Swiss TPH

Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

Department of Epidemiology and Public Health
Health Systems Research and
Dynamical Modelling Unit

Modelling Heterogeneity

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Workshop on Mathematical Models of Climate Variability,
Environmental Change and Infectious Diseases
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- In the basic SIR-type models, we have assumed that the population is homogeneous, that is, everyone is considered to be identical (except for disease status) and to have random contacts.
- In general, disease systems contain many heterogeneities such as,
  - Population heterogeneity
  - Spatial heterogeneity
  - Temporal heterogeneity (seasonality).

Populations can be heterogeneous in terms of (model parameters)

- Susceptibility and infectivity
- Rate of recovery and acquired immunity
- Contact rates
- Mortality and disease-induced mortality.

Heterogeneity (in model parameters) may depend on demographic characteristics such as

- Age
- Socioeconomic status
- Occupation
- Degree of contacts
- Gender
- Species
- Individual characteristics.

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We determine parameter values for each demographic category.
We can do this in three ways.

1. We can replicate the SIR model equations for different groups representing different values of a demographic parameter leading to high-dimensional ODE models with multiple groups.
2. We can assume that the demographic parameter is continuous leading to partial integrodifferential equations.
3. We can assign a particular value for a number of different demographic parameters to each individual in the population and numerically simulate the interactions of the individuals within the population and the subsequent progress of the disease, leading to an individual-based model.

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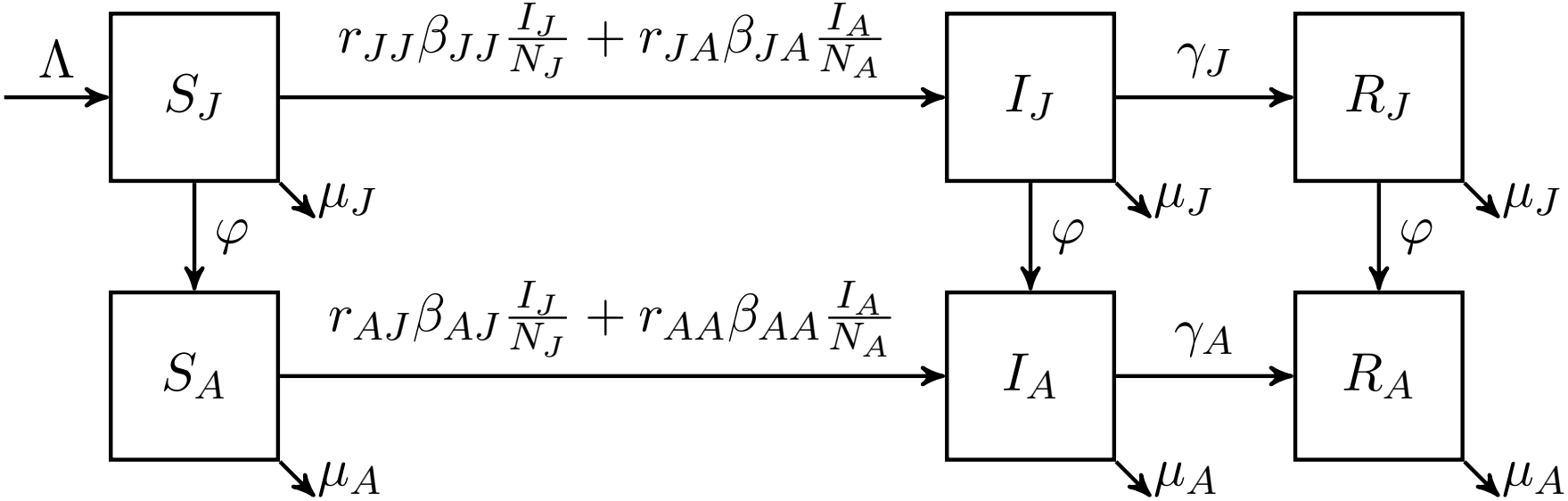


S_J:	Susceptible Juveniles	S_A:	Susceptible Adults
I_J:	Infectious Juveniles	I_A:	Infectious Adults
R_J:	Recovered Juveniles	R_A:	Recovered Adults

Λ: Recruitment rate of new juveniles.

r_{kl}: Number of contacts per time between an individual in group k with individuals in group l.

β_{kl}: Probability of disease transmission per contact between an infectious in group l with a susceptible in group k.

γ_k: Recovery rate of individuals in group k.

φ: Development rate (from juveniles to adults).

μ_k: Death rate of individuals in group k.

N_k: Total population of group k. $N_k = S_k + I_k + R_k$.

for $k = J$ or $k = A$ and $l = J$ or $l = A$.

$$\frac{\mathrm{d}S_J}{\mathrm{d}t} = \Lambda - \left(r_{JJ}\beta_{JJ}\frac{I_J}{N_J} + r_{JA}\beta_{JA}\frac{I_A}{N_A}\right) S_J - (\varphi + \mu_J)S_J$$

$$\frac{\mathrm{d}I_J}{\mathrm{d}t} = \left(r_{JJ}\beta_{JJ}\frac{I_J}{N_J} + r_{JA}\beta_{JA}\frac{I_A}{N_A}\right) S_J - (\gamma_J + \varphi + \mu_J)I_J$$

$$\frac{\mathrm{d}R_J}{\mathrm{d}t} = \gamma_J I_J - (\varphi + \mu_J)R_J$$

$$\frac{\mathrm{d}S_A}{\mathrm{d}t} = \varphi S_J - \left(r_{AJ}\beta_{AJ}\frac{I_J}{N_J} + r_{AA}\beta_{AA}\frac{I_A}{N_A}\right) S_A - \mu_A S_A$$

$$\frac{\mathrm{d}I_A}{\mathrm{d}t} = \varphi I_J + \left(r_{AJ}\beta_{AJ}\frac{I_J}{N_J} + r_{AA}\beta_{AA}\frac{I_A}{N_A}\right) S_A - (\gamma_A + \mu_A)I_A$$

$$\frac{\mathrm{d}R_A}{\mathrm{d}t} = \varphi R_J + \gamma_A I_A - \mu_A R_A$$

$$K = \begin{pmatrix} K_{JJ} & K_{JA} \\ K_{AJ} & K_{AA} \end{pmatrix}$$

K_{JJ}: Number of new juvenile individuals infected by one infectious juvenile individual assuming a fully susceptible population through the duration of the infectious period.

K_{JA}: Number of new juvenile individuals infected by one infectious adult individual assuming a fully susceptible population through the duration of the infectious period.

K_{AJ}: Number of new adult individuals infected by one infectious juvenile individual assuming a fully susceptible population through the duration of the infectious period.

K_{AA}: Number of new adult individuals infected by one infectious adult individual assuming a fully susceptible population through the duration of the infectious period.

R_0 is the spectral radius of K (eigenvalue with the maximum absolute value).

$$R_0 = \frac{1}{2}\left(\sqrt{K_{JJ}^2 + K_{AA}^2 - 2K_{JJ}K_{AA} + 4K_{AJ}K_{JA}} + K_{JJ} + K_{AA}\right)$$

where

$$K_{JJ} = \frac{r_{JJ}\beta_{JJ}}{\gamma_J + \varphi + \mu_J}$$

$$K_{JA} = \frac{r_{JA}\beta_{JA}}{\gamma_A + \mu_A}$$

$$K_{AJ} = \frac{r_{AJ}\beta_{AJ}}{\gamma_J + \varphi + \mu_J}$$

$$K_{AA} = \frac{r_{AA}\beta_{AA}}{\gamma_A + \mu_A}$$

- We can divide the population into any number of groups.
- We could include more than one demographic parameter but the equations then become complicated.
- We need to determine the contact matrix for each model.
- However, the population is still assumed to be homogeneous within each group.

$$\frac{\partial S}{\partial a} + \frac{\partial S}{\partial t} = -\left(\frac{\int_0^\infty r(a,\tilde{a})\alpha(a)\beta(\tilde{a})I(\tilde{a},t)\,d\tilde{a}}{\int_0^\infty N(\tilde{a},t)\,d\tilde{a}} + \mu(a) \right) S,$$

$$\frac{\partial I}{\partial a} + \frac{\partial I}{\partial t} = \left(\frac{\int_0^\infty r(a,\tilde{a})\alpha(a)\beta(\tilde{a})I(\tilde{a},t)\,d\tilde{a}}{\int_0^\infty N(\tilde{a},t)\,d\tilde{a}} \right) S - (\gamma + \mu(a))I,$$

$$\frac{\partial R}{\partial a} + \frac{\partial R}{\partial t} = \gamma I - \mu(a)R,$$

where $r(a,\tilde{a}) = r(\tilde{a},a)$ is the contact rate between hosts of age a and $\tilde{a}$; $\alpha(a)$ is the susceptibility of hosts of age a; $\beta(a)$ is the infectivity of hosts of age a; and $N(a,t) = S(a,t) + I(a,t) + R(a,t)$; with specified initial conditions, and boundary conditions,

$$S(0,t) = \int_0^\infty f(a)N(a,t)\,da,$$

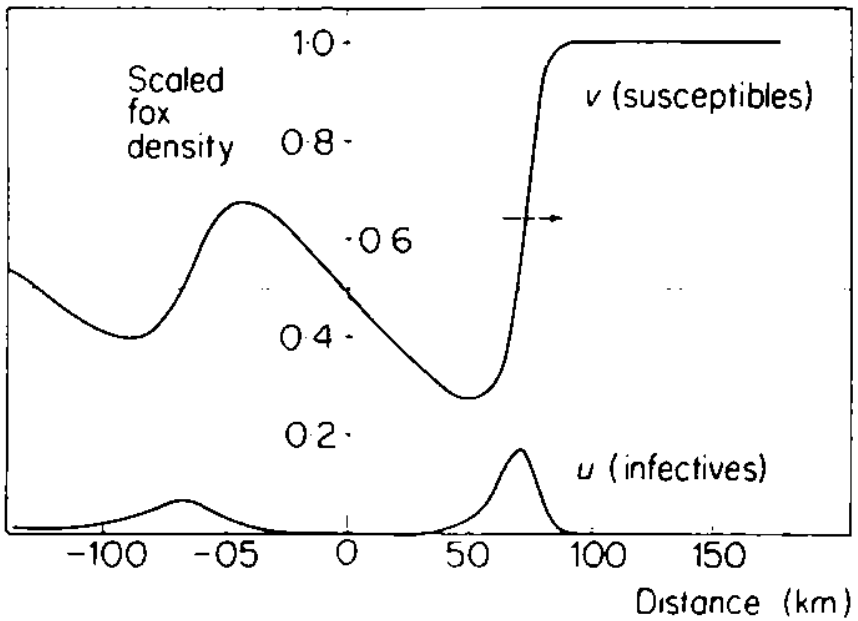
and $I(0,t) = 0$, $R(0,t) = 0$. And, $N(t) = \int_0^\infty N(a,t)\,da$.

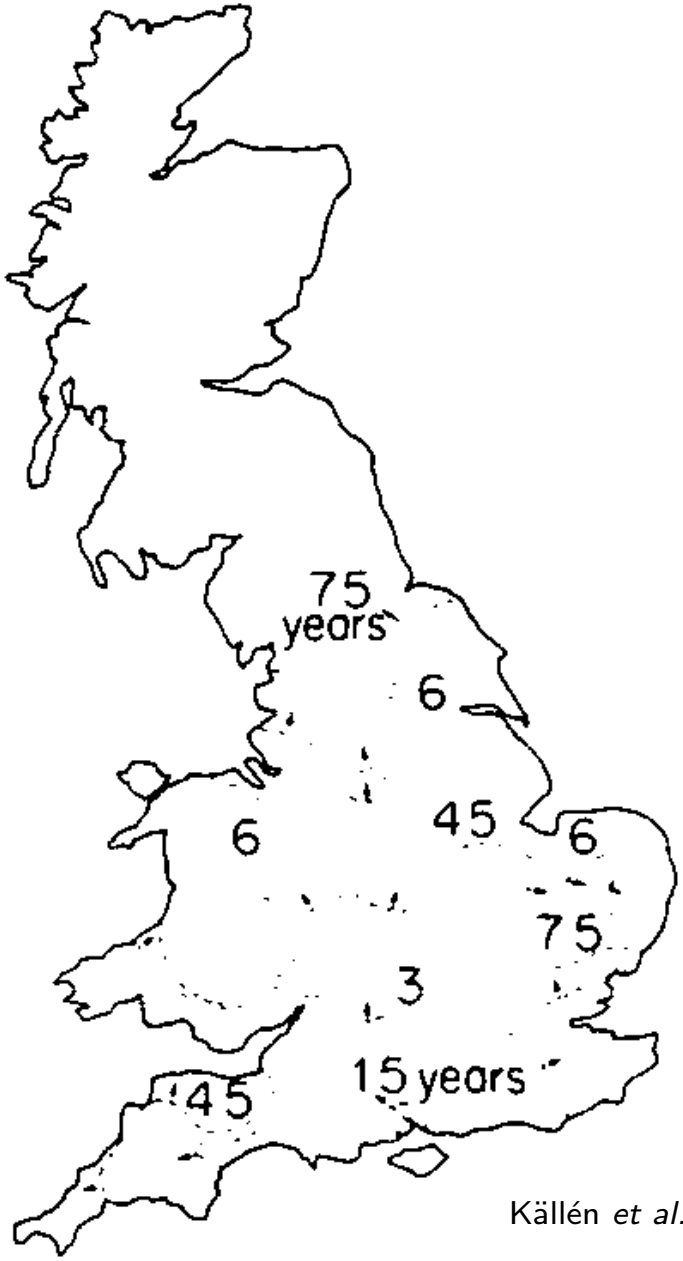
Adapted from Hethcote (2000)

- Modeling spatial heterogeneity is similar to modeling population heterogeneity but we divide the population by spatial location instead of by demographic characteristics.
- We can model space as continuous or discrete.
  - Continuous space leads to partial integrodifferential equations.
  - Discrete space leads to multi-group ODE models (for example, patch models) or cellular automata.
- We can model movement of hosts or of infection.

$$\frac{\partial S}{\partial t} = -KIS$$

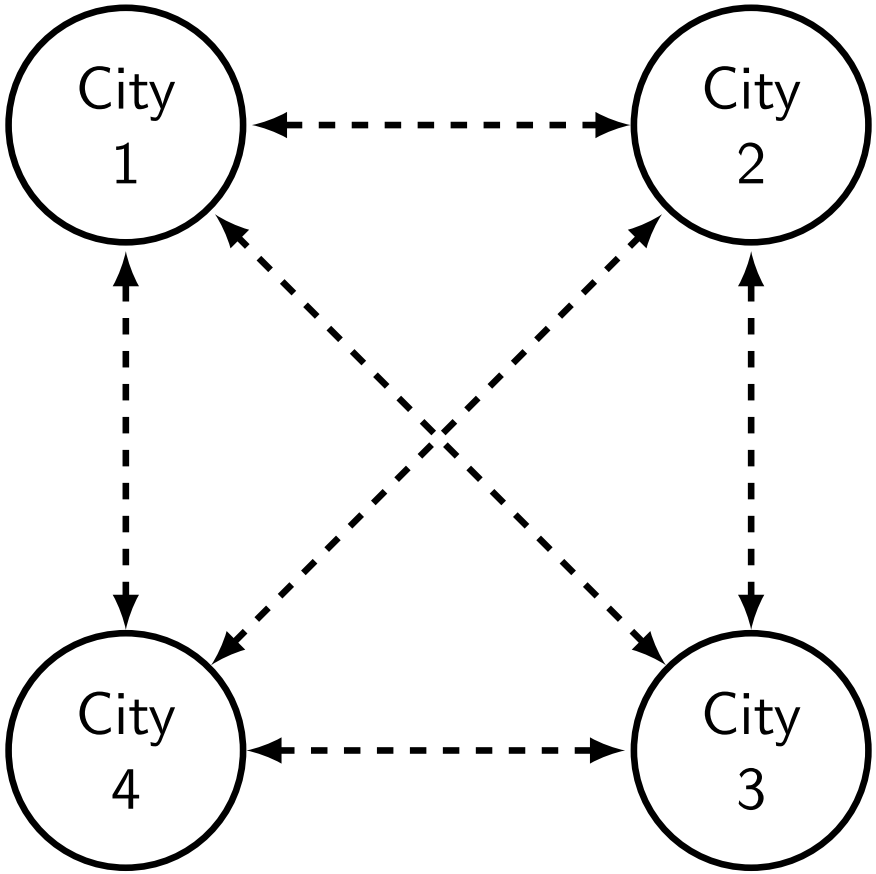
$$\frac{\partial I}{\partial t} = D\frac{\partial^2 I}{\partial x^2} + KIS - \mu I$$





Källén *et al.* (1985)

- Models of interacting populations.
- For example, multiple connected SIR models for the spread of influenza across cities.



Rabies in N'Djamena, Chad

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Vaccination Campaigns

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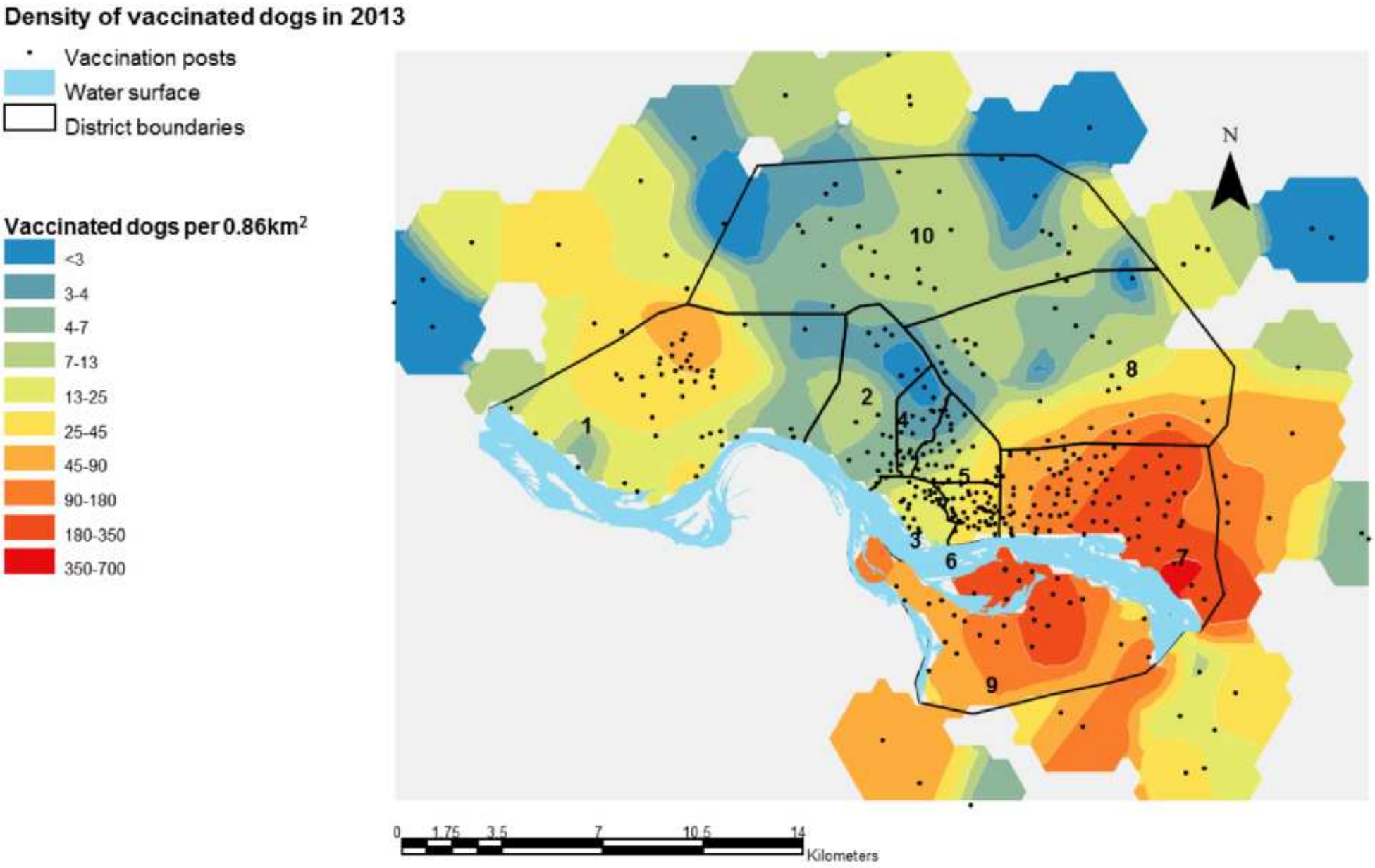
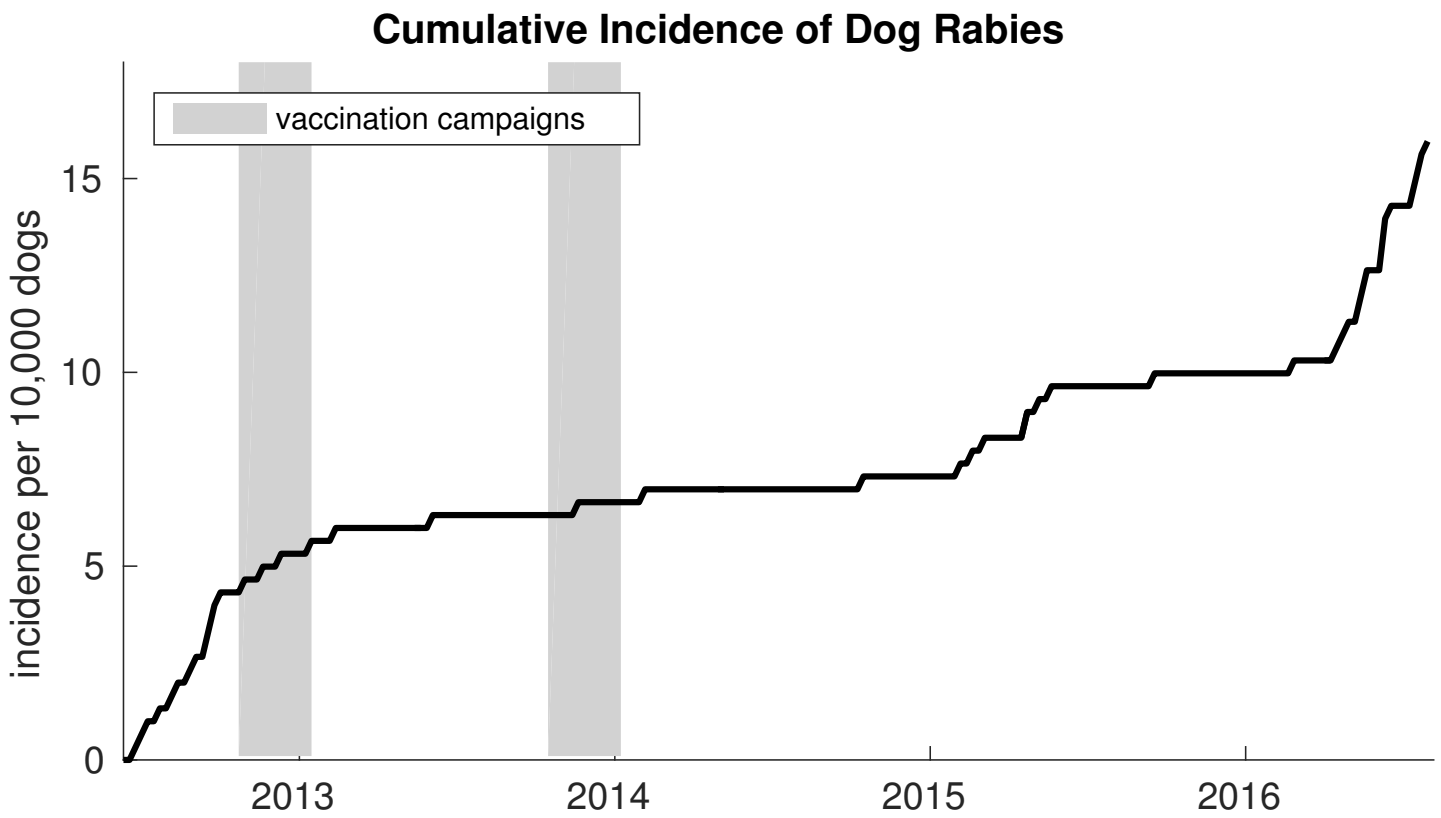
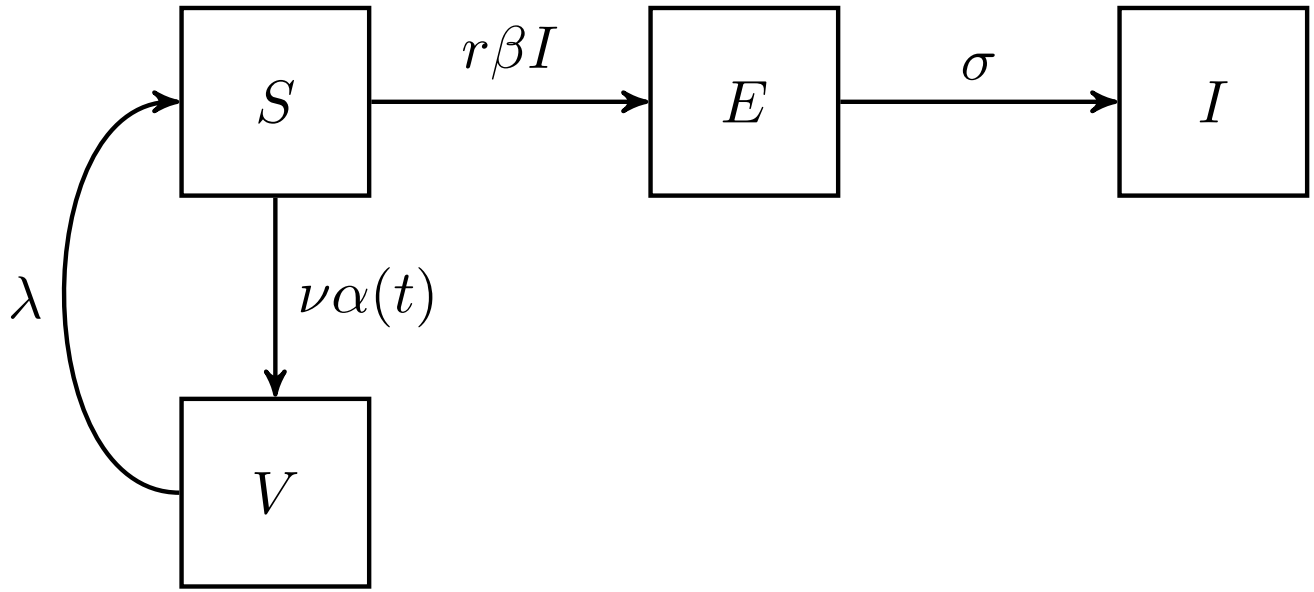




- Different models were fit to 4 years of weekly incidence data from N'Djamena.

(from Mirjam Laager)

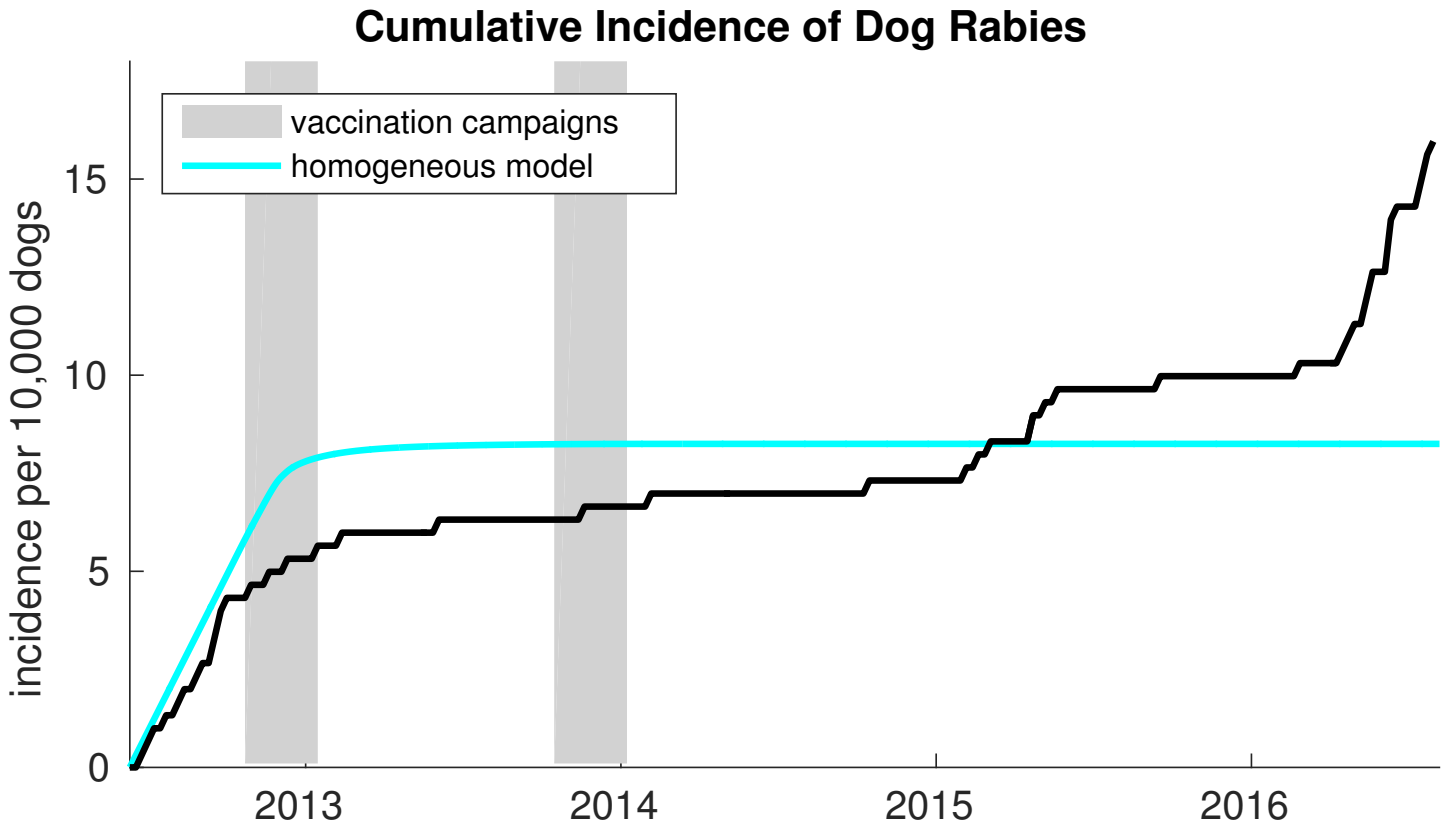


S: Susceptible, E: Exposed, I: Infective, V: Vaccinated
μ: birth/death, δ: disease induced death, ε: importation
$\nu\alpha(t)$: vaccination, λ: immunity loss, β: transmission,
σ: rate of progression from exposed stage

$$\frac{dS(t)}{dt} = \mu N_0 + \lambda V(t) - (\nu\alpha(t) + \mu)S(t) - \beta S(t)I(t),$$
$$\frac{dE(t)}{dt} = \beta S(t)I(t) - (\sigma + \mu)E(t) + \varepsilon,$$
$$\frac{dI(t)}{dt} = \sigma E(t) - (\delta + \mu)I(t),$$
$$\frac{dV(t)}{dt} = \nu\alpha(t)S(t) - (\lambda + \mu)V(t).$$

In the absence of importation ($\varepsilon = 0$):

$$R_0 = \frac{\sigma\beta N_0}{(\sigma + \mu)(\delta + \mu)}$$



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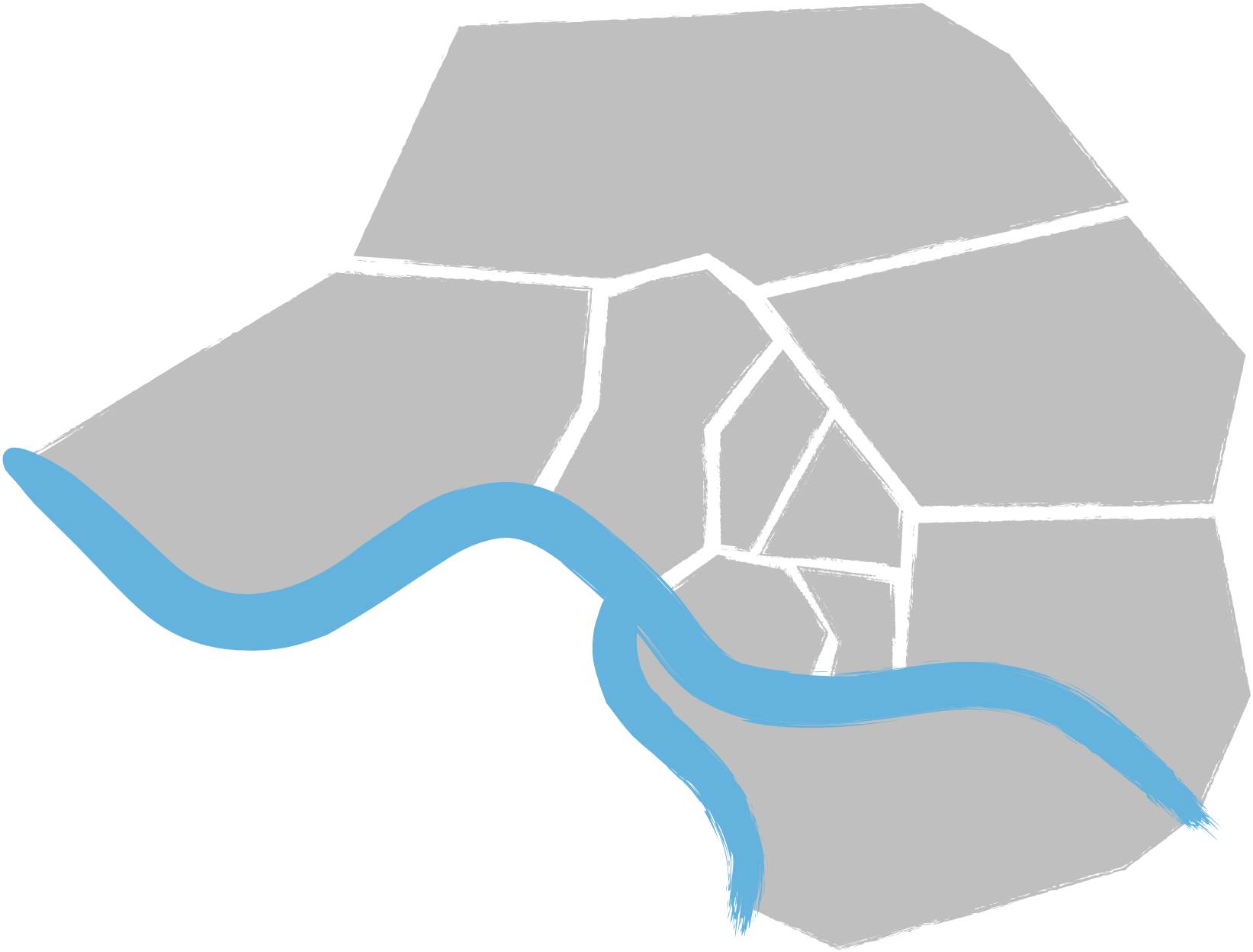
Metapopulation Model

Swiss TPH



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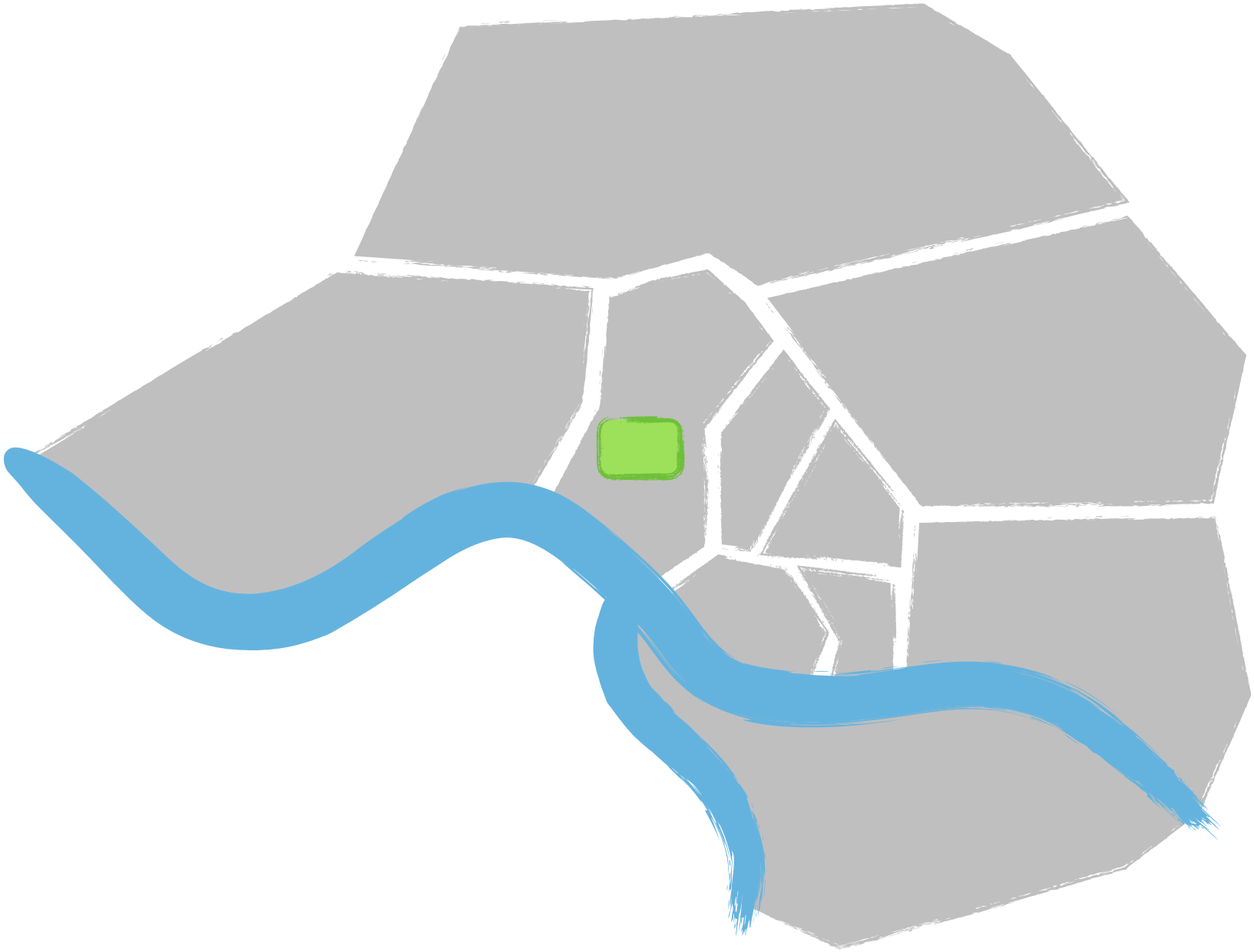

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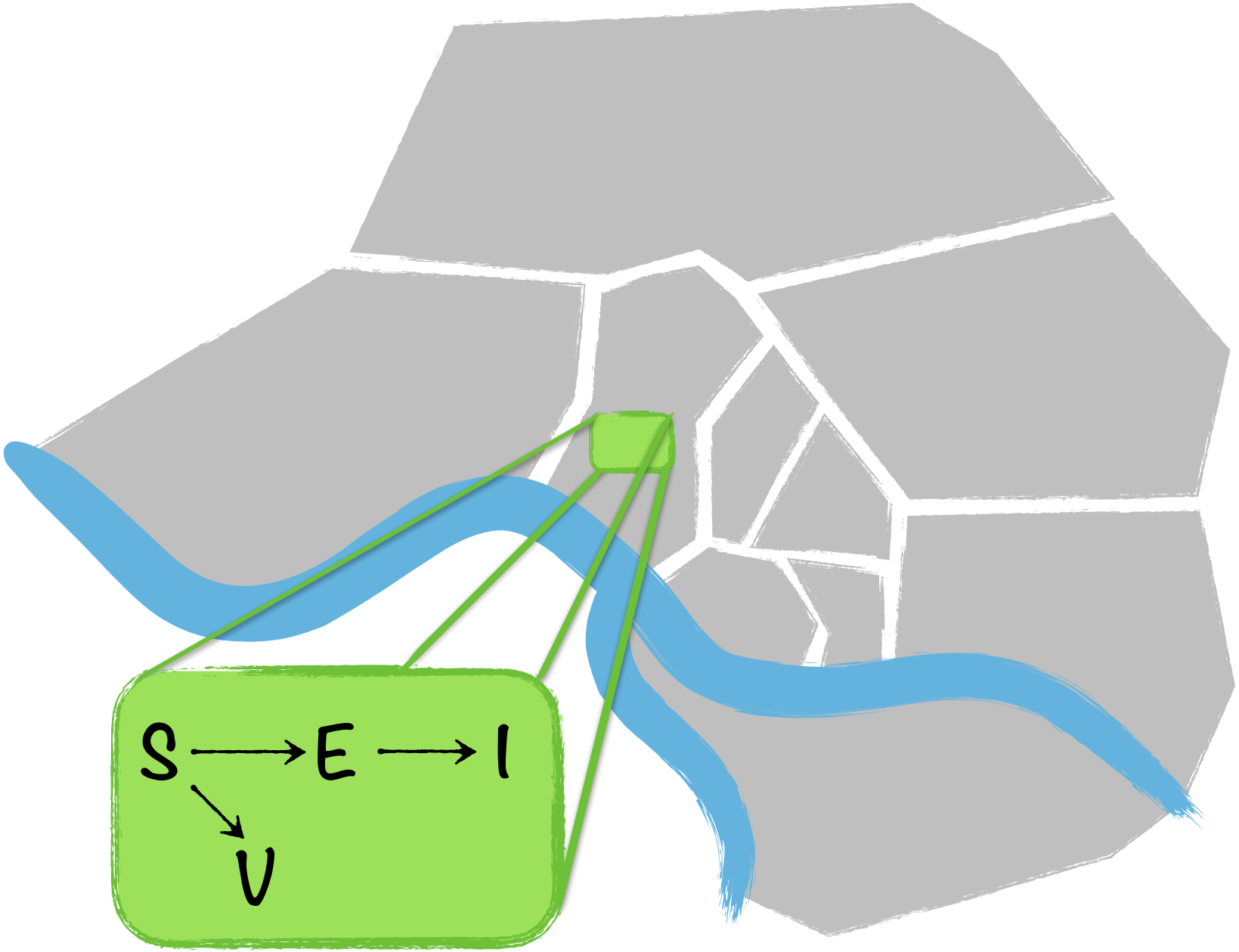

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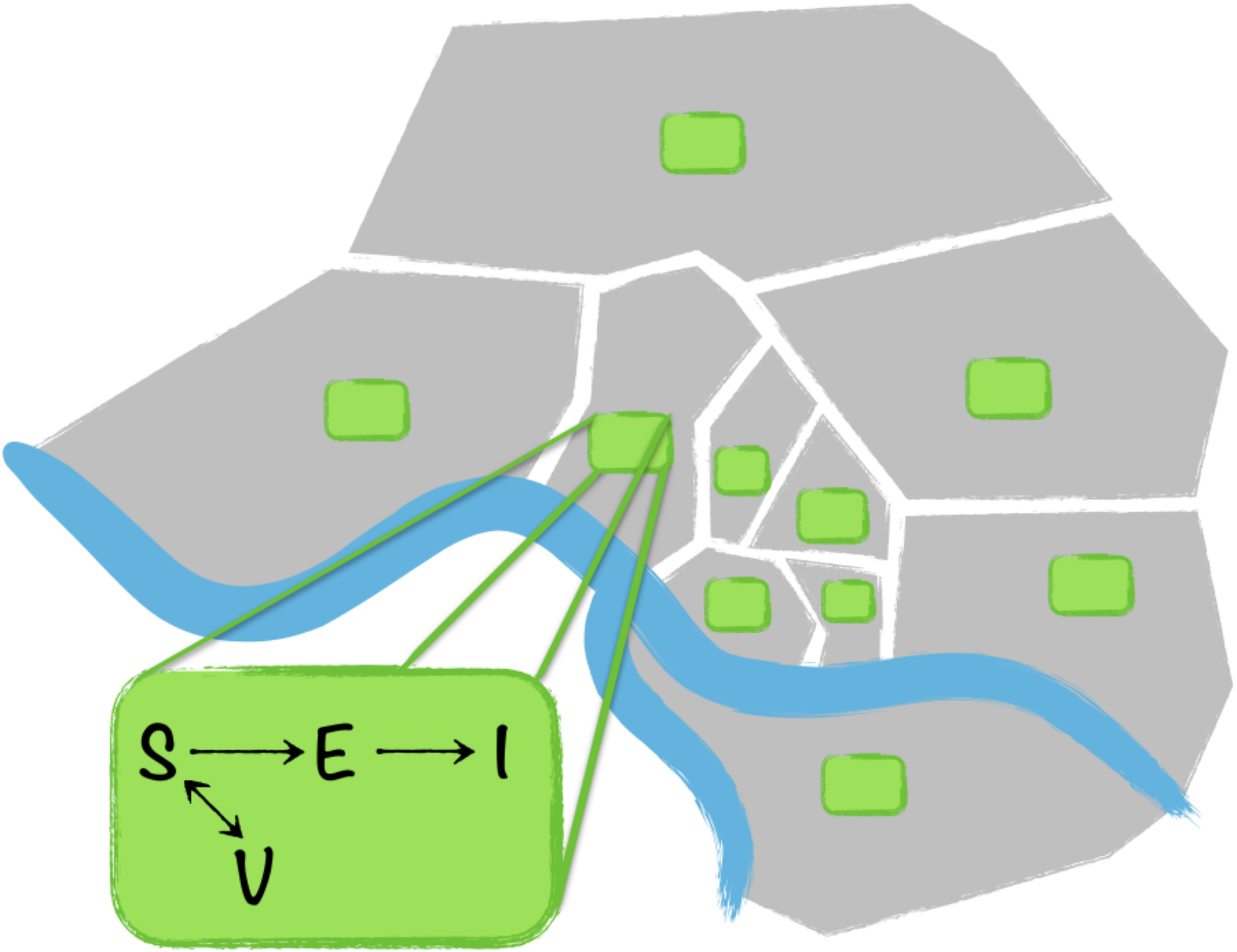

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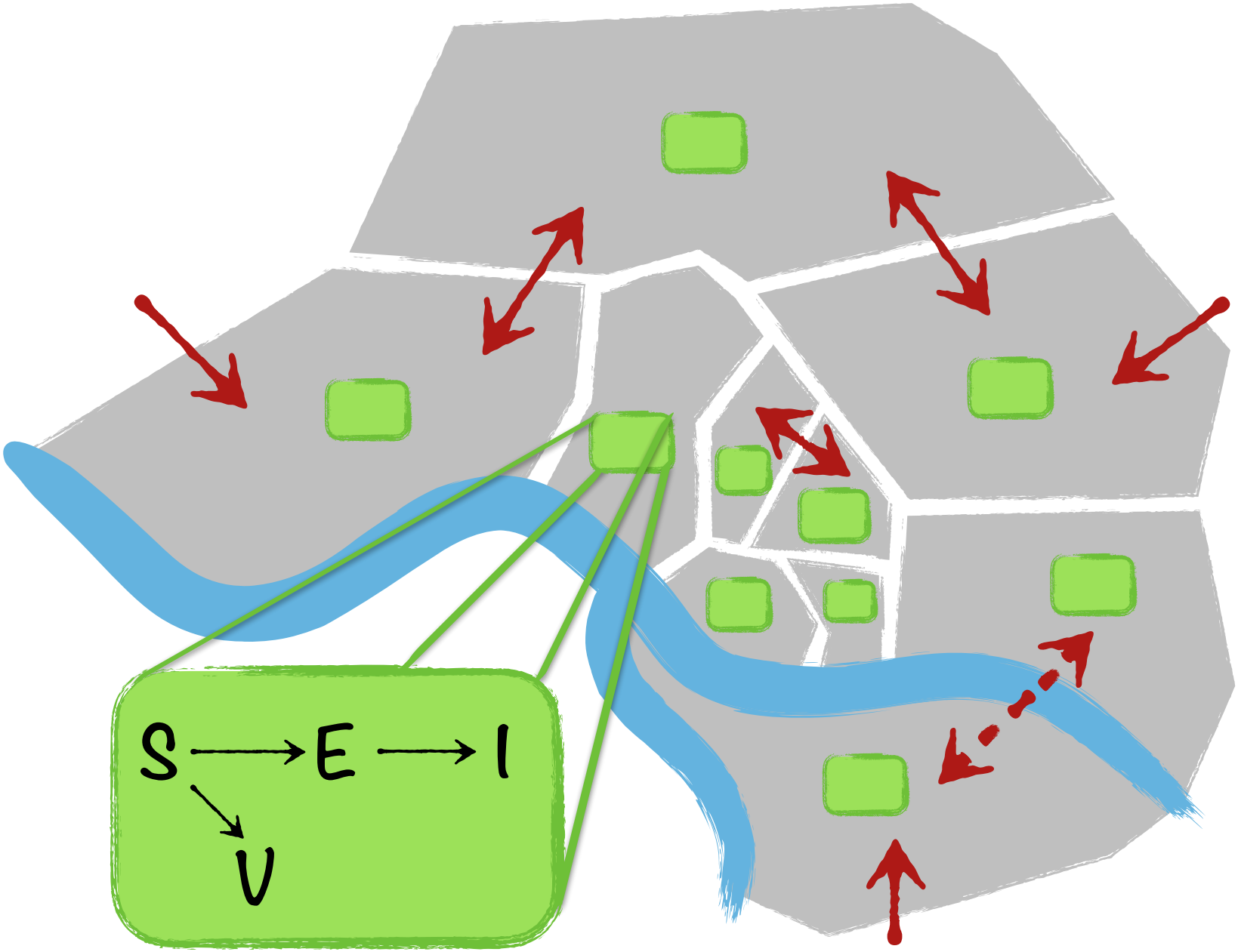


Consider n subpopulations.

$$\frac{dS_k(t)}{dt} = \mu N_{0k}(t) + \lambda V_k(t) - (\nu\alpha_k(t) + \mu)S_k(t) - \beta_k S_k(t)\sum_{j=1}^{n} m_{kj} I_j(t),$$

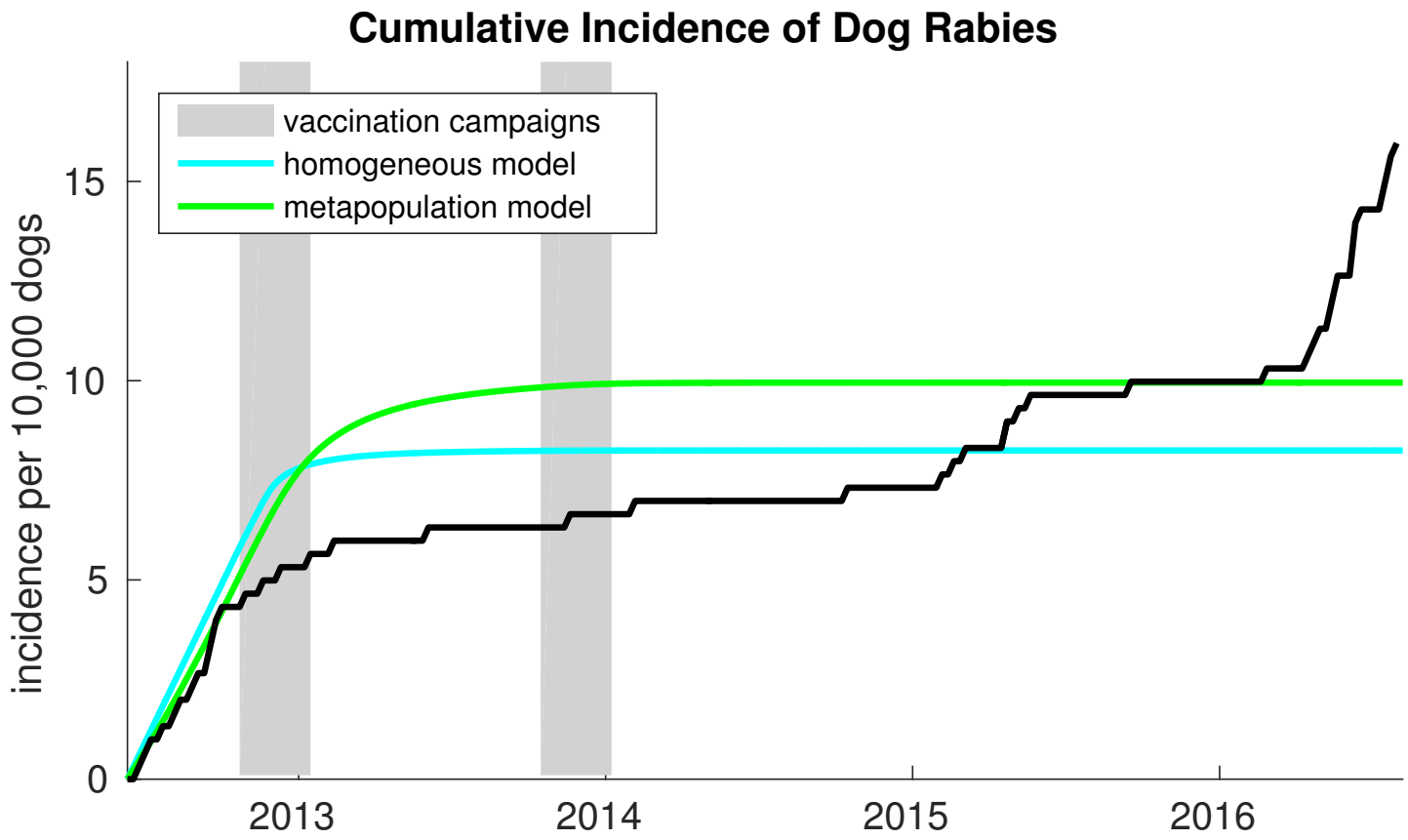
$$\frac{dE_k(t)}{dt} = \beta_k S_k(t)\sum_{j=1}^{n} m_{kj} I_j(t) - (\sigma + \mu)E_k(t),$$

$$\frac{dI_k(t)}{dt} = \sigma E_k(t) - (\delta + \mu)I_k(t),$$

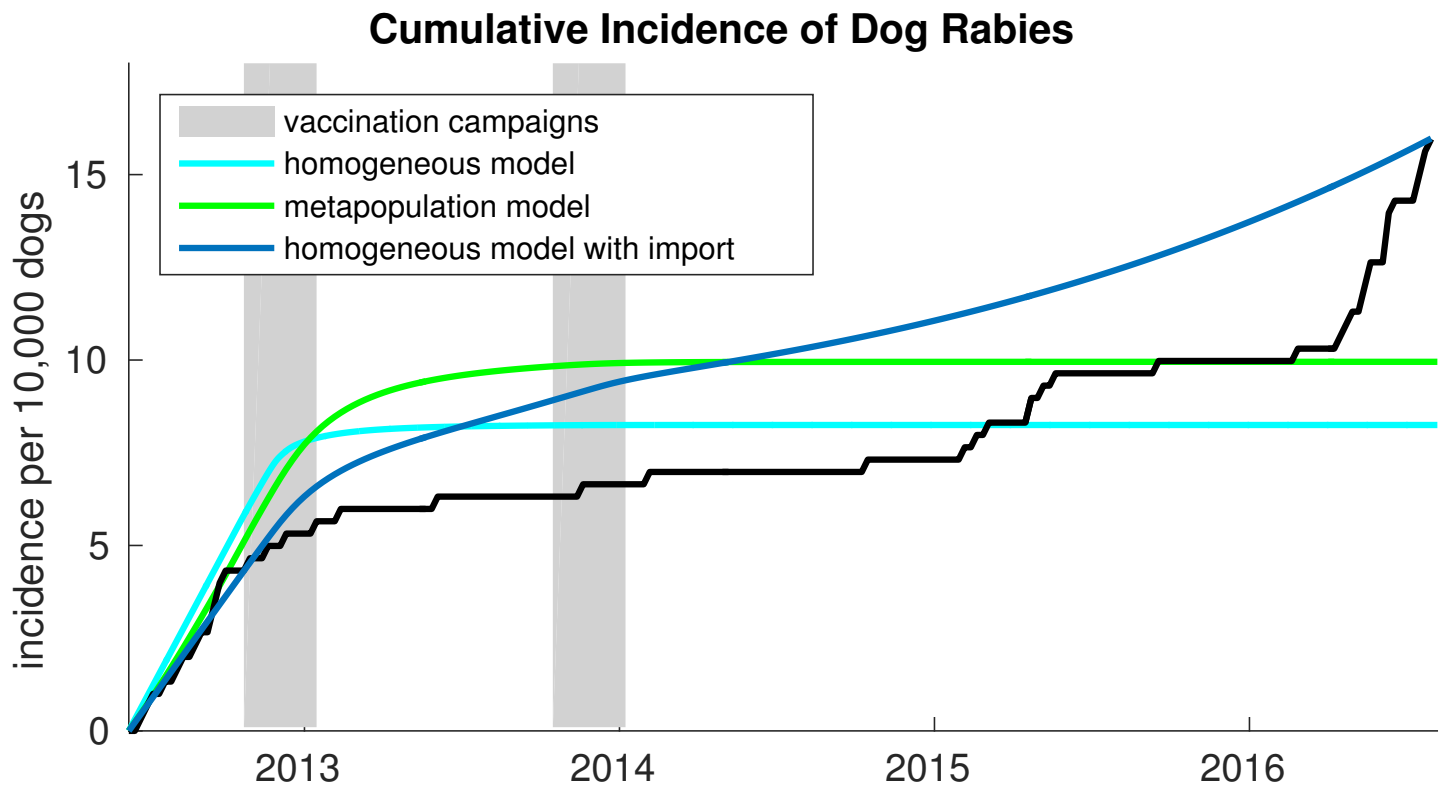
$$\frac{dV_k(t)}{dt} = \nu\alpha_k(t)S_k(t) - (\lambda + \mu)V_k(t),$$

with M such that

1. $m_{ij} = m_{ji}$ for all i, j
2. $m_{ii} \geq m_{ij}$ for all j
3. $\sum_{j=1}^{n} m_{kj} = 1$ for all k



- Different models were fit to 4 years of weekly incidence data from N'Djamena.



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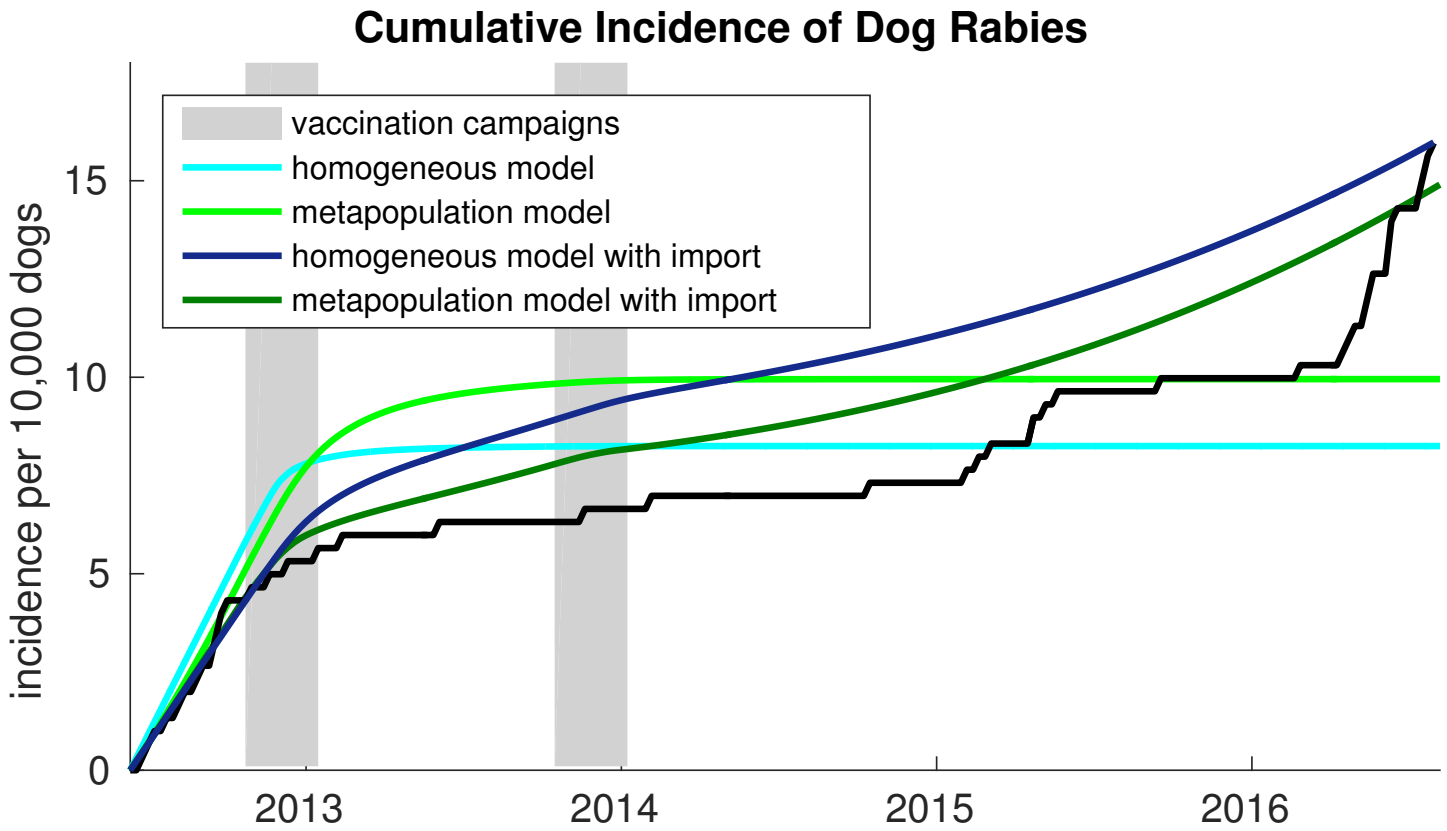


- Different models were fit to 4 years of weekly incidence data from N'Djamena.

- Continuous time models are easier to analyse than discrete-time models. However, for some diseases, or certain situations, discrete time may be more appropriate.
  - Reproduction of falciparum malaria blood stage parasites is on a 2 day cycle.
  - Mosquitoes have discrete stages in their feeding cycle that can be modeled with a one day time step.
- Discrete-time models consist of difference equations.
- Numerically integrating differential equations converts them to difference equations.

$$S(t+1) = S(t)(1 - r\beta I(t)/N)$$
$$I(t+1) = I(t)(1 + r\beta S(t)/N - \kappa)$$
$$R(t+1) = R(t) + \kappa I(t)$$

r: Number of contacts made in one time step.

β: Probability of disease transmission per contact.

κ: Proportion of infectious individuals that recover in one time step.

$N = S + I + R$ is the total population size.

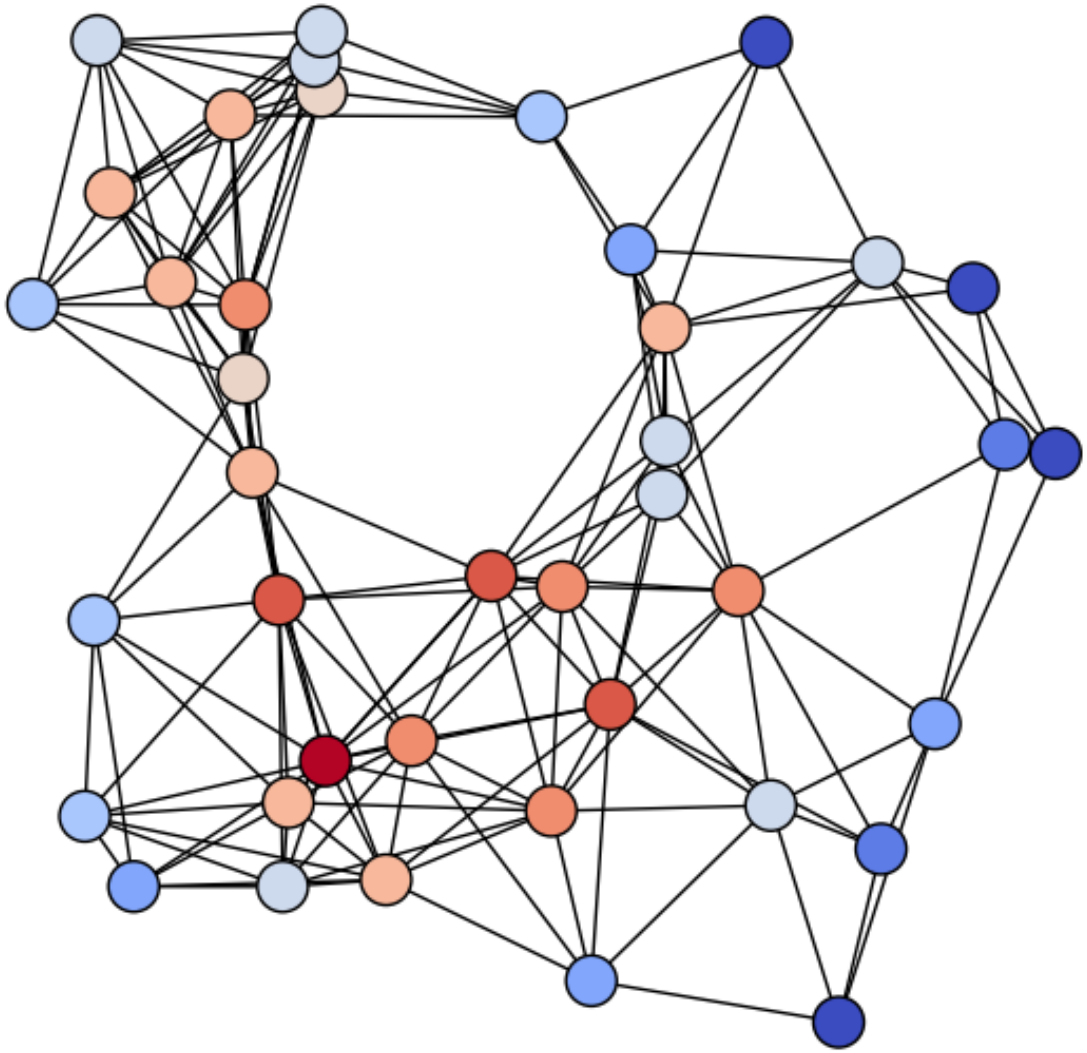
- Simulate the dynamics of infection in each individual at discrete time steps.
- Stochastic models because mean field approximation is no longer possible.

Advantages

- Include many different demographic characteristics.
- Include superinfection and dynamics of individual infections.
- Include temporal variation and other sources of heterogeneity.

Disadvantages

- Little mathematical analysis is possible.
- Can be computationally expensive.



Contacts between individuals are usually not equally likely but occur on networks.

- OpenMalaria is an open source C++ platform to simulate falciparum malaria immunology, epidemiology, and control with an ensemble of individual-based models.
- Developed at the Swiss TPH and Liverpool School of Tropical Medicine.
- `https://github.com/SwissTPH/openmalaria/wiki`
- Allows the comparison of the effectiveness and cost-effectiveness of multiple malaria control intervention strategies in reducing transmission and disease.

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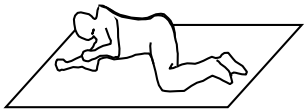
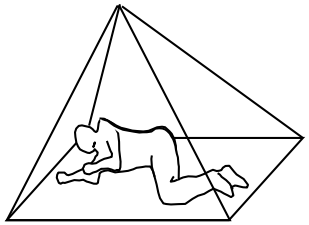
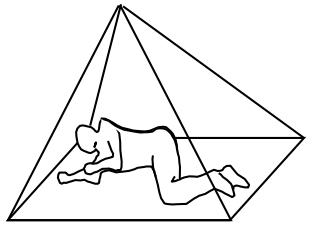
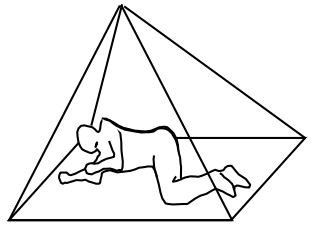
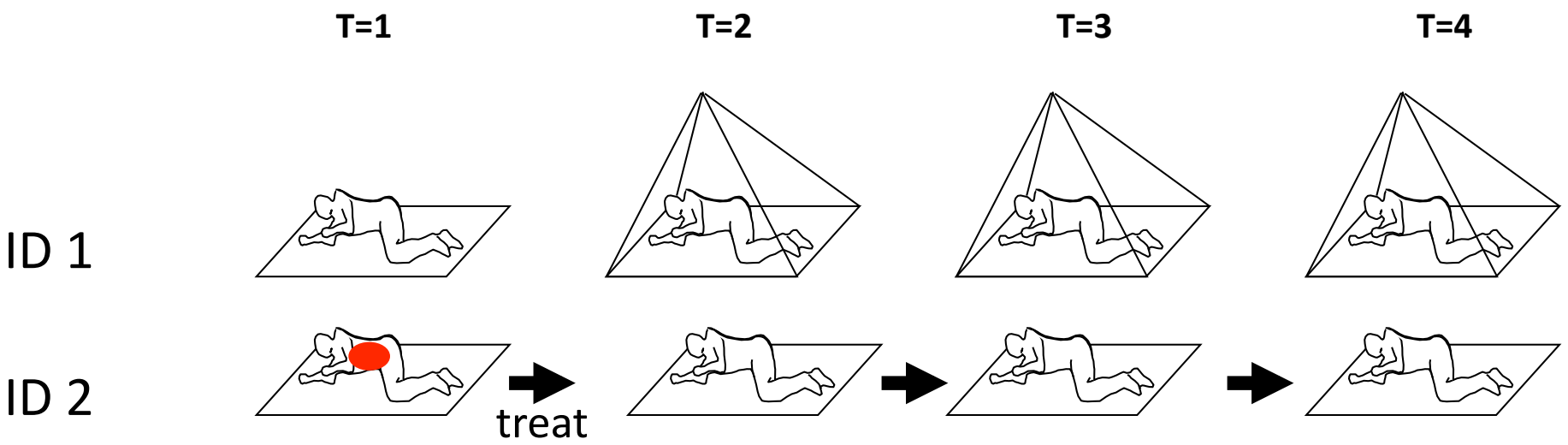
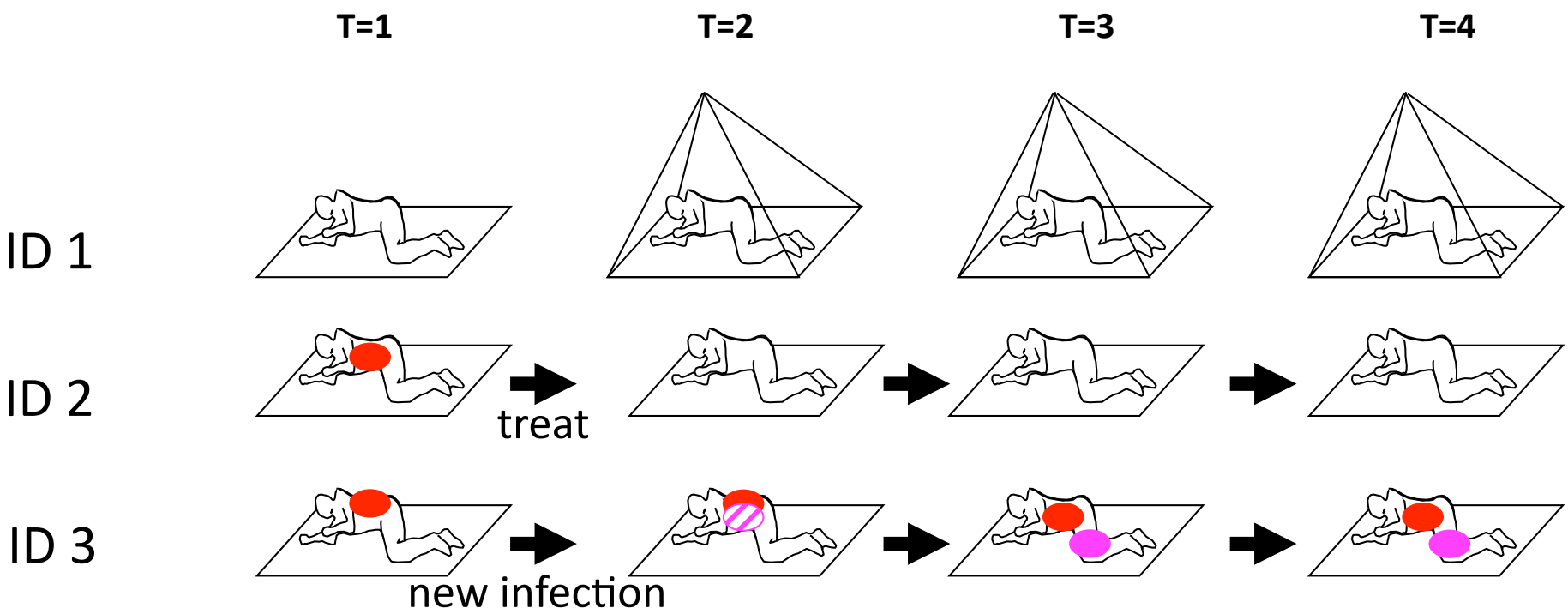
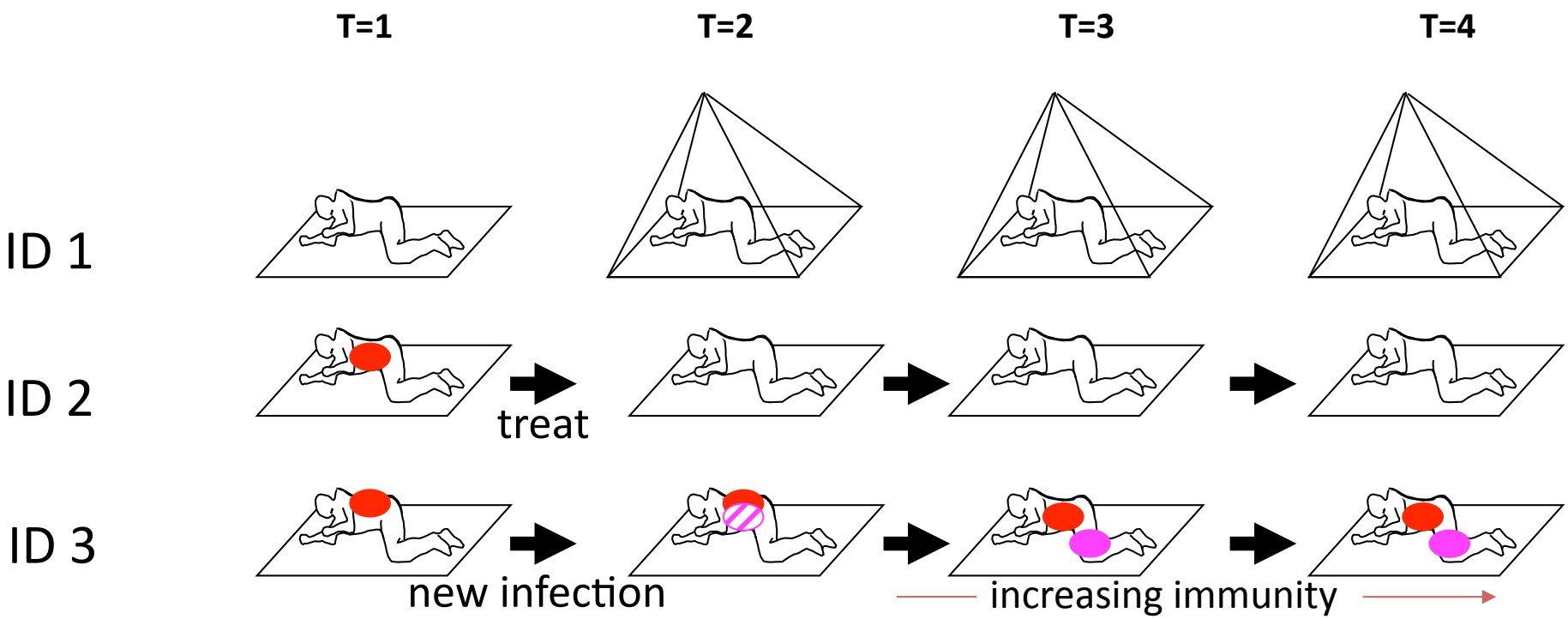
ID 1				


T=1
T=2
T=3
T=4
ID 1
ID 2
treat

Swiss TPH

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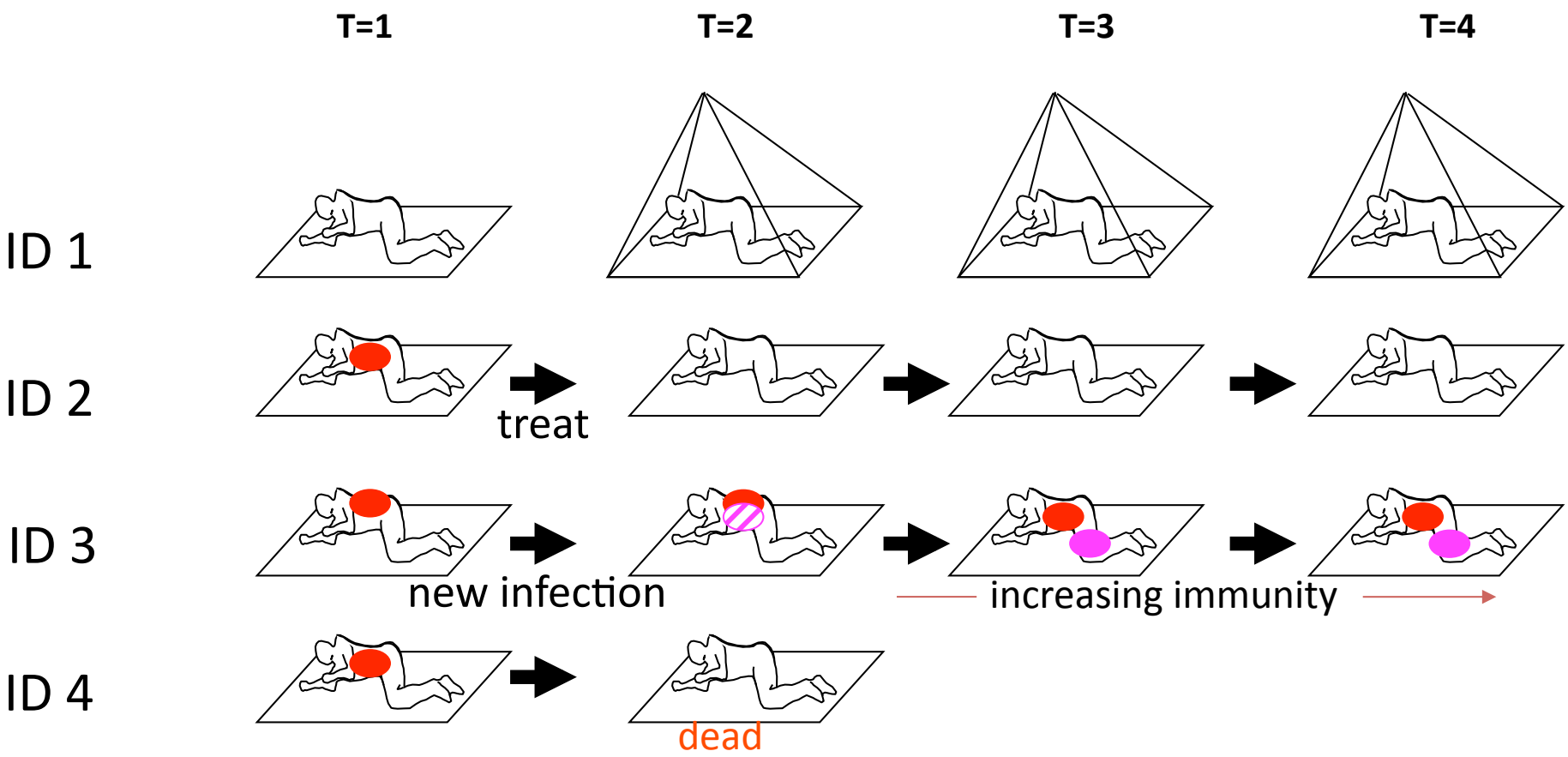
T=2
T=3
T=4
ID 1
ID 2
ID 3
treat
new infection
increasing immunity


T=1
T=2
T=3
T=4
ID 1
ID 2
ID 3
ID 4
treat
new infection
increasing immunity
dead

Model Overview

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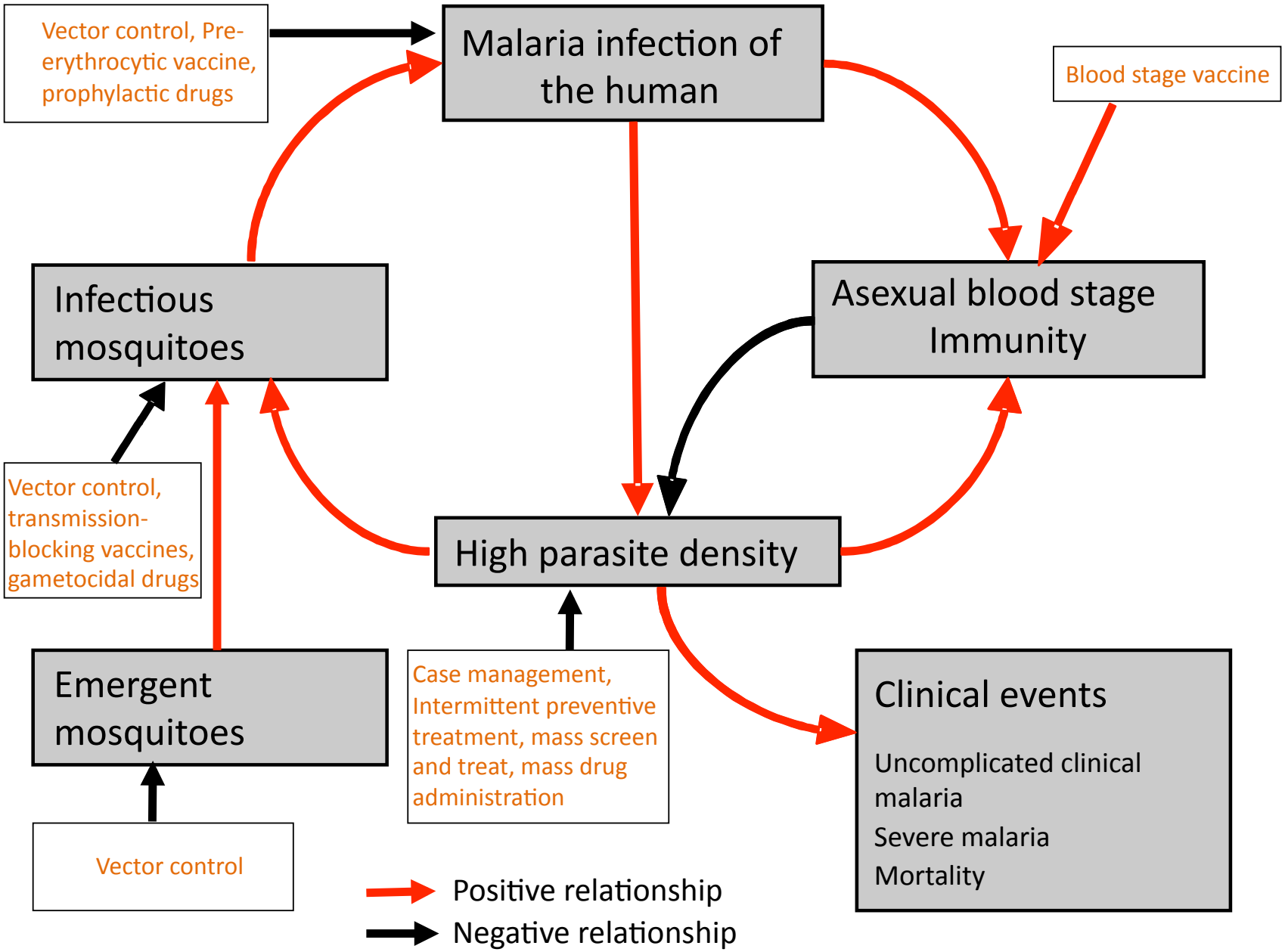

Stochasticity in Outcomes

- Multiple random seed values

Parameter Uncertainty

- Model fitting
- One-dimensional/multi-dimensional sensitivity analysis
- Probabilistic sensitivity analysis

Model Uncertainty

- Ensembles of different models

- Mass-action models for single infections
- Decay of blood-stage immunity
- Case management models
- Morbidity models
- Correlations in heterogeneity and variation in force of infection, comorbidity and access to treatment

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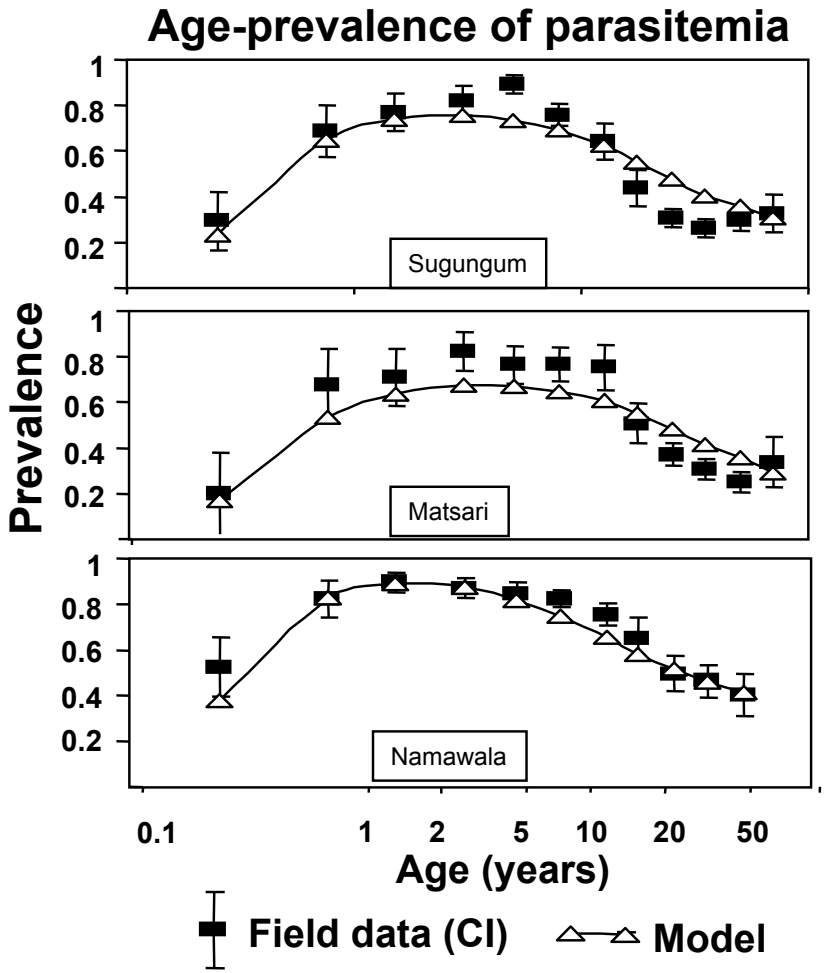
Use 61 data sets from field studies with different objectives to fit up to 27 parameters

- Incidence of infection
- Age-prevalence of parasitemia
- Seasonality of parasitemia
- Age-density of parasites
- Age-incidence of clinical disease, hospitalisation and mortality.

Models components are validated separately and the entire model is validated in certain geographically specific settings.



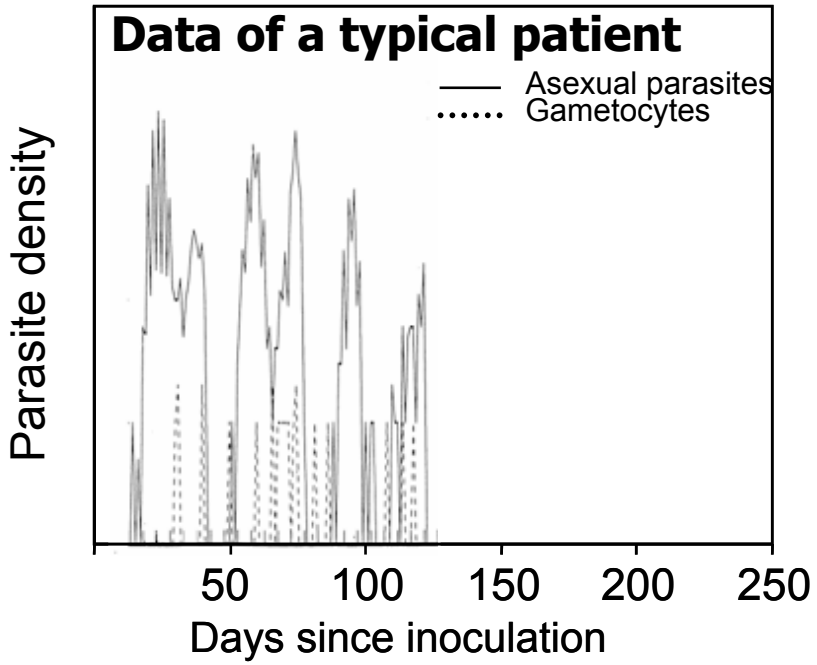
Maire *et al.* (2006)

- Human age structure is set to local demographic data.
- The population size and age distribution is kept constant through the simulation through migration.
- Humans are simulated through one life span to determine immune status.

- Each infection in each individual is modeled separately:
  - Empirical model (Maire *et al.*, 2006)
  - Stochastic mass-action (difference equation) models fit to descriptive statistics (Molineaux *et al.*, 2001)
  - Stochastic mass-action (difference equation) model fit to both individual level data and population level data. (Penny *et al.*, unpublished)
- Asexual parasite densities fit to malaria therapy data.
- Infectivity to mosquitoes weighted sum of past asexual parasite density.
- Immunity (Dietz *et al.*, 2006)
  - Reduces force of infection
  - Decreases asexual blood stage parasite densities
  - Increases pyrogenic threshold

Swiss TPH

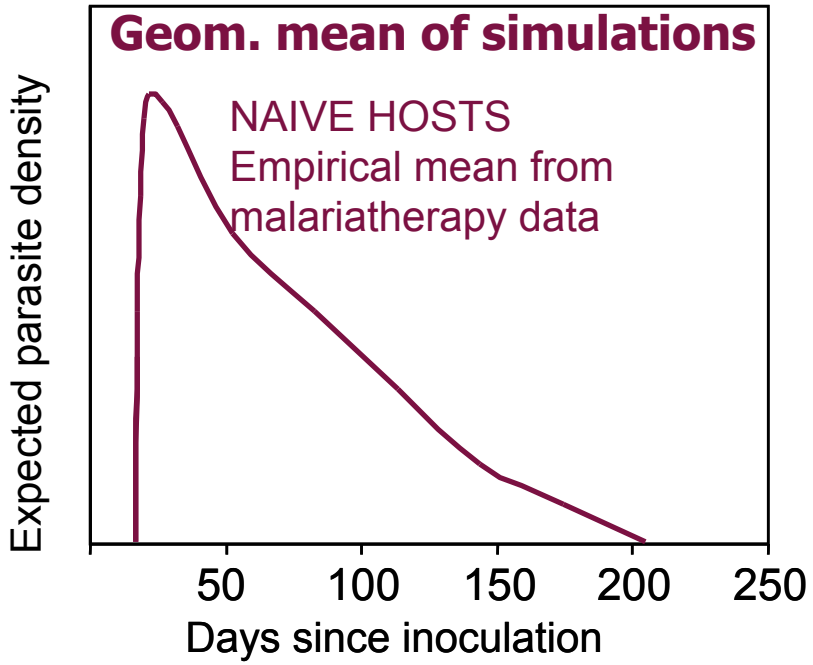
- Starting point is the empirical distributions of densities by age of infection for untreated patients (malariatherapy)
- Choice of exposure proxy made empirically (by fitting models to field data)
- Simulated densities are sampled from a distribution centred on the expected parasite density.



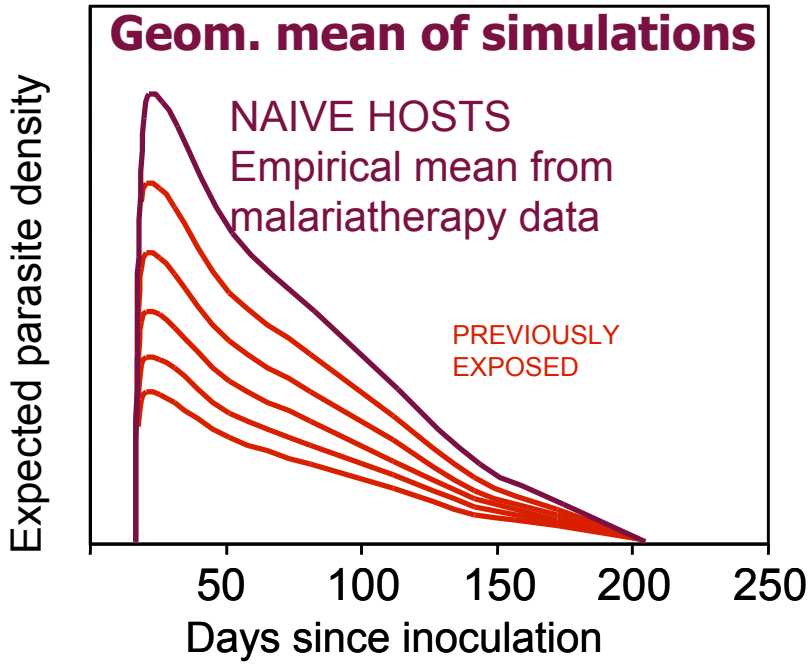
Empirical Within-Host Model

Swiss TPH

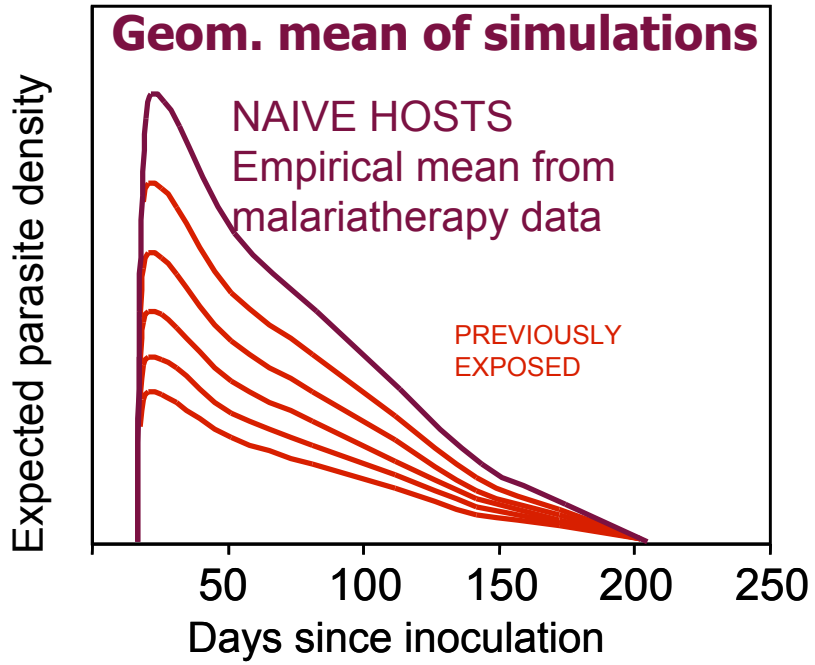
- Starting point is the empirical distributions of densities by age of infection for untreated patients (malariatherapy)
- Choice of exposure proxy made empirically (by fitting models to field data)
- Simulated densities are sampled from a distribution centred on the expected parasite density.

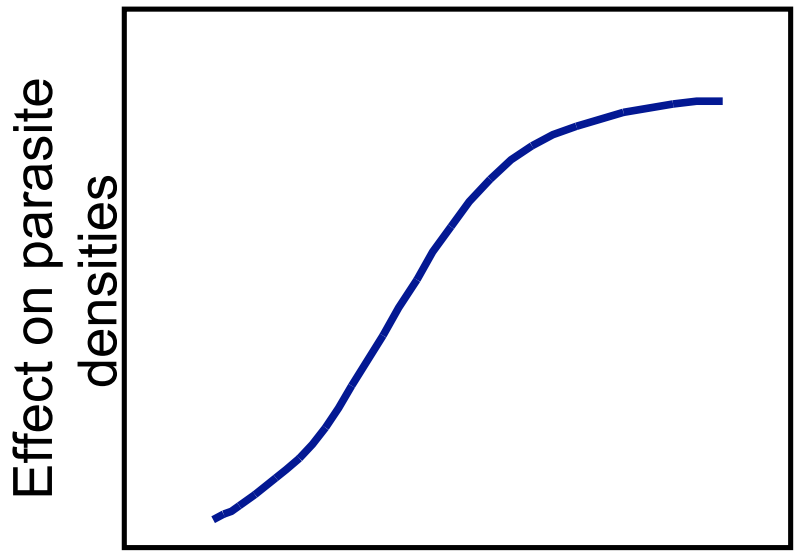


- Starting point is the empirical distributions of densities by age of infection for untreated patients (malariatherapy)
- Choice of exposure proxy made empirically (by fitting models to field data)
- Simulated densities are sampled from a distribution centred on the expected parasite density.



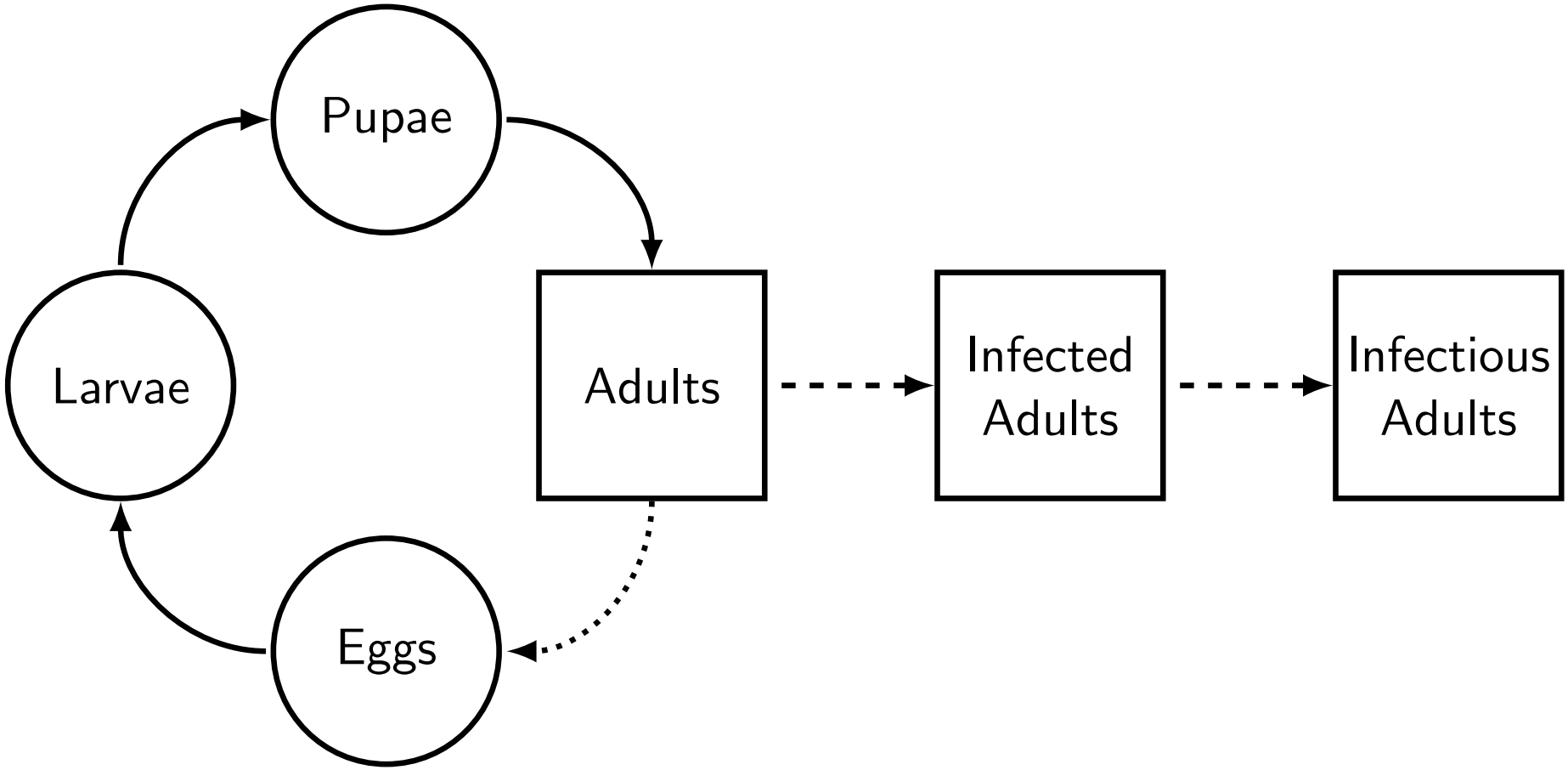
- Starting point is the empirical distributions of densities by age of infection for untreated patients (malariatherapy)
- Choice of exposure proxy made empirically (by fitting models to field data)
- Simulated densities are sampled from a distribution centred on the expected parasite density.





- Humans in any of five possible states
  - Not sick
  - Uncomplicated fever (malarial or non-malarial with or without parasites)
  - Severe malaria
  - Dead (malaria, indirect, non-malaria death)
  - Out-migrated
- Clinical malaria is determined by parasite density and fever threshold (dependent on immune status)
- Probability of non-malarial disease is determined by local health systems data.
- A decision tree model determines events in case of an illness using local health systems data.

- Model mosquito feeding cycle and malaria infection in female mosquitoes with periodically forced difference equations
- Extensions of pre-existing models (Saul *et al.* (1991), Saul (2003), and Killeen and Smith (2007))
- Heterogeneous population of hosts
  - Individual humans
  - Any number and type of non-human hosts
- Allow multiple mosquito species or types
- Include annual seasonality
- Evaluate key entomological quantities to compare to field data
- Include various coverage levels of different interventions
- Include decay of effectiveness of interventions over time (resulting equations are no longer periodic)


Pupae
Larvae
Adults
Infected Adults
Infectious Adults
Eggs

Effects of Vector Control Interventions

Swiss TPH

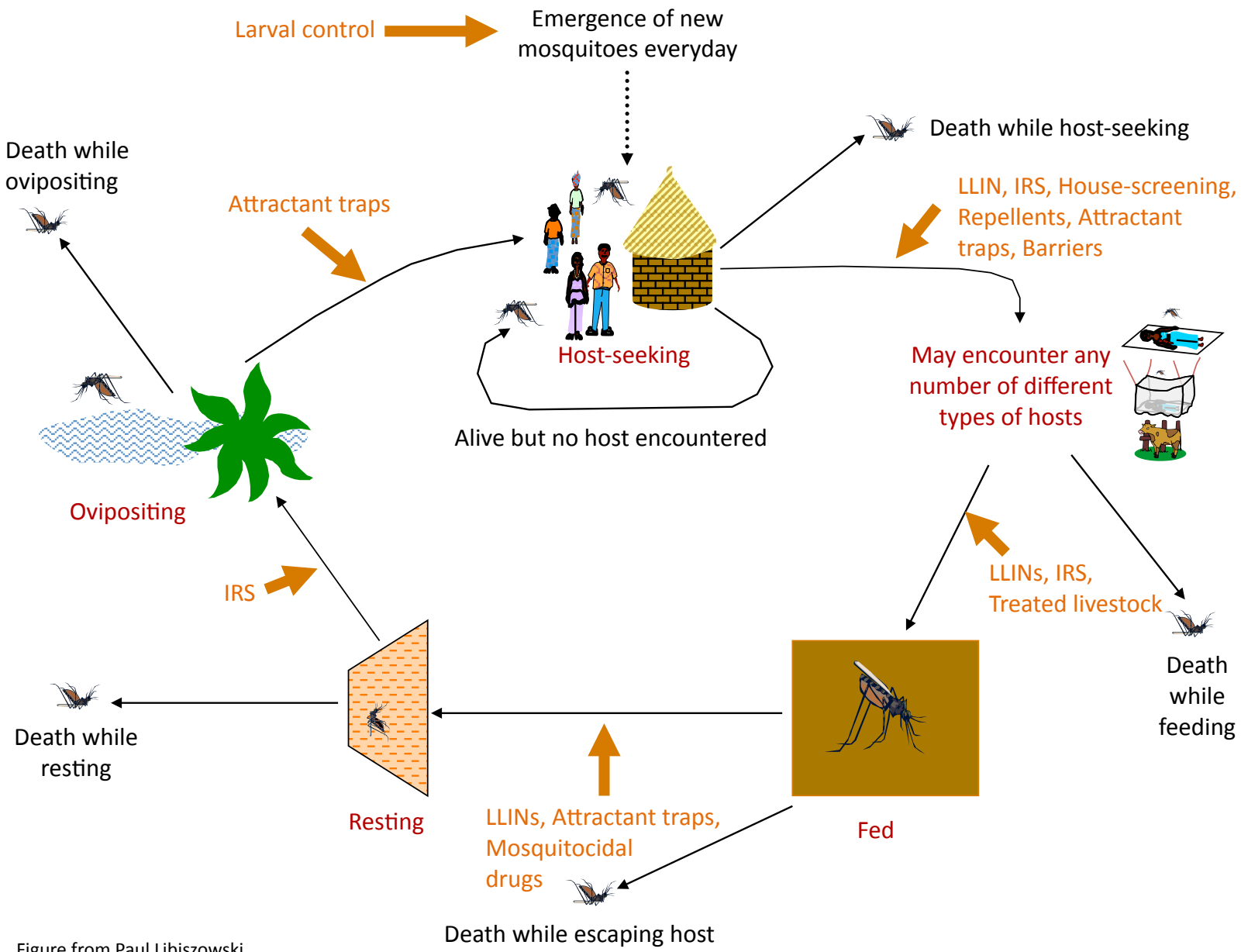
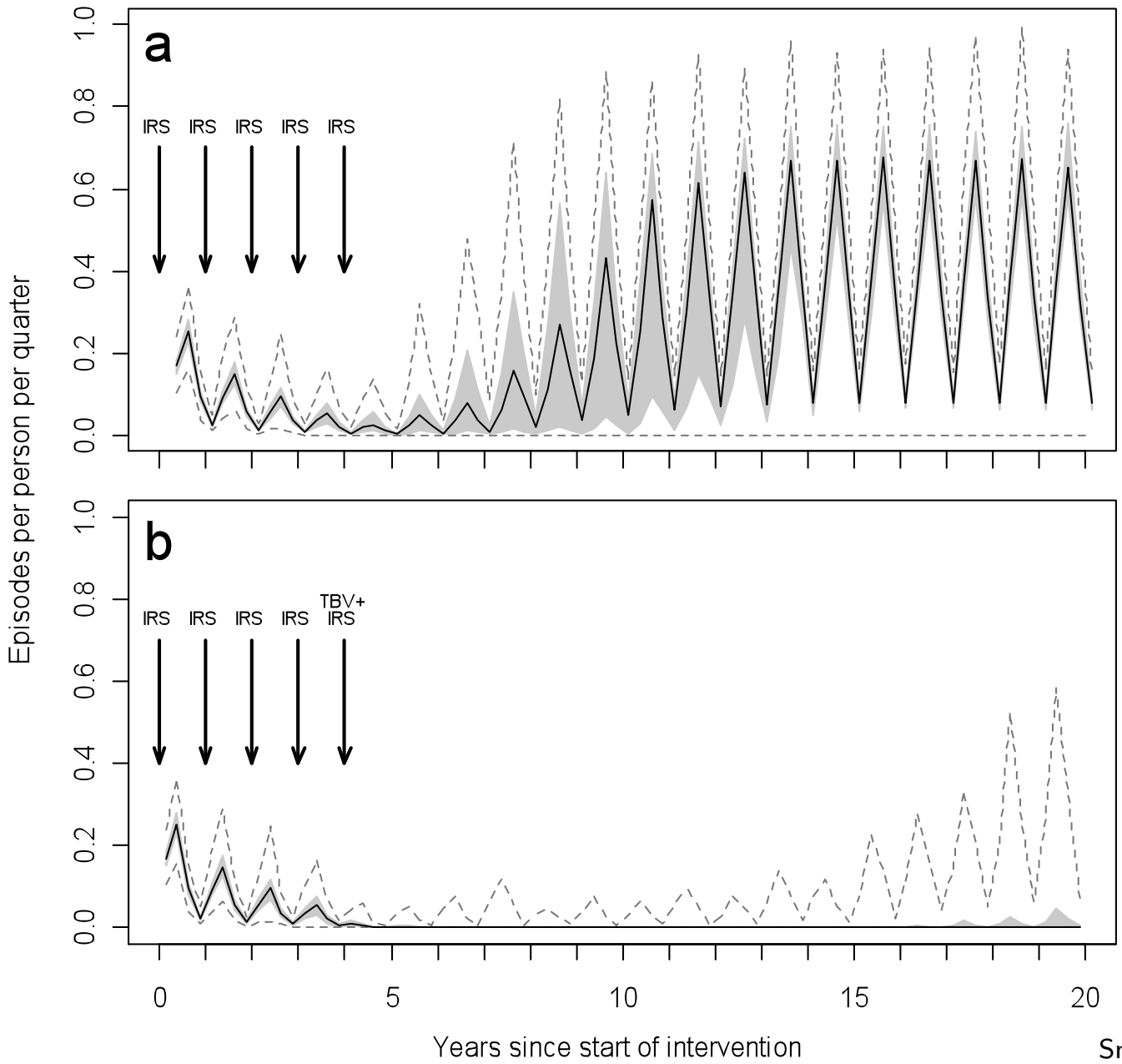


Figure from Paul Libiszowski

LLINs: long-lasting insecticidal nets; IRS: indoor residual spraying

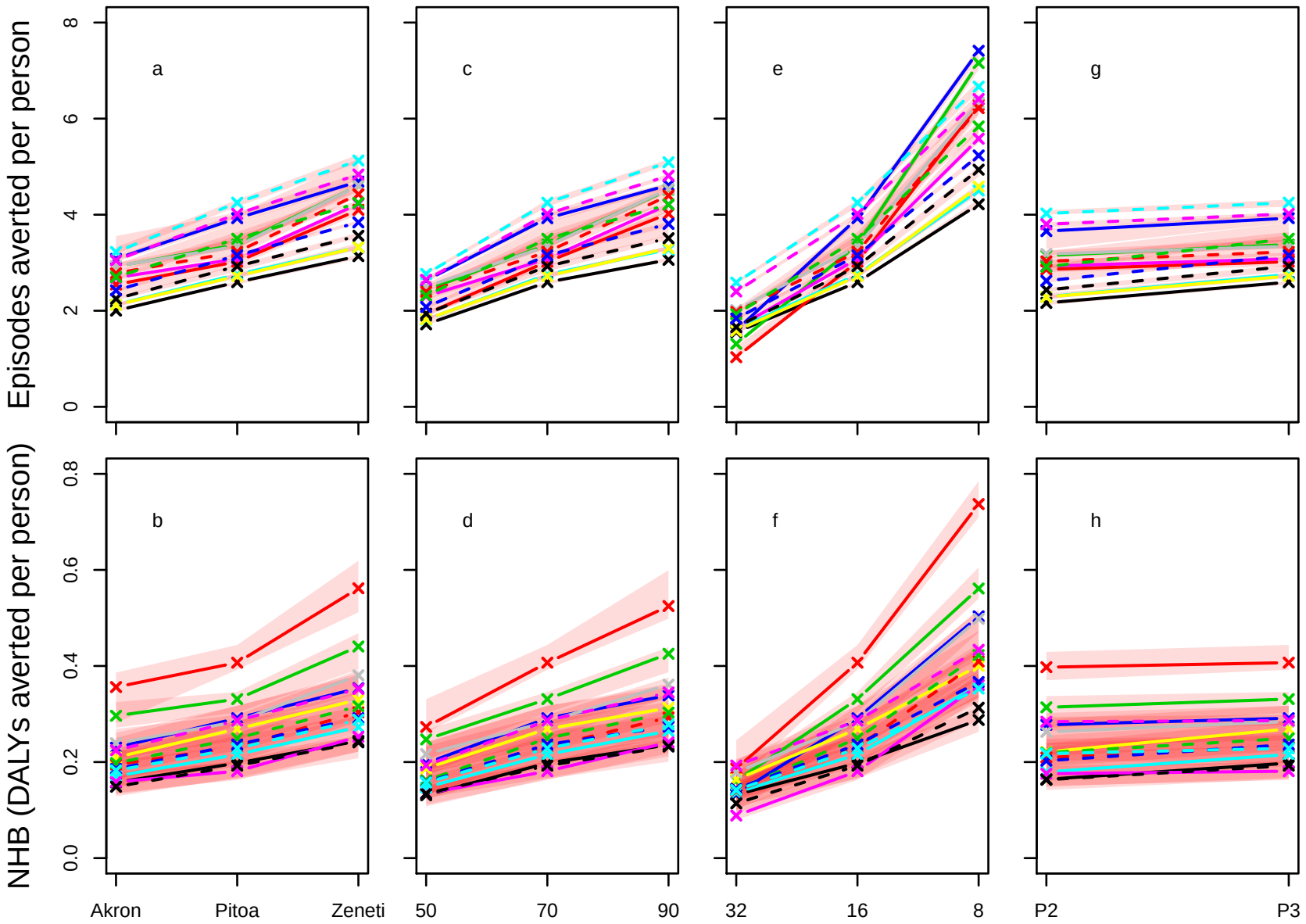
Elimination with a Transmission Blocking Vaccine

Swiss TPH



Smith *et al.* (2011)

Sensitivity of Net Effectiveness



Briët *et al.* (2013)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