Adaptive Malaria Control

Adaptive Management for Malaria Programs

David L Smith, January 31, 2025

https://faculty.washington.edu/smitdave/

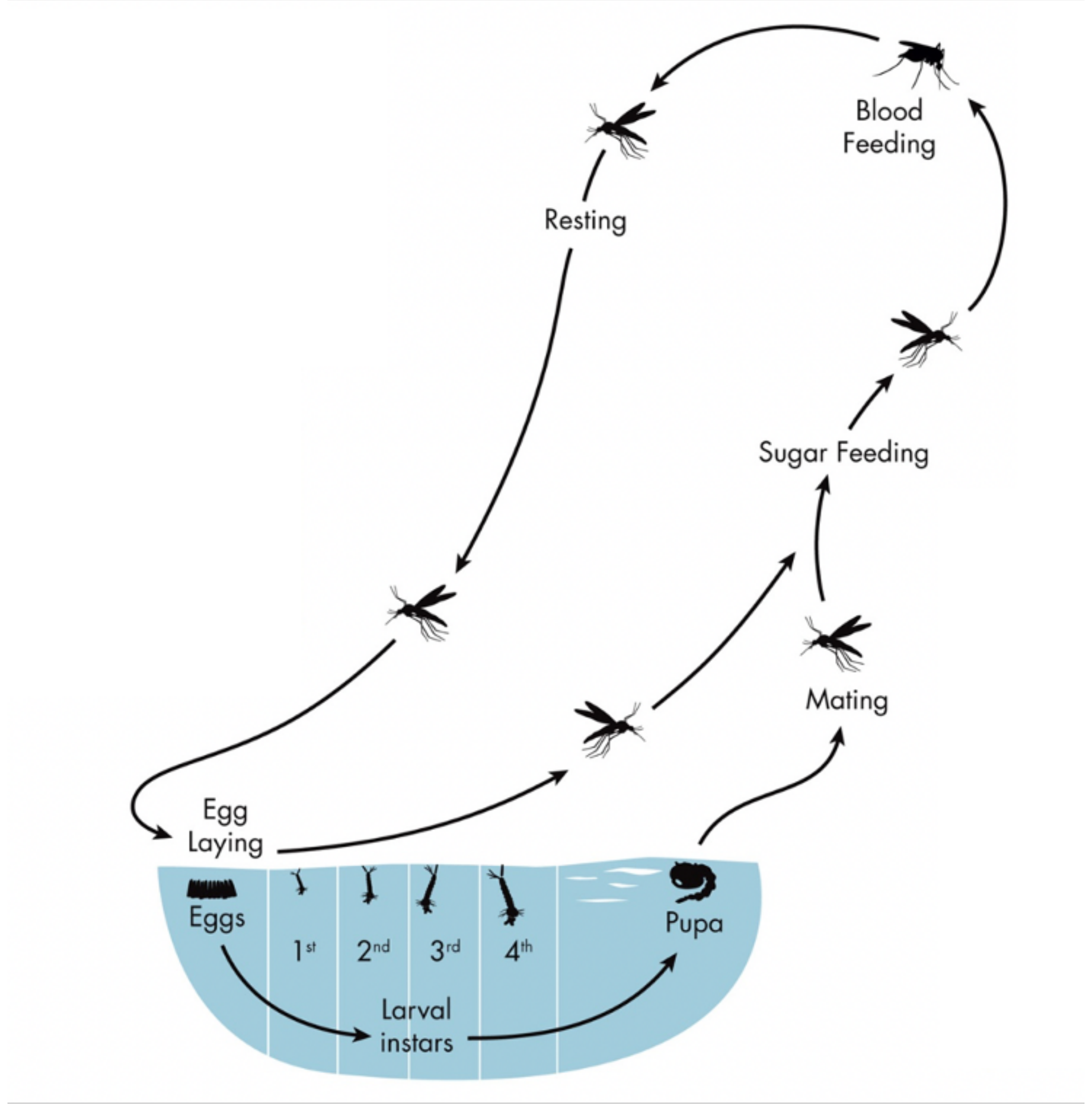
smitdave@uw.edu

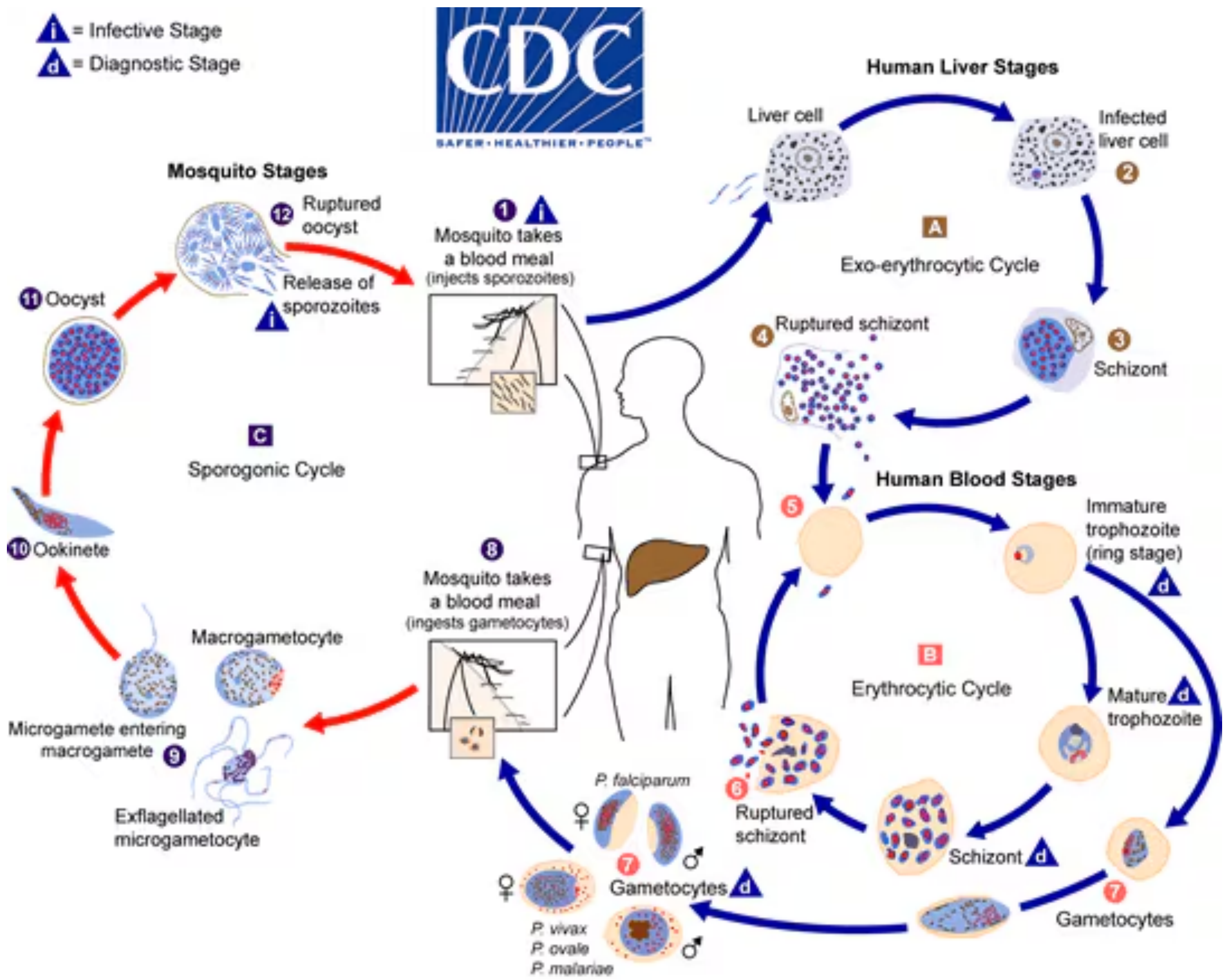
Download this talk:

https://faculty.washington.edu/smitdave/talks/DavidLSmith_SAFS_2025Jan31.pdf

The Global Burden of Malaria

Human malaria can be understood as a set of loosely spatially coupled, managed, complex adaptive systems with multiple interacting agents (*i.e.*, mosquitoes, parasites, humans, & managers), non-linear interactions (*e.g.,* mosquito population regulation, blood feeding & transmission, immunity), and exogenous forcing by weather & malaria control. The systems change over time because resistance evolves to drugs & insecticides, weather is changing, and human populations are developing socio-economically.





…*malaria is so moulded and altered by local conditions that it becomes a thousand different diseases and epidemiological puzzles. Like chess, it is played with a few pieces, but is capable of an infinite variety of situations*.

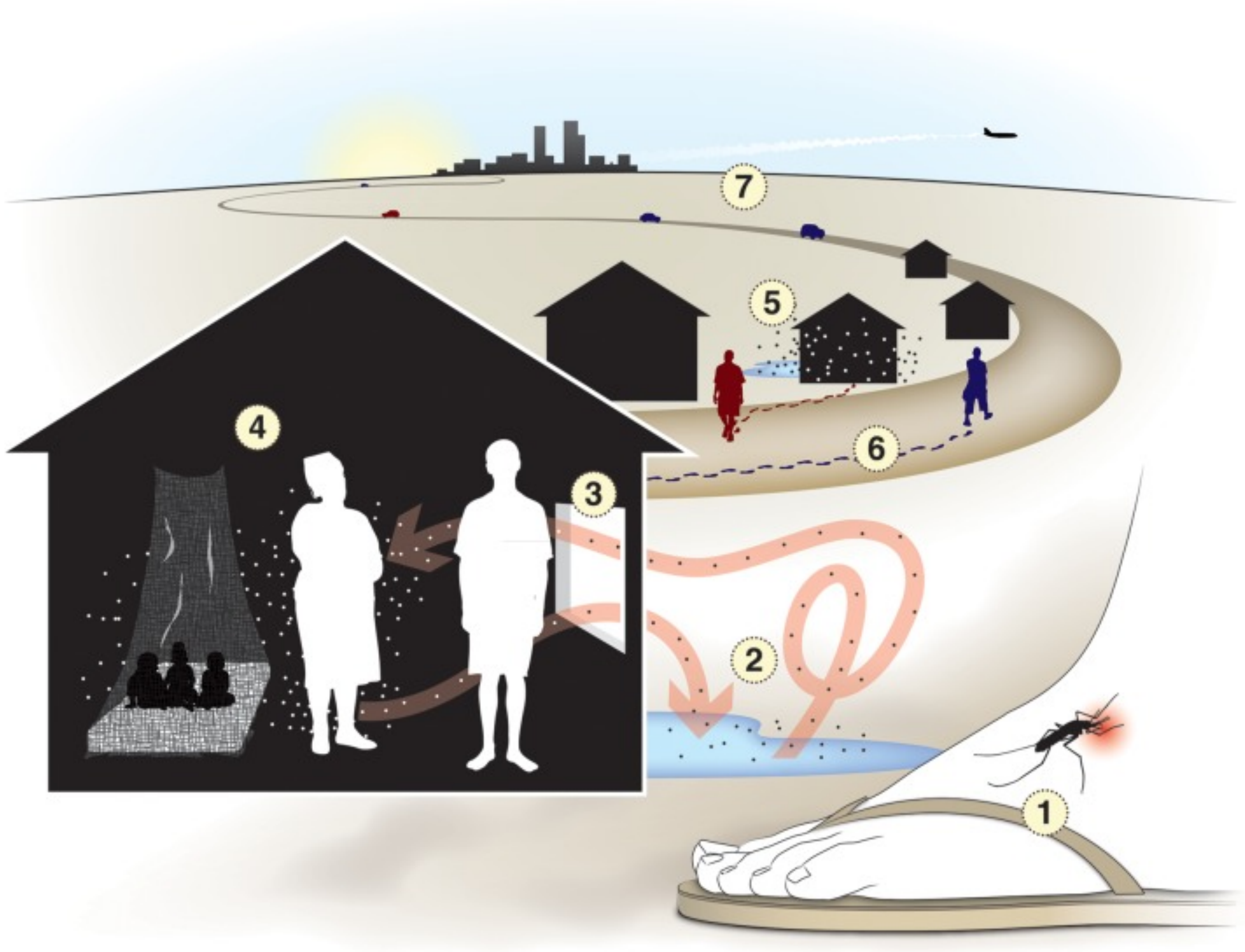
Lewis Hackett, 1937

Malaria Theory

Measuring Malaria &

Understanding Malaria Transmission

Dynamics and Control



Recasting the theory of mosquito-borne pathogen transmission dynamics and control
https://academic.oup.com/trstmh/article/108/4/185/1924536

Ronald Ross
1899-1911

1911

THE PREVENTION OF MALARIA

SOME QUANTITATIVE STUDIES IN EPIDEMIOLOGY.

$$\frac{dz}{dt} = k'z'(p - z) + qz$$

$$\frac{dz'}{dt} = kz(p' - z') + q'z'$$

These studies require to be developed much further; but they will already be useful if they help to suggest a more precise and quantitative consideration of the numerous factors concerned in epidemics. At present medical ideas regarding these factors are generally so nebulous that almost any statements about them pass muster, and often retard or misdirect important preventive measures for years. RONALD ROSS.

George Macdonald
1950-1969

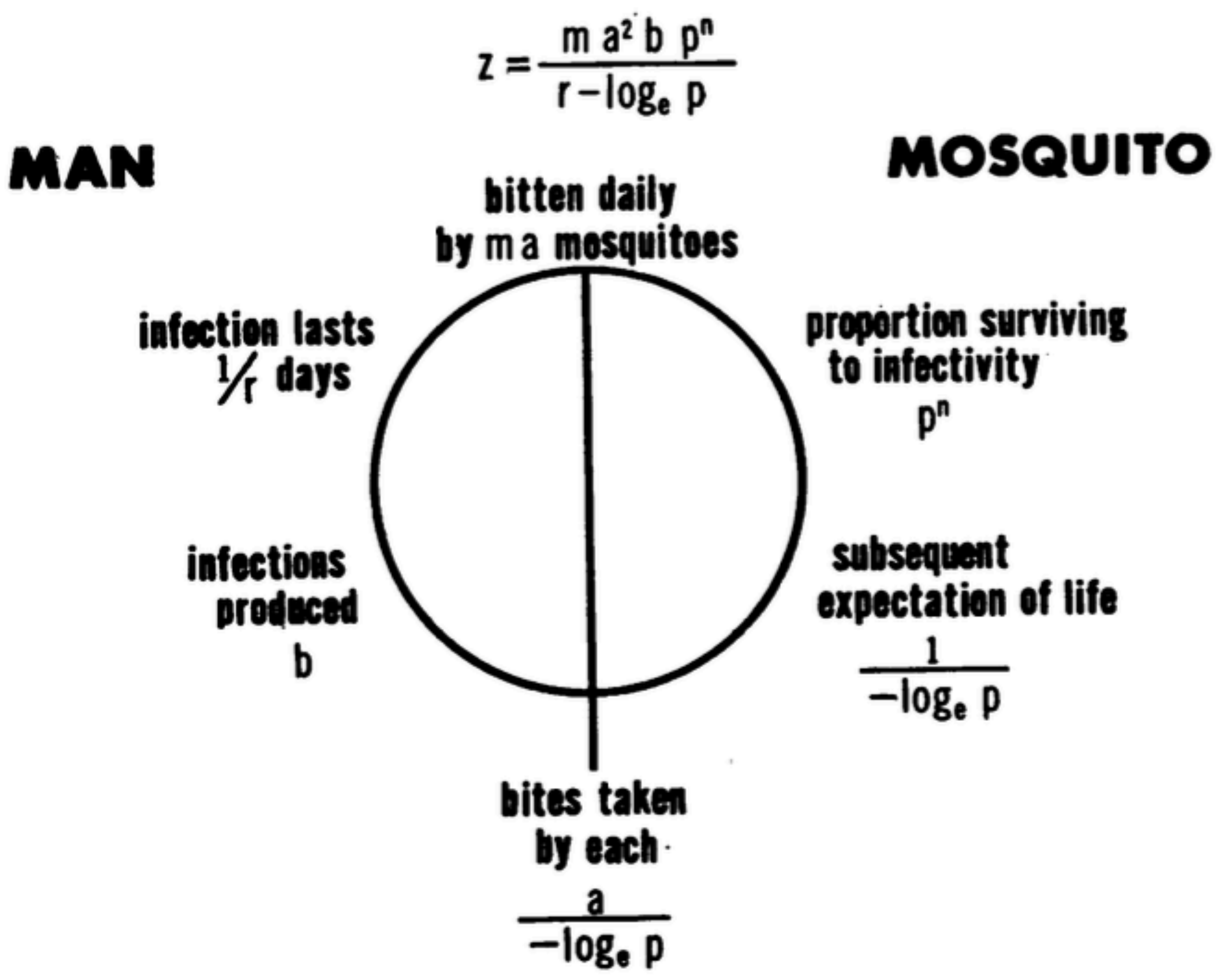
TABLE I

Values of p^n and $-\log_e p$

Value of p:—	0·95	0·9	0·85	0·8	0·75	0·7	0·65	0·6	0·55	0·5
p^8	0·6633	0·4304	0·2725	0·1677	0·1002	0·0577	0·0318	0·0168	0·0084	0·0039
p^9	0·6302	0·3875	0·2316	0·1342	0·0751	0·0404	0·0207	0·0101	0·0046	0·0019
p^{10}	0·5987	0·3486	0·1967	0·1075	0·0564	0·0283	0·0135	0·0060	0·0025	0·0010
p^{11}	0·5687	0·3138	0·1673	0·0859	0·0423	0·0198	0·0087	0·0036	0·0014	0·0005
p^{12}	0·5402	0·2823	0·1422	0·0687	0·0317	0·0138	0·0057	0·0022	0·0008	0·0002
p^{13}	0·5134	0·2542	0·1209	0·0550	0·0238	0·0097	0·0037	0·0013	0·0004	0·0001
p^{14}	0·4876	0·2288	0·1028	0·0440	0·0178	0·0068	0·0024	0·0008	0·0002	
p^{15}	0·4632	0·2059	0·0874	0·0352	0·0134	0·0047	0·0016	0·0005	0·0001	
p^{16}	0·4401	0·1853	0·0743	0·0281	0·0102	0·0033	0·0010	0·0003		
p^{17}	0·4181	0·1667	0·0631	0·0225	0·0075	0·0023	0·0007	0·0002		
p^{18}	0·3972	0·1501	0·0536	0·0180	0·0053	0·0016	0·0004	0·0001		
p^{19}	0·3773	0·1351	0·0456	0·0144	0·0042	0·0011	0·0003			
p^{20}	0·3585	0·1215	0·0388	0·0115	0·0032	0·0008	0·0002			
$-\log_e p$	0·0513	0·1054	0·1625	0·2232	0·2877	0·3567	0·4308	0·5108	0·5979	0·6932

Note : The fact that $-\log_e p$ is a *positive* number must be borne in mind.

Figure 3. The basic reproduction rate



Ross, Macdonald, and a Theory for the Dynamics and Control of Mosquito-Transmitted Pathogens
https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1002588

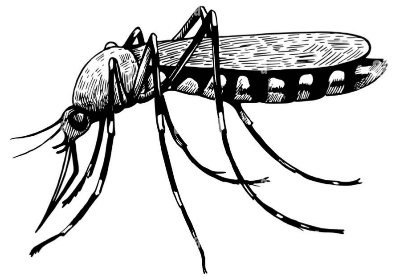
1916

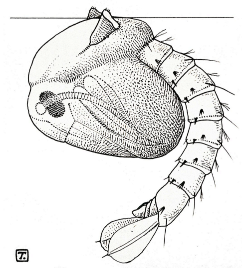
An Application of the Theory of Probabilities to the Study of a priori *Pathometry.*—Part I.

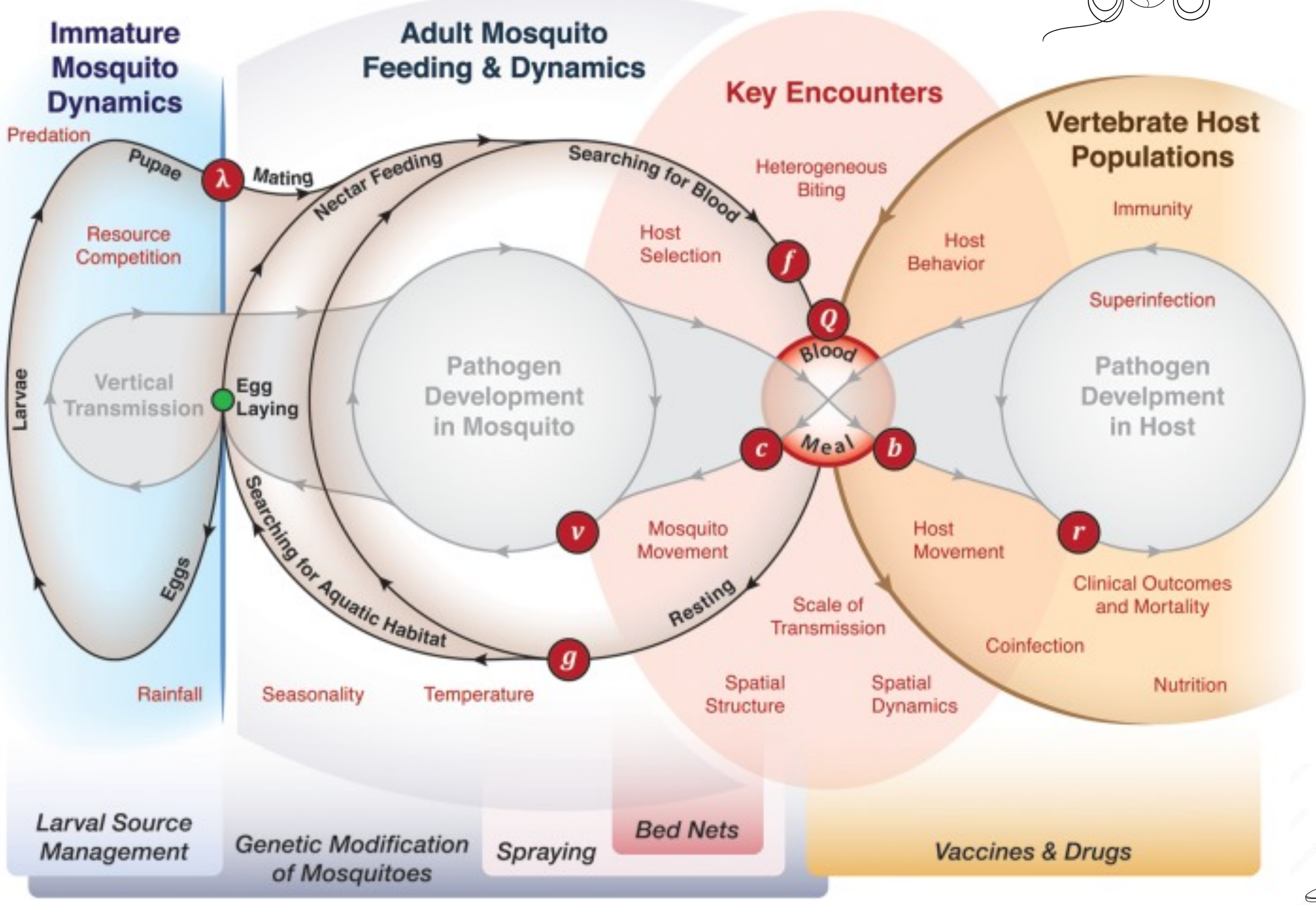
By Lieut.-Colonel Sir Ronald Ross, K.C.B., F.R.S., R.A.M.C.T.F.

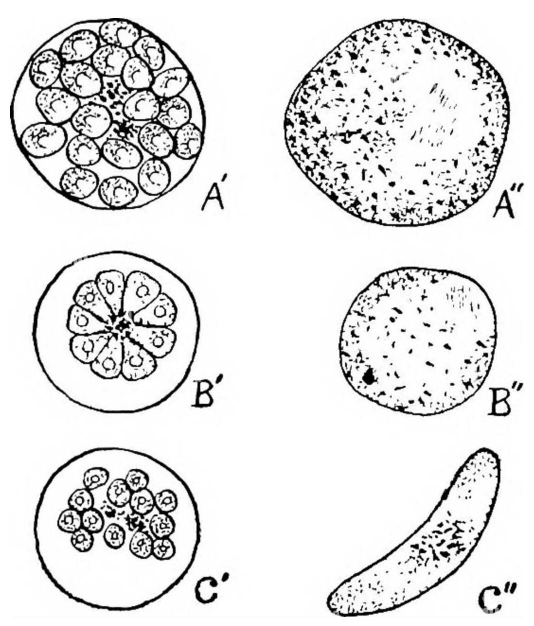
The whole subject is capable of study by two distinct methods which are used in other branches of science, which are complementary of each other, and which should converge towards the same results—the *a posteriori* and the *a priori* methods. In the former we commence with observed statistics, endeavour to fit analytical laws to them, and so work backwards to the underlying cause (as done in much statistical work of the day); and in the latter we assume a knowledge of the causes, construct our differential equations on that supposition, follow up the logical consequences, and finally test the calculated results by comparing them with the observed statistics.

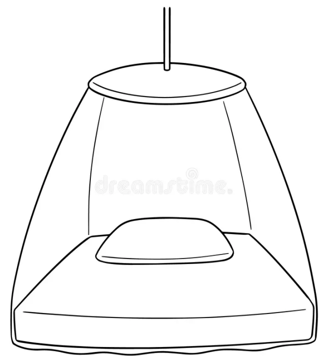
Malaria Theory









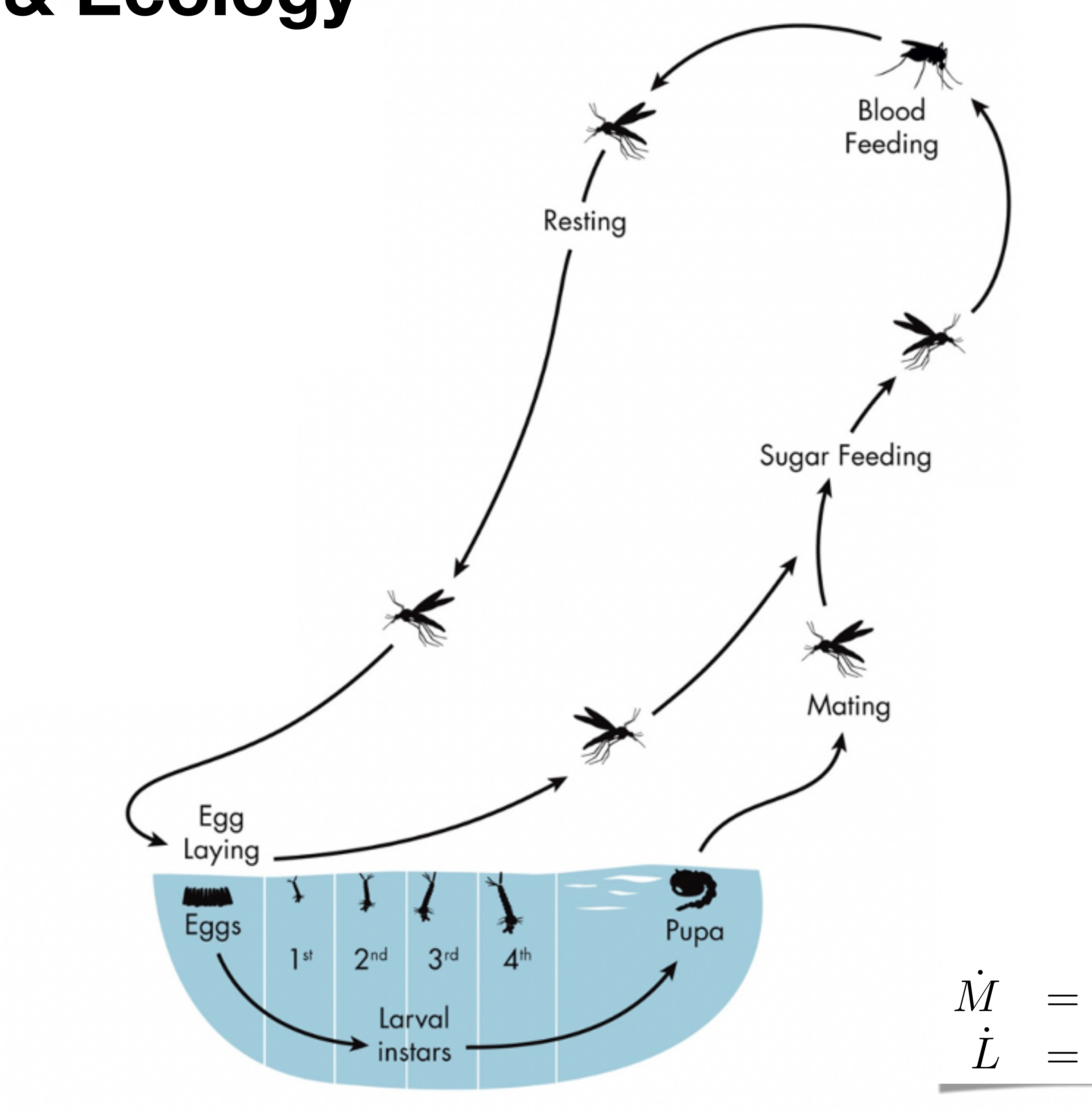


A systematic review of mathematical models of mosquito-borne pathogen transmission: 1970–2010
https://royalsocietypublishing.org/doi/full/10.1098/rsif.2012.0921

Mosquitoes

Feeding Cycle, Life Cycle, & Ecology

- Adult, Female — the gonotrophic cycle
  - Mate
  - Blood feed
  - Lay eggs
  - Sugar Feed
- Immature Mosquitoes — aquatic habitats
  - Eggs
  - Four Larval Instars
  - Pupae



$$\dot{M} = \sum \alpha L - gM$$
$$\dot{L} = \nu f p M - (\alpha + \gamma + \psi L)L$$

Mosquito Population Regulation and Larval Source Management in Heterogeneous Environments

David L. Smith, T. Alex Perkins, Lucy S. Tusting, Thomas W. Scott, Steven W. Lindsay

Vectorial Capacity

 # infectious bites arising, per host, per day

$$V = \lambda S^2 P$$

$$V = \frac{\Lambda}{H} \frac{f^2 q^2}{g^2} e^{-gn}$$

- a - the human blood feeding rate $(a = fq)$
  - f - the human blood feeding rate
  - q - the human fraction
- n - the extrinsic incubation period (EIP)
- g - the mosquito mortality rate
- Λ - the mosquito emergence rate
- H - the mosquito emergence rate

$$\lambda = \Lambda / H$$

emerging adult mosquitoes, per human, per day

$$S = \frac{fq}{g}$$

human blood meals, per mosquito (lifetime)

$$P = e^{-gn}$$

fraction surviving through the EIP

Statics and dynamics of malaria infection in Anopheles mosquitoes

https://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-3-13

Reproductive Numbers

$$R_0 = bVD$$

$$V\kappa = E\,(1 + S\kappa)$$

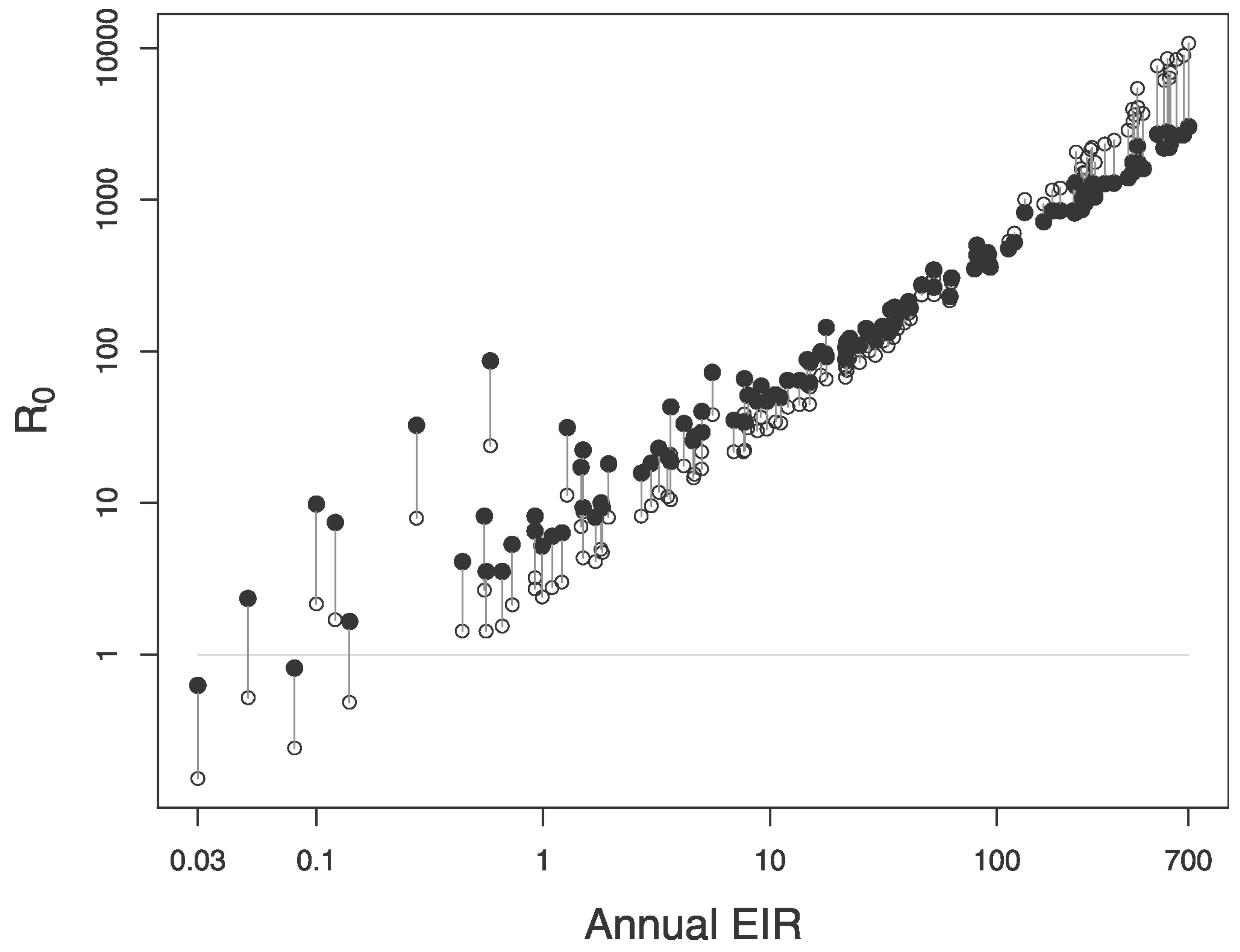
- V - vectorial capacity
  (# bites arising, per person, per day)

- E - entomological inoculation rate
  (# bites received, per person, per day)

- κ - net infectiousness

- x - the prevalence of malaria (parasite rate)

$$\kappa = F_\kappa(x)$$



Revisiting the Basic Reproductive Number for Malaria and Its Implications for Malaria Control

https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0050042

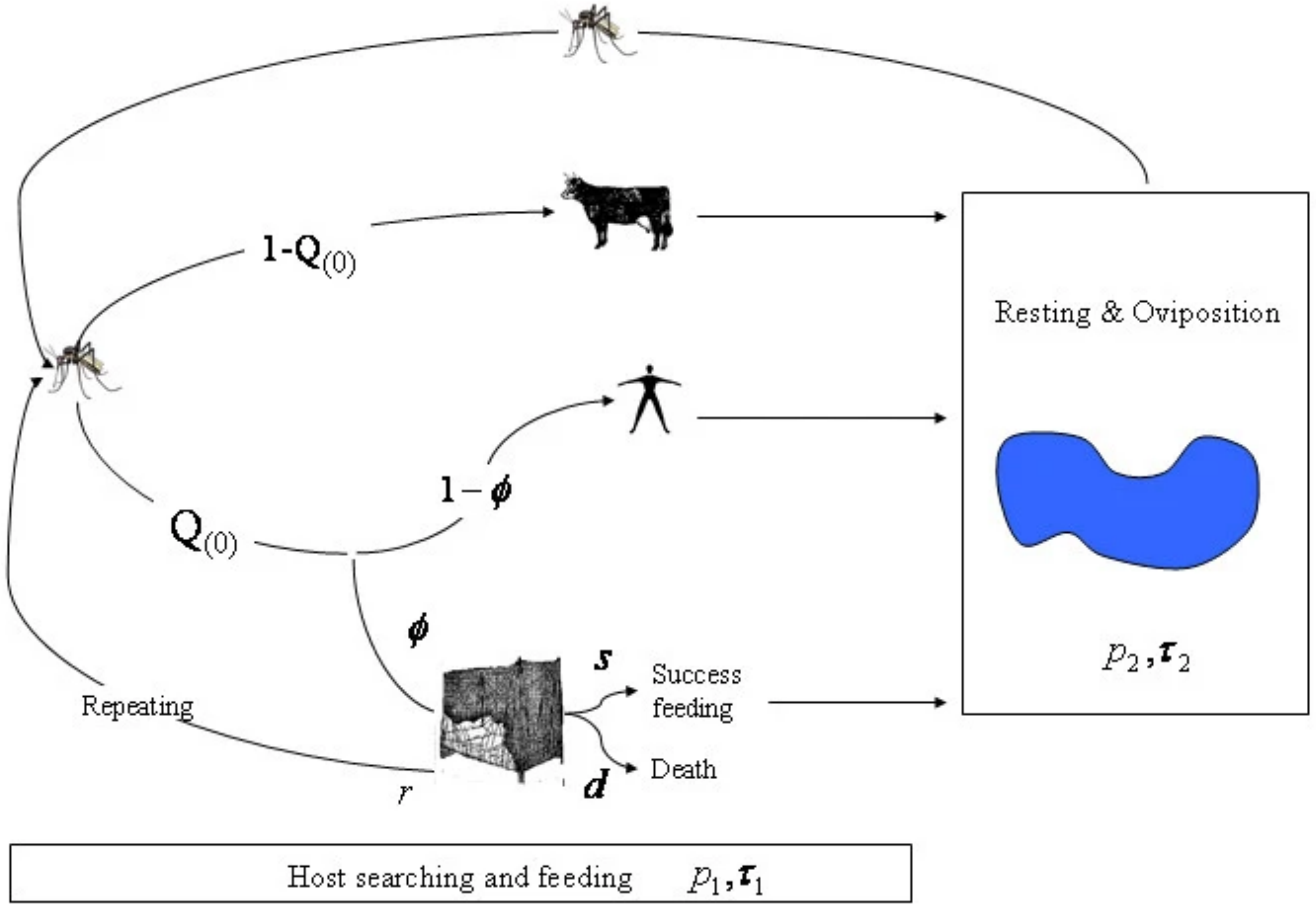
Coverage *vs.* Effect Sizes

…on potential transmission

$$\frac{V(\phi)}{V(0)} = \frac{\Lambda(\phi)}{\Lambda(0)} \frac{f(\phi)^2 q(\phi)^2}{f(0)^2 g(0)^2} \frac{g(0)^2 e^{g(0)n}}{g(\phi)^2 e^{g(\phi)n}}$$

ϕ - "coverage"

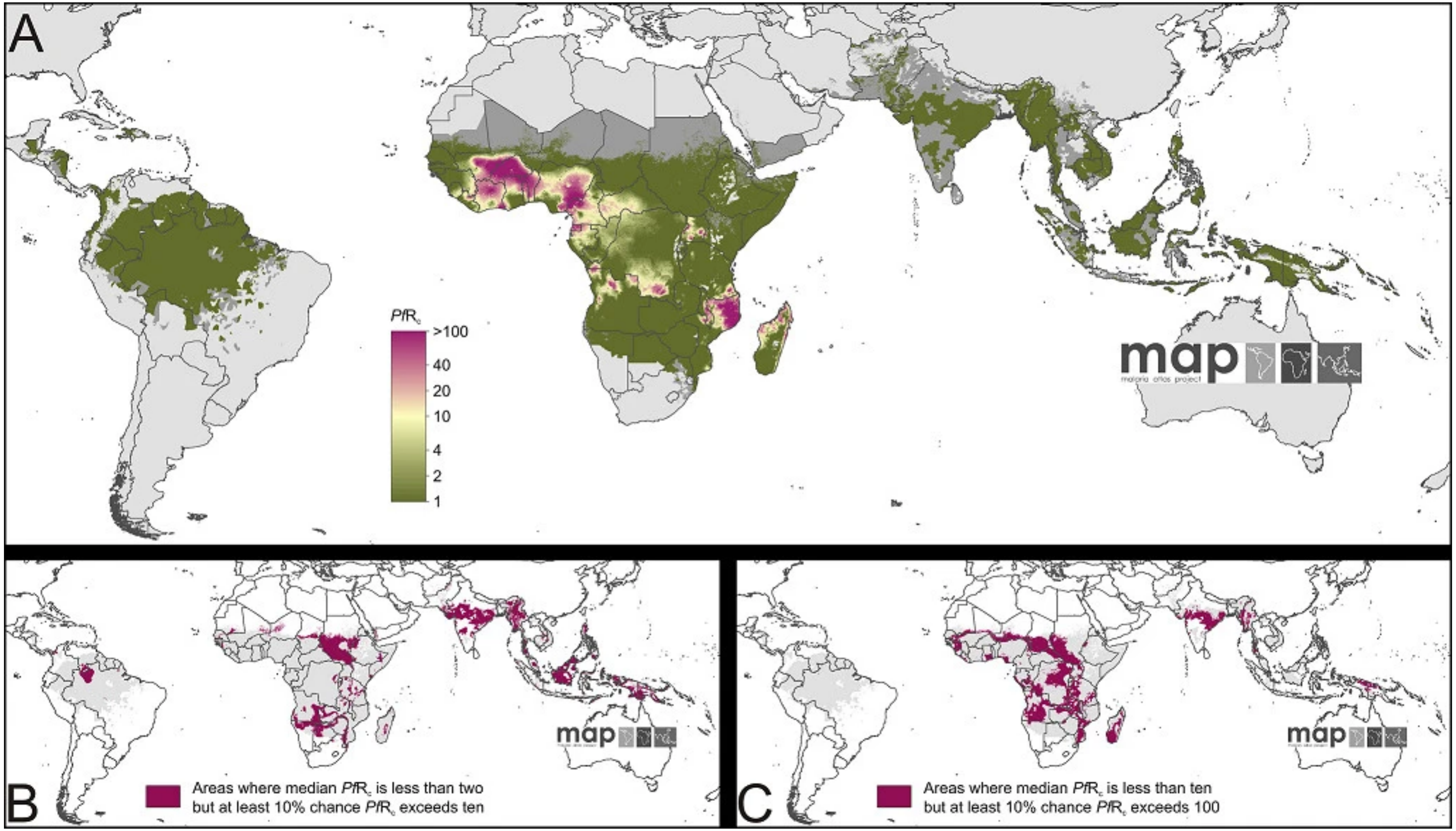
The fraction of times a mosquito encounters a human that is protected by a bednet



An elaborated feeding cycle model for reductions in vectorial capacity of night-biting mosquitoes by insecticide-treated nets

https://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-6-10

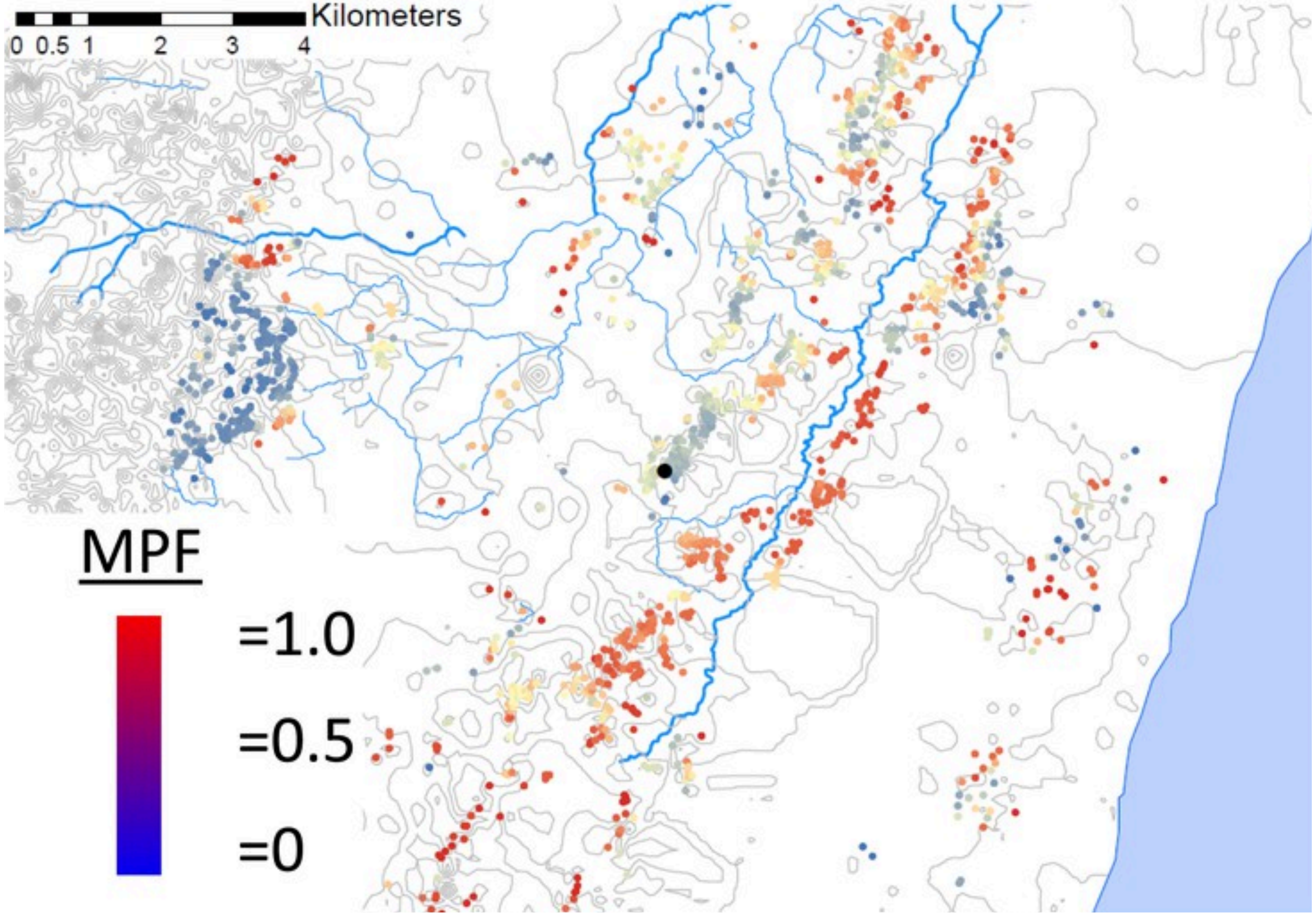
The spatial distribution of *Plasmodium falciparum* basic reproductive number under control (*PfR*c) in 2010



A new world malaria map: *Plasmodium falciparum* endemicity in 2010

https://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-10-378

Malaria Positive Fraction (MPF): among all hospital visits from 2003-2011 in which febrile patients from each homestead tested positive for malaria



A micro-epidemiological analysis of febrile malaria in Coastal Kenya showing hotspots within hotspots

https://doi.org/10.7554/eLife.02130

Adaptive Malaria Control

Iterative, Robust Analytics for Malaria Policy

Malaria Control

Tailor Interventions to Context (under a Budget Constraint)

Vector Control

- Insecticide Treated Bed Nets
- Indoor Residual Spraying
- Larval Source Management
- Attractive Toxic Sugar Baits
- Environmental Management

Health Systems

- Case Management
- Chemoprophylaxis
- Intermittent Preventative Therapy
- Mass Treatment (*e.g.* outbreak response)
- Vaccines

Robust Analytics for Adaptive Malaria Control

Defining malaria analytics

- **Malaria Analytics** → systematic analysis of data for decision support or to develop malaria policy advice
- **Robust Analytics for Malaria Policy (RAMP)**
  - A bespoke inferential system that combines conventional and simulation-based analytics to develop robust policy advice & decision support for malaria
  - Advice is ***robust*** in the sense that it would not change if the analysis had been done in some other reasonable way
  - A goal for robust analytics is to characterize & quantify uncertainty (ontological, epistemic, & aleatoric) and propagate it through the analysis including its effects on advice
- **Adaptive Malaria Control** → adaptive management for malaria: iterative, robust analytics with a feedback loop to modify surveillance or conduct studies to reduce uncertainty over time

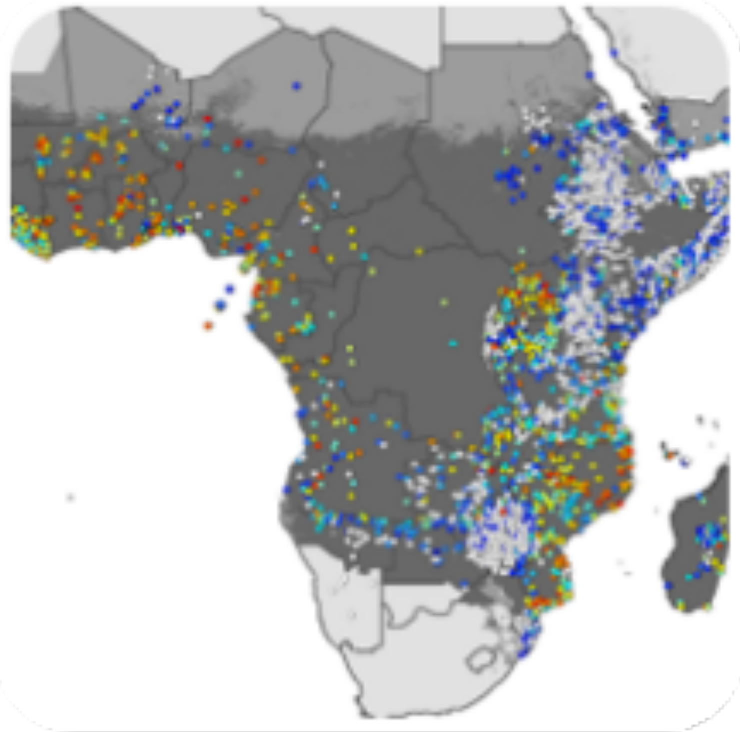
Malaria Intelligence

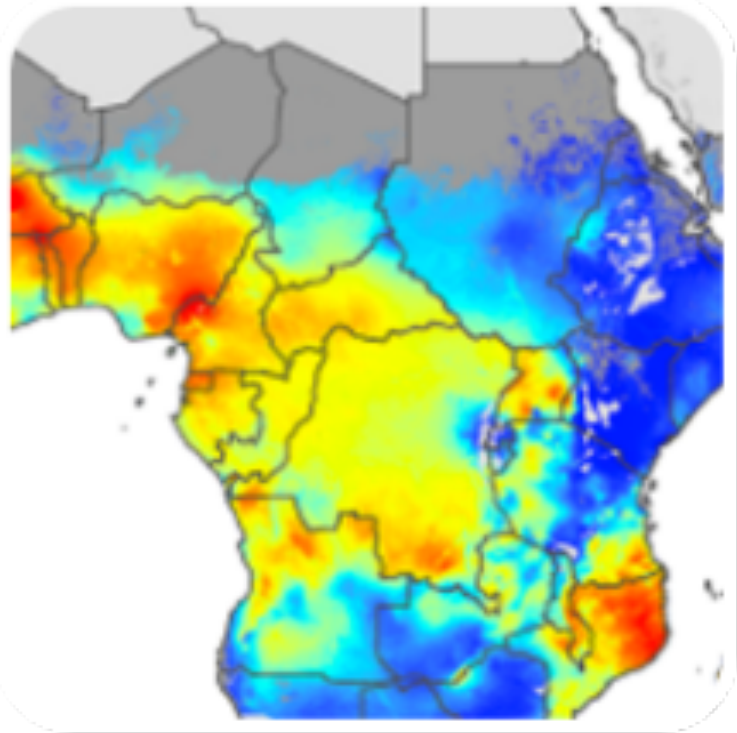
Information for Malaria Policies

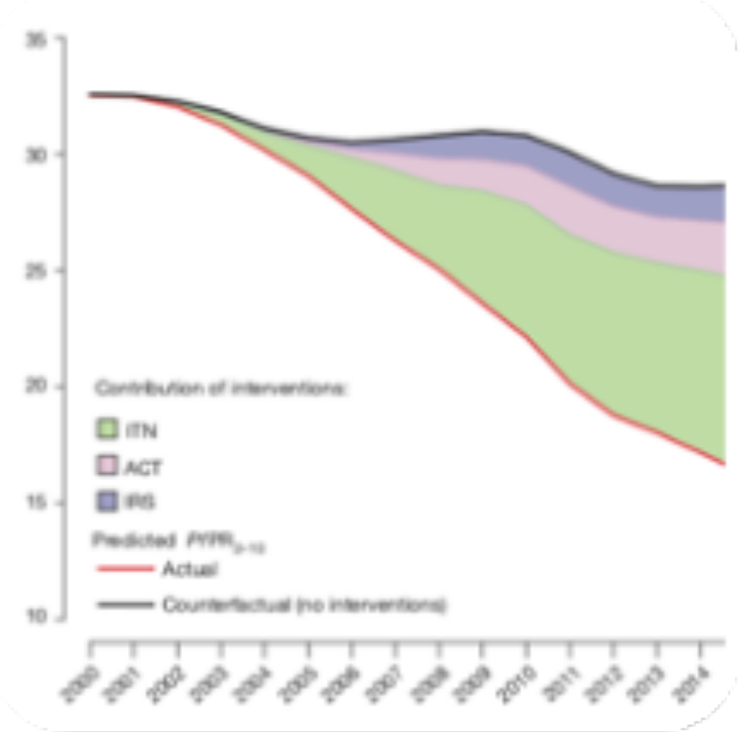
- ***Information*** is data that has been given meaning through analysis
- ***Intelligence*** is information needed to support policy:
  - Timely: up to date
  - Question Driven Design: theory → model building → simulation-based analytics
  - Checkpoints: informative metrics for decision support (PR, EIR, …)
  - Geographical / Temporal Completeness: algorithms to fill information gaps in space & time

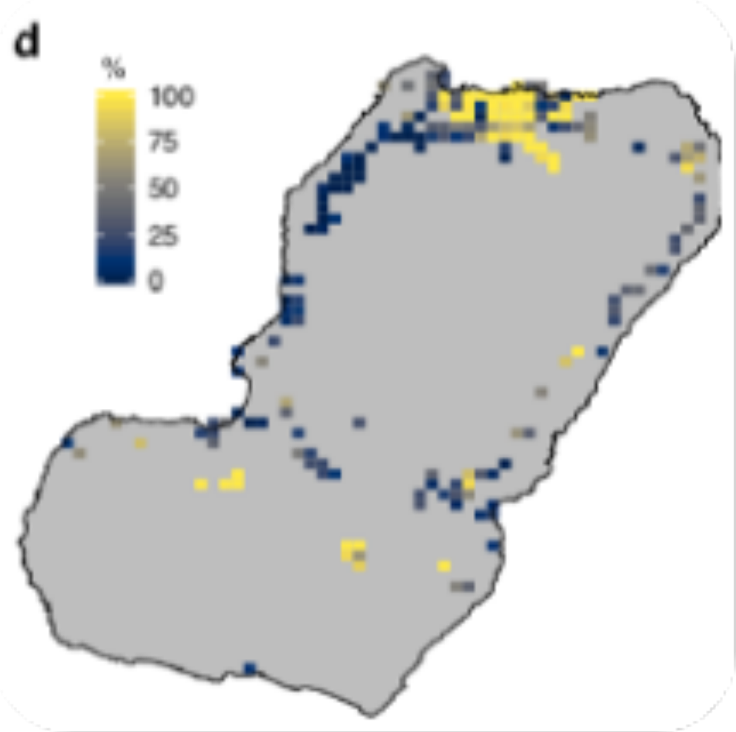
Malaria Analytics

What does it mean to be a professional malaria analyst?









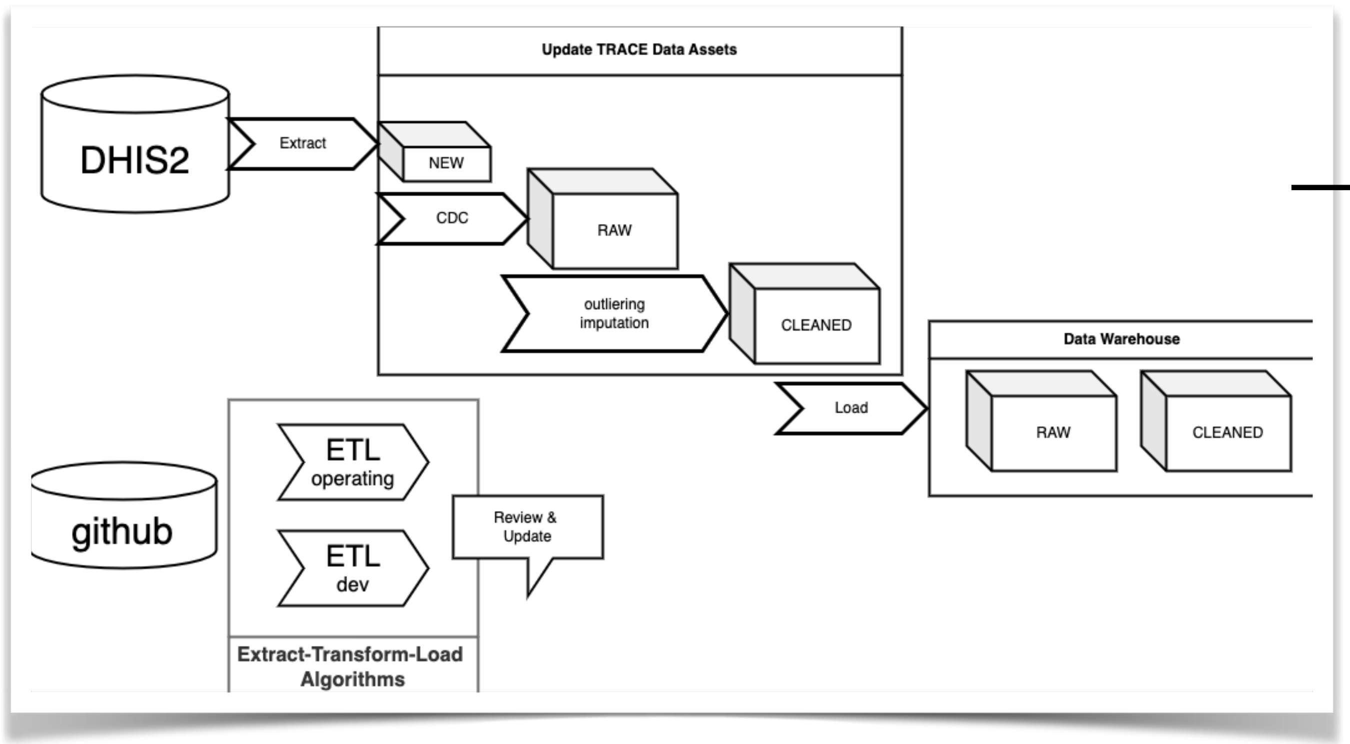
Malaria Policy: Temporal Epochs

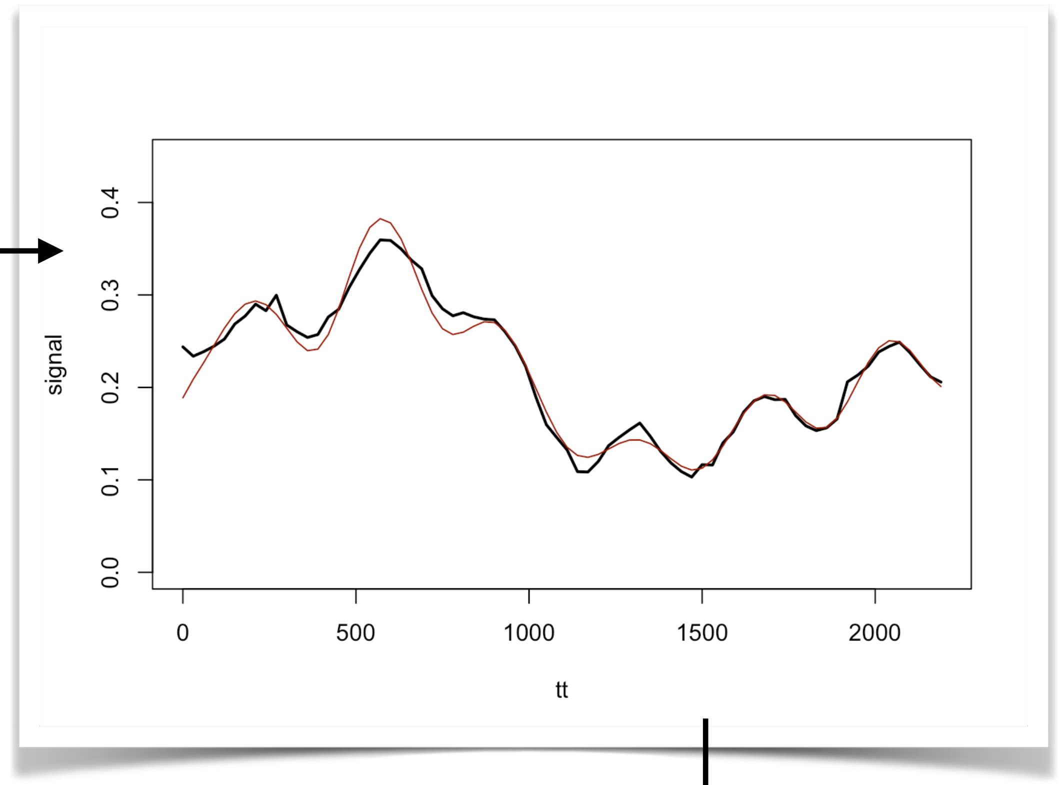
Use evidence / history to asses impact, respond to changing conditions, & guide the future

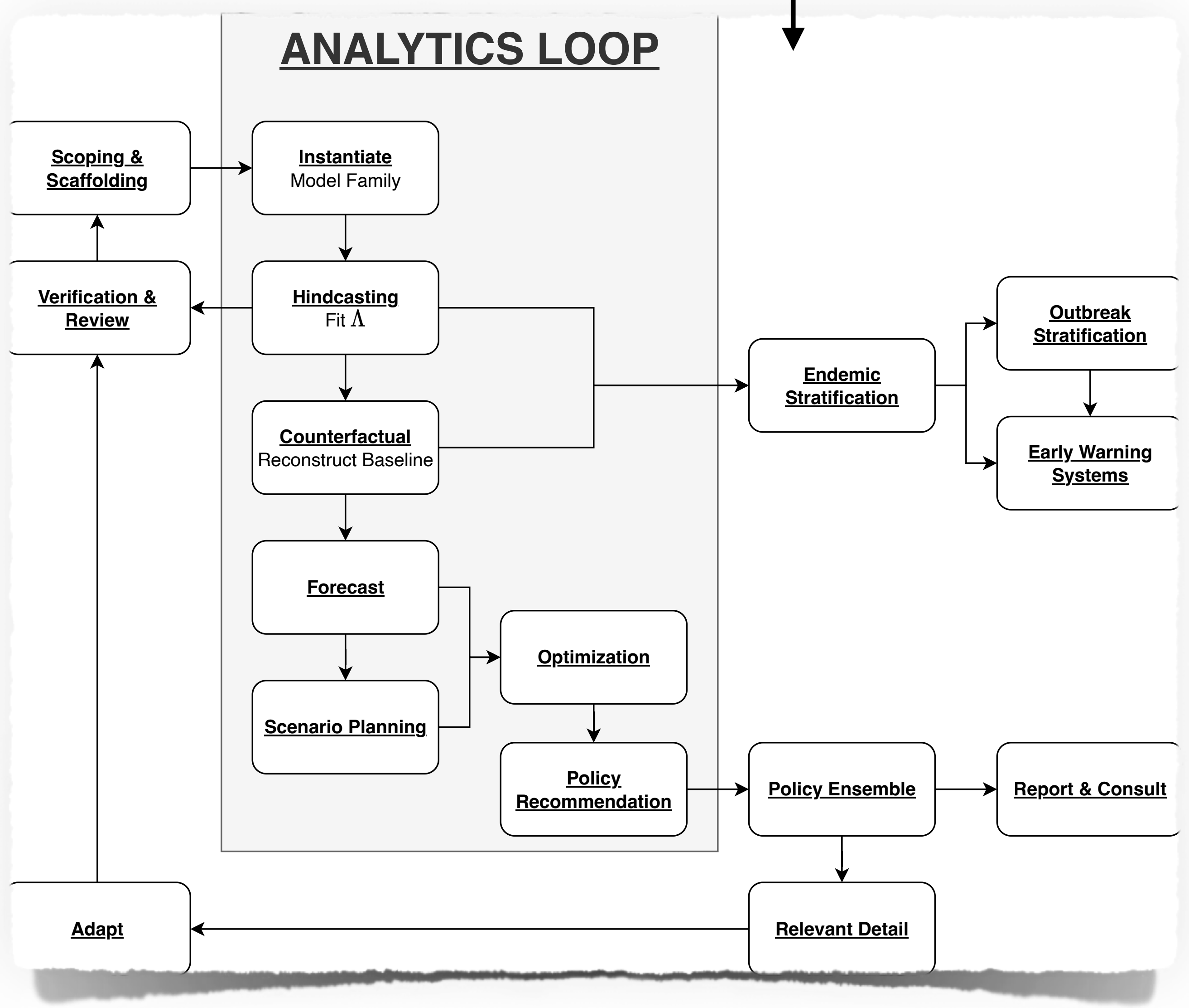
Epoch	Methods	Outputs	Programmatic Needs
Past	Statistical Analysis Model Fitting	Transmission History *Intensity, Seasonality, Stability, Trends*	Monitoring & Evaluation Burden
	Estimation	Counterfactual History	Averted Burden
Present	Nowcasting Outbreak Identification	Routine Reports Outbreak Stratification **Malaria Intelligence**	Logistics Support Early Warning Systems Outbreak Response
Future	Forecasting Simulation Optimization	Malaria Forecasts Scenario Planning	Stratification Strategic Planning Optimized Allocation

Bespoke Decision Support Systems

Flexibility, Accountability, Robustness, Efficiency







Malaria Intelligence Systems

- Data Processing Pipelines
- Routine Analysis / Outbreaks
- Robust, Progressive Estimation

Robust, Simulation-Based Analytics

- Analytics Pipelines
- Ensemble Policy Analyses

Nimble Model Building / Scaling Complexity

What makes a model / framework / analysis good for policy?

Nimble

- Models are integrated into well-organized information systems: data processing pipelines; algorithms for routine analysis; and up-to-date *malaria intelligence* assessments
- A framework enables model building to rapidly develop simulation-based analyses fit-for-purpose

Relevant Detail

- Pipelines are developed that propagate uncertainty through ensembles of simulation-based policy analyses
- The ensembles are analyzed to identify parameters that affect the policy advice
- If the uncertainty could be narrowed, what would resolve uncertainty about what to do?

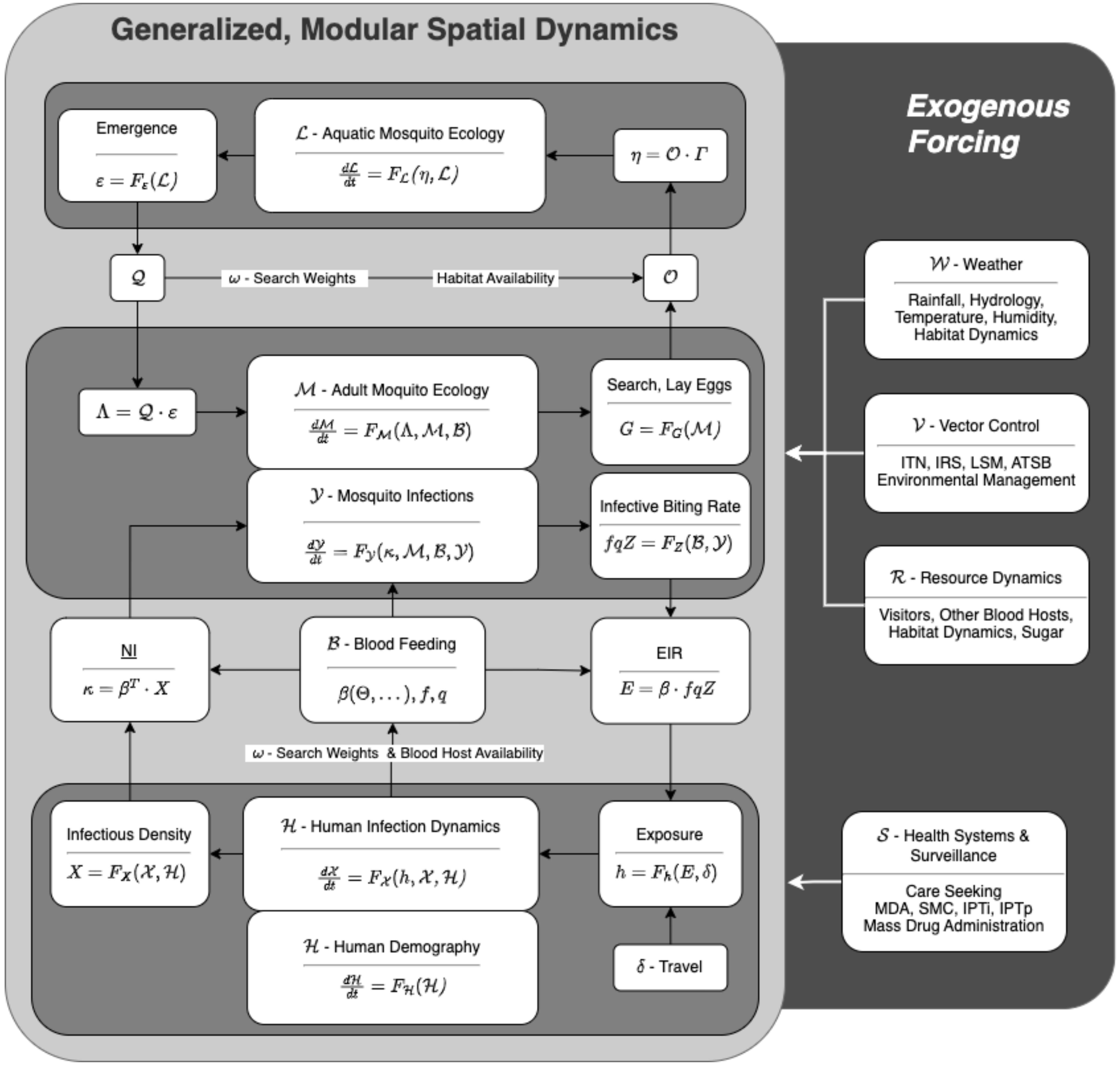
Immature Mosquito Dynamics
Maturation & Population Regulation

Egg Laying & Emergence

Adult Mosquito Dynamics
Demography & Behavior
Infection Dynamics

Blood Feeding & Transmission

Humans
Malaria Epidemiology
Demography



Environment
Habitat Dynamics,
Resource Dynamics,
Weather

Malaria Control
Vector Control, Vaccines,
Mass Therapy

Health Systems
Primary Healthcare &
Surveillance

Spatial dynamics of malaria transmission
https://doi.org/10.1371/journal.pcbi.1010684

SimBA

*Software for **Sim**ulation-**B**ased **A**nalytics*

R packages on GitHub

- **ramp.xds** → e**X**tensible **D**ynamical **S**ystems for malaria and mosquito-borne pathogens: setup & solve autonomous and non-autonomous systems of ordinary & delay differential and difference equations with spatial dynamics, including stochastic difference equations (replaces *exDE & MicroMoB*)

- **ramp.library** → reusable code library of (perhaps slightly modified) published / peer reviewed models, imported as dynamical modules for the major components

- **ramp.control** → reusable code library of algorithms implementing malaria control, including most forms of vector control & mass distribution of therapeutics

- **ramp.forcing** → reusable code library of peer reviewed algorithms implementing exogenous forcing by weather & other factors

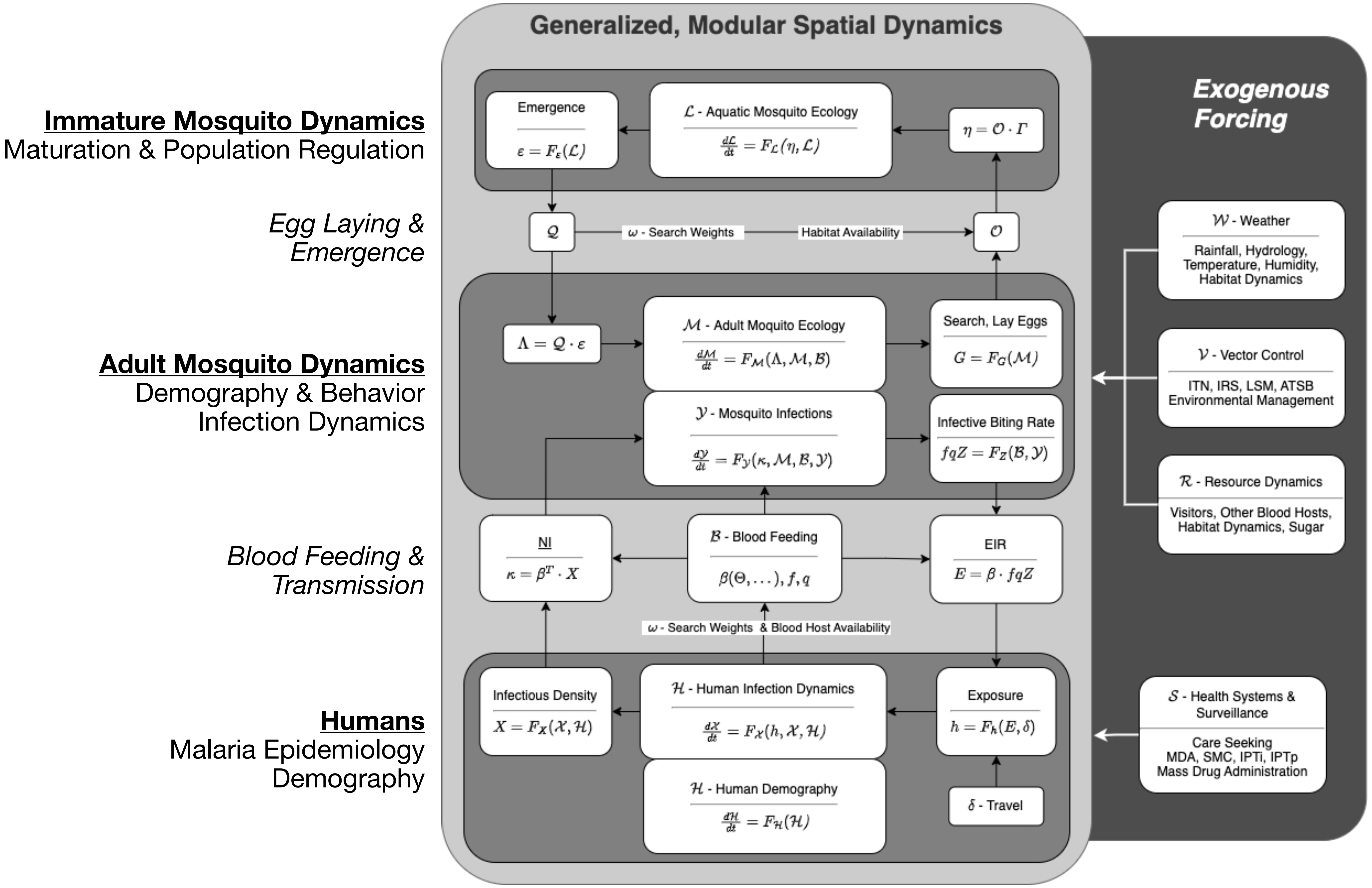
- **ramp.work** → algorithms to accomplish specific tasks

https://faculty.washington.edu/smitdave/simba/index.html

SimBA Software Design & Features

Nimble Model Building & Scalable Complexity

- **Modular**
  - 3 dynamical ***components*** (independent sub-systems) representing 5 distinct sets of biological processes
  - 2 rigorous ***interfaces:*** blood feeding and egg laying (for patch-based meta-population dynamics)
  - internalize lags for delay differential equations
- **Structurally Flexible & Extensible**
  - Plug-and-play design, including trivial modules
  - arbitrary numbers of human population strata, patches & aquatic habitats
  - multiple vector / host species
  - boundary conditions (malaria importation)
- **Built-in Computational Algorithms**
  - Required: output standard metrics. (observational process model)
  - Model Fitting
  - Numerical computation of thresholds, connectivity, …



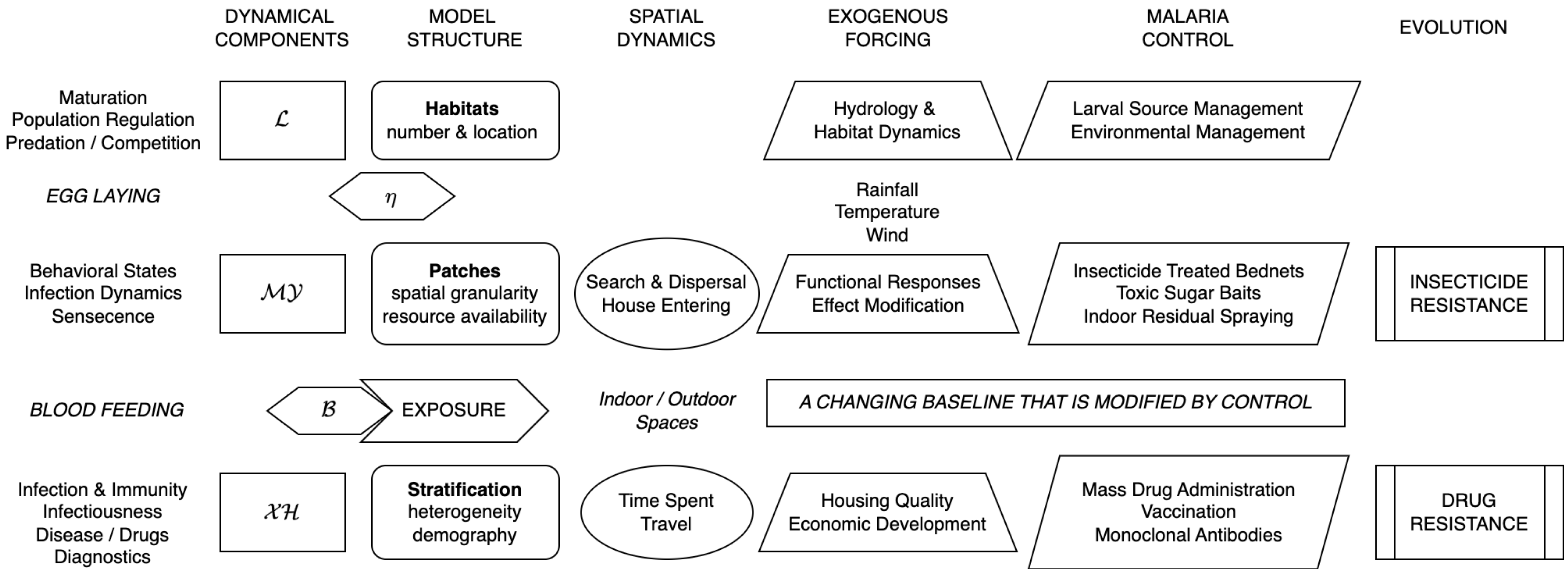
https://faculty.washington.edu/smitdave/simba/index.html

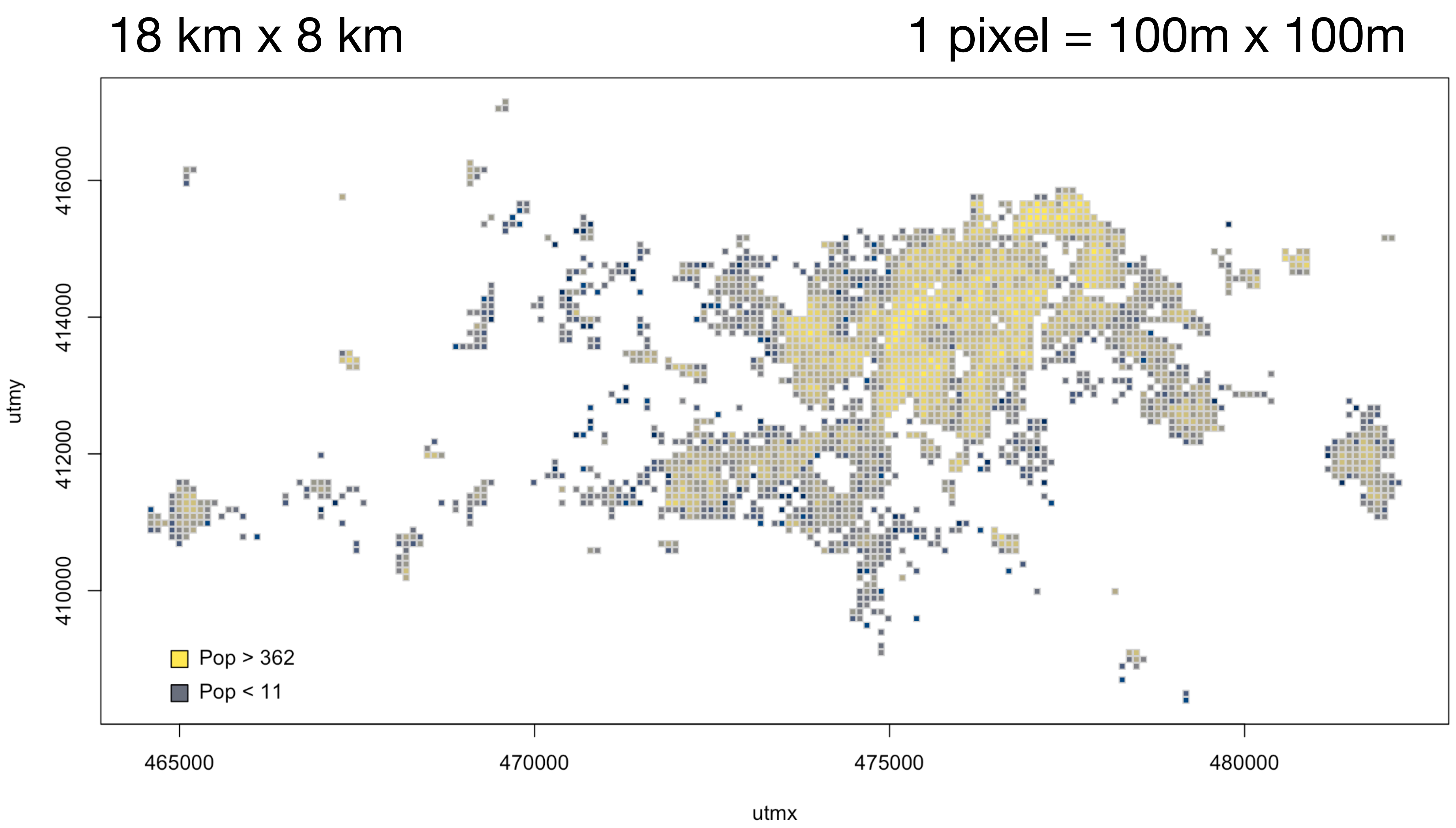
Scaling Complexity

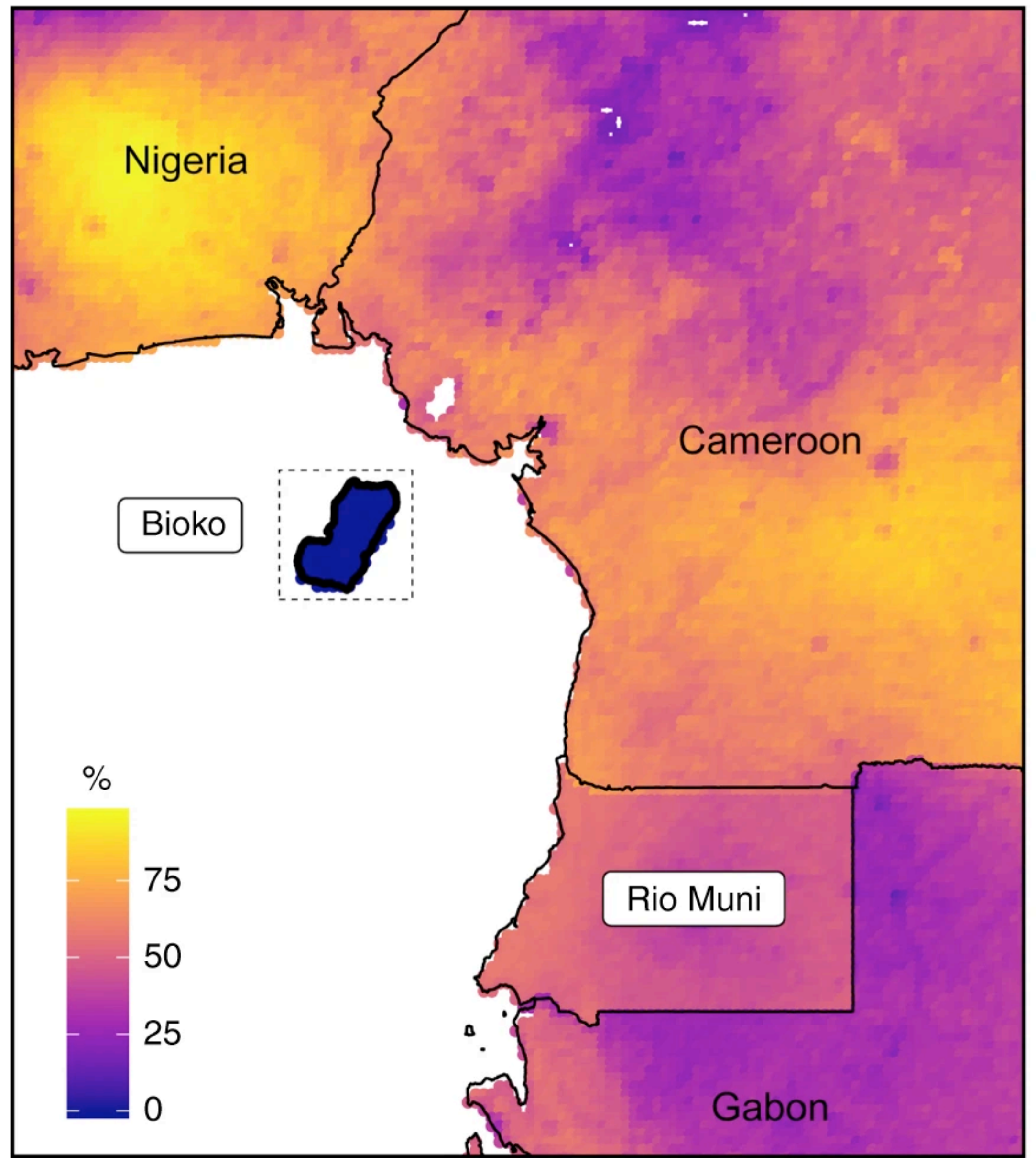
$$\frac{dz}{dt} = k'z'(p - z) + qz$$
$$\frac{dz'}{dt} = kz(p' - z') + q'z'$$

→ *Increasing Realism & Complexity*

Model Building Rubric

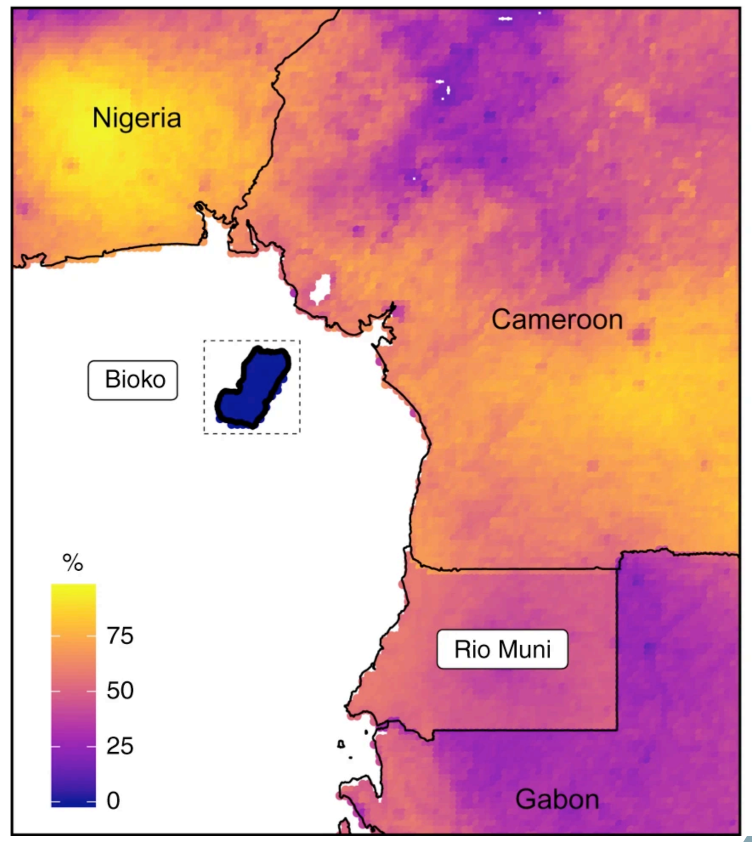


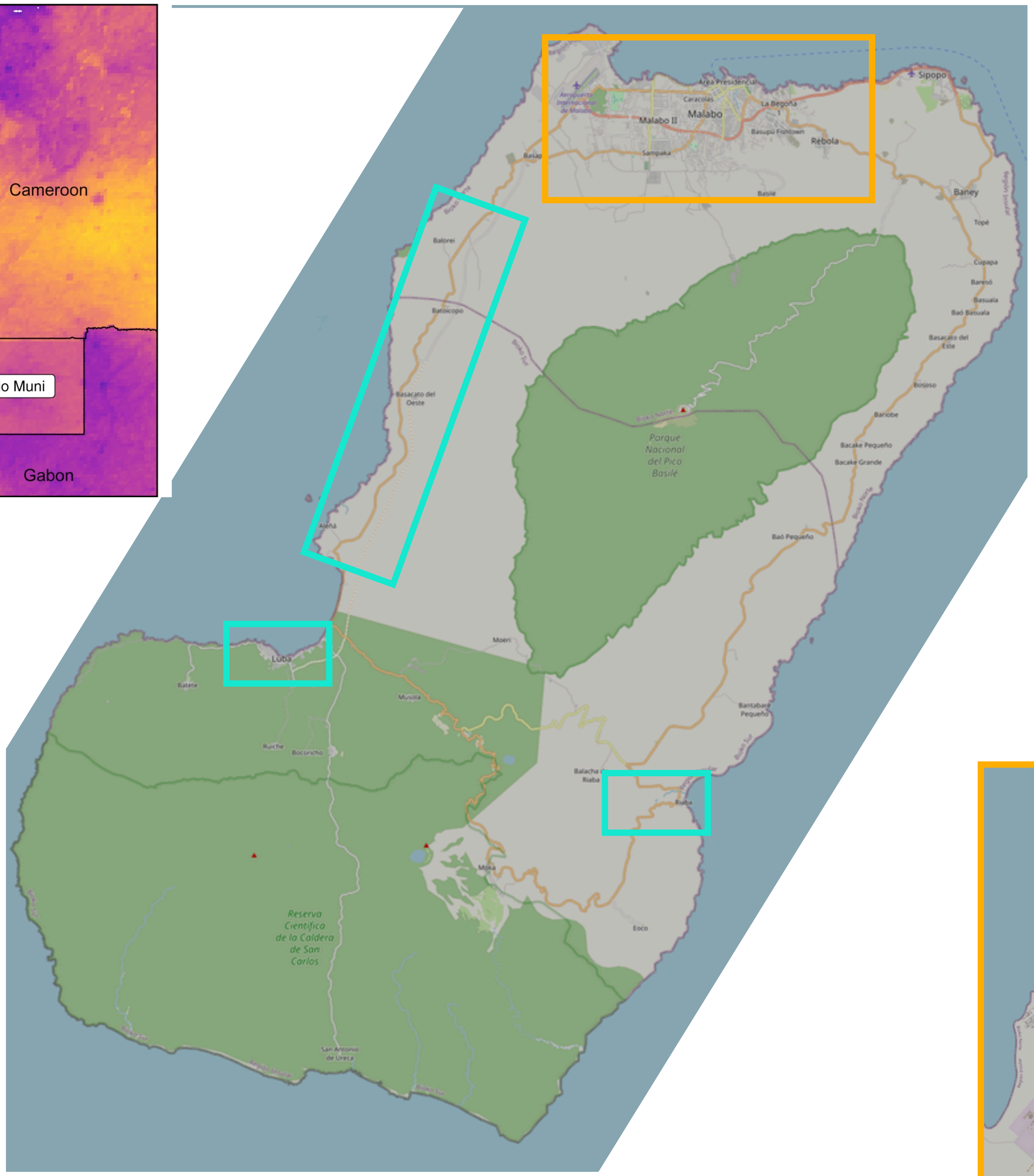




Adaptive Vector Control

Adaptive Malaria Control for Small Areas





Bioko Island

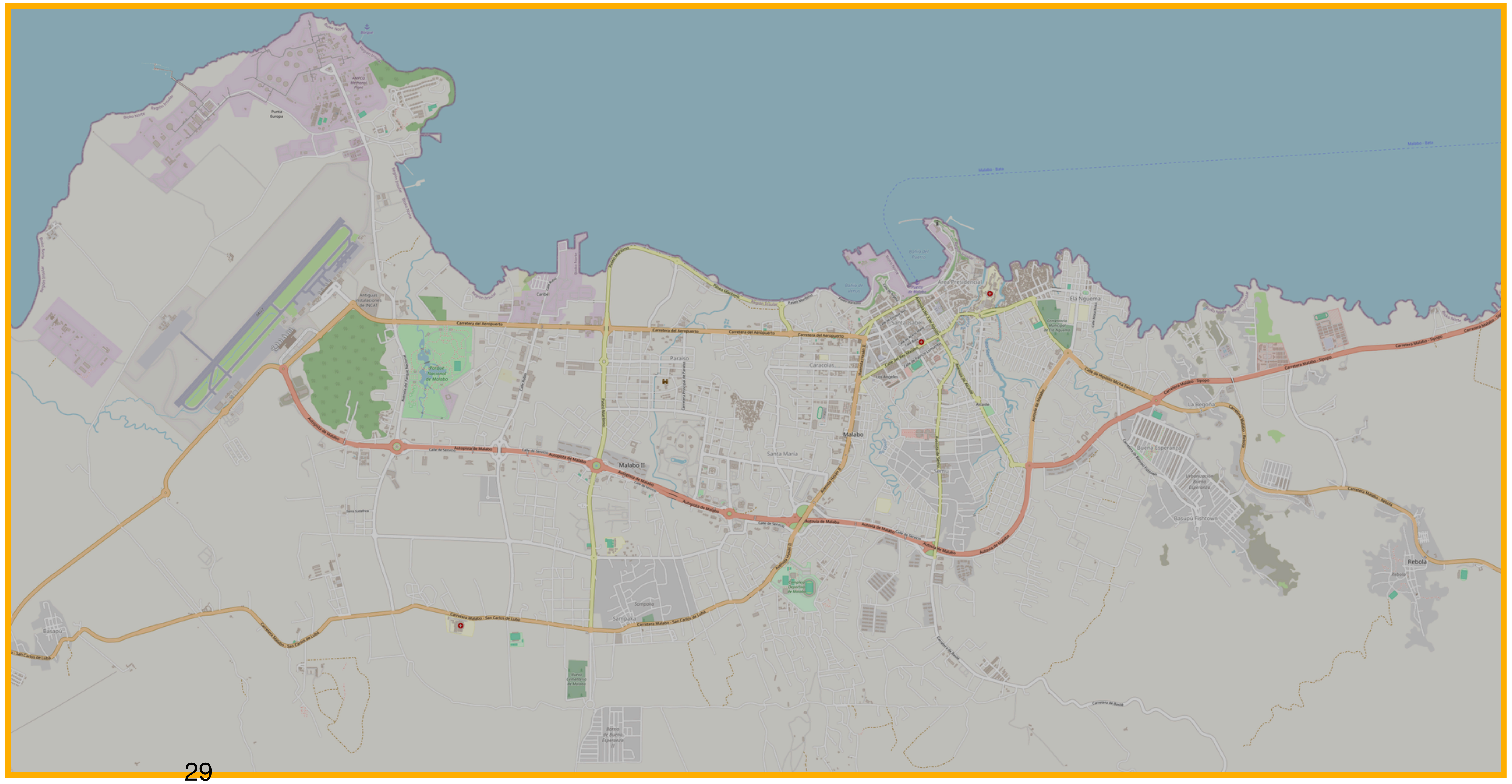
35 km x 72 km

population: ~330,000

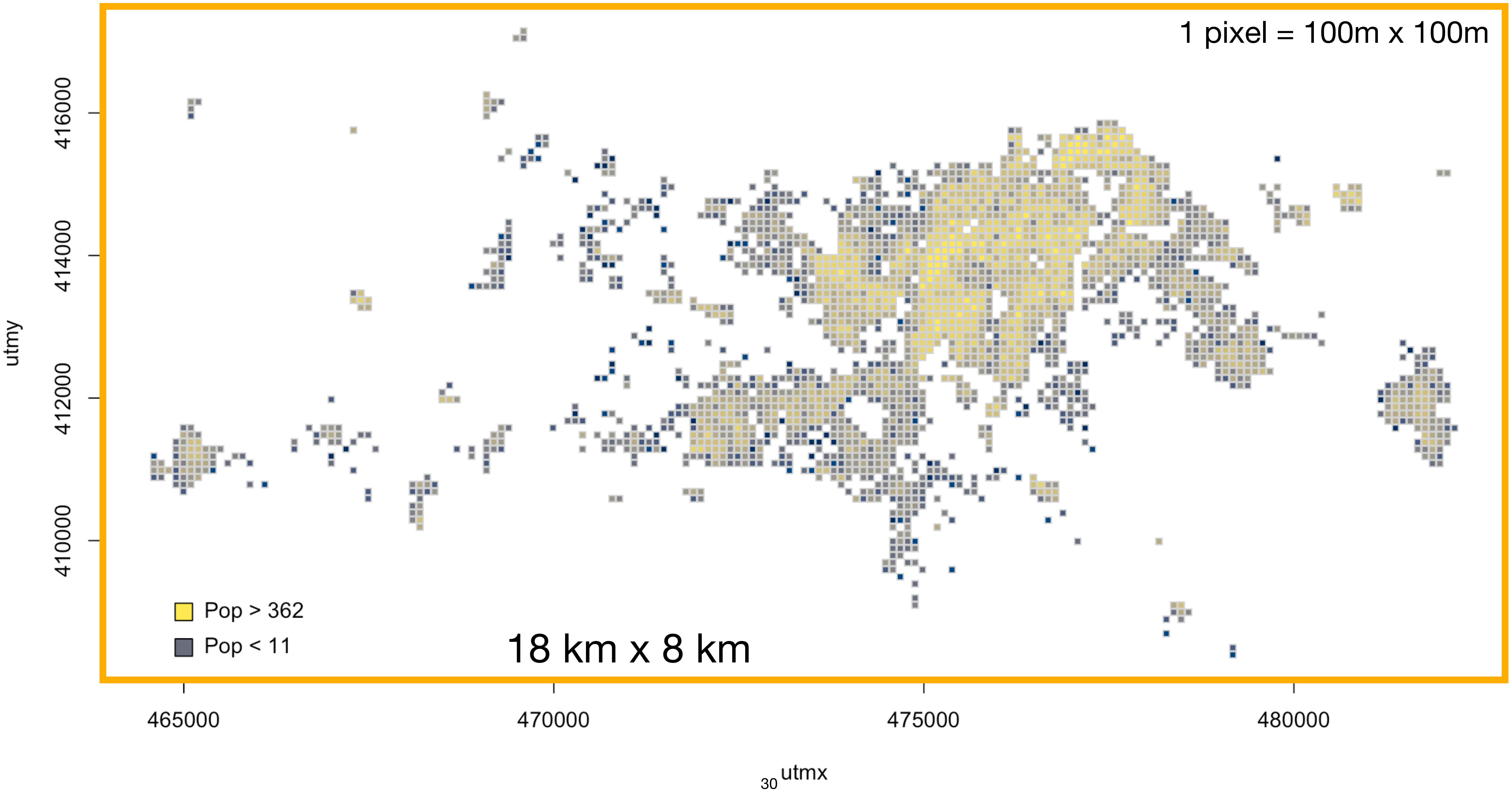
Malabo

18 km x 8 km

population: ~300,000



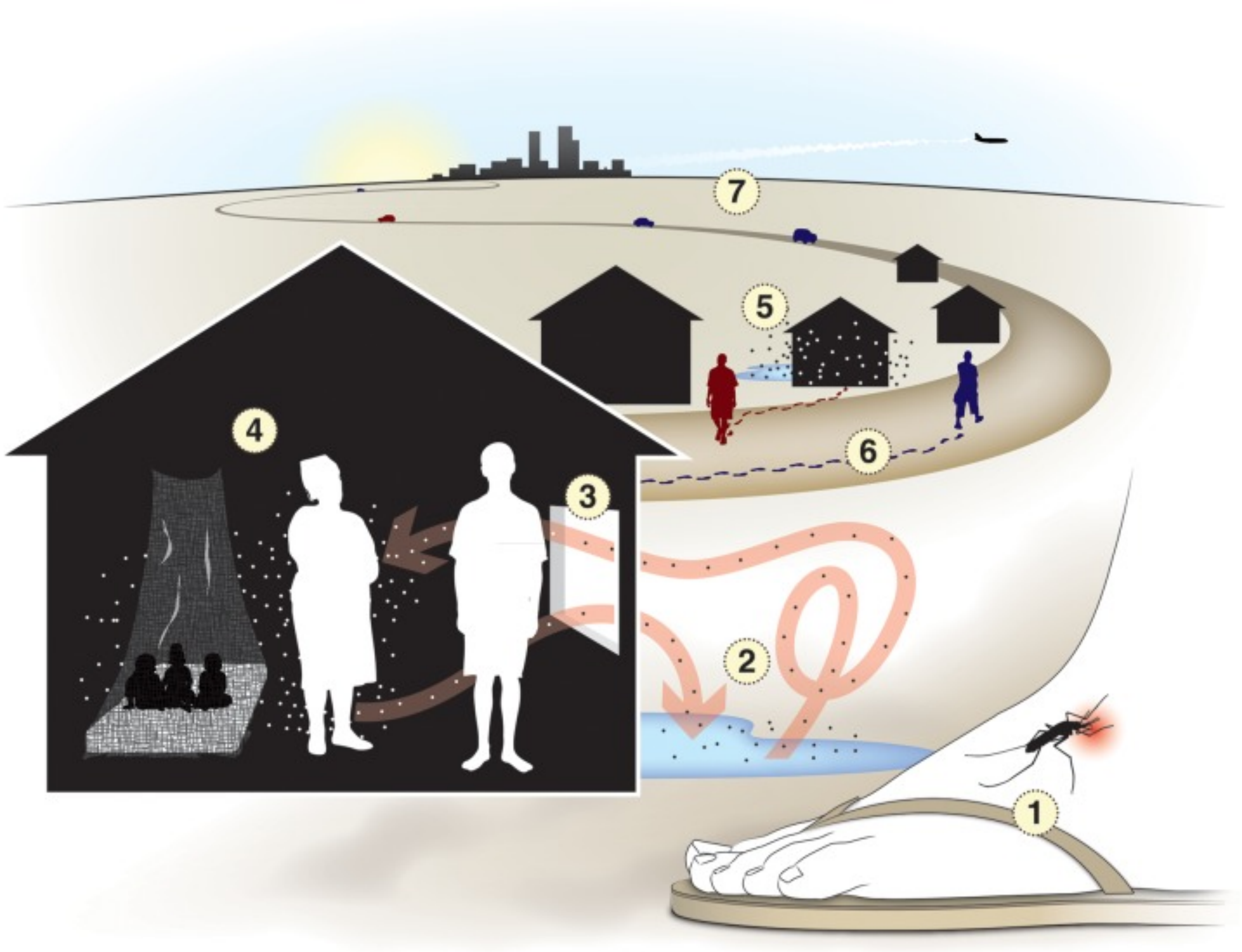
Occupied Sectors / Human Population Density



Transmission Dynamics

The Robust Approach

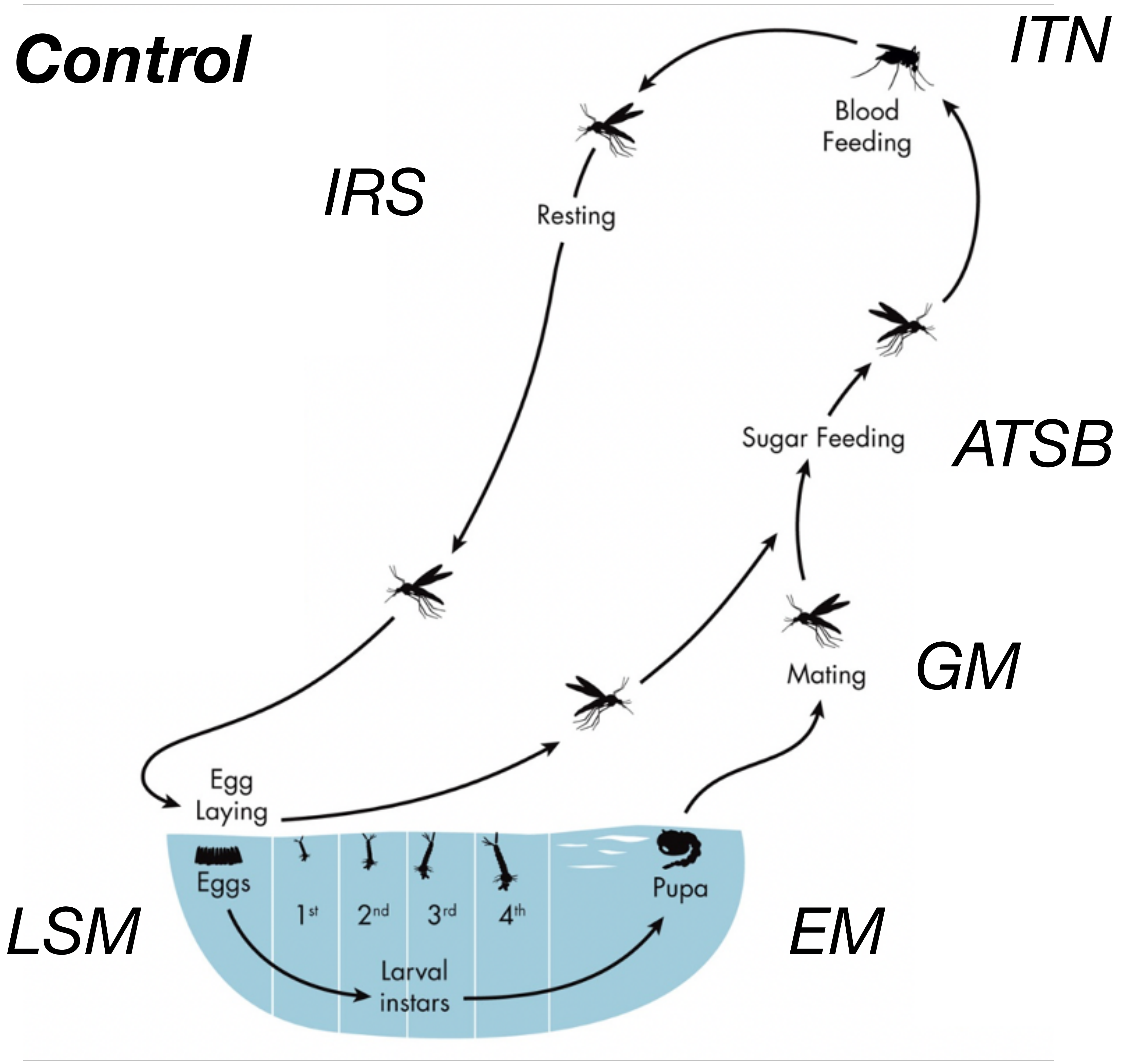
- How far do mosquitoes move?
- What spatial scales are appropriate for modeling transmission?
- What, if anything, is a malaria population?
- What, if anything, is a focus?
- Is all malaria transmission focal?

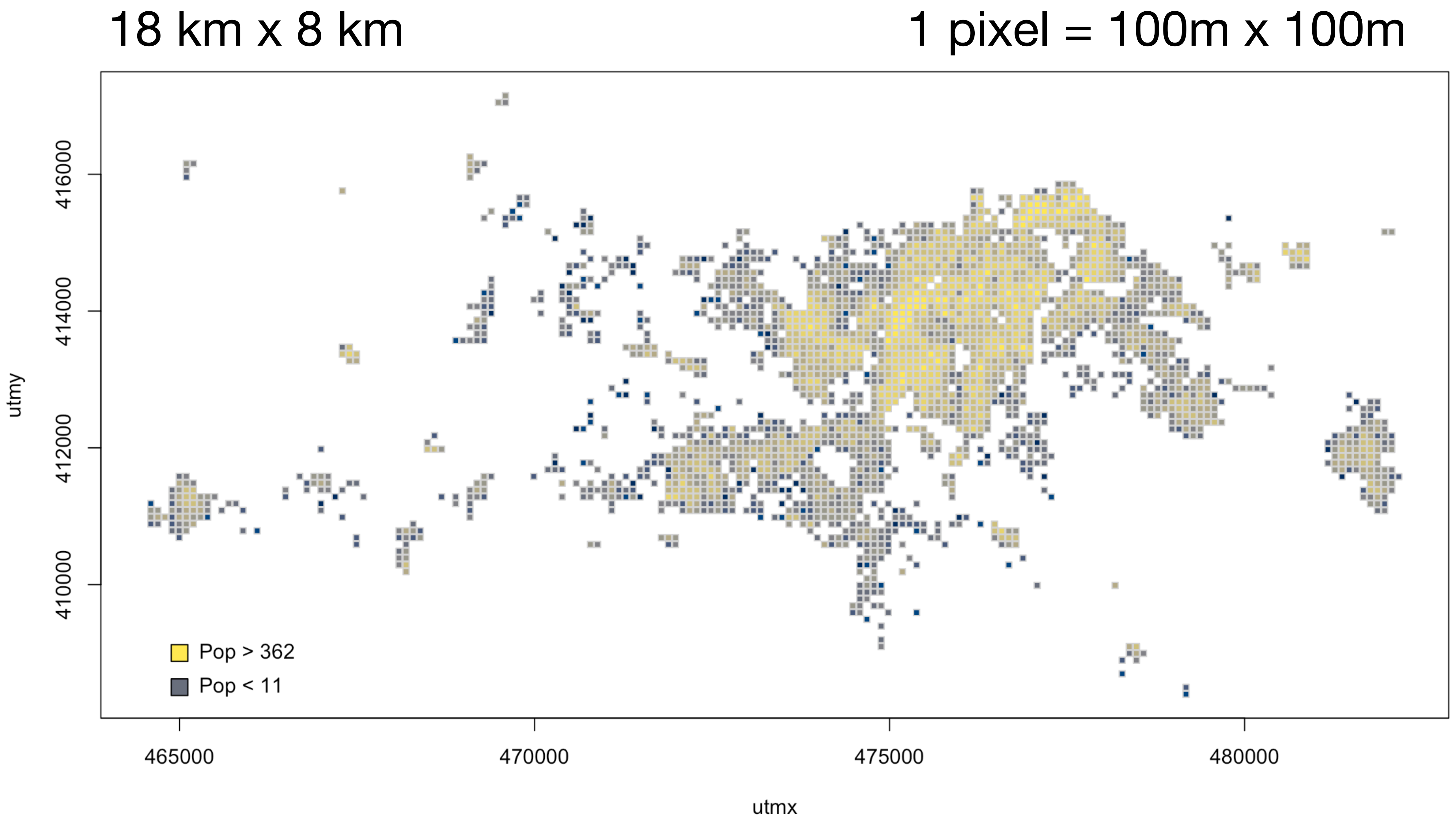


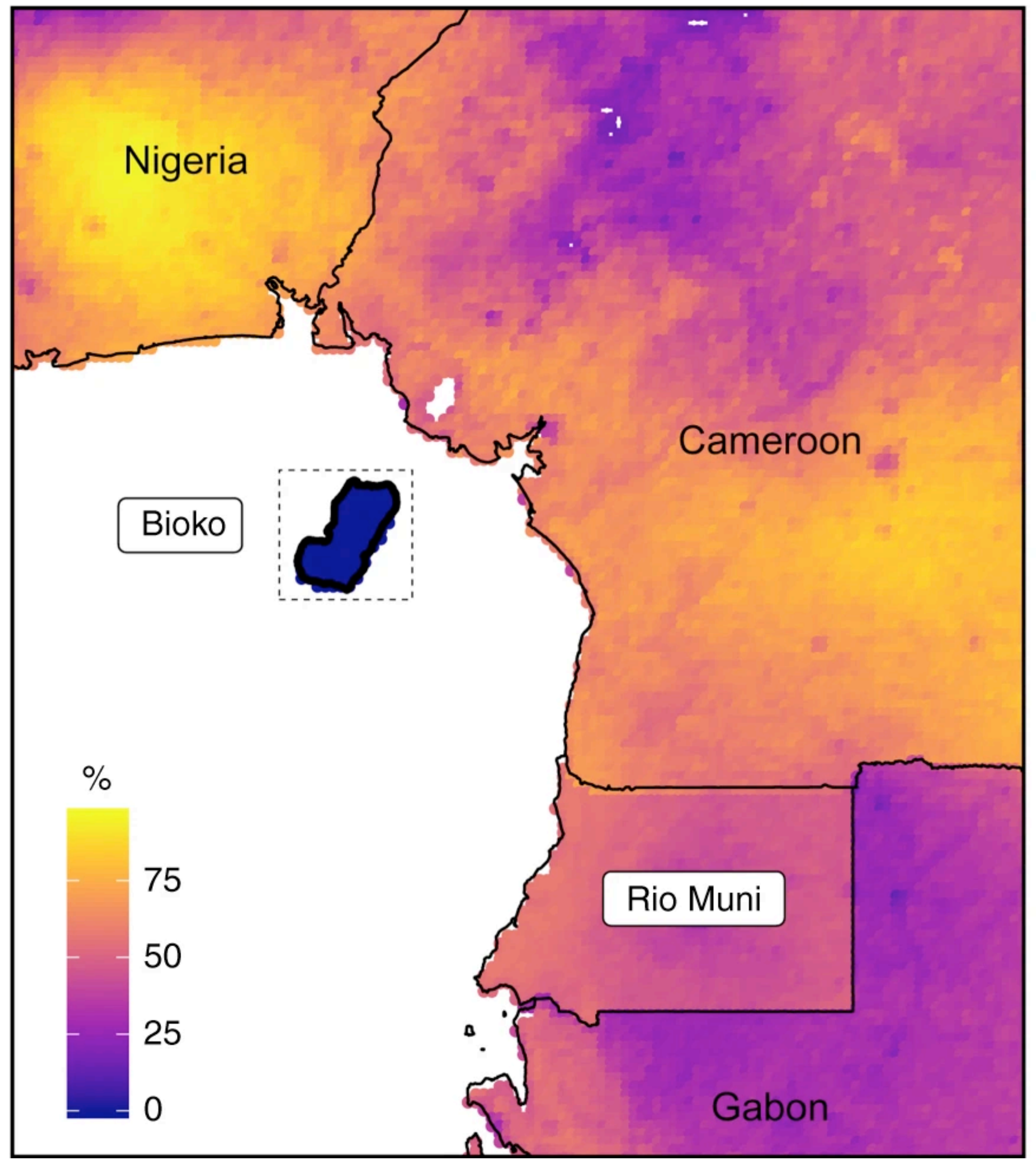
Vector Control

Annual Planning for Integrated Vector Control

- Indoor Residual Spraying (IRS)
- Insecticide Treated Bed Nets (ITN)
- Attractive Toxic Sugar Baits (ATSB)
- Larval Source Management (LSM)
- Environmental Management (EM)
- Genetic Modification (GM)

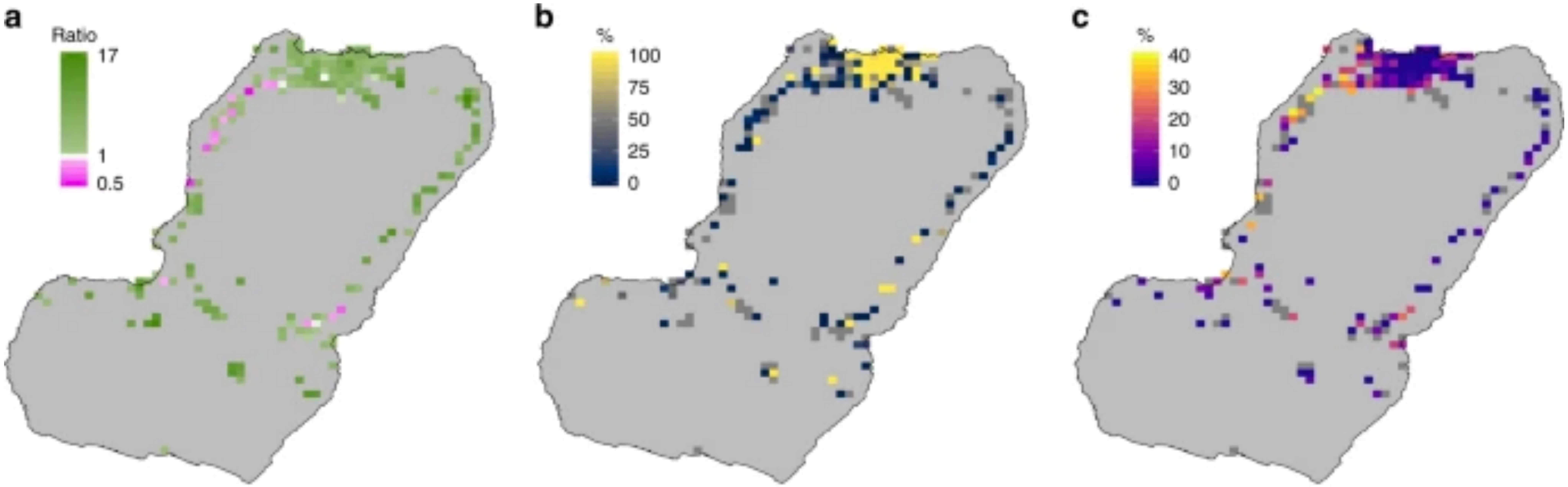






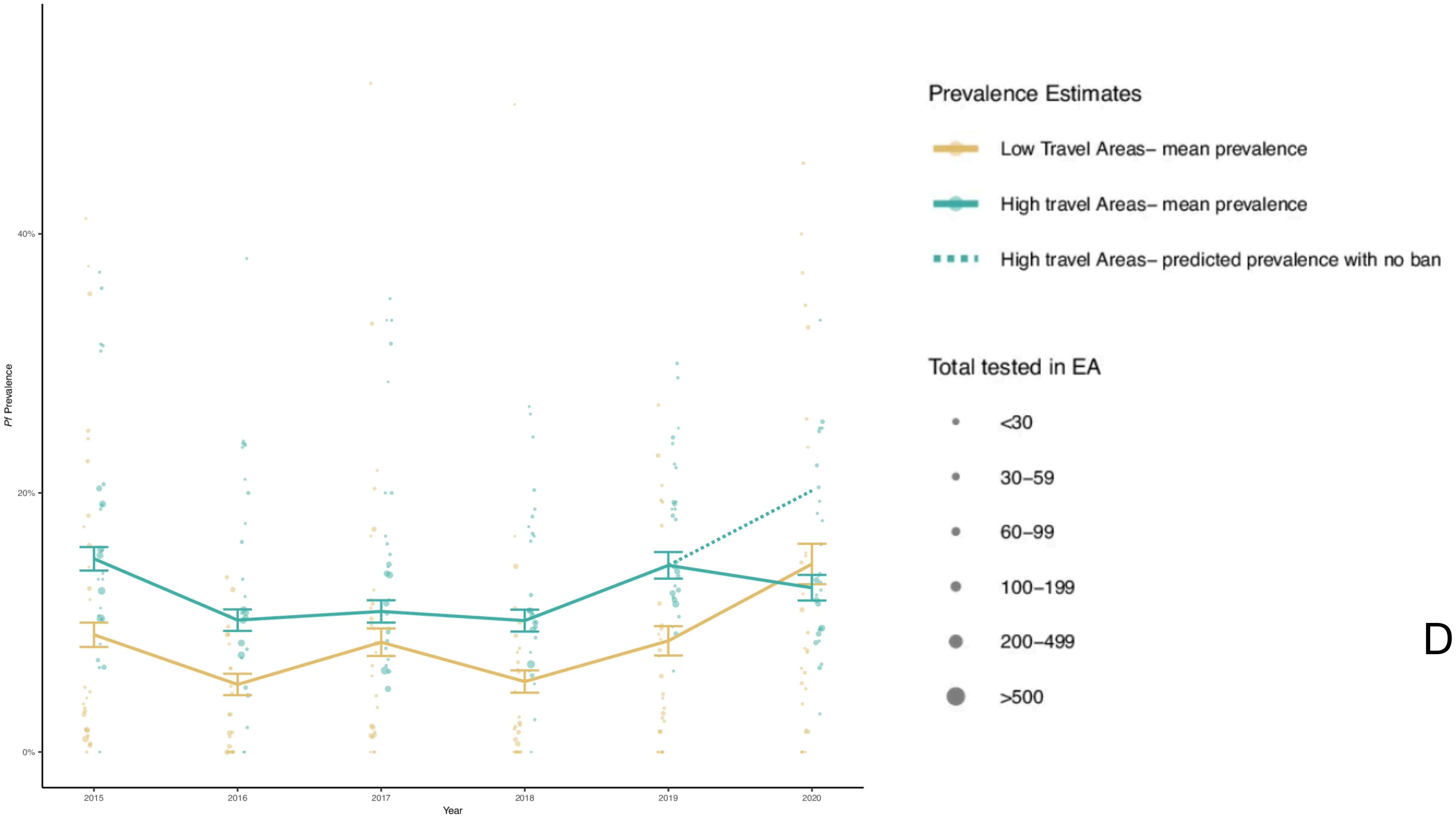
Local Transmission *vs.* Imported Malaria

a) imported:local *b) travel fraction* *c) counterfactual local*



Human mobility patterns and malaria importation on Bioko Island

https://www.nature.com/articles/s41467-019-10339-1



Dianna Hergott, *et al.*

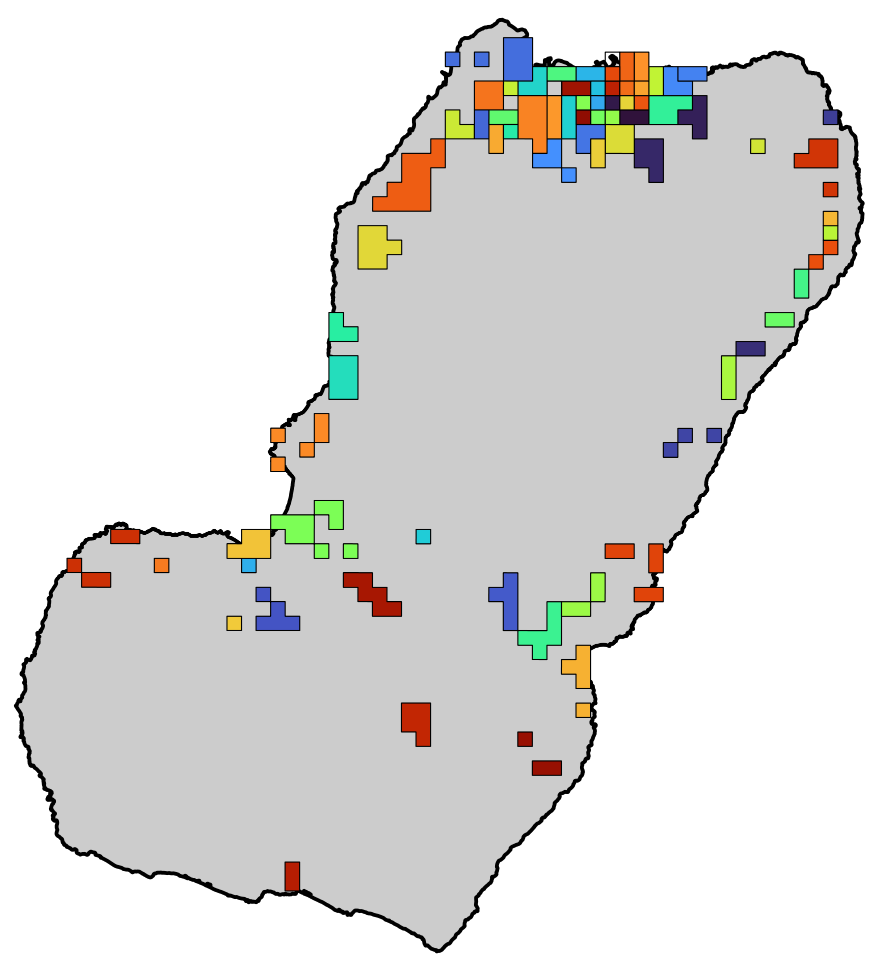
Impact of six-month COVID-19 travel moratorium on *Plasmodium falciparum* prevalence on Bioko Island, Equatorial Guinea

https://www.nature.com/articles/s41467-024-52638-2

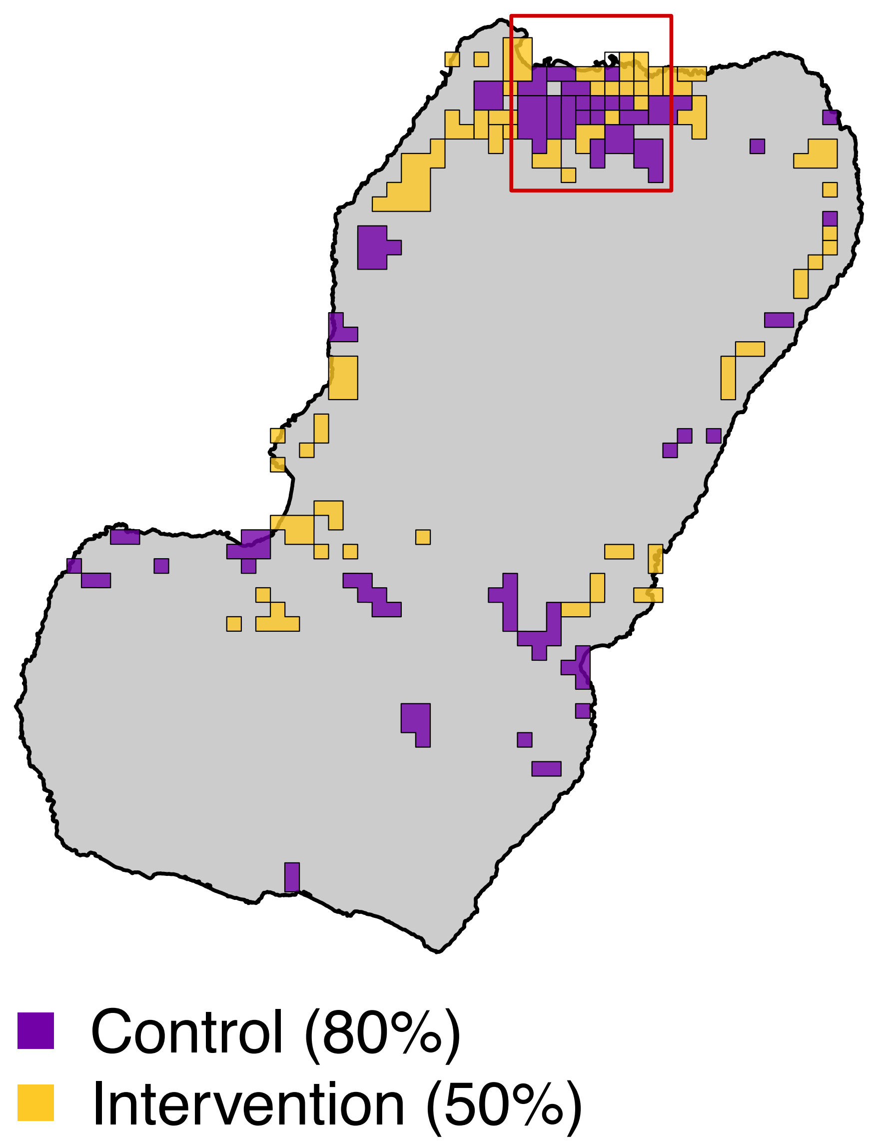
Indoor Residual Spraying

Spatial Targeting & Coverage

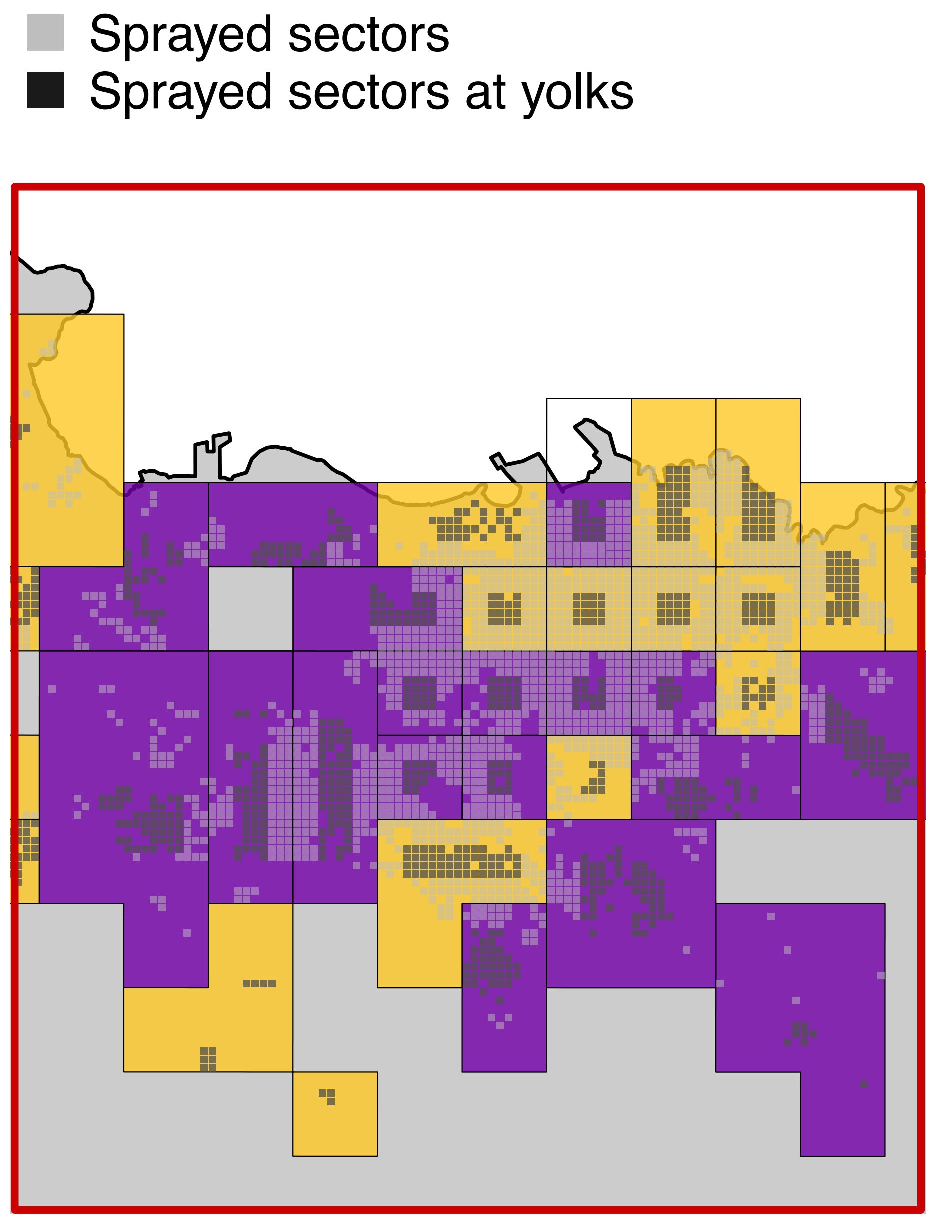
Clusters

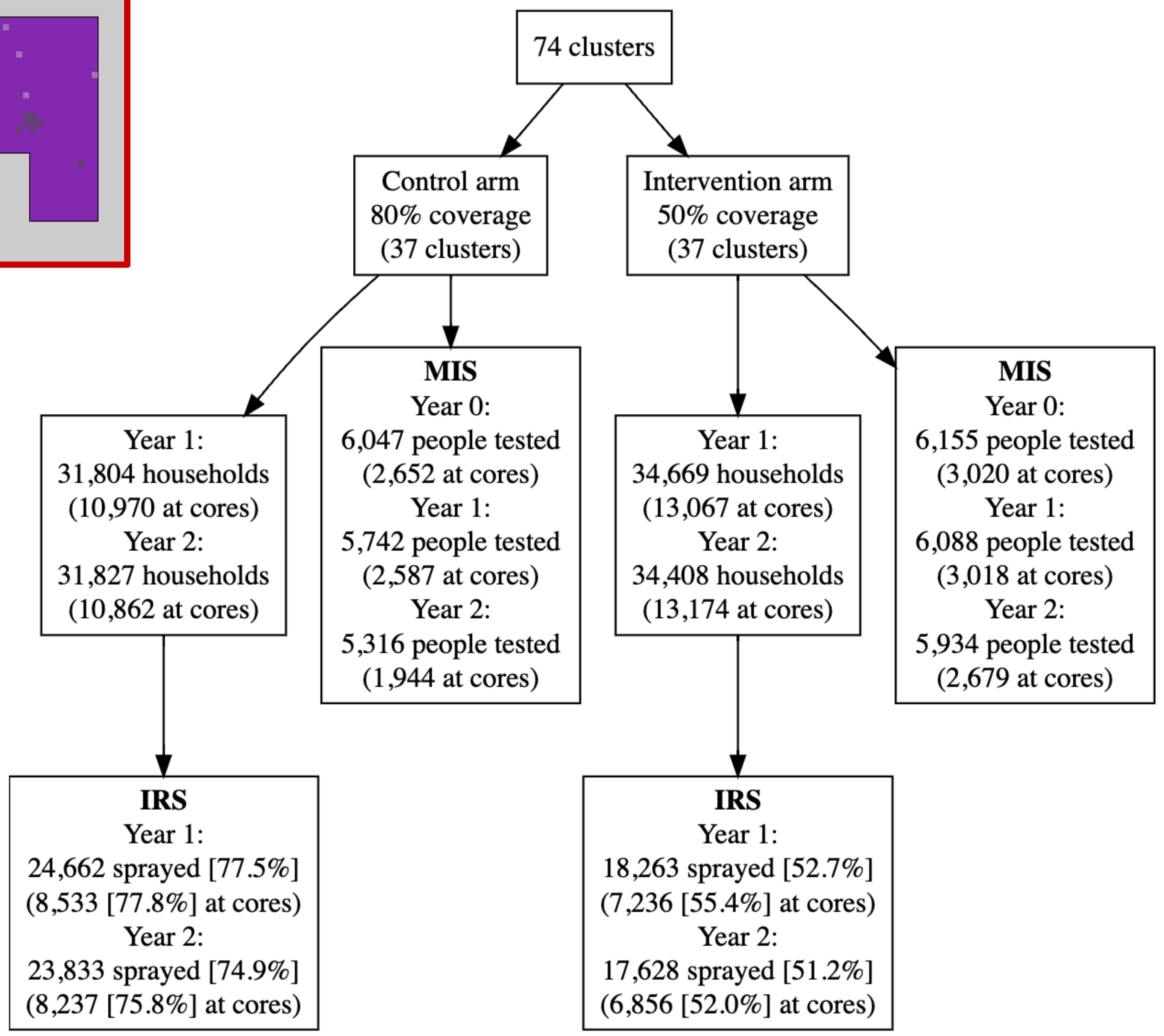


Arms



Yolks



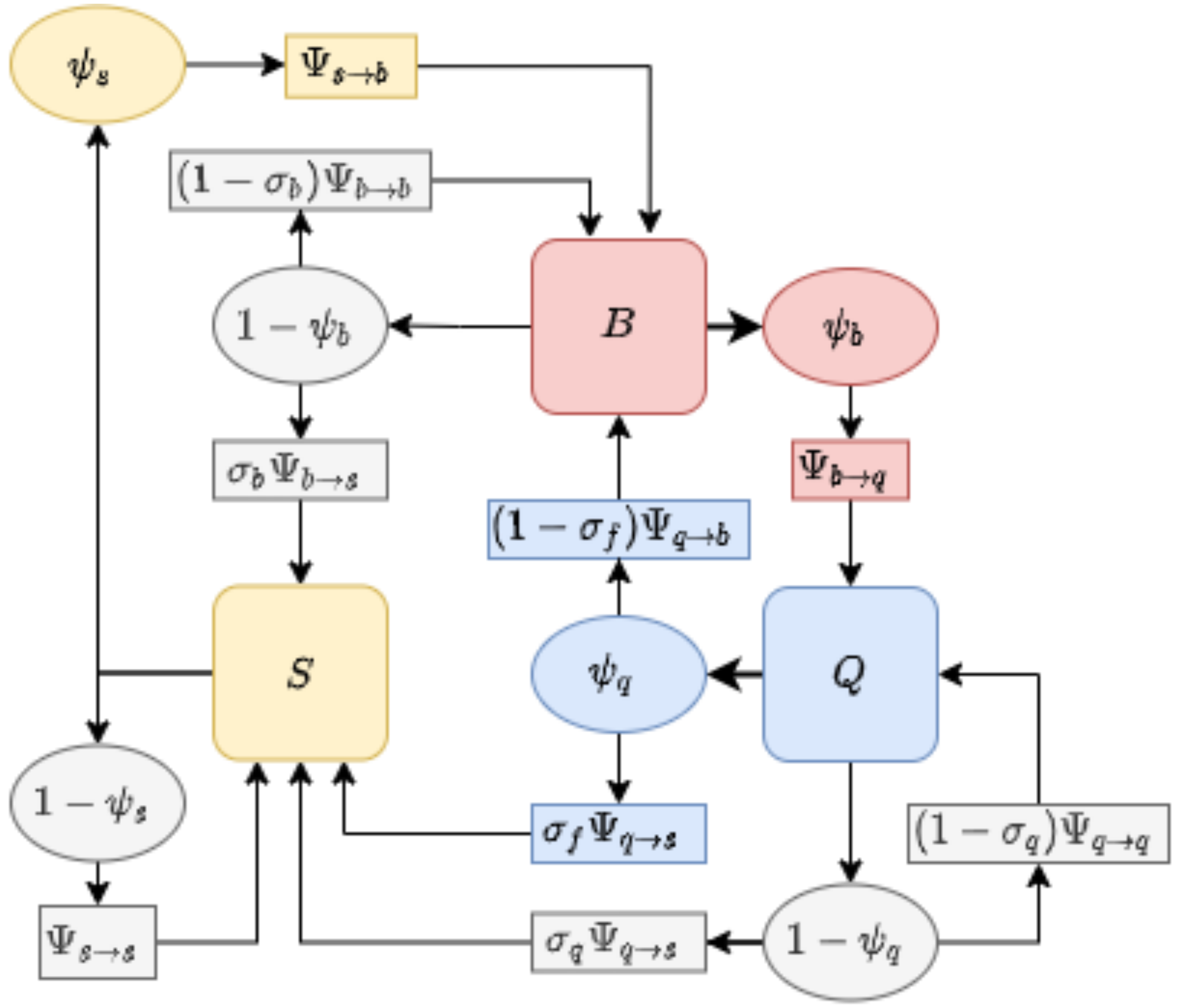


Rethinking indoor residual spraying coverage targets: An operational trial testing the non-inferiority of 50% against 80%

Mosquito Ecology

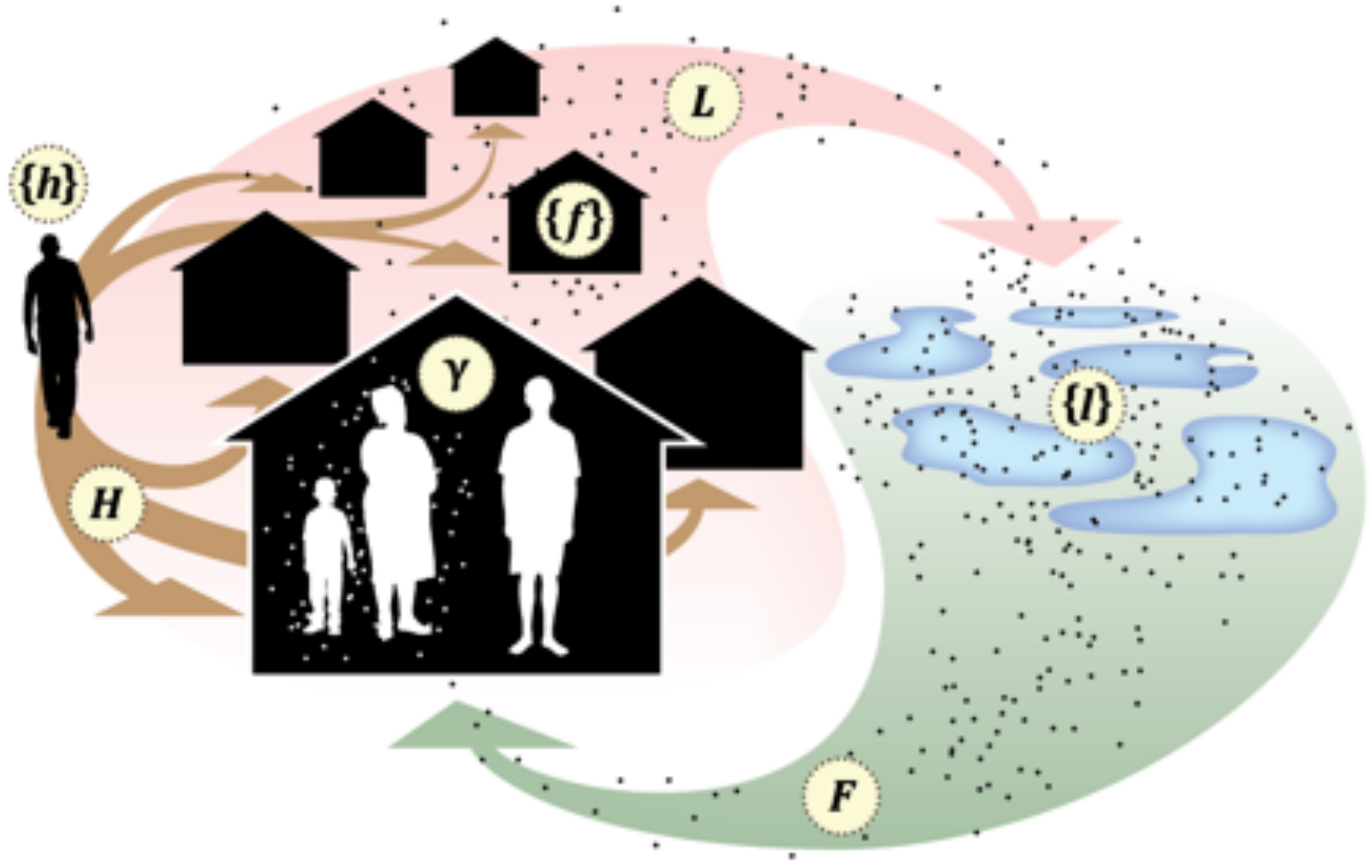
The Robust Approach

Mosquito Behavioral State Models



Microsimulation

Transmission dynamics on point sets



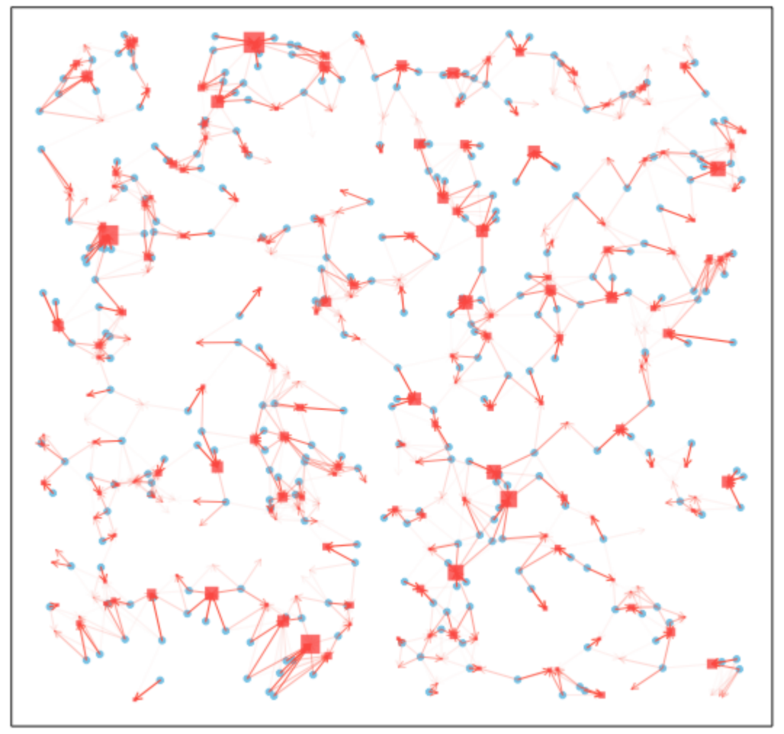
Heterogeneity, Mixing, and the Spatial Scales of Mosquito-Borne Pathogen Transmission

https://doi.org/10.1371/journal.pcbi.1003327

Mosquito Ecology

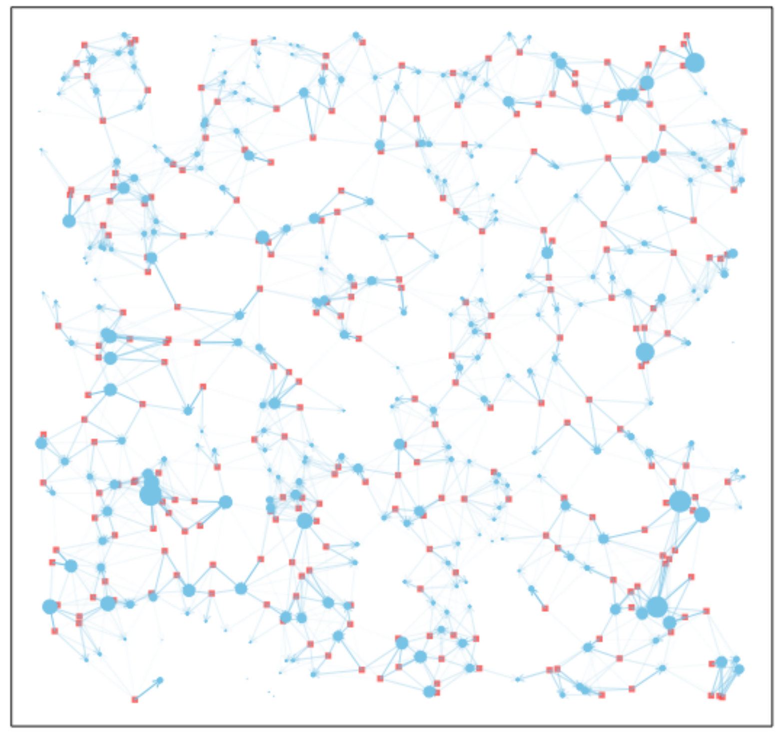
Deep Dive: `ramp.micro`

$\Psi_{b \leftarrow q}$



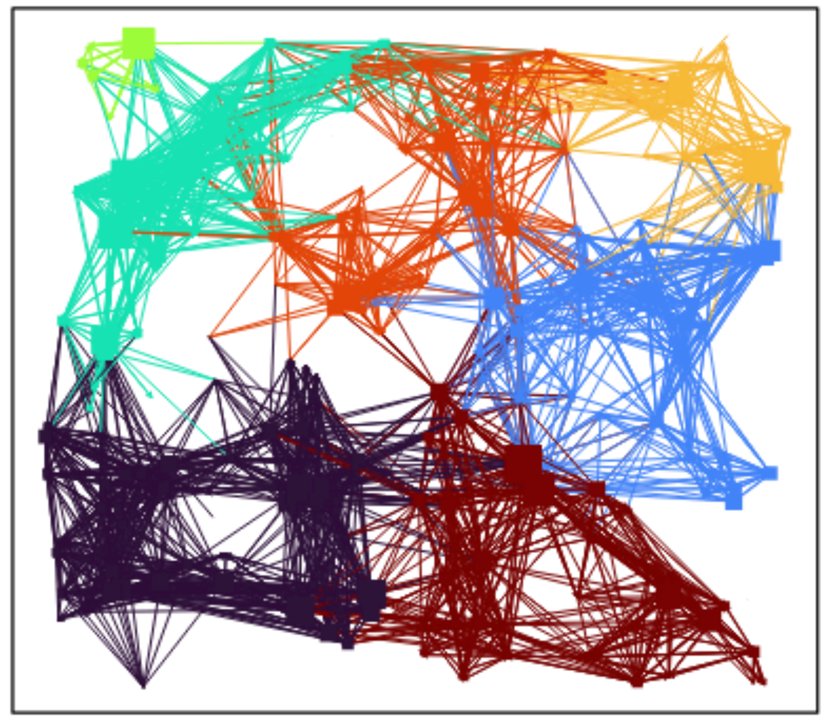
Dispersal while Searching
for Blood Hosts

$\Psi_{q \leftarrow b}$

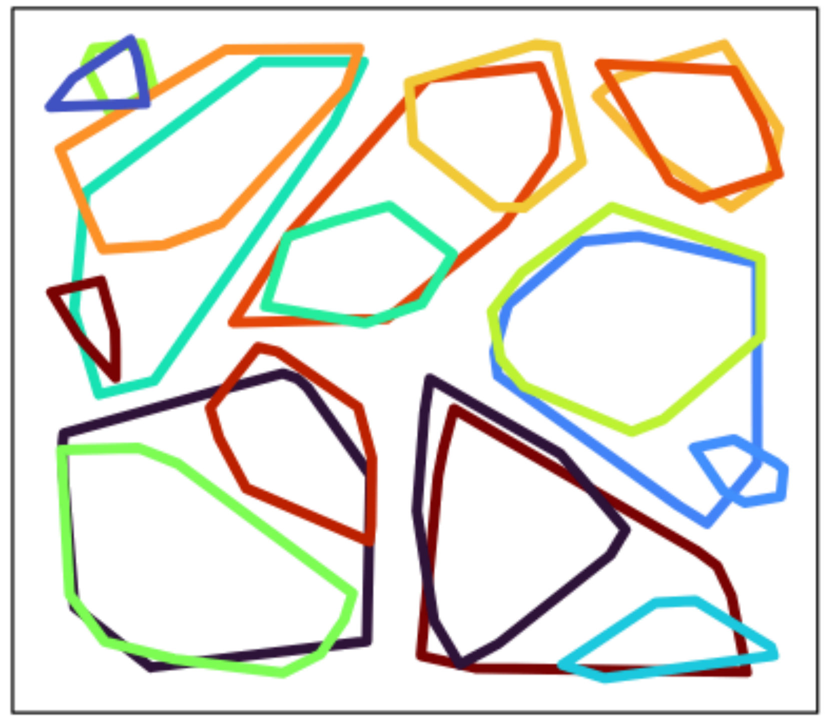


Dispersal while Searching
for Aquatic Habitats

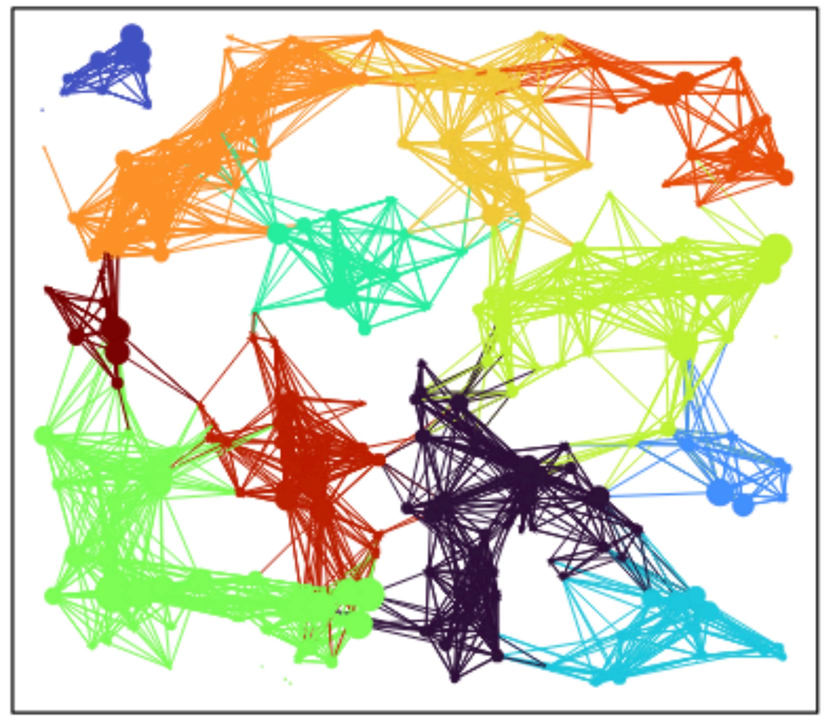
Potential Parasite Dispersal, Population



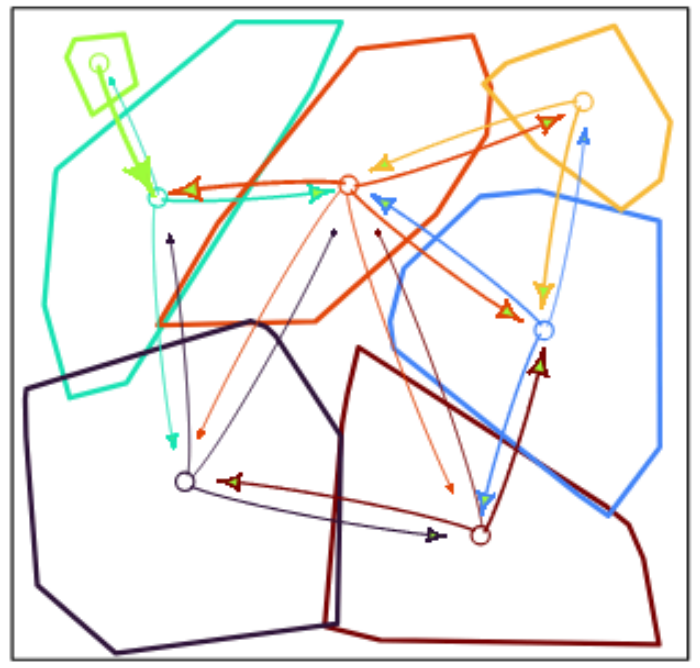
Convex Hulls



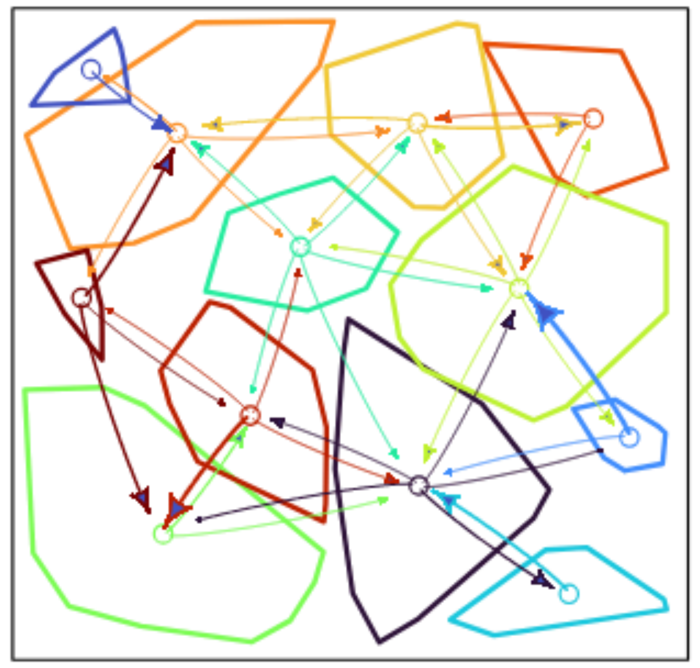
Lifetime Egg Dispersal, Population



Potential Parasite Dispersal, Population



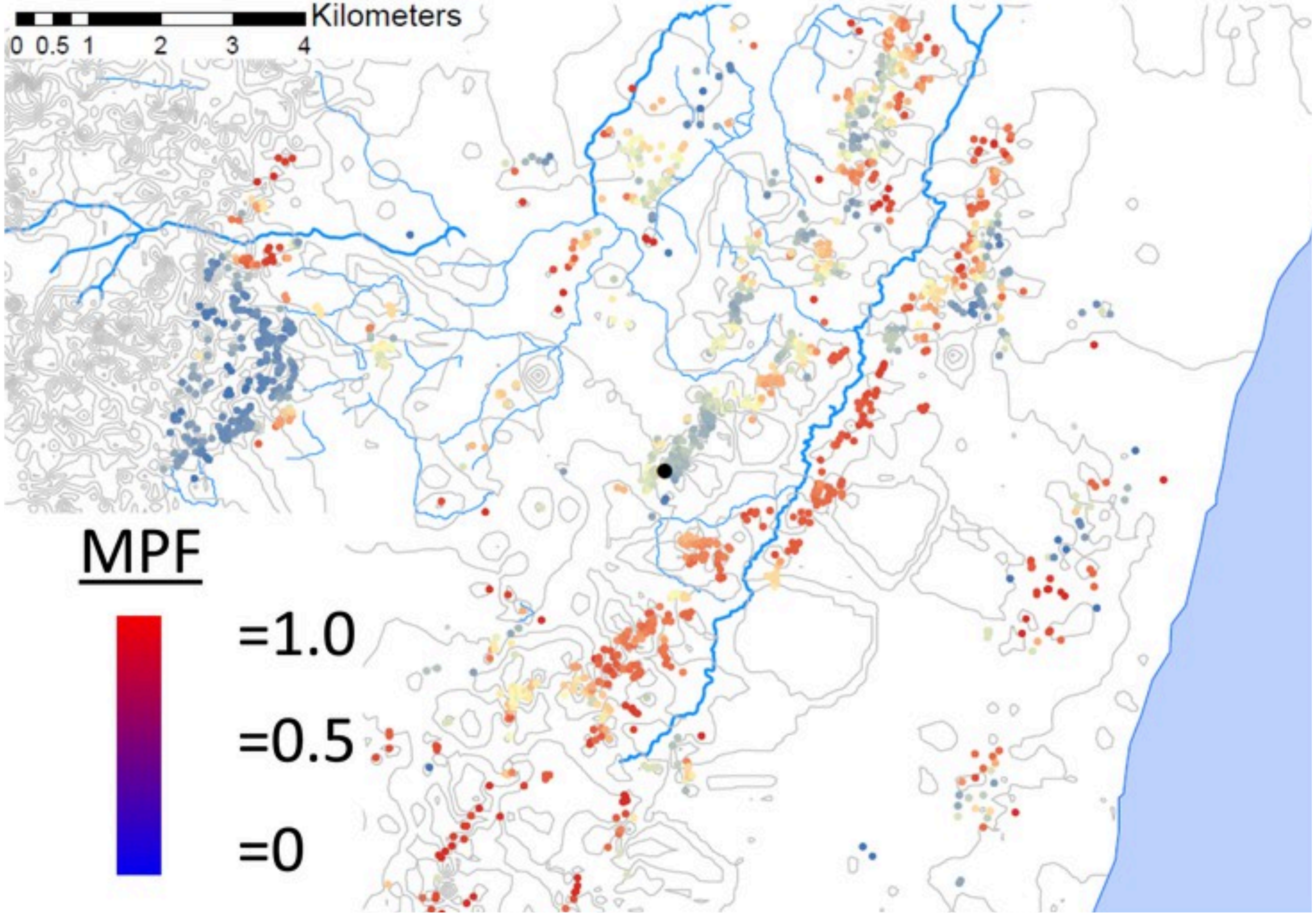
Lifetime Egg Dispersal, Population



MGSurvE: A framework to optimize trap placement for genetic surveillance of mosquito population

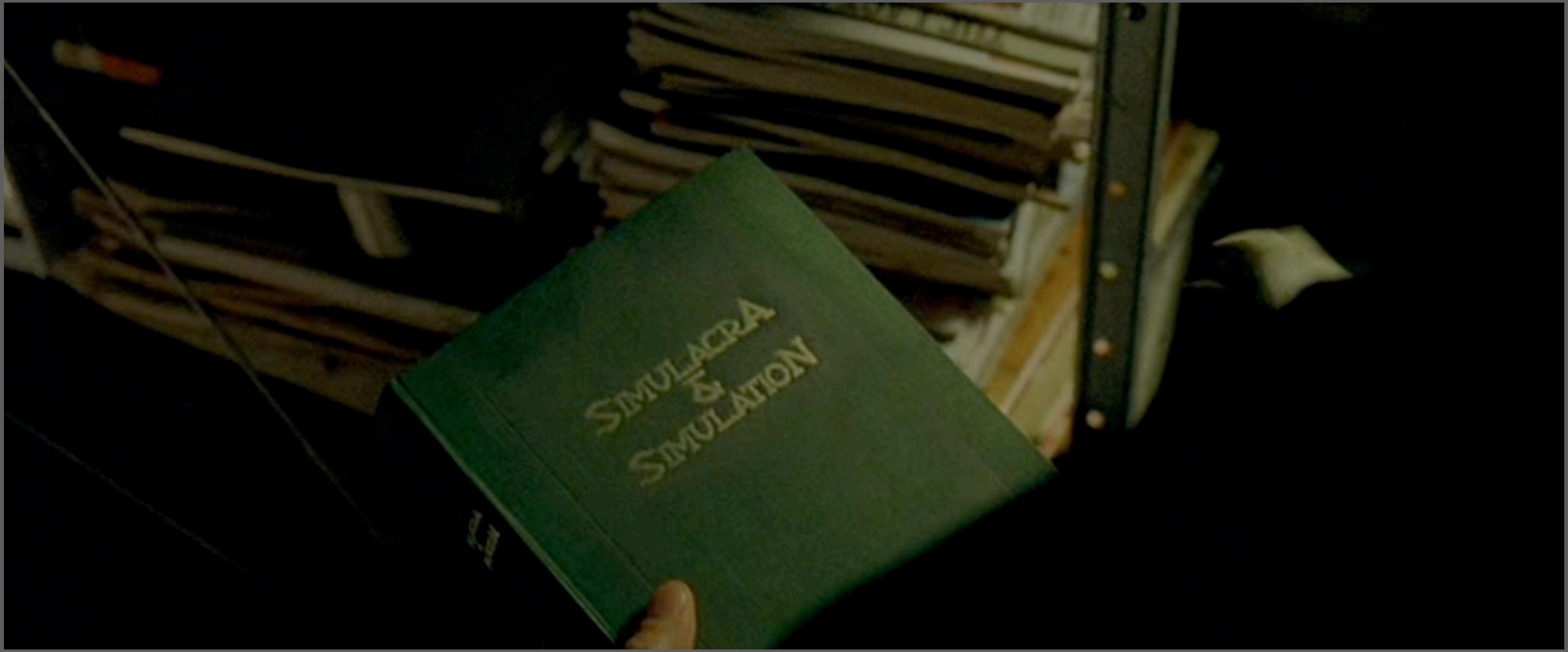
https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1012046

Malaria Positive Fraction (MPF): among all hospital visits from 2003-2011 in which febrile patients from each homestead tested positive for malaria



A micro-epidemiological analysis of febrile malaria in Coastal Kenya showing hotspots within hotspots

https://doi.org/10.7554/eLife.02130


SIMULACRA
&
SIMULATION

The Team

University of Washington: John M. Henry, Sean L. Wu, Dianna Hergott, Austin R. Carter, Daniel T Citron

Uganda: John Rek, Doreen Mbabazi Ssebuliba, Juliet Nakakawa Nsumba, Jaffer Okiring, Meddy Rutayisire, Thomas Eganyu, Jimmy Opigo, Paul Mbaka

Bioko Island Malaria Elimination Program: Guillermo Garcia, Carlos Guerra, David Galick

Download this talk:

https://faculty.washington.edu/smitdave/talks/DavidLSmith_SAFS_2025Jan31.pdf

smitdave@uw.edu

ACKNOWLEDGEMENTS

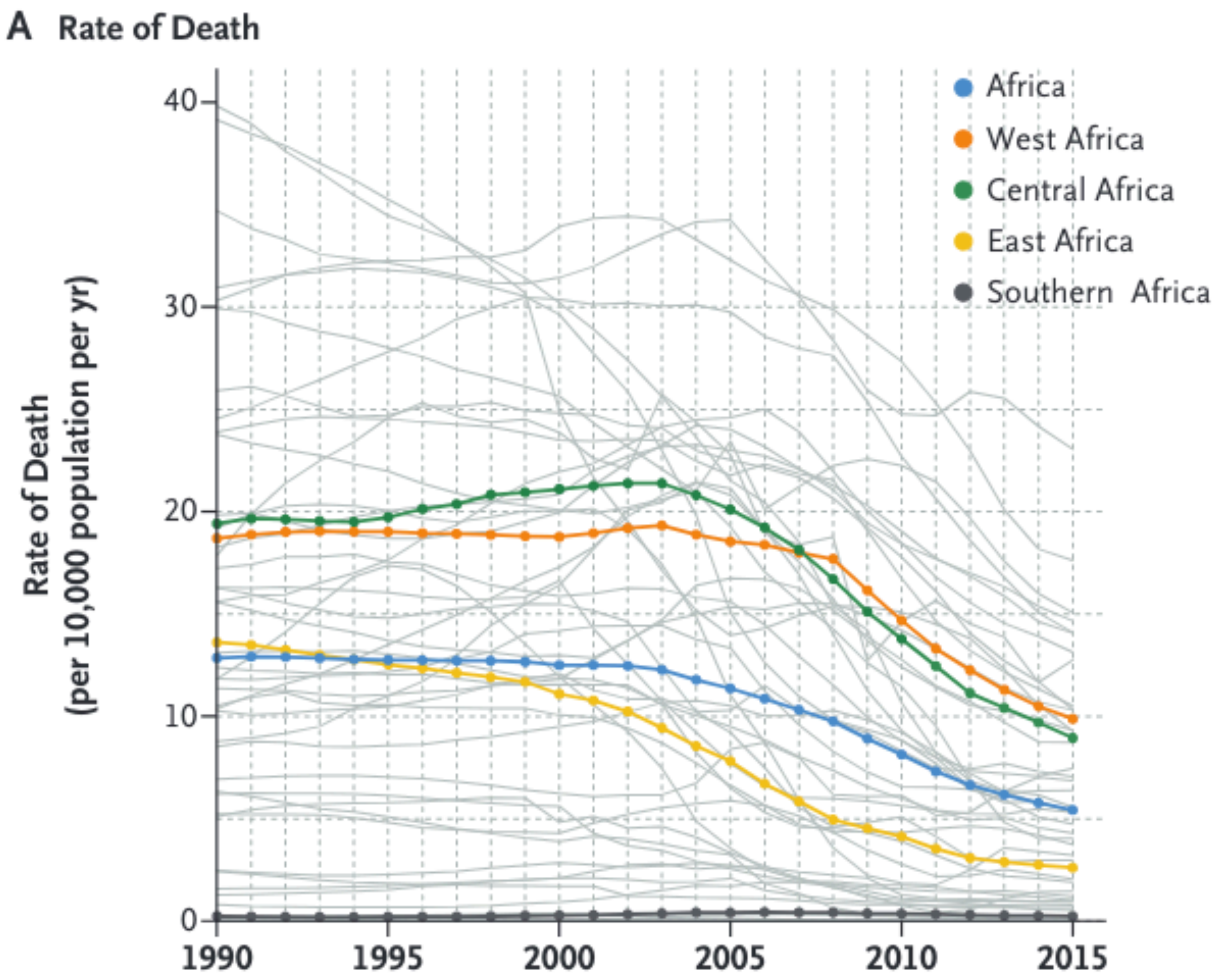
- The Uganda project was supported by a grant from the Bill and Melinda Gates Foundation, **Modeling for Adaptive Malaria Control** (INV 030600, PI = David L Smith, University of Washington).
- Adaptive Vector Control for Bioko Island is funded by grant **Spatial Targeting and Adaptive Vector Control for Residual Transmission and Malaria Elimination in Urban African Settings** (R01 AI163398, PI = David L Smith), from US National Institute of Allergies and Infectious Diseases (NIAID).
- Development of adaptive vector control was supported through a collaboration with the **Bioko Island Malaria Elimination Program**
- Development of adaptive malaria control e was supported through a collaboration with Uganda's **National Malaria Control Division** and **Department of Health Information** in the Uganda Ministry of Health
- Development of this software benefited from funding and collaboration with the NIAID grant **Program for Resistance, Immunology, Surveillance & Modeling of Malaria in Uganda** (PRISM) (2U19AI089674, PIs = Grant Dorsey, University of California San Francisco; and Moses Kamya, Infectious Diseases Research Collaboration), which was part of the **International Centers of Excellence in Malaria Research** (ICEMR) program.
- Funding to develop models of West Nile Virus to support Harris County Public Health was funded by the NSF as part of a project, Computing the Biome (PI = Janos Sztipanovits). The project was part of the Convergence Accelerator program of the National Science Foundation, Directorate for Technology, Innovation, and Partnerships (TIP) (NSF 2040688 and NSF 2040688, PI=Janos Sztipanovits, Vanderbilt University).
- We acknowledge the important formative role played by the mosquito working groups of **RAPIDD** (Research and Policy for Infectious Disease Dynamics), which was sponsored by the Fogarty International Center, NIH, and the Department of Homeland Security. The mosquito working groups were led by Professor Thomas Scott. RAPIDD was led by F. Ellis McKenzie.

Malaria Analytics

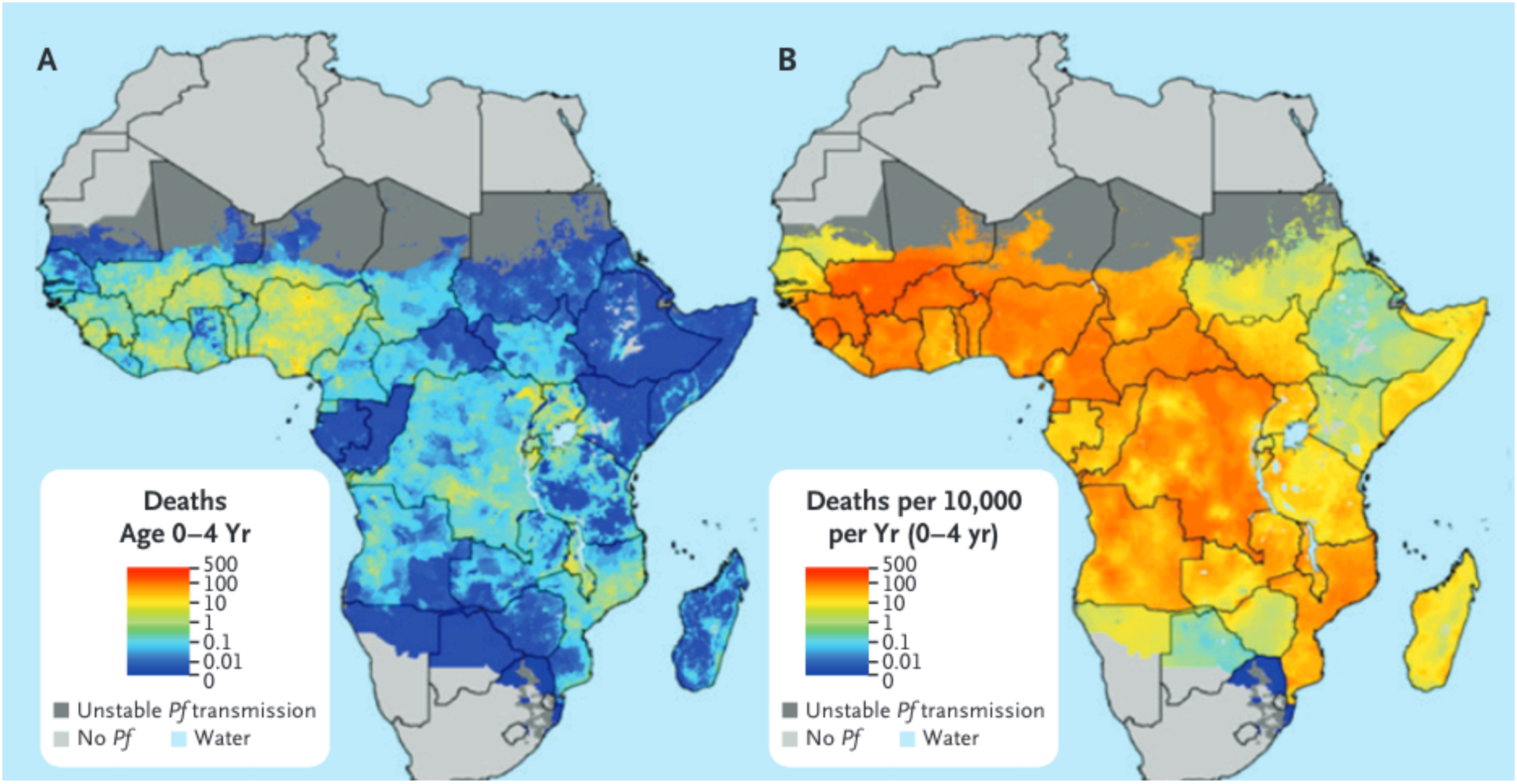
What makes a model / framework / analysis good for policy?

- **Timely** → *Nimble*
- **Responsive** → Fit for Purpose; Realistic
- **Accurate** → Models Observational Process; Fitted to Data
- **Useful** → Specific Advice; Output Thresholds, Burden, Avertable Burden, …
- **Accountable** → Replicable; Repeatable; Transparent
- **Thorough** → *Robust Analytics;* Ensemble Analyses
- **Adaptive** → Evolving; *Relevant Details*

Mapping *Plasmodium falciparum* Mortality in Africa between 1990 and 2015



~631,000 deaths in Africa, 2015

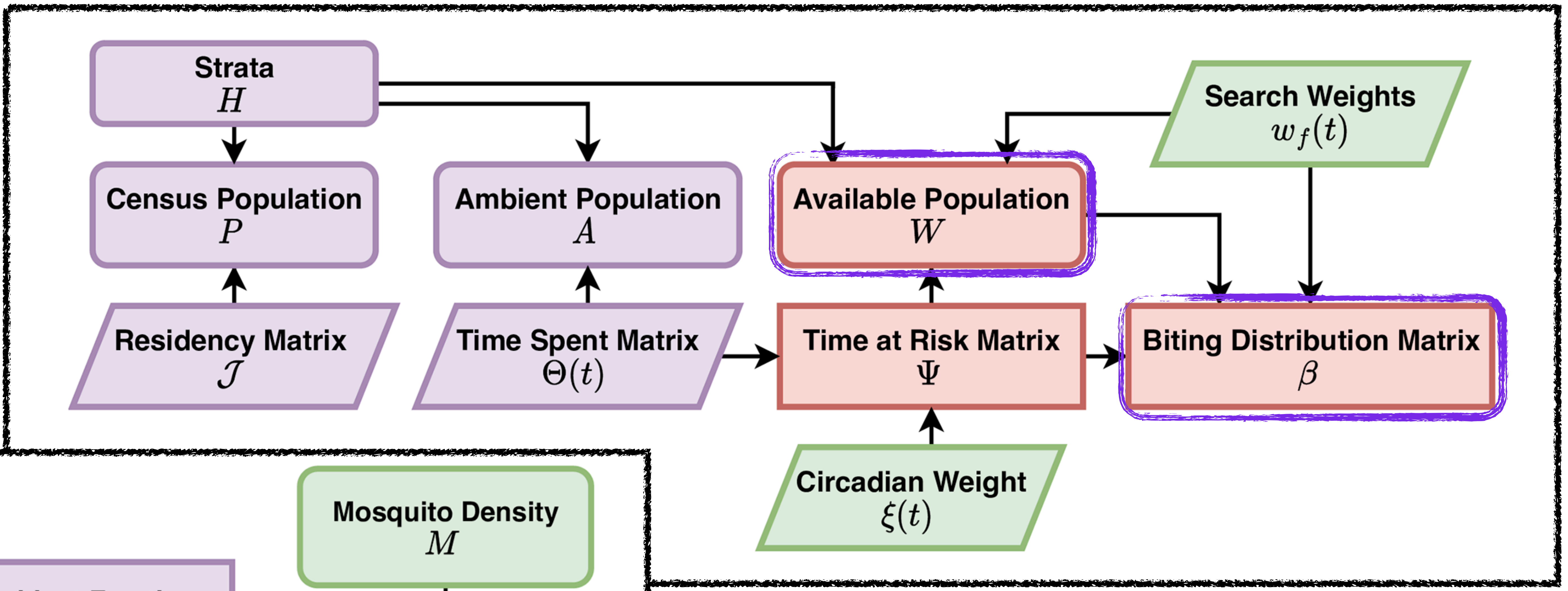


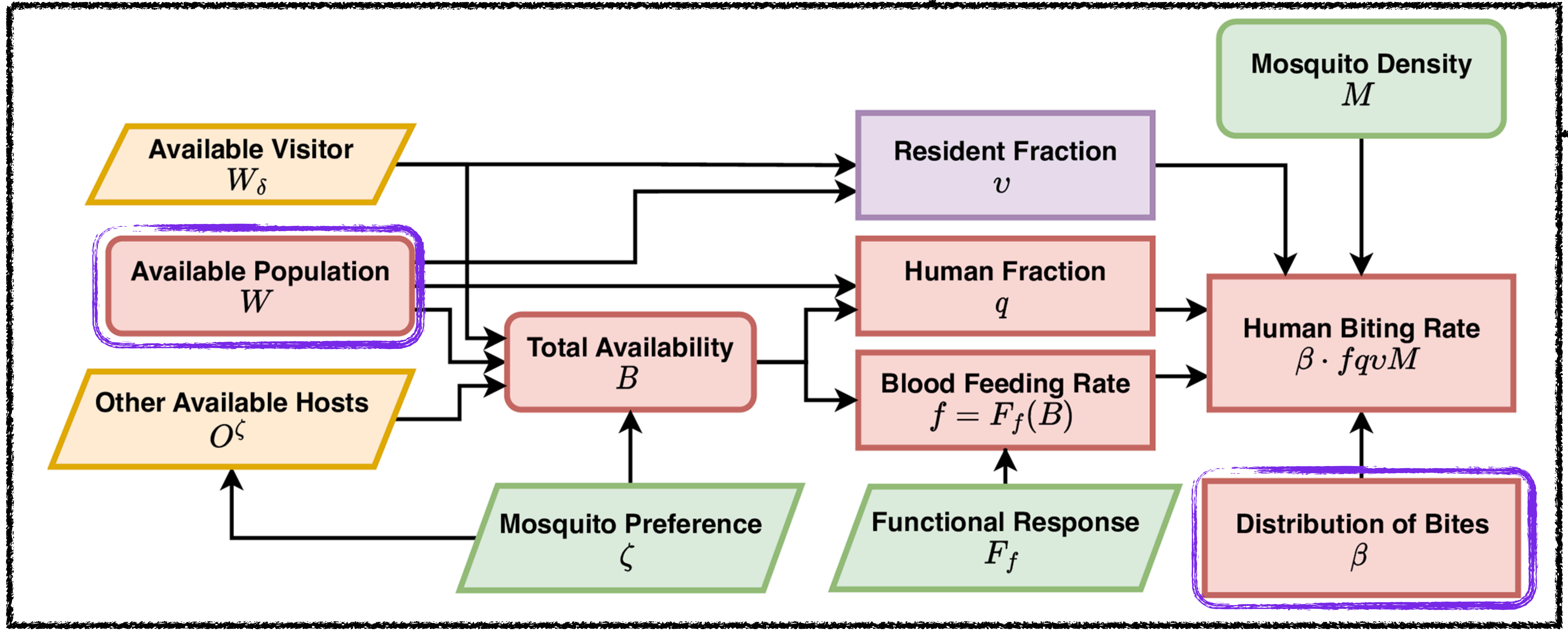
https://www.nejm.org/doi/full/10.1056/NEJMoa1606701

Blood Feeding & Transmission

Blood Feeding Rates and Habits. The Biting Distribution Matrix (β)

Humans Spend Time





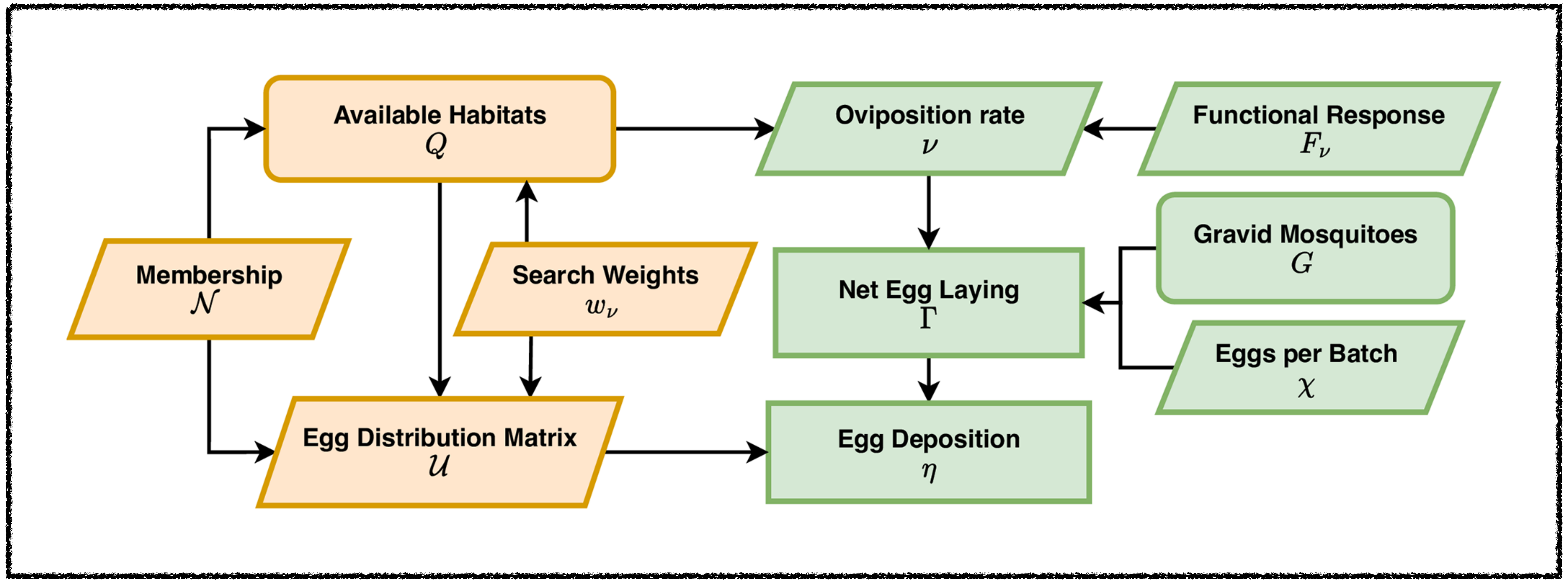
Mosquitoes Search for Blood Hosts

Spatial dynamics of malaria transmission

https://doi.org/10.1371/journal.pcbi.1010684

Egg Laying & Emergence

- **Aquatic habitats are located in patches (an arbitrary number)**
- **Eggs laid by adults in the patch are distributed among aquatic habitats in that patch**
- **Egg laying, blood feeding, and emigration can not occur if the resource is unavailable**

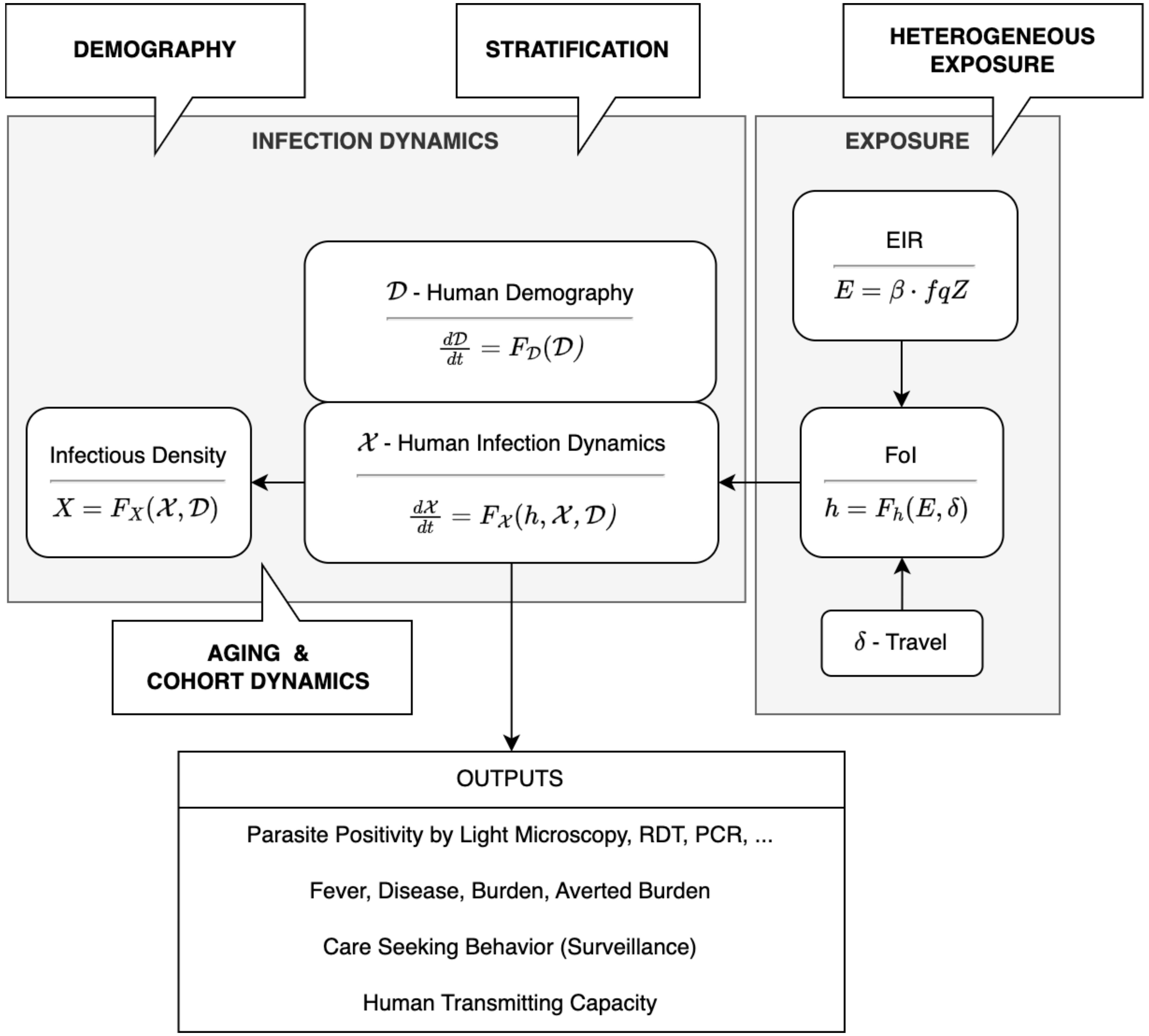


Spatial dynamics of malaria transmission
https://doi.org/10.1371/journal.pcbi.1010684

Malaria Epidemiology

The Robust Approach

- Exposure
- Dynamics of Infection & Immunity
- Human Demography
  - Births, Deaths, Migration
  - Aging / Cohort Dynamics
- Heterogeneity / Stratification
- **Outputs**
  - Research Metrics
  - Surveillance Metrics
  - Analysis

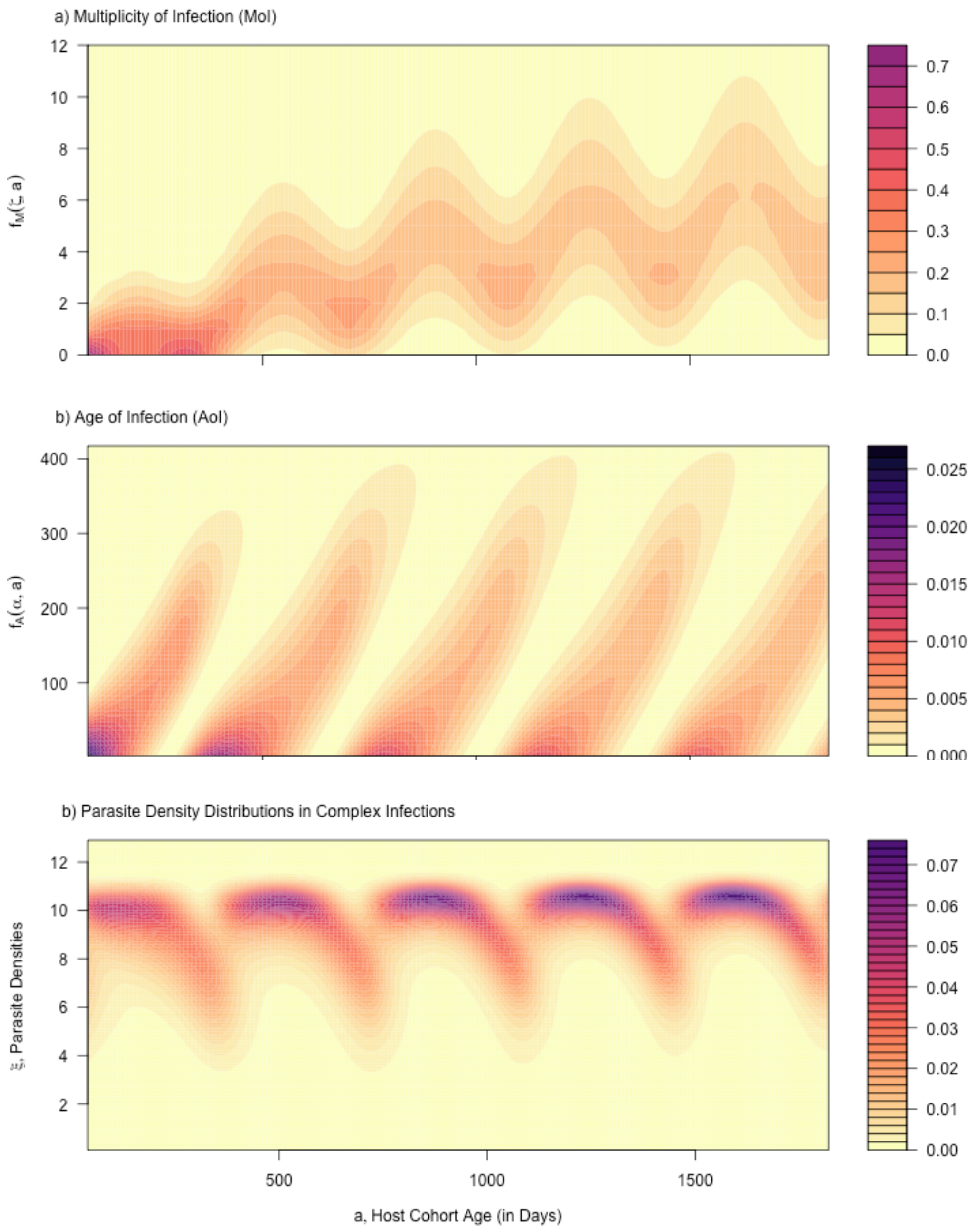


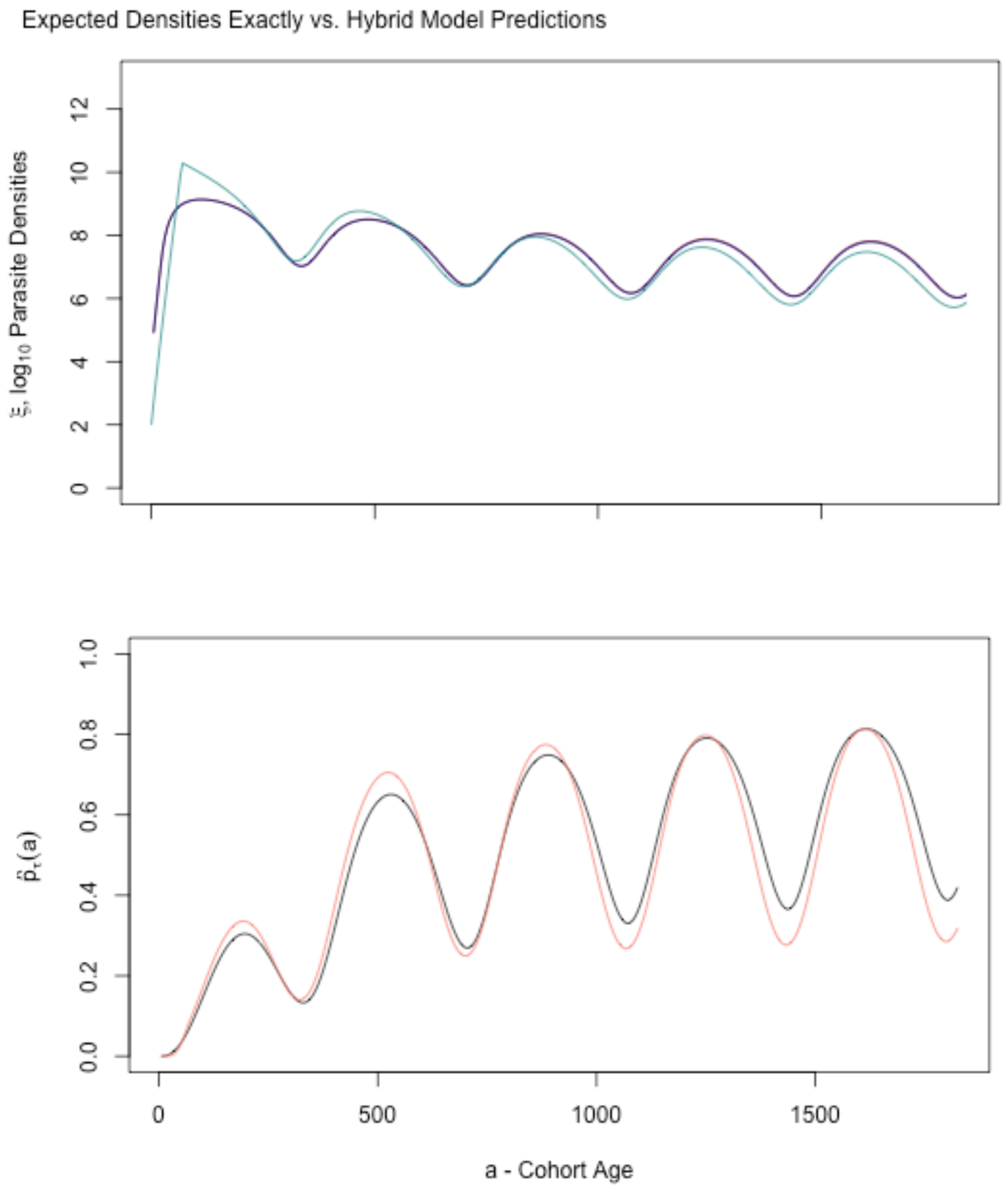
Malaria Epidemiology

Deep Dive: `ramp.falciparum`

$$E[P_\tau(a)] = \int_0^b \xi f_P(\xi; a, \tau | h) d\xi \approx F_\mu(x_\tau(a))$$
$$E[B_\tau(a)] = \int_0^b \xi f_B(\xi; a, \tau | h) d\xi \approx F_\mu(y_\tau(a))$$

$$\frac{dm}{da} = h - rm$$
$$\frac{dx}{da} = 1 - x\frac{h}{m}$$
$$\frac{dy}{da} = 1 - y\frac{h}{p} + \phi(r, m)x$$





PhD Thesis:

John M. Henry

GitHub R Package

`ramp.falciparum`

https://dd-harp.github.io/ramp.falciparum/

Where are the mosquitoes?

Science *vs.* Policy

Robust Analytics for Malaria Policy

- ***Spatial heterogeneity in mosquito densities & blood feeding***
  - *Concepts* — What is a malaria population?
  - *Heterogeneous Exposure* — Existing models are *way* too homogeneous
  - *Sampling Methods* are not up to the task of measuring spatial heterogeneity
- ***Malaria Epidemiology***
  - The concept of *disease* is far more complex and difficult than we have considered using existing simple models
  - The effects of waxing and waning immunity are poorly documented in data

Scaling Complexity for Malaria Analytics

Mathematics / Scientific Research / Analytics

- **Mathematics** → Formulate new classes of dynamical systems. Critically evaluate equations. Develop new methods or algorithms for computation or analysis. Qualitative analysis. Prove conjectures. Verify model or computational methods. **What can we understand about the dynamical behavior of the equations?**

- **Scientific Research** → Build models to understand malaria or address focused research questions. Prefer simple, analytic models. Analyze models to understand something about malaria. Estimate parameters, measure transmission. Fit models to aggregated data. Model selection & parsimony. Make general conclusions about *how things work* or *what we know.* Identify critical knowledge gaps. How accurate is the model? **What does the model teach us about malaria?**

- **Analytics** → Build models to address policy questions. Fit models to data describing malaria *in situ.* Make recommendations about *what to do now* or *strategic plans* affecting malaria. Identify critical data gaps affecting malaria policy. Is the policy advice robust to uncertainty? **What does the analysis suggest is the best malaria policy?**

Robust Analytics for Malaria Policy

Characterize, Quantify, and Propagate Uncertainty

- ***Ontological*** — *lack of knowledge about the states of a system, including from unconscious use of inappropriate methodology or belief systems*
    - How do we represent *disease* (*including* mild, moderate, & severe) across the spectrum of intensity?
    - How are malaria *and* anemia related?
- ***Epistemic*** — *a lack of knowledge about a system or phenomenon*
    - How do malaria transmission systems work? How does malaria transmission work *here*?
    - How frequently are people taking drugs? What fraction adhere to proper drug regimens?
    - Where / when are the mosquitoes blood feeding?
    - What factors affect seasonality, inter-annual variability in transmission?
    - What factors affect the prevalence of malaria by age / sex?
- ***Aleatoric*** — *due to the inherent randomness of a system*
    - How much does process uncertainty (*i.e.* from stochasticity) is there in malaria prevalence?
    - How will weather conditions and mosquito ecology change malaria in the future?