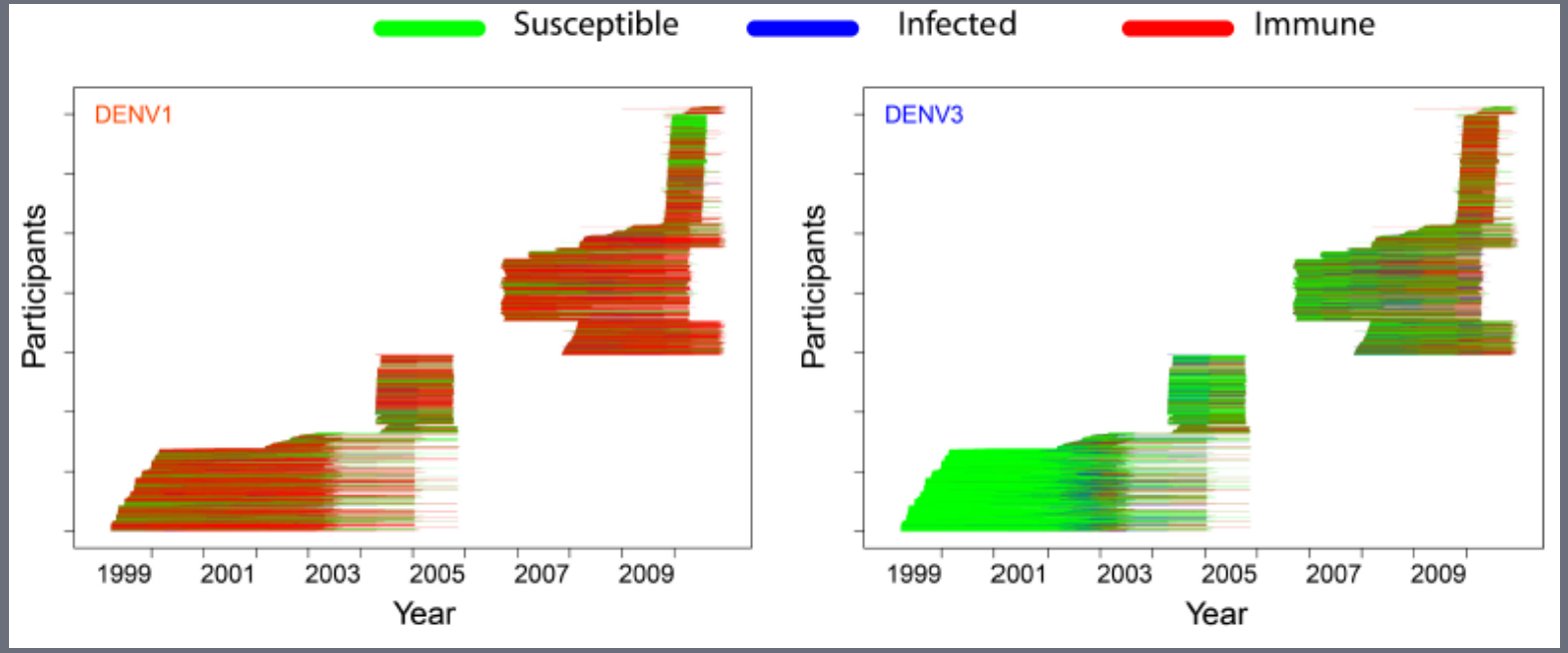
Long-Term and Seasonal Dynamics of Dengue in Iquitos, Peru

Steven T. Stoddard[1,2*], Helen J. Wearing[3], Robert C. Reiner Jr.[1,2], Amy C. Morrison[1,4], Helvio Astete[4], Stalin Vilcarromero[4], Carlos Alvarez[5], Cesar Ramal-Asayag[6], Moises Sihuincha[7], Claudio Rocha[4], Eric S. Halsey[4], Thomas W. Scott[1,2], Tadeusz J. Kochel[8], Brett M. Forshey[4]



Iquitos, Peru

- Yearly outbreak size and timing of DENV cases vary year-to-year. But again, "cases" represent a small proportion of dynamics.



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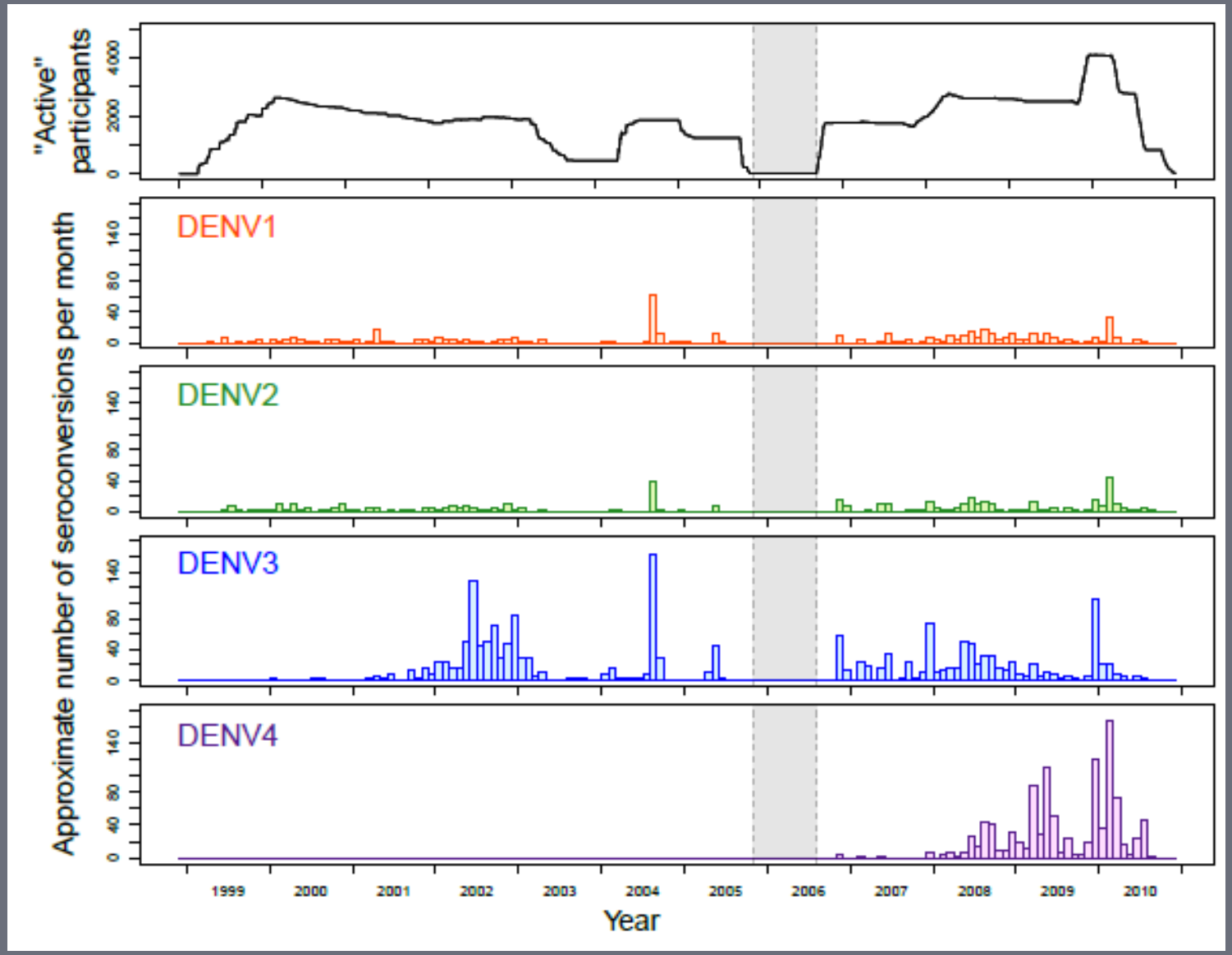
Iquitos, Peru



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- Around 15,000 participant's serotype-specific serostatus was measured several (2-14) times (over 47,00 blood samples)

Force of infection

PNAS

Time-varying, serotype-specific force of infection of dengue virus

Robert C. Reiner, Jr.[a,b,1], Steven T. Stoddard[a,b], Brett M. Forshey[c], Aaron A. King[a,d], Alicia M. Ellis[a,e], Alun L. Lloyd[a,f], Kanya C. Long[b,g], Claudio Rocha[c], Stalin Vilcarromero[c], Helvio Astete[c], Isabel Bazan[c], Audrey Lenhart[h,i], Gonzalo M. Vazquez-Prokopec[a,j], Valerie A. Paz-Soldan[k], Philip J. McCall[h], Uriel Kitron[a,j], John P. Elder[l], Eric S. Halsey[c], Amy C. Morrison[b,c], Tadeusz J. Kochel[c], and Thomas W. Scott[a,b]

[a]Fogarty International Center, National Institutes of Health, Bethesda, MD 20892; [b]Department of Entomology and Nematology, University of California, Davis, CA 95616; [c]US Naval Medical Research Unit No. 6 Lima and Iquitos, Peru; [d]Department of Ecology and Evolutionary Biology, University of Michigan, Ann Arbor, MI 48109; [e]Rubenstein School of Environment and Natural Resources, University of Vermont, Burlington, VT 05405; [f]Department of Mathematics and

‘Key transmission parameters’

- The force of infection (***FoI***, denoted λ) is the rate at which susceptible individuals become infected. In the simplest ‘catalytic’ model of transmission, if $s(t)$ is the percent of individuals that are susceptible at time t, then

$$\frac{ds(t)}{dt} = -\lambda(t)s(t) \quad \Leftrightarrow \quad \frac{dF(t)}{dt} = \lambda(t)(1 - F(t))$$

- We can use our censored data, methods derived from reliability and B-splines to estimate the pdf of infection times

$$f(t) = \frac{dF(t)}{dt}$$

which we can then use to estimate the force of infection.

‘Key transmission parameters’

- Left Censored (***L***)

$$\text{LIKELIHOOD} = \int_{-\infty}^{t_1} f(t)dt$$

where t_1 was the time of the first test (which in these cases was positive)

- Interval Censored (***C***)

$$\text{LIKELIHOOD} = \int_{t_1}^{t_2} f(t)dt$$

where t_1 was the time of the last negative test and t_2 was the time of the first positive test

- Right Censored (***R***)

$$\text{LIKELIHOOD} = 1 - \int_{-\infty}^{t_2} f(t)dt$$

where t_2 was the time of the last test (which in these cases was negative)

‘Key transmission parameters’

We cannot estimate f before 1999. However, since infections that occurred before 1999 will appear as left censored infections, we can estimate the percent of the population that was exposed previous to 1999. With t_0 representing the beginning of the study, we write:

$$\kappa = \int_{-\infty}^{t_0} f(s)ds$$

Combining this with the equations above, the log-likelihood of the data for a given serotype is

$$l(f,\kappa) = \sum_{j\in L} \log\left(\kappa + \int_{t_0}^{t_{j,1}} f(s)ds\right) + \sum_{k\in C} \log\left(\int_{t_{k,1}}^{t_{k,2}} f(s)ds\right) + \sum_{l\in R} \log\left(1-\kappa-\int_{t_0}^{t_{j,2}} f(s)ds\right)$$

‘Key transmission parameters’

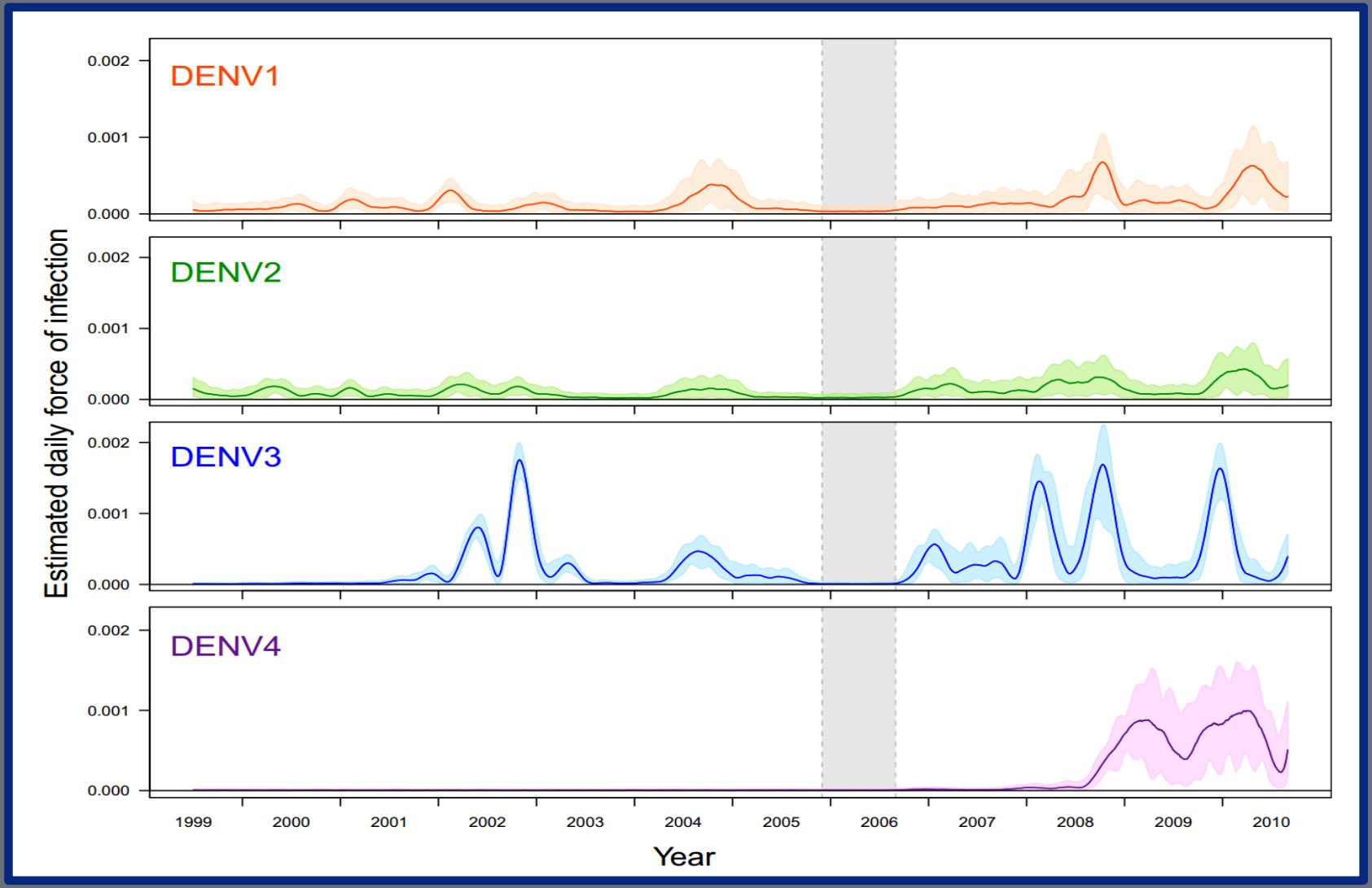
The basic reproductive number (denoted R_0) is the number of secondary infections which one infection would produce in a completely susceptible population. Once the pathogen has invaded and some individuals have been infected and become immune, the expected number of secondary infections from a single infection is called the effective reproductive rate (denoted $R(t)$) and

$$R_0 = \frac{R(t)}{s(t)}.$$

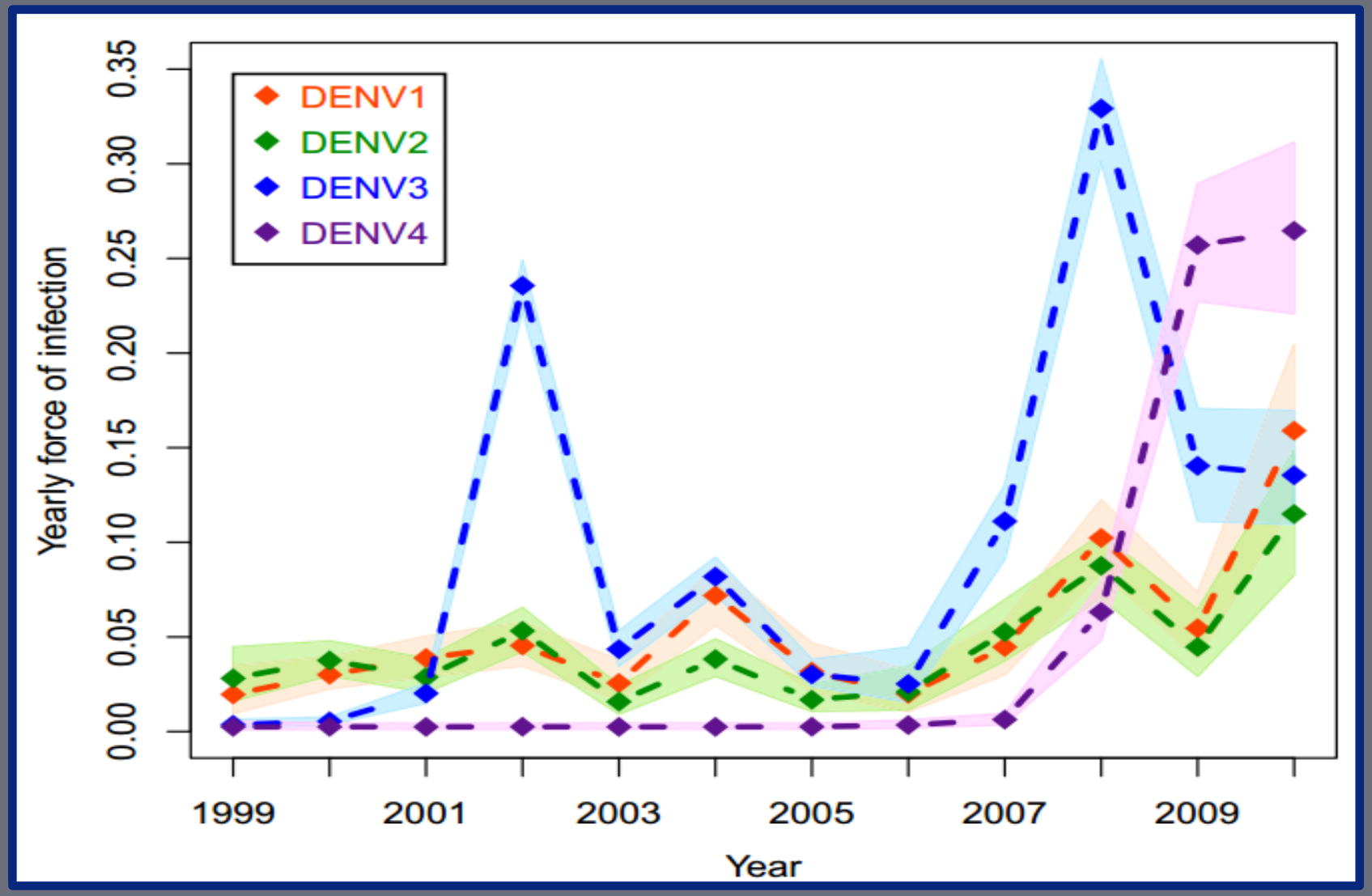
Using the mean time between successive DENV infections (i.e., serial interval) of 15-17 days, and letting $s_P(t)$ be the fraction of the entire population susceptible at time t, we approximate the effective reproductive rate as:

$$R(d) \approx \hat{R}(d) = \frac{\int_{d+15}^{d+18} s_P(u)\lambda(u)du}{3 * \int_{d}^{d+1} s_P(u)\lambda(u)du}$$

Force of Infection

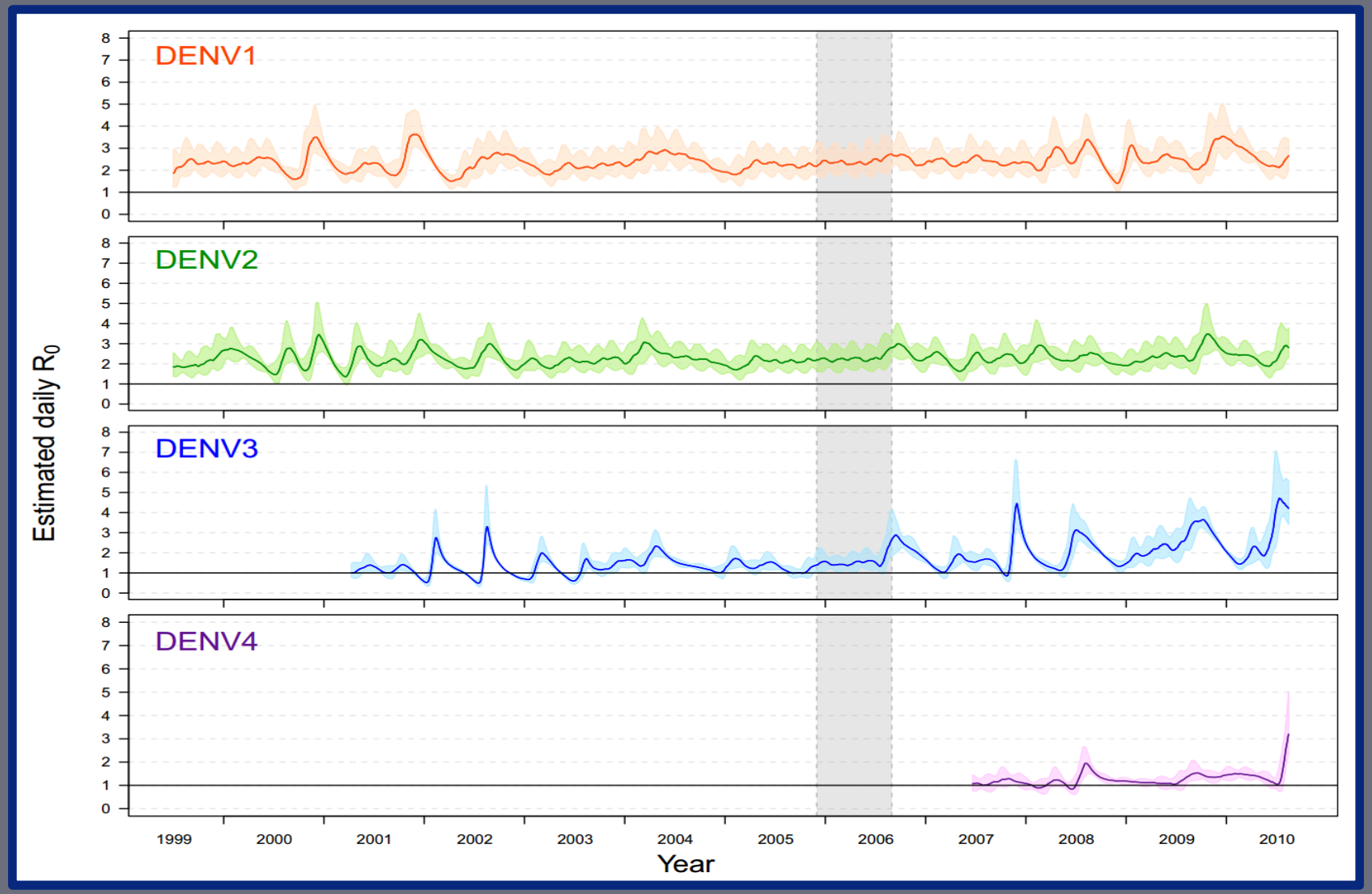


FoI


DENV1
DENV2
DENV3
DENV4
Yearly force of infection
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
1999
2001
2003
2005
2007
2009
Year

FoI

Force of Infection



R_0

Force of infection

- Novel serotypes appear to disrupt previous ***FoI*** patterns.
- There appear to be some serotype-independent dynamics
- Synchronization appears to be able to occur between any subsets of serotypes.
- R_0 vary through time and across serotypes from 1 up to 5

Temporary Cross-Immunity/Cross-Protection

Temporary Cross-Immunity/Cross-Protection

In the 1950's, Albert Sabin identified the existence of short term heterologous protection for dengue virus.

When challenged with a different serotype 2-3 months after already being infected by a first, individuals who were infected with one virus **did** develop viremia. However they did not develop severe symptoms.

These results, cross-protection from severe illness, lasted at least 9 months in his samples.

Interactions between serotypes of dengue highlight epidemiological impact of cross-immunity

Nicholas G. Reich, Sourya Shrestha, Aaron A. King, Pejman Rohani, Justin Lessler, Siripen Kalayanarooj, In-Kyu Yoon, Robert V. Gibbons, Donald S. Burke and Derek A. T. Cummings

J. R. Soc. Interface 2013 **10**, 20130414, published 3 July 2013

Much more recently, Reich et al quantified temporary cross-protection to disease using 38 years of case data from Bangkok. They fit a TSIR model

$$S_{t,i} = B_{t-d} + S_{t-1,i} - I_{t,i} - \delta Q_{t,L,-i}$$

where the form of the temporary cross-protection was either:

1. Fixed duration for all individuals with an imperfect protection

2. Exponential duration where protection was perfect

Temporary Cross Protection

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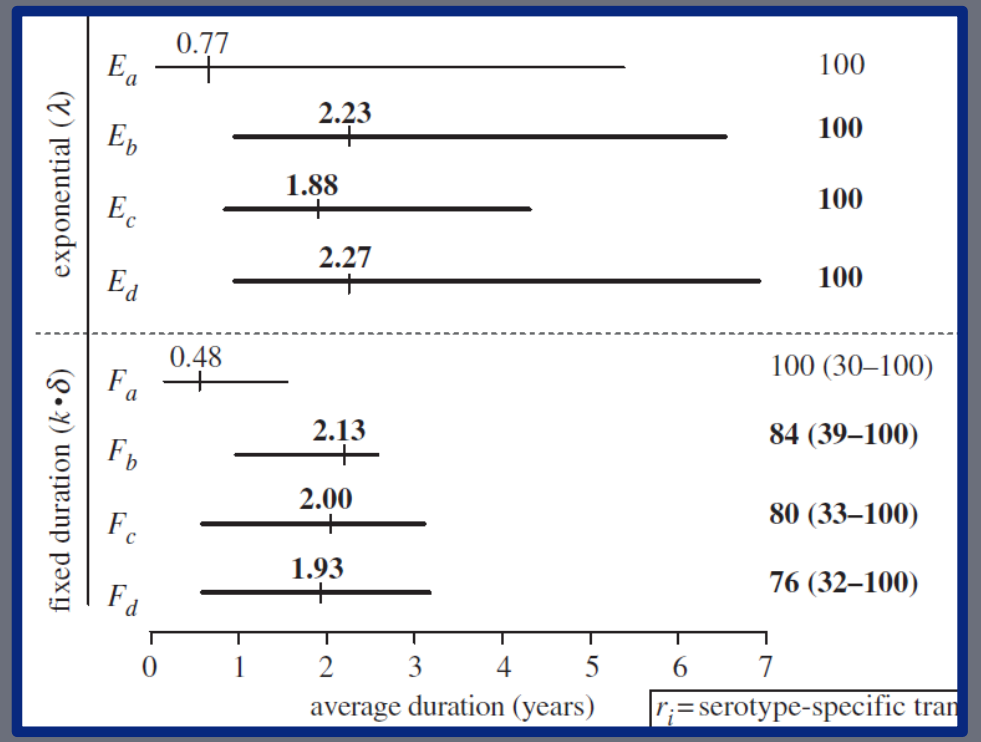

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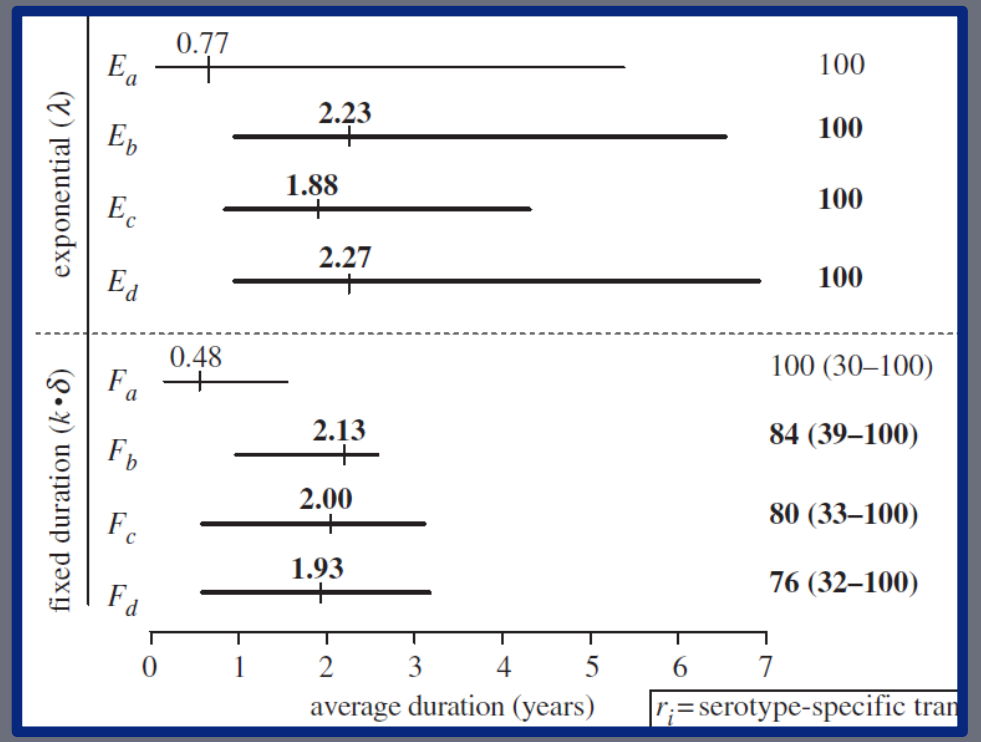

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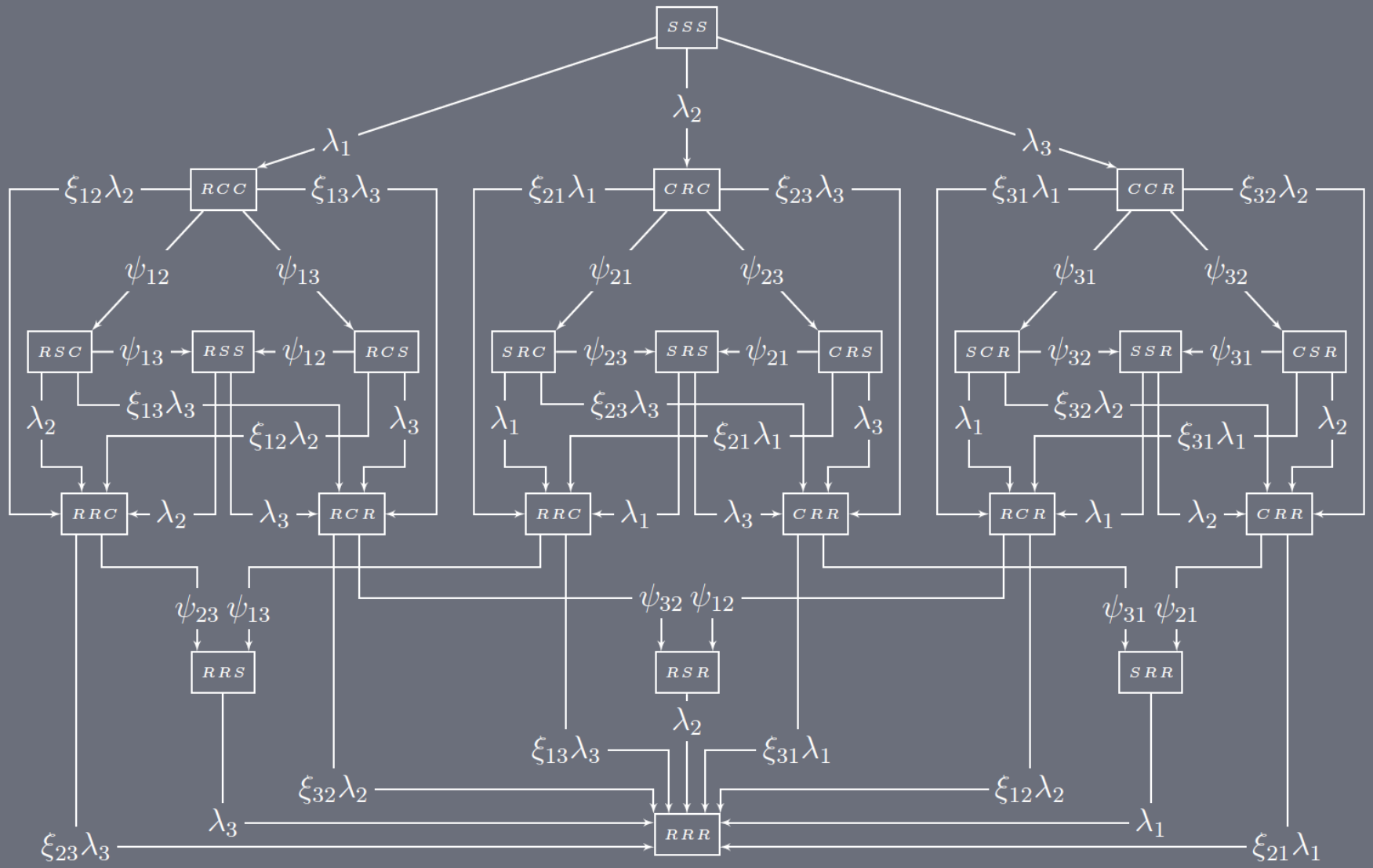
Their model found that serotype-specific dynamics were not significantly better than a model that only adjusted for seasonality

The best fixed duration and exponential duration models indicated heterologous disease protection lasted 2.00 and 1.88 years respectively

Model Assumptions

- Since there were only 3 serotypes circulating in Iquitos before 2007 we can simplify the model.



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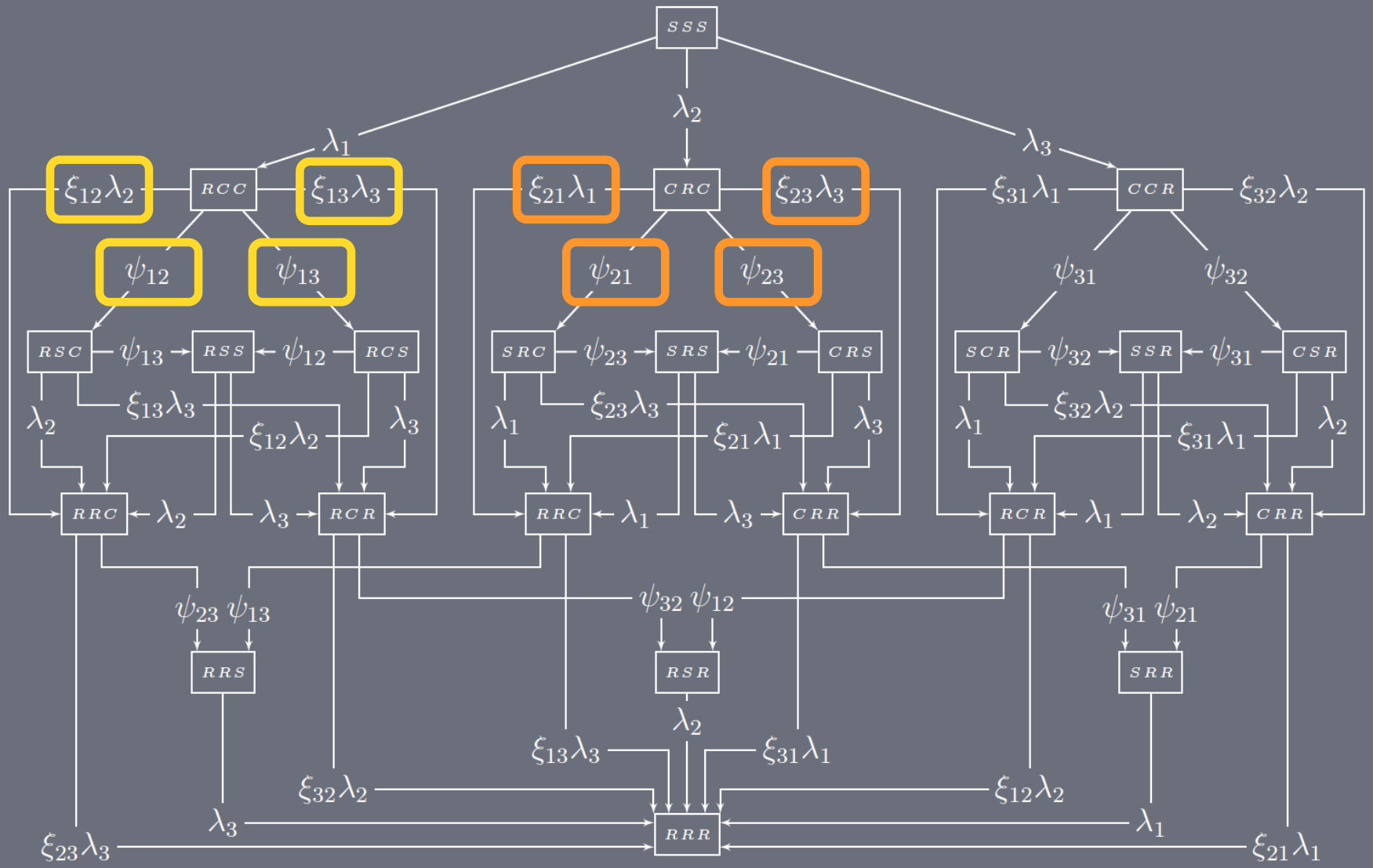

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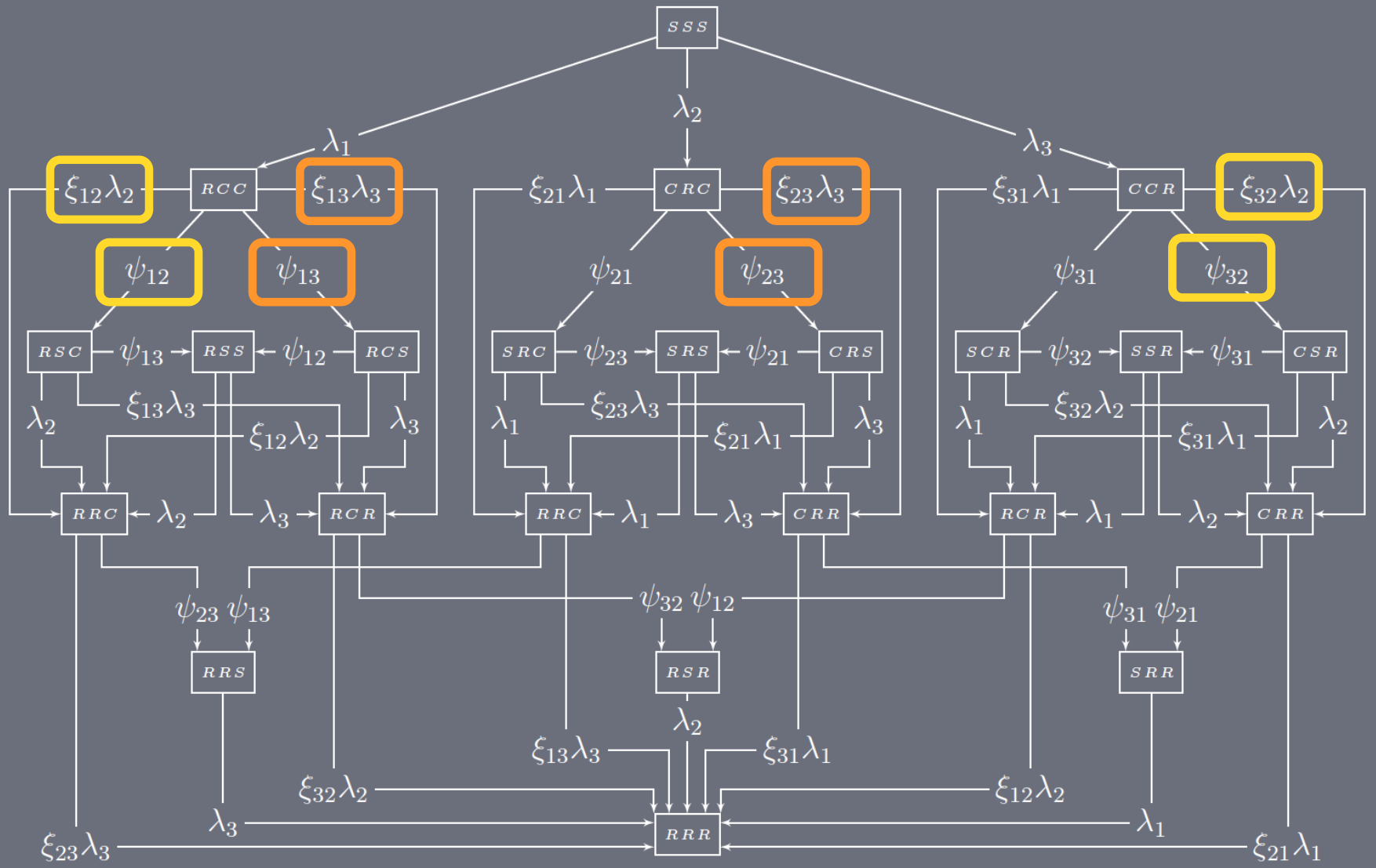

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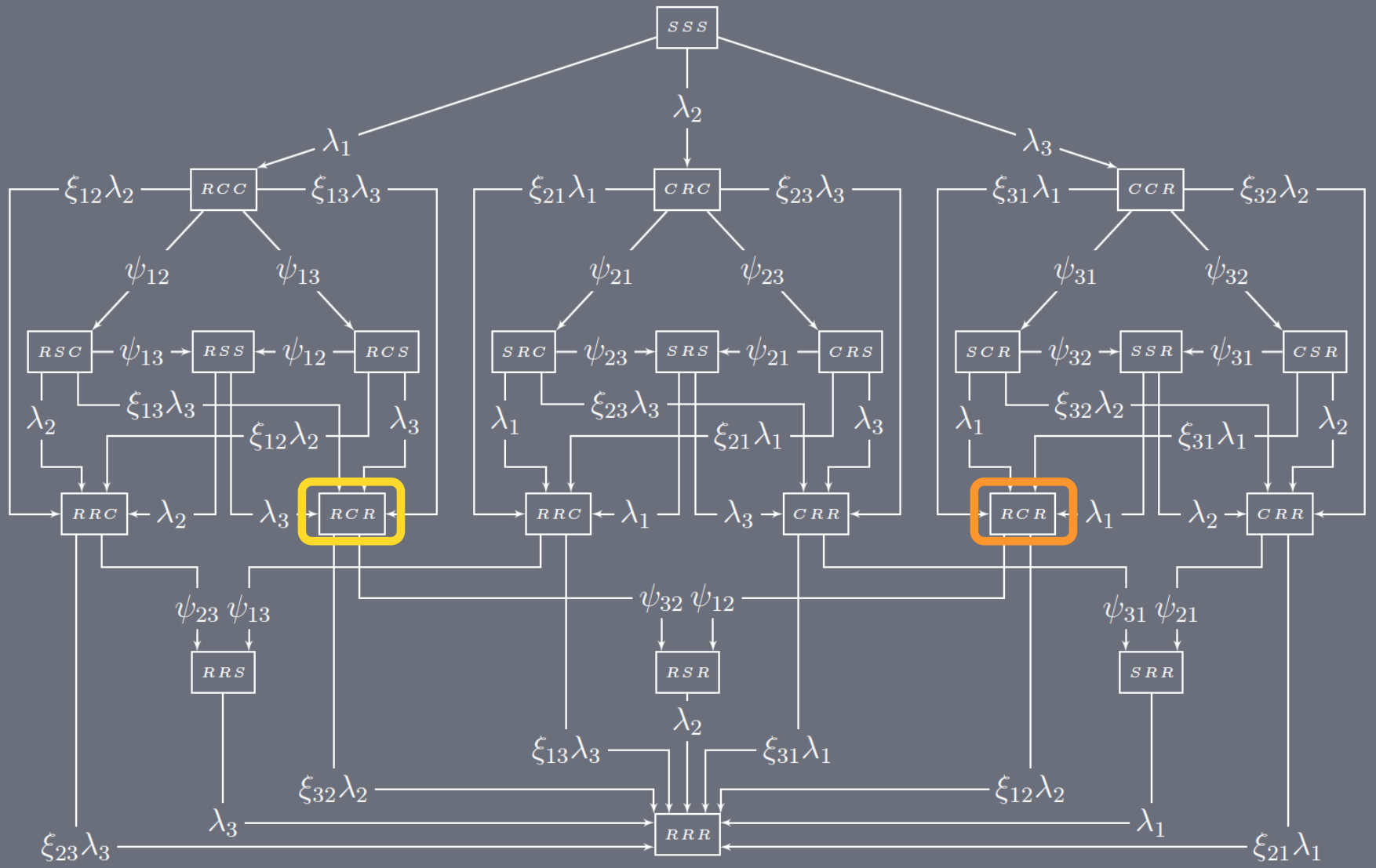

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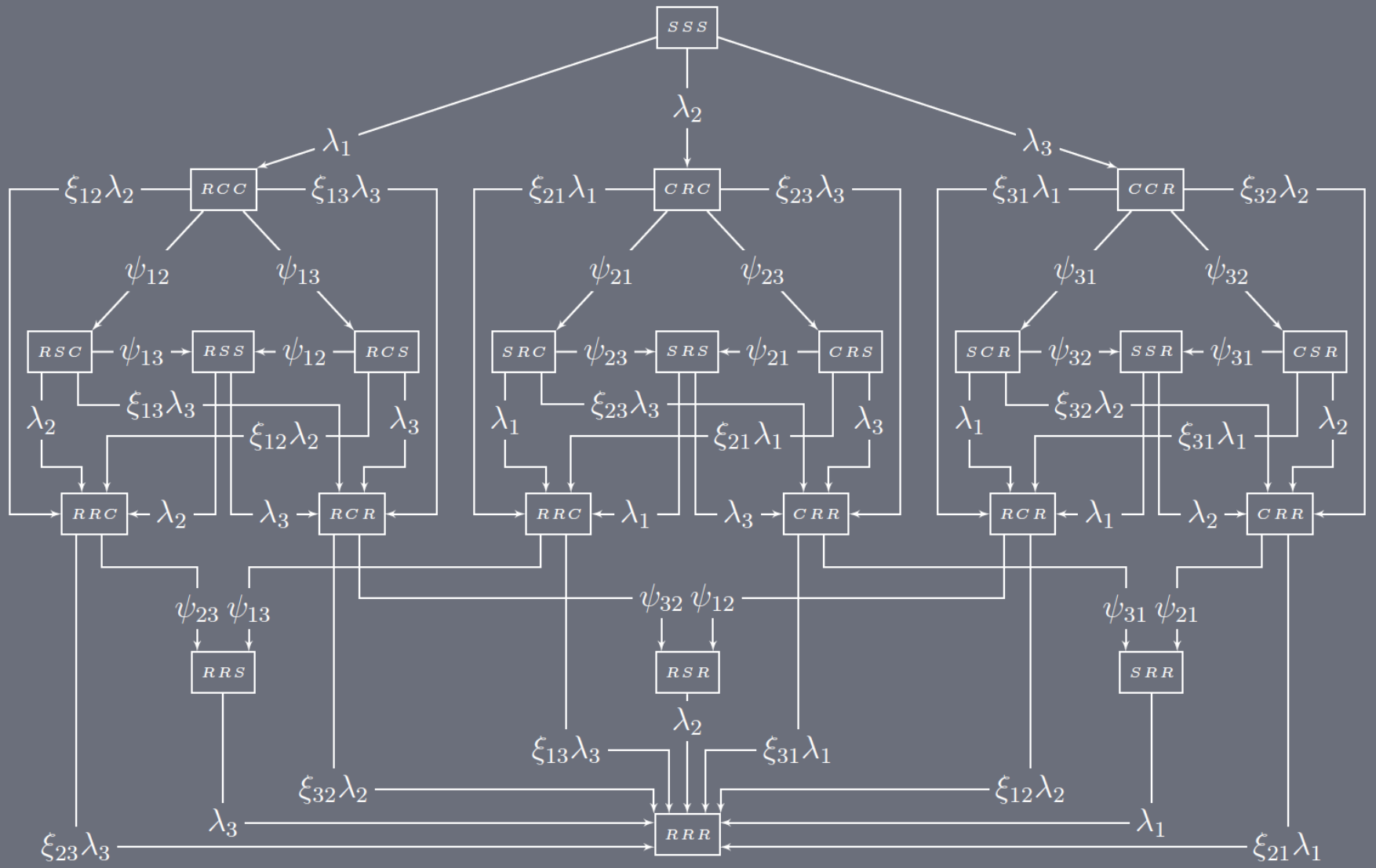

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- An individual's serostatus isn't necessarily the only information required to evaluate future risk
- Force of infections are functions of time and are fit simultaneously to ξ and ψ

Model fitting

We essentially have two types of censored data: interval censored and right censored

Interval Censored

One serotype

$$P\left(t_1^1 < X_1 < t_1^2\right) = \int_{t_1^1}^{t_1^2} f_1(s)ds$$

Model fitting

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Interval Censored

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Two serotypes

$$P\left(t_1^1 < X_1 < t_1^2, t_2^1 < X_2 < t_2^2\right) = \int_{t_1^1}^{t_1^2}\int_{t_2^1}^{t_2^2} \delta(s_1, s_2)\, f_1(s_1) f_2(s_2) ds_2 ds_1$$

$$\text{where} \quad \delta(s_1, s_2) = \begin{cases} 1 & \text{if } |s_1 - s_2| > \psi \\ \xi & \text{if } |s_1 - s_2| \leq \psi \end{cases}$$

Model fitting

We essentially have two types of censored data: interval censored and right censored

Interval Censored

Three serotypes

$$P\left(t_1^1 < X_1 < t_1^2, t_2^1 < X_2 < t_2^2, t_3^1 < X_3 < t_3^2\right)$$

$$= \int_{t_1^1}^{t_1^2} \int_{t_2^1}^{t_2^2} \int_{t_3^1}^{t_3^2} \delta(s_1, s_2)\delta(s_1, s_3)\,\delta(s_2, s_3)\, f_1(s_1) f_2(s_2) f_3(s_3) ds_3 ds_2 ds_1$$

Model fitting

Right Censored

One serotype

$$P\left(X_1 > t_1^2\right) = 1 - \int_{t_1^0}^{t_1^2} f_1(s)ds$$

Model fitting

Right Censored

Two serotypes — One interval censored, one right censored

$$P\left(t_1^1 < X_1 < t_1^2, X_2 > t_2^2\right) = \int_{t_1^1}^{t_1^2} f_1(s)ds - \int_{t_1^1}^{t_1^2}\int_{t_2^0}^{t_2^2} \delta(s_1, s_2) f_1(s_1)\, f_2(s_2) ds_2 ds_1$$

Model fitting

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Two right censored

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Model fitting

Right Censored

Three serotypes

Math omitted

Model fitting

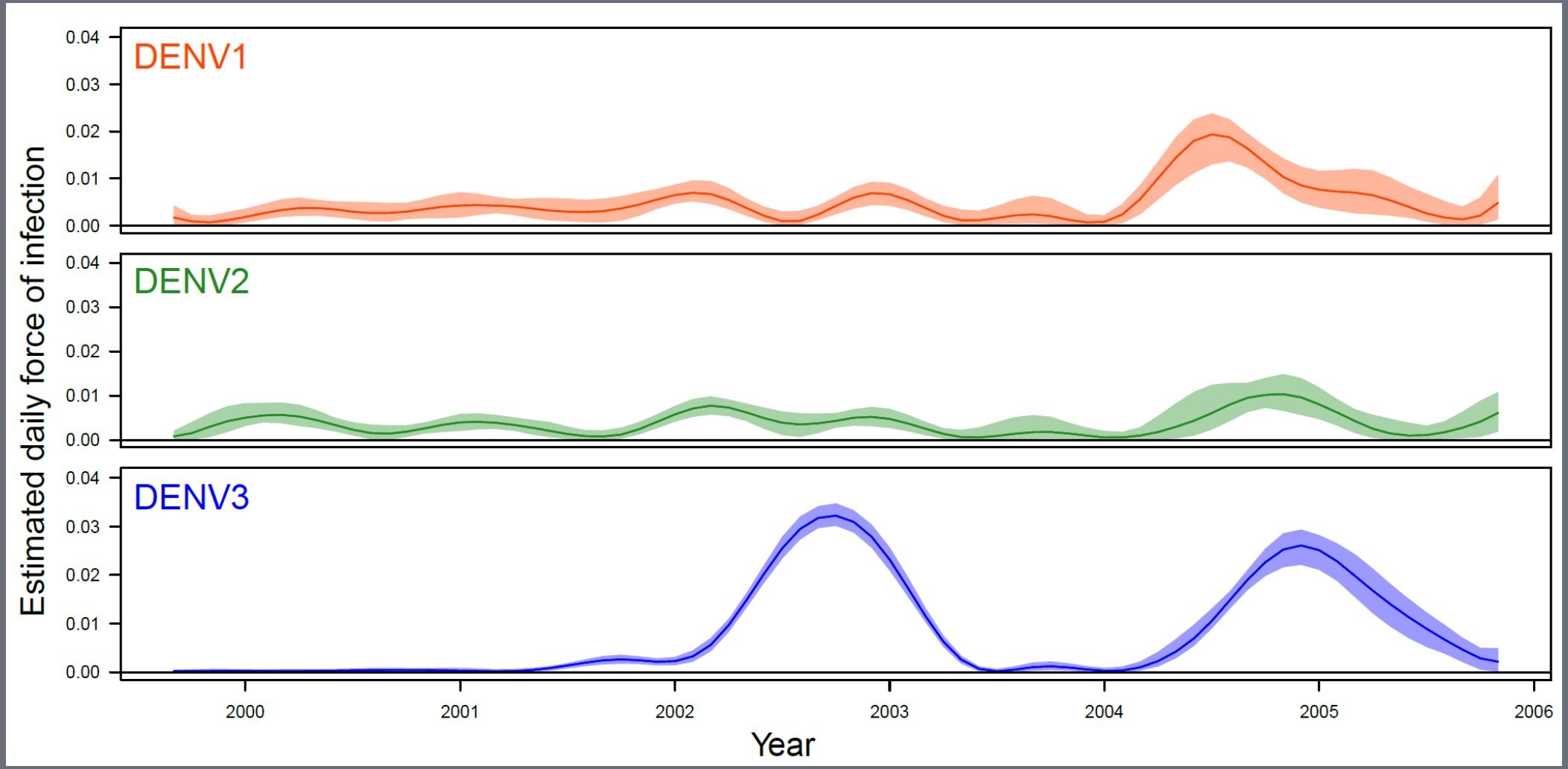
Right Censored

Three serotypes

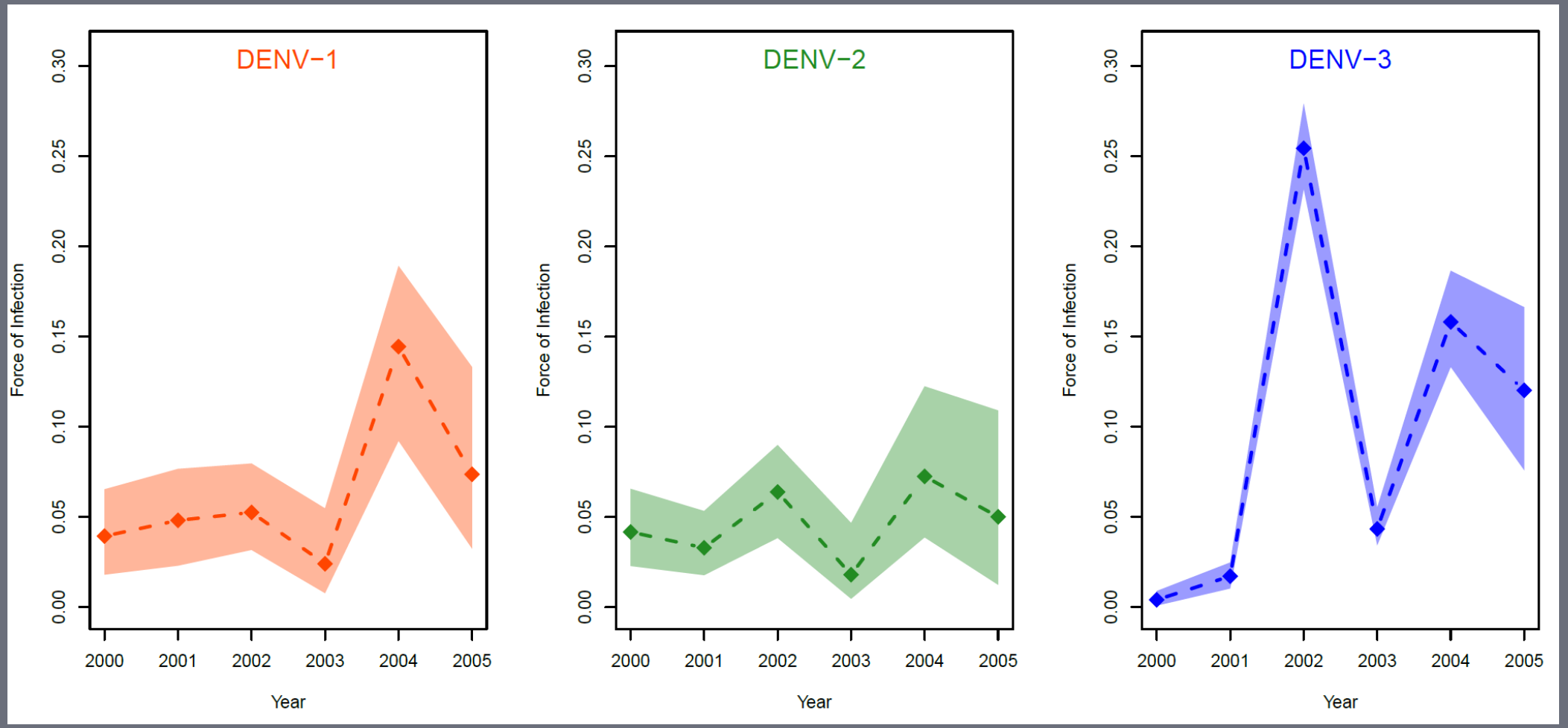
Math omitted

We use adaptive Gibbs-within-Metropolis MCMC to estimate the parameters governing durations and strengths of temporary cross-protection for each serotype/serotype combination as well as the temporally varying serotype-specific forces of infection

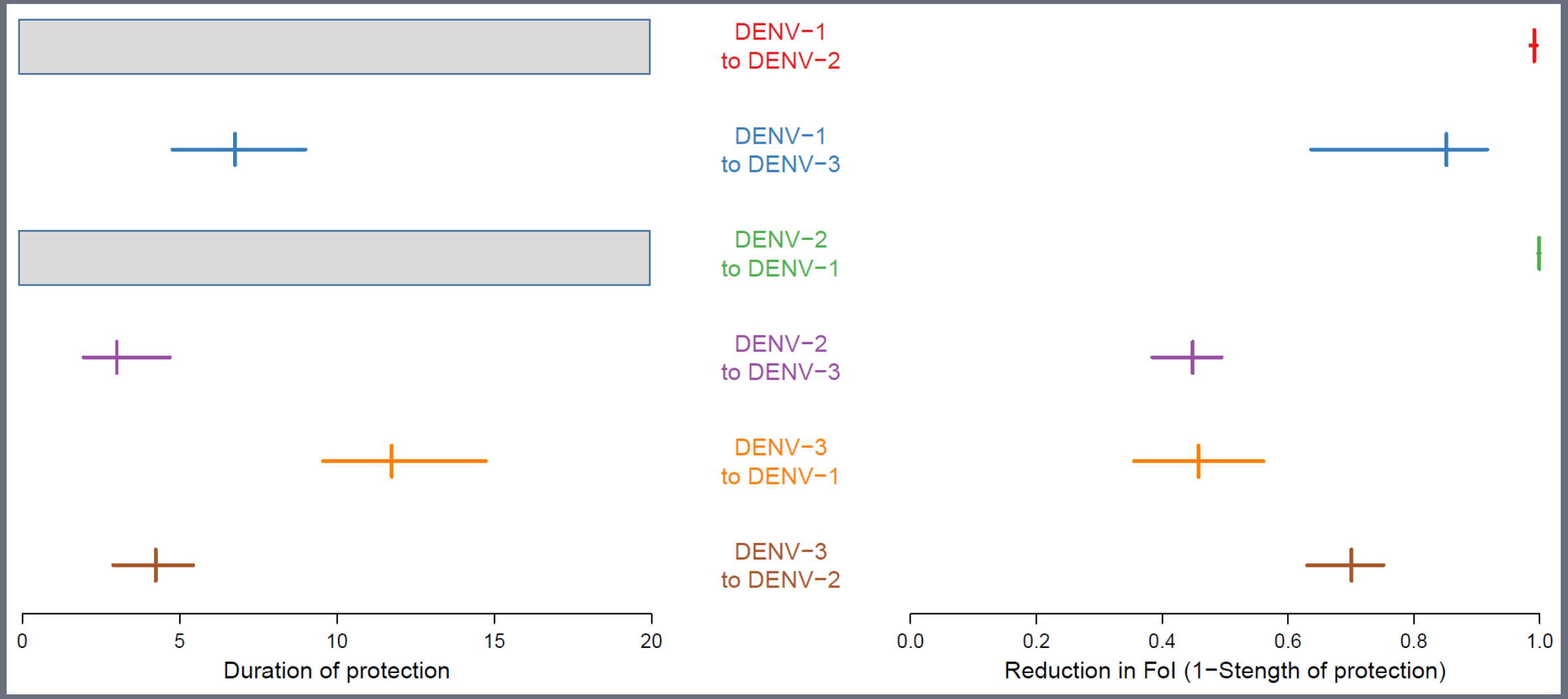
Force of Infection



Force of Infection



Temporary Cross-Protection



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Conclusions and Future Work

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Next Steps

- Use values to simulate populations
  - Evaluate statistical significance versus practical importance
  - Interpretation of results in context of vaccination protection
- Explore sub-models with greedy algorithms
- Add DENV-4 (include data from 2008)
- Add Asian-American DENV-2 (include data from 2011)
- Antibody-dependent enhancement may increase infectability
- Evaluate functional form of TCI
- Incorporate finer scale of FoI

Obrigado!!!

Questions?