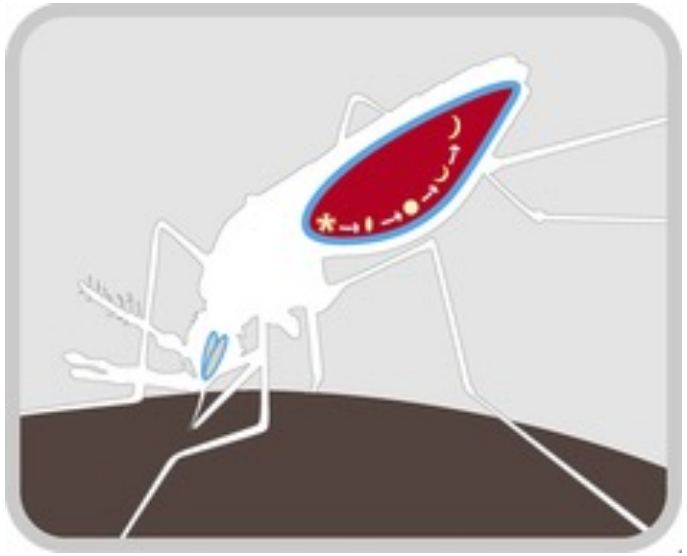
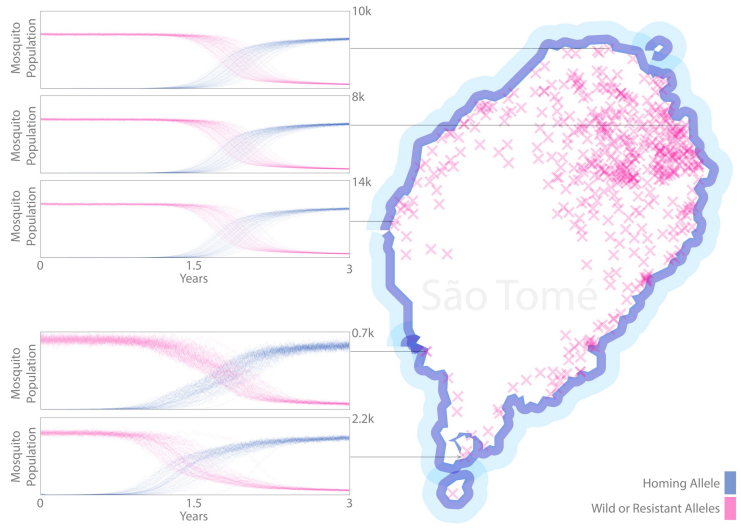
Modeling priorities as gene drive mosquito projects transition from lab to field

John M. Marshall, Héctor M. Sánchez C., Ace R. North





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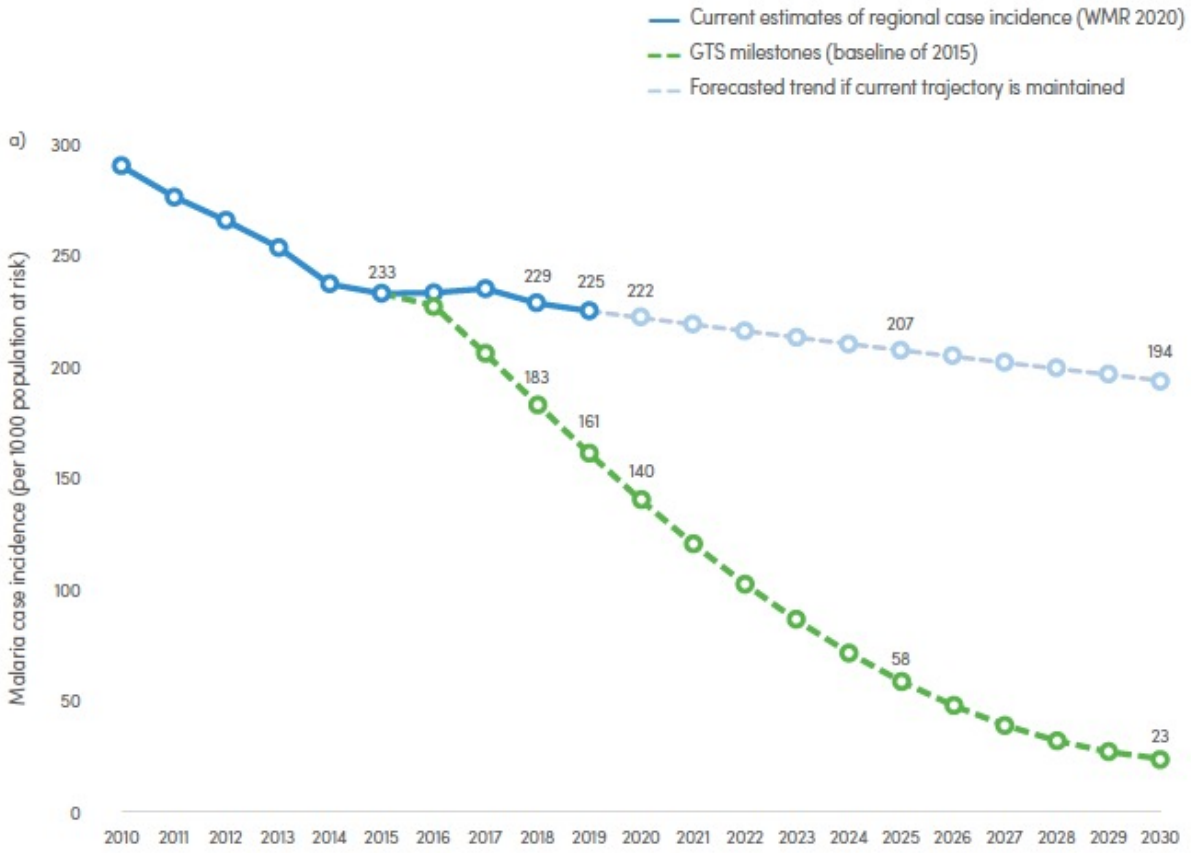
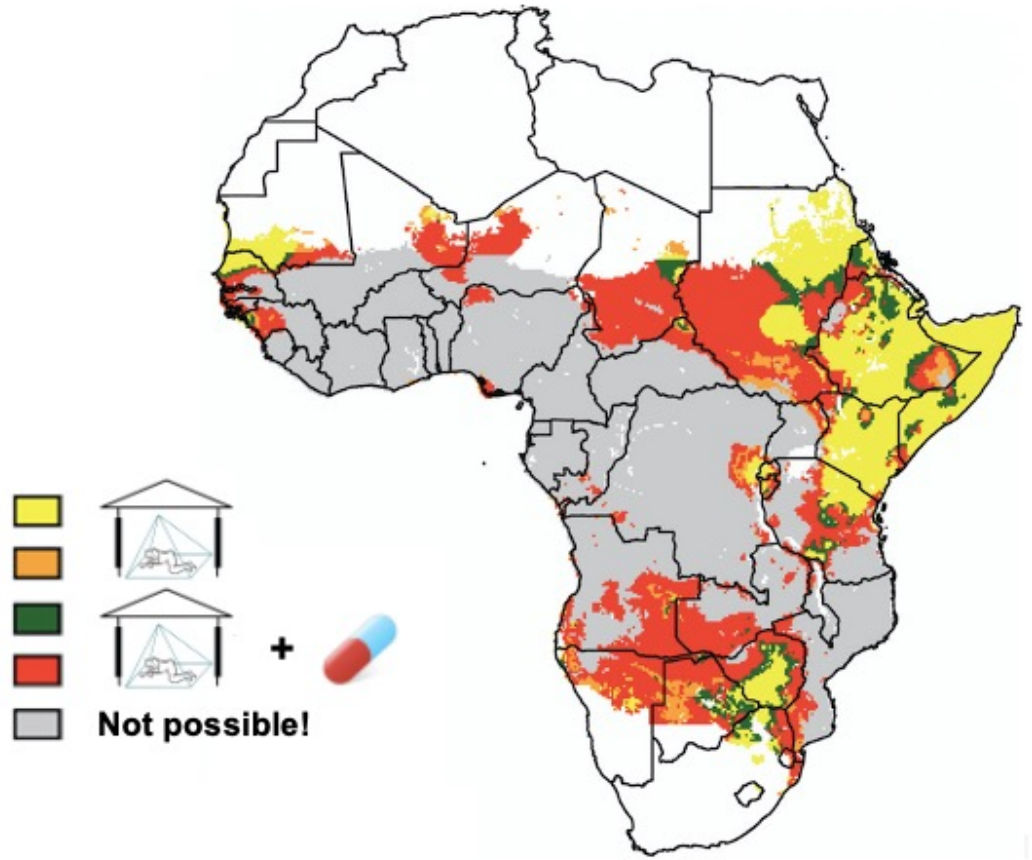
Malaria burden stagnating, elimination difficult



GTS: *Global technical strategy for malaria 2016–2030*; WHO: World Health Organization; WMR: world malaria report.



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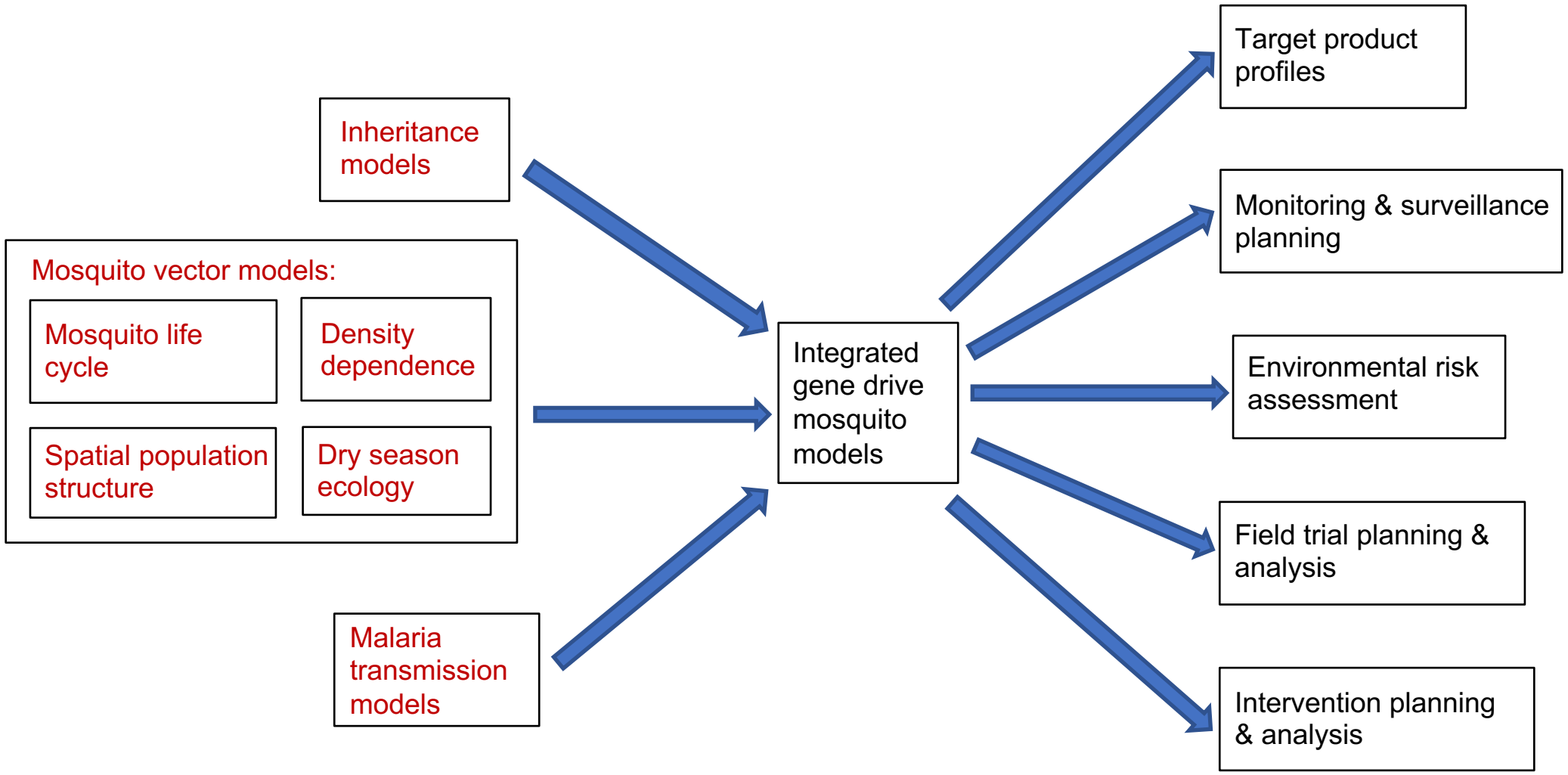
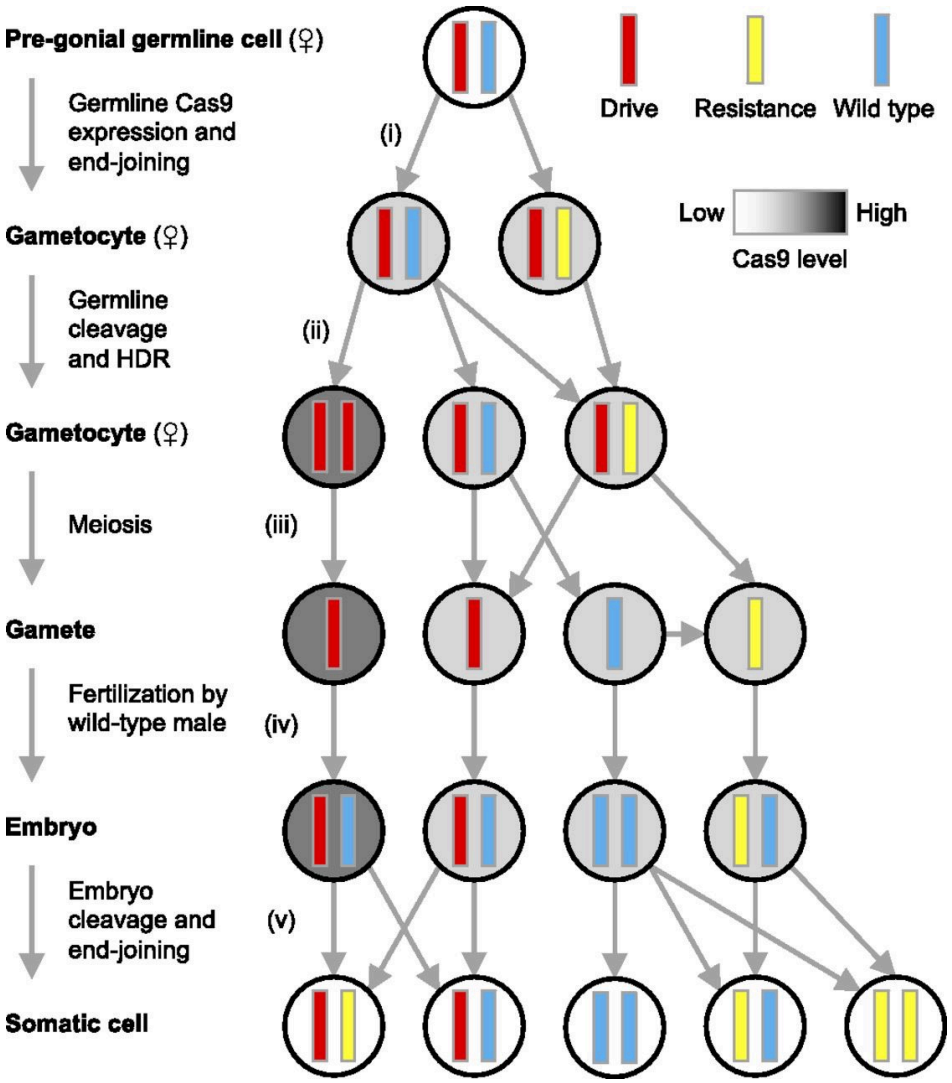
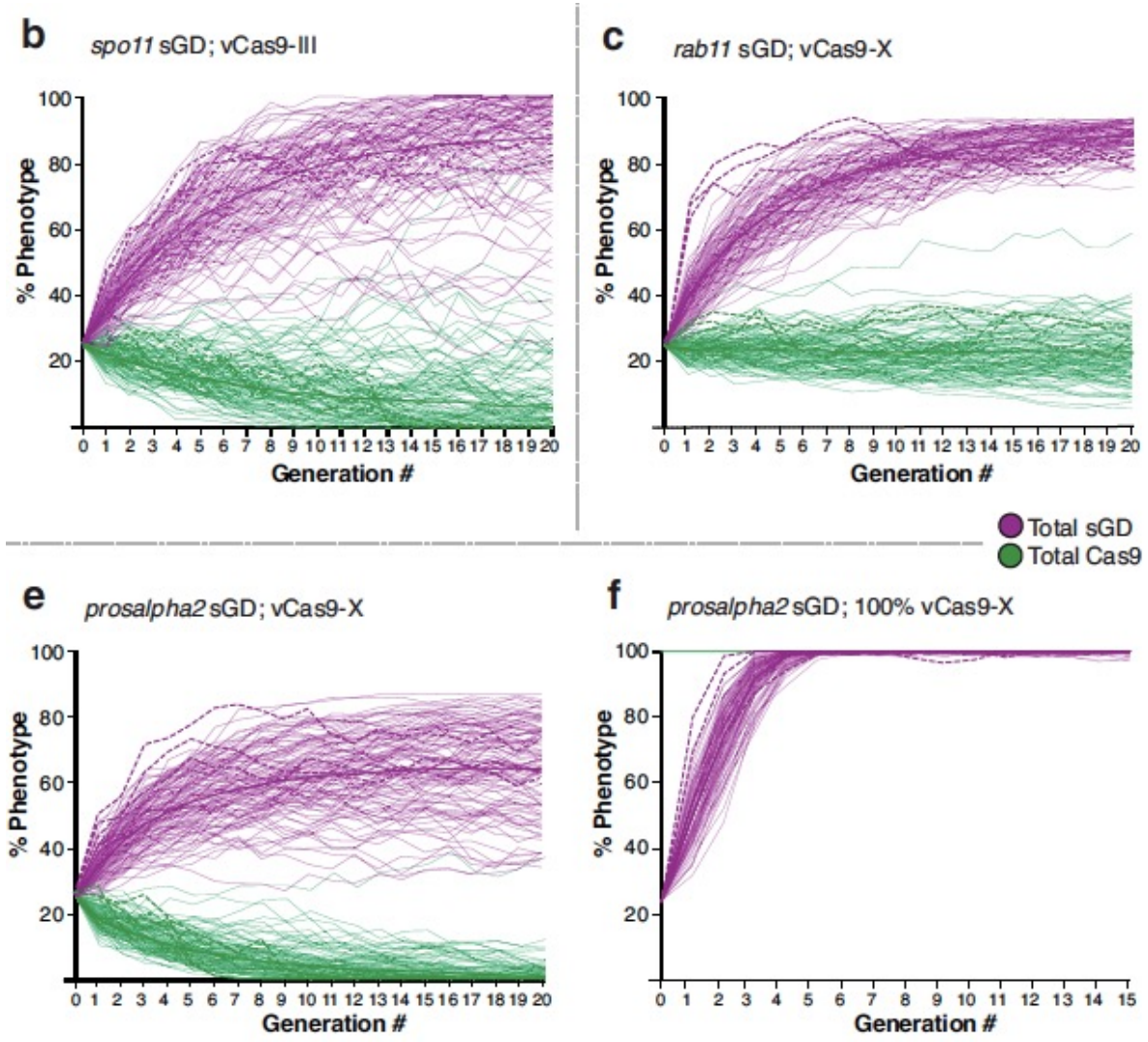
From lab to field: Model building priorities



- Marshall JM, North AR (in press) Gene Drives and the Malaria Eradication Agenda

Understanding resistance alleles & Cas9 dynamics





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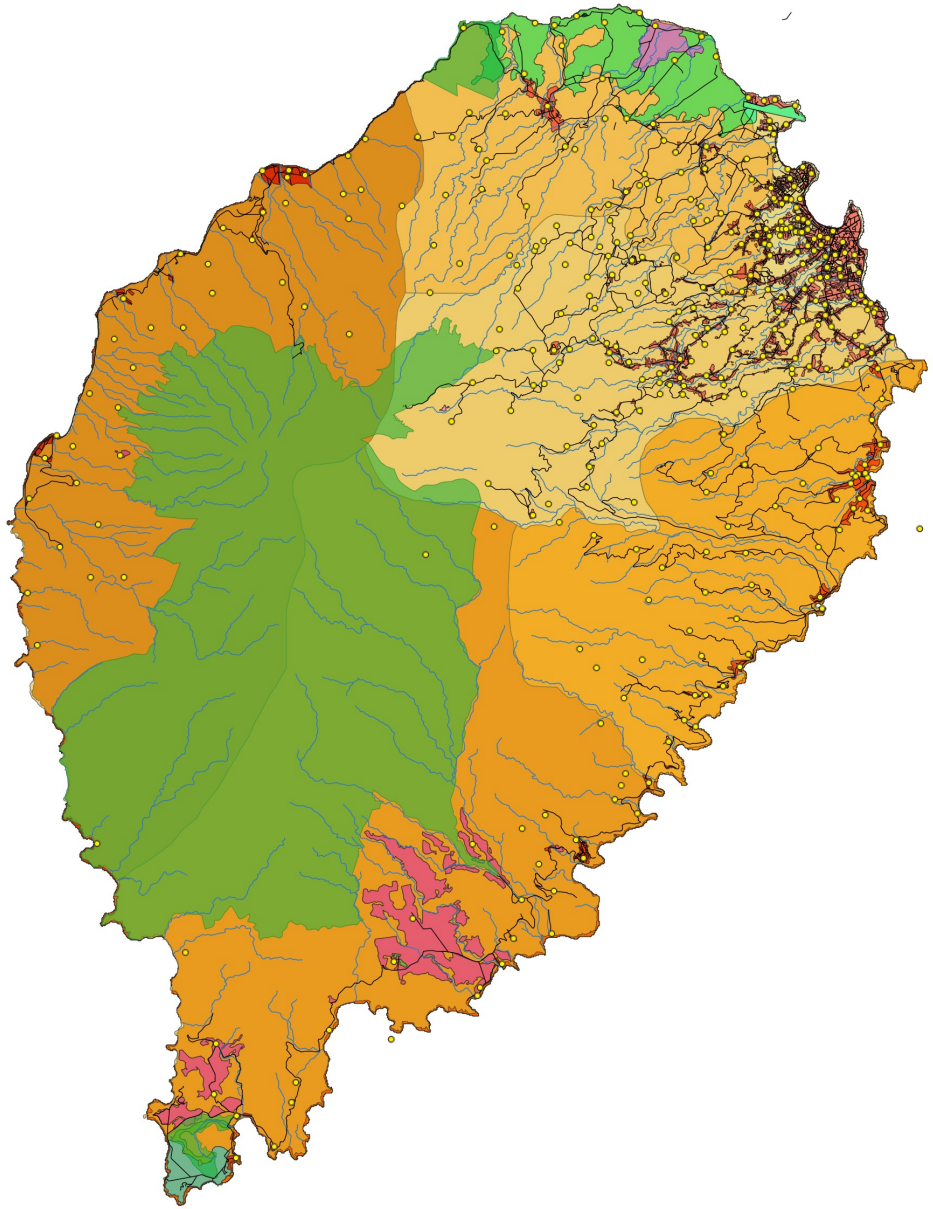
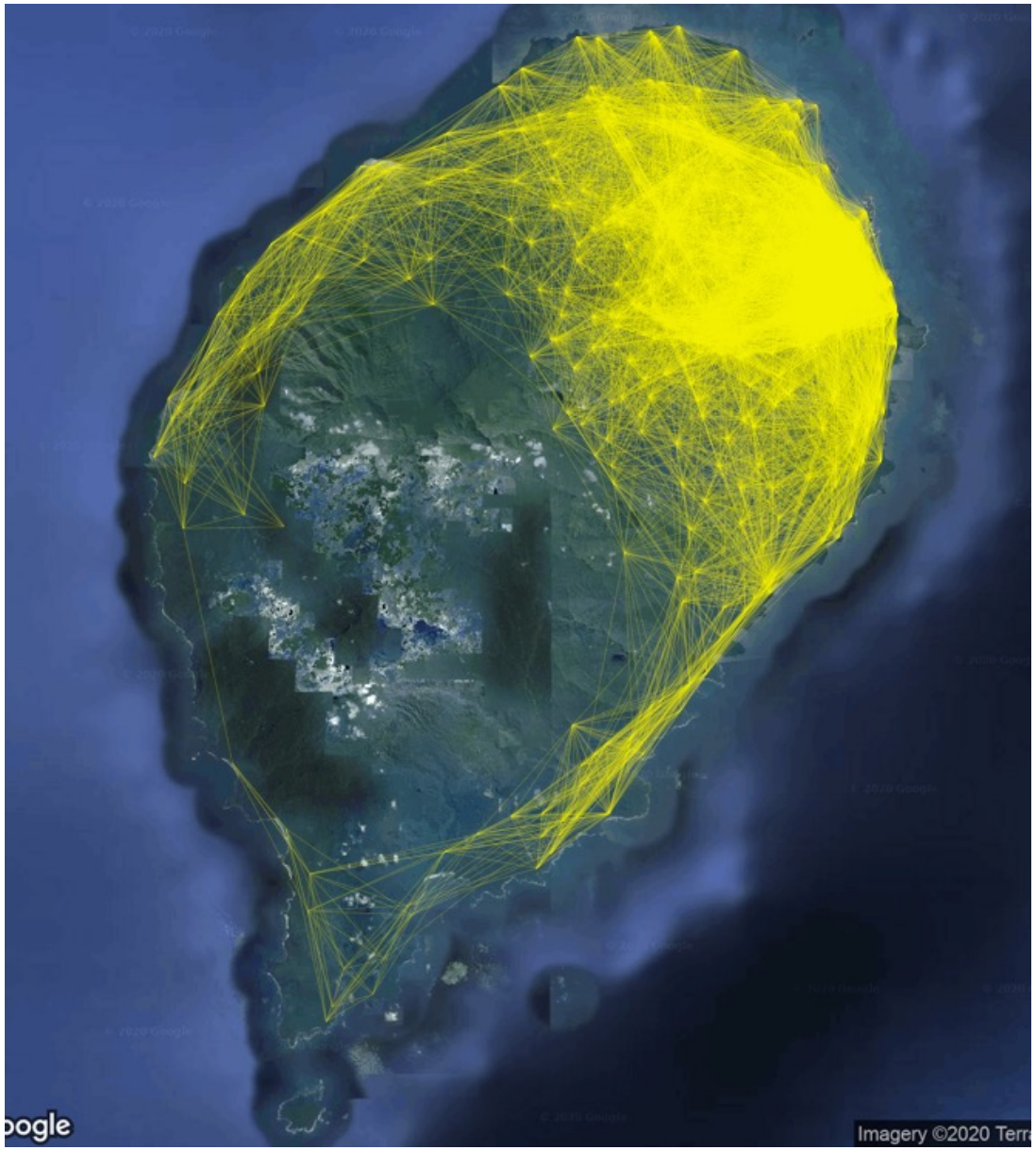
Spatial population structure

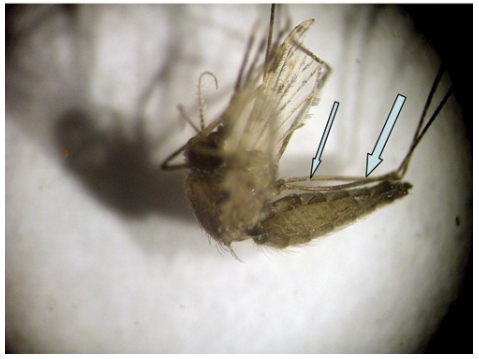




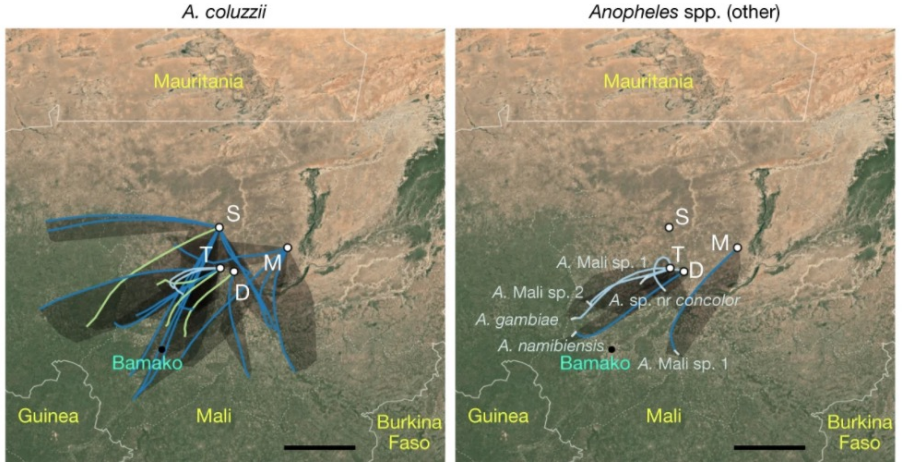
Spatial population structure

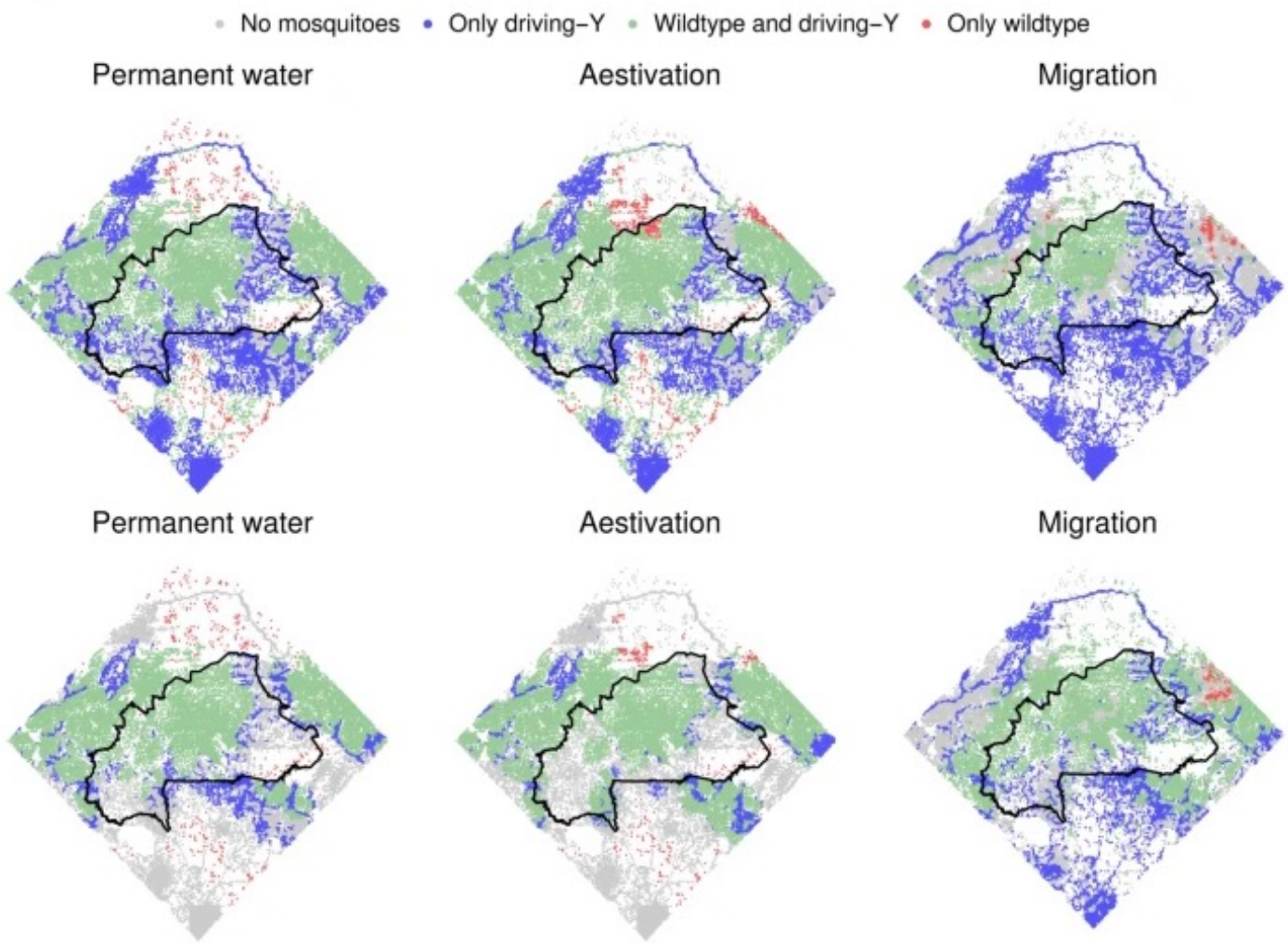
Dry season ecology

Aestivating female caught ~7 months after being marked:



Trajectories of flights for *Anopheles* capture events:





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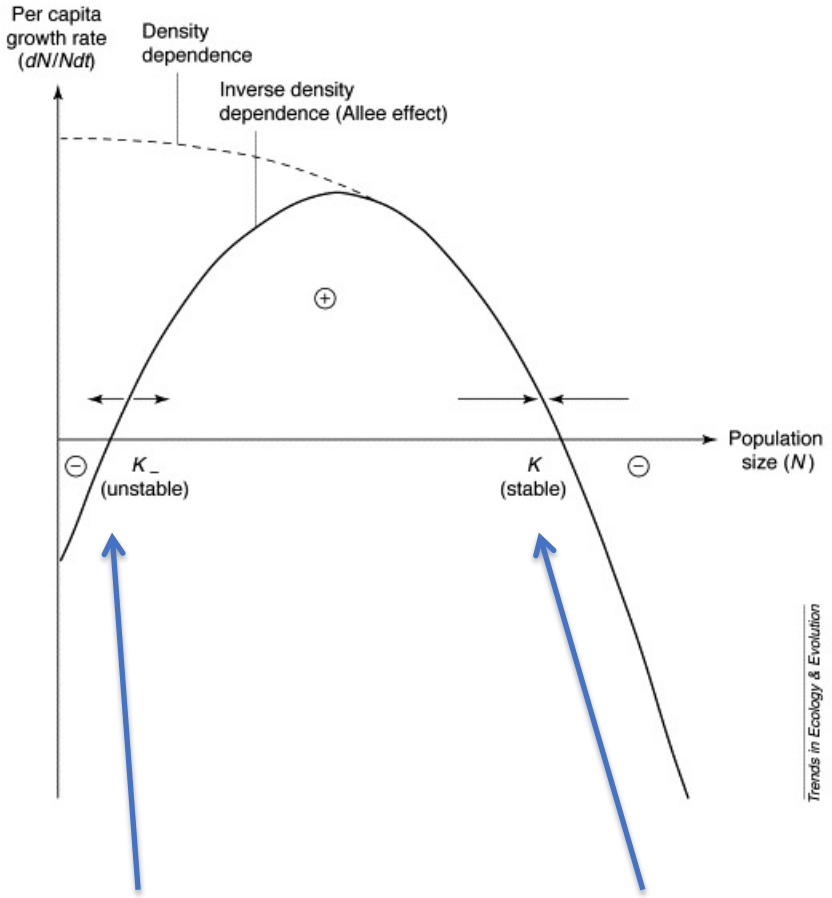
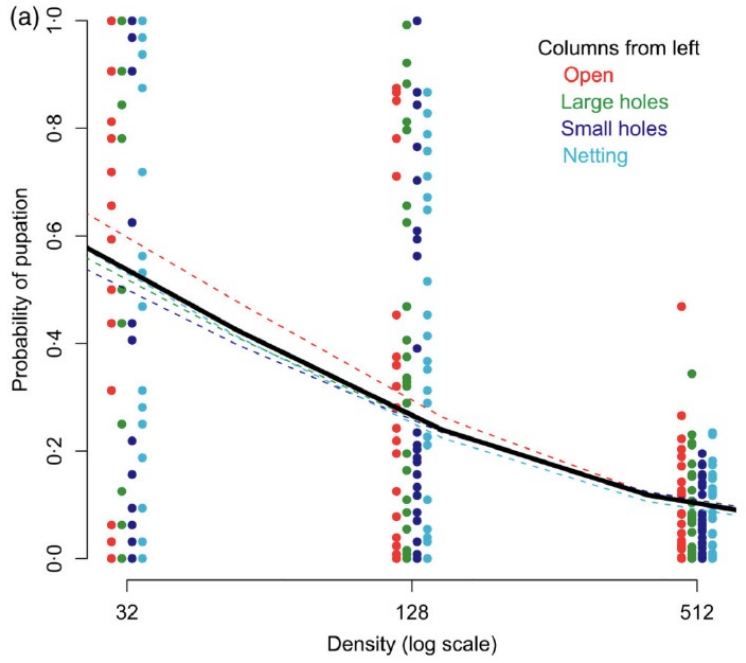
Density dependence

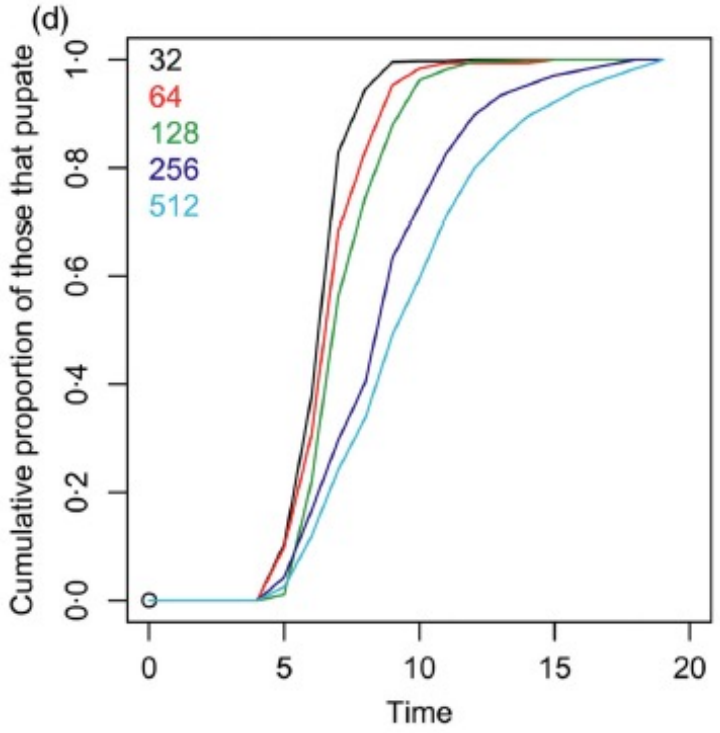


More difficult to form swarms & find mates at low densities

Crowding of larvae leads to increased competition for space & resources

Higher larval density leads to less pupation & longer time to pupation:





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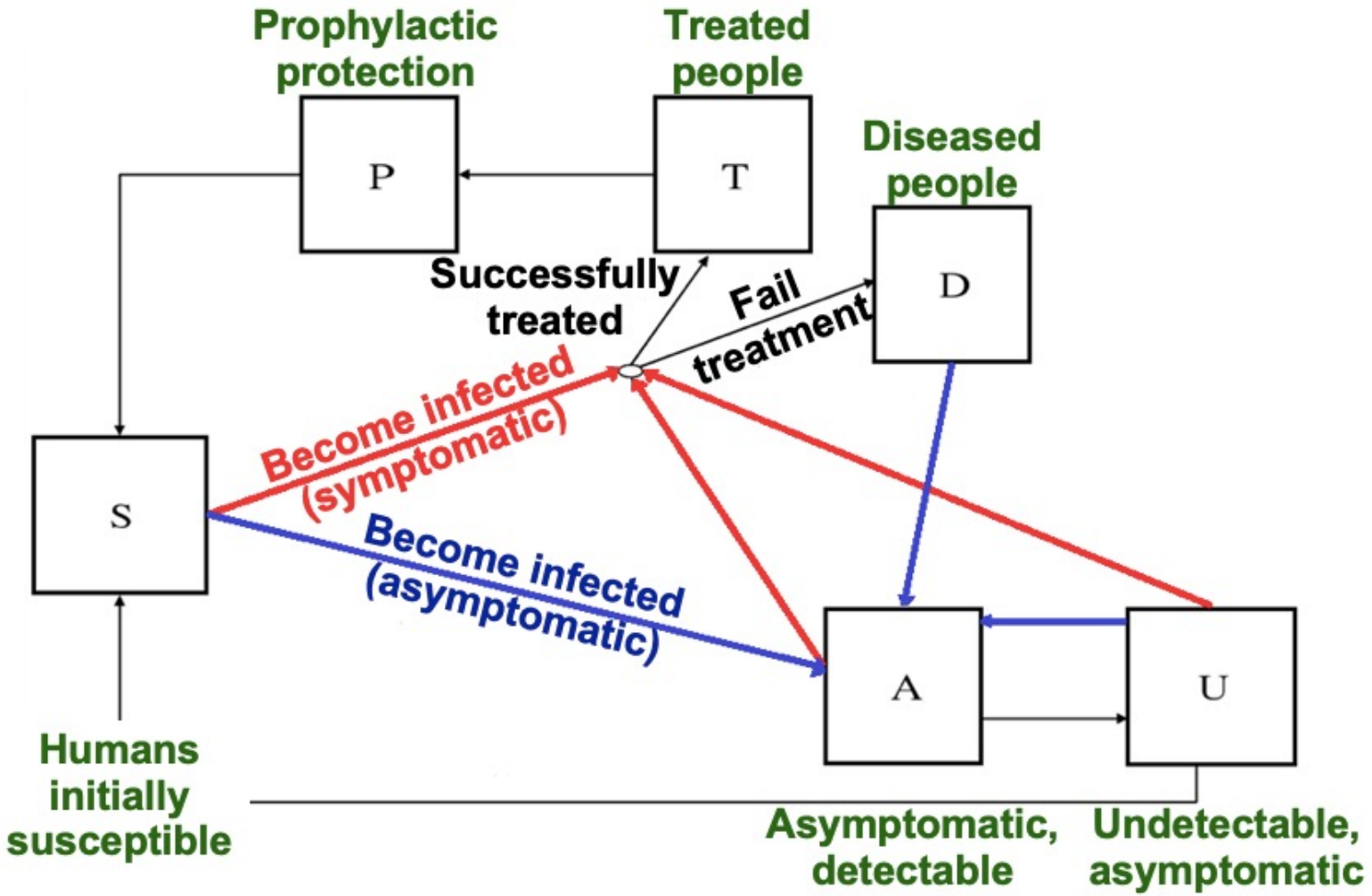
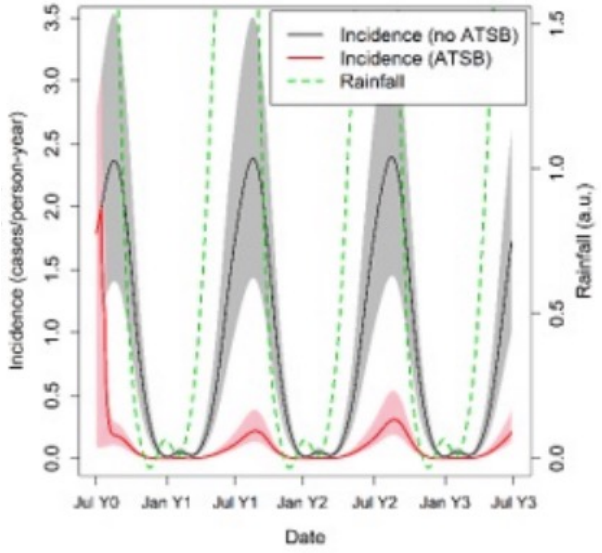
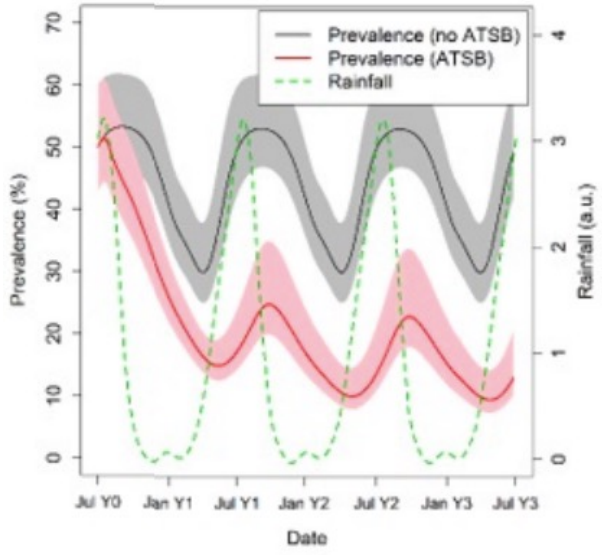
Malaria transmission models







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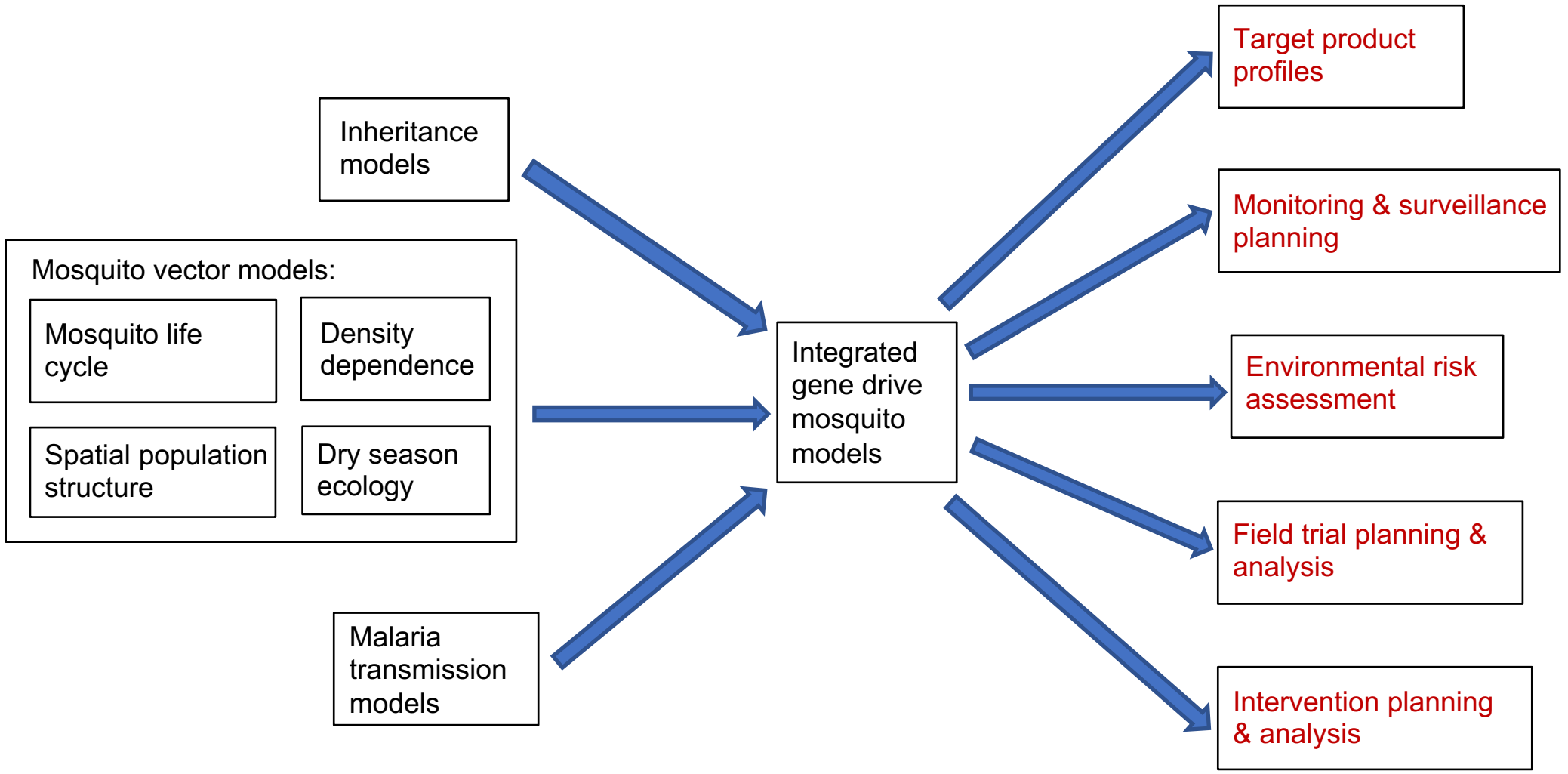
From lab to field: Model application priorities



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Target product profiles

TABLE 1. PROPOSED CRITERIA FOR PREFERRED PRODUCT CHARACTERISTICS OF GENE DRIVE-MODIFIED MOSQUITOES

1. Indication—target vector and parasite species
2. Epidemiological efficacy goal—reduction in clinical incidence of malaria
3. Entomological efficacy goal—reduction in vectorial capacity commensurate with epidemiological protection goal
4. Duration of protection—time over which the epidemiological efficacy impact will be evident
5. Time to impact—time required for the product to achieve epidemiological and entomological goals over a specified area
6. Safety for human health and the environment

TABLE 2. PROPOSED EFFICACY PARAMETERS FOR TARGET PRODUCT PROFILES OF GENE DRIVE-MODIFIED MOSQUITOES

1. Homing rate—predictor of rate of spread and time to impact
   a. Deviation from Mendelian expectation of inheritance in cages
2. Life history and reproductive success—predictor of rate of spread and time to impact
   a. Adult longevity
   b. Adult biting rate
   c. Mating efficiency
   d. Egg clutch size and hatching rate
   e. Sex ratio of progeny
   f. Development and mortality rate at different life stages
3. Construct functionality—predictor of entomological and epidemiological efficacy
   a. Population suppression—population decline in cages
   b. Population replacement—reduction in carriage of the target parasite species
4. Functional resistance—predictor of duration of protection
   a. Population suppression and replacement—functional resistance to the drive
   b. Population replacement—parasite resistance to the effector(s)

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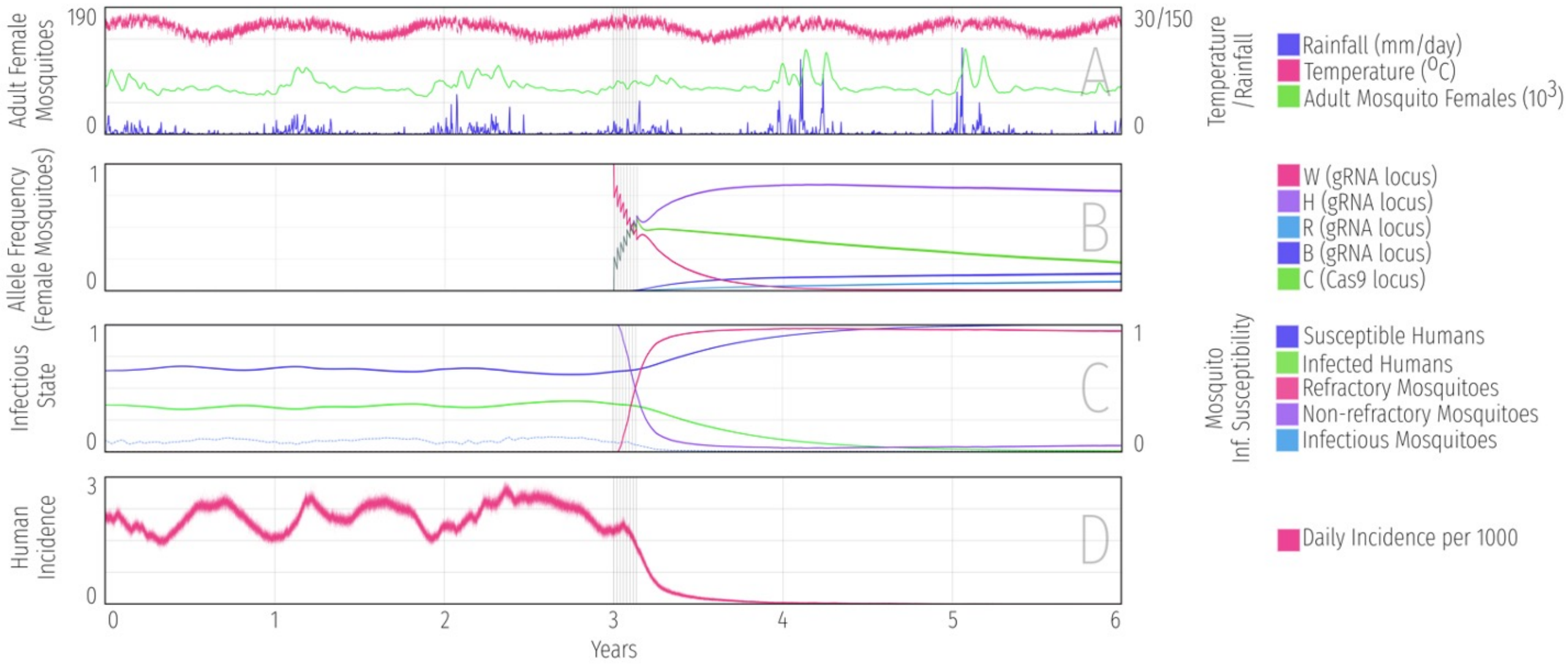
Target product profile:



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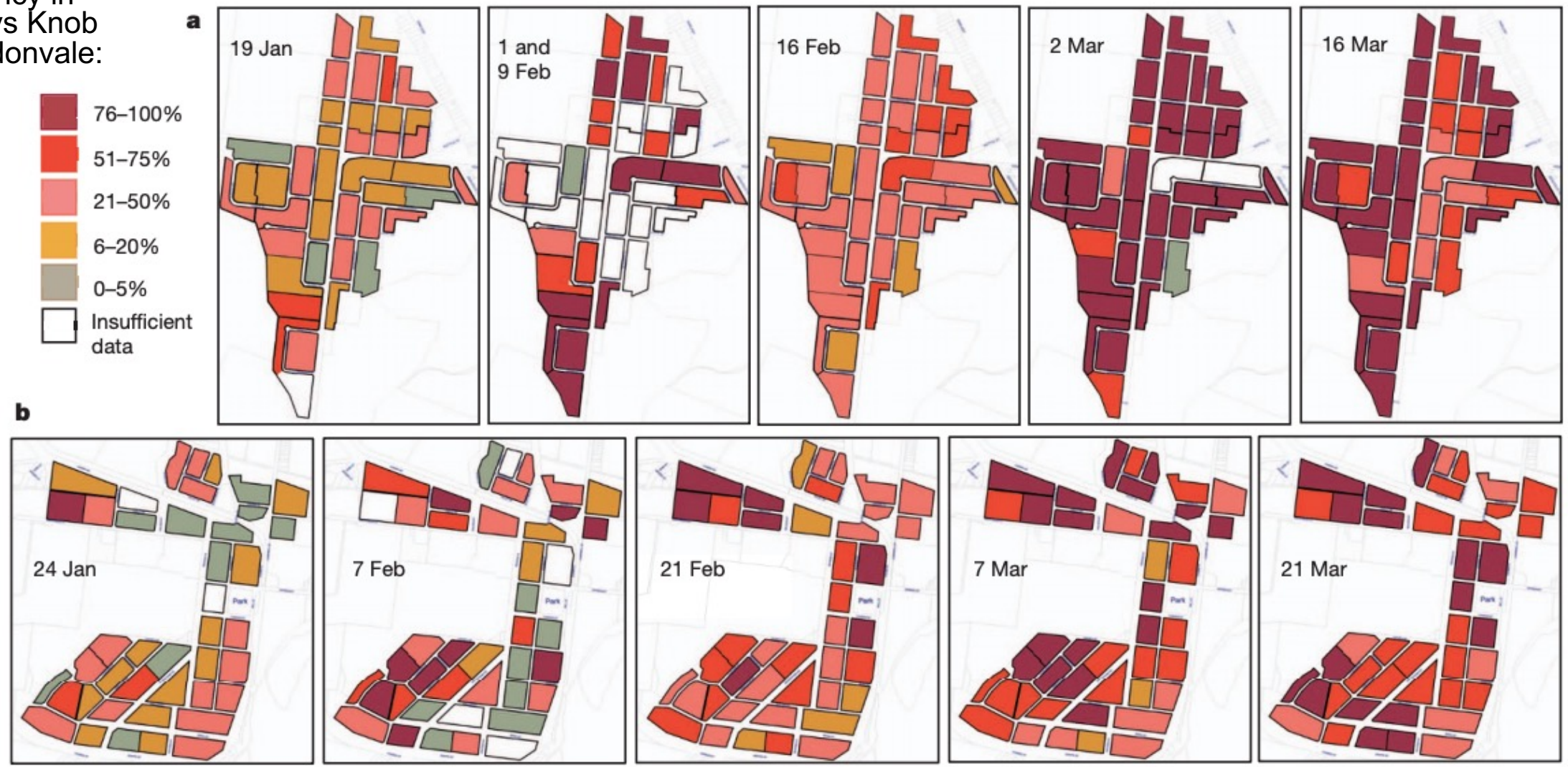
Monitoring needs: Heterogeneity in spread

Wolbachia frequency in Yorkeys Knob & Gordonvale:



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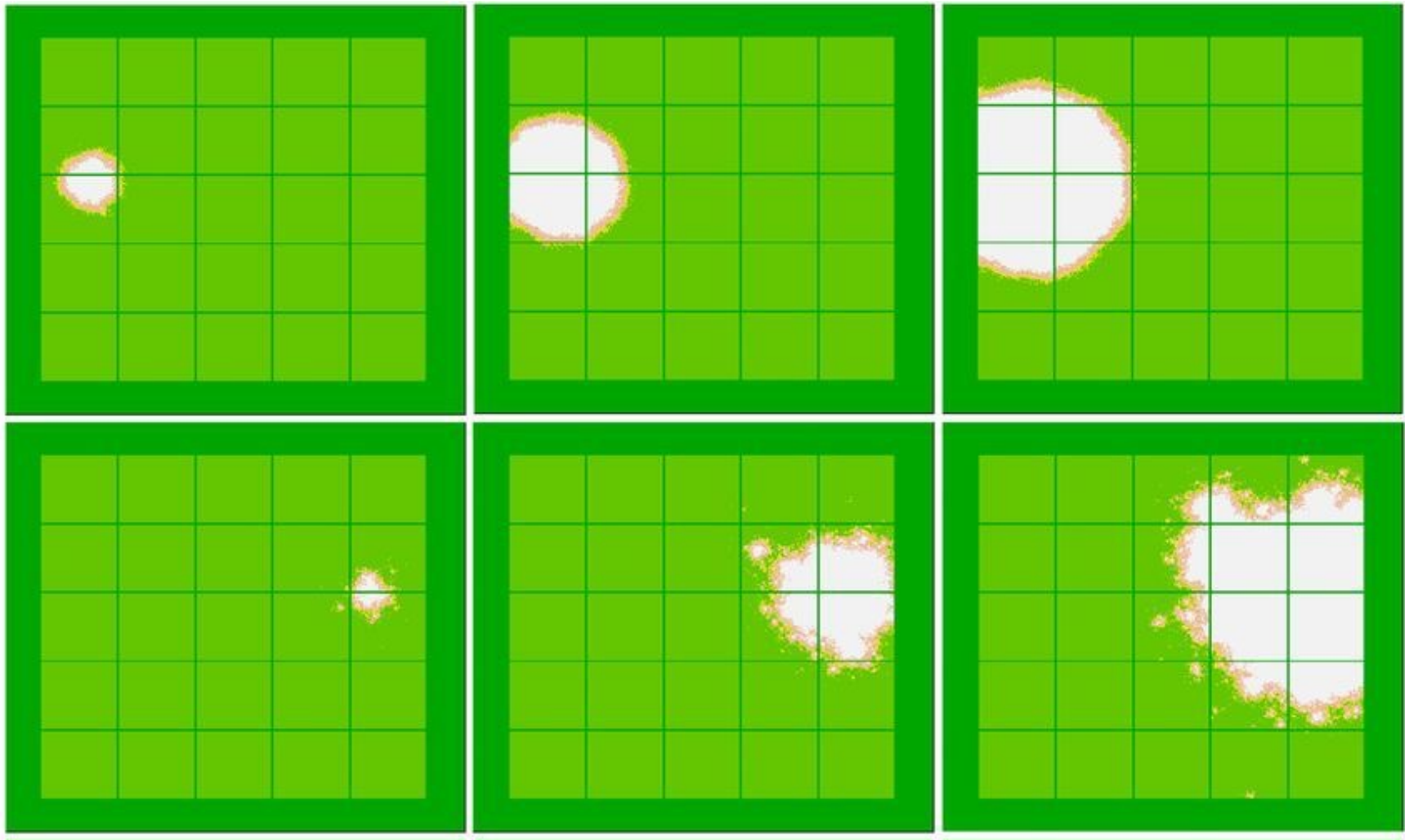
Surveillance needs: Detecting resistance alleles / unintended spread



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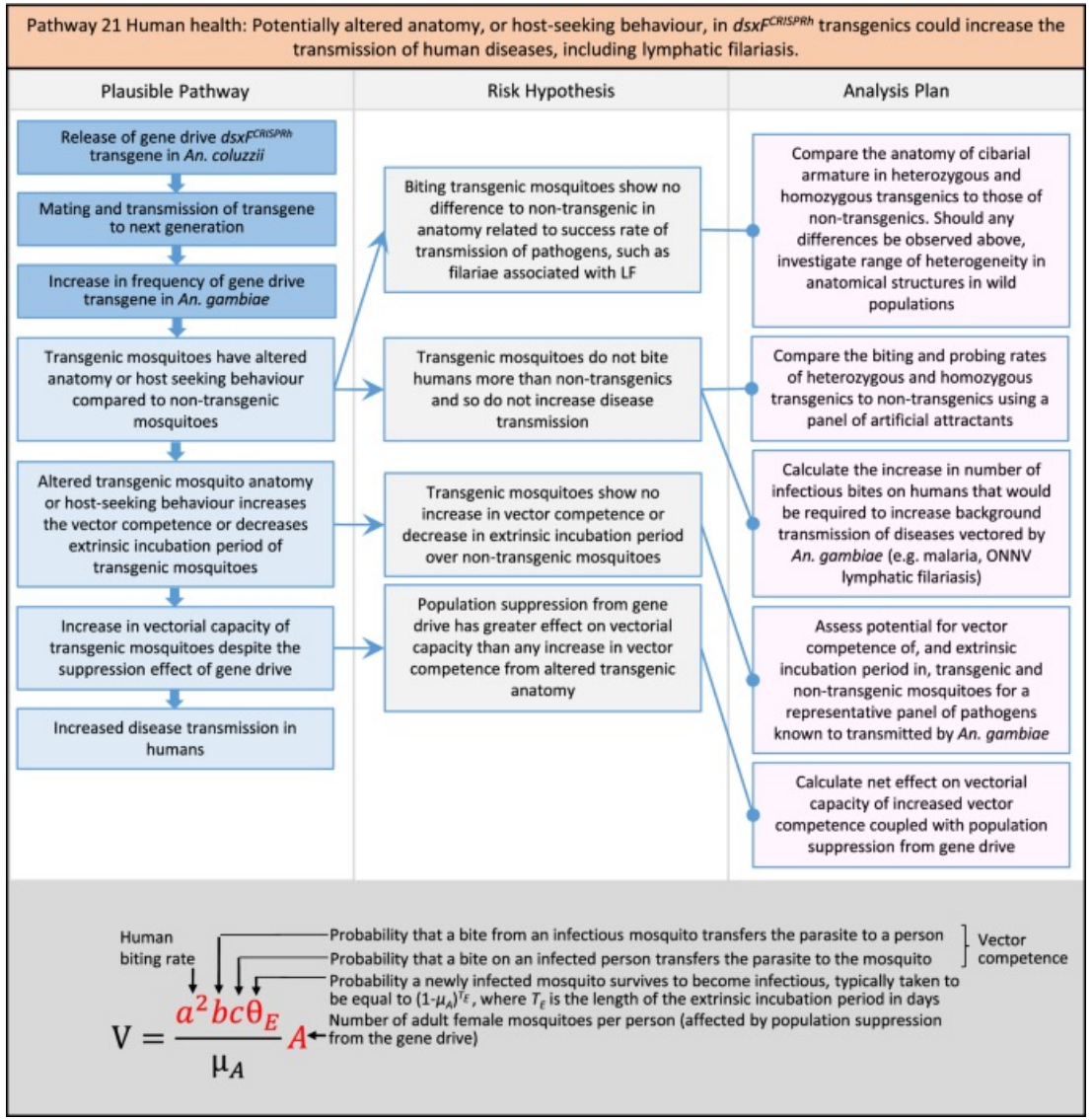
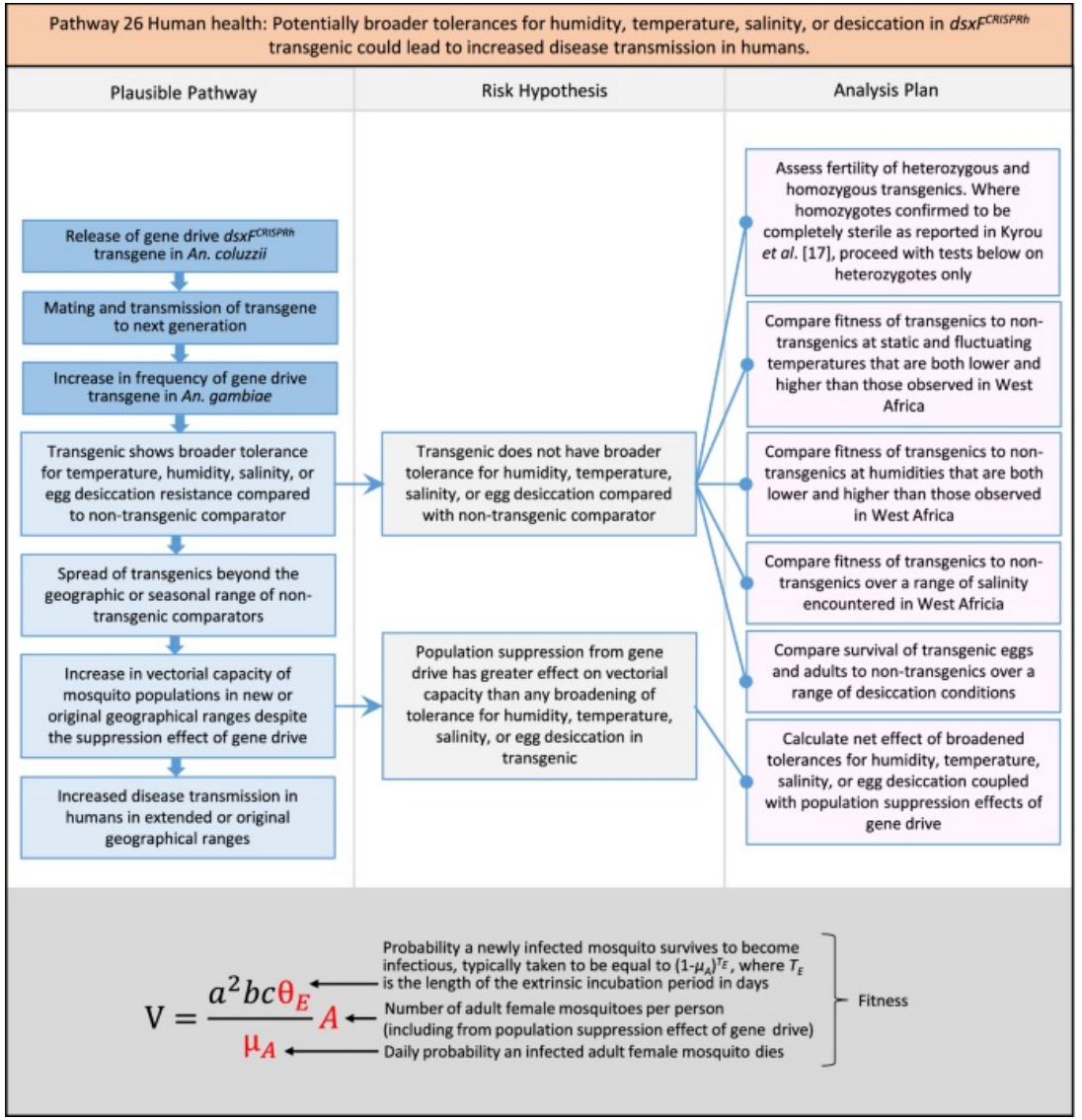
Risk assessment





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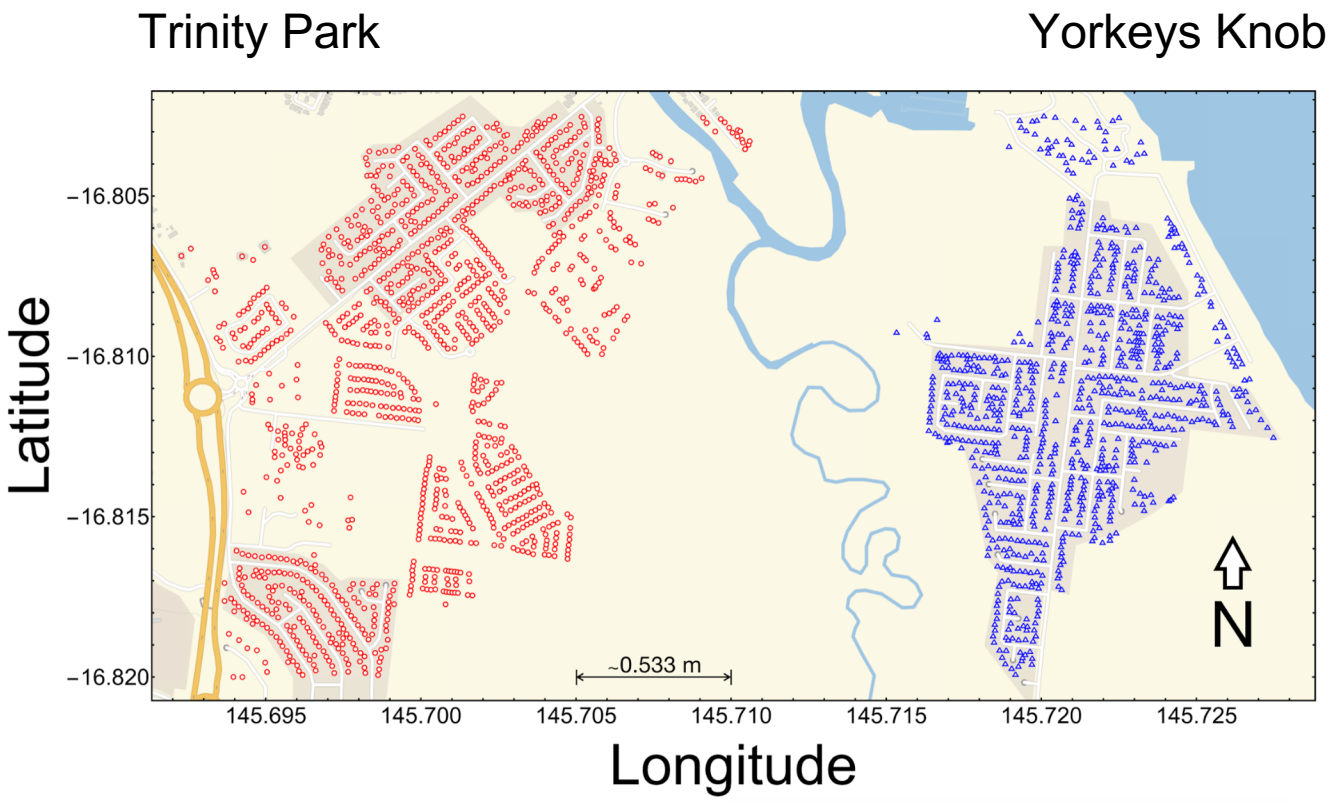
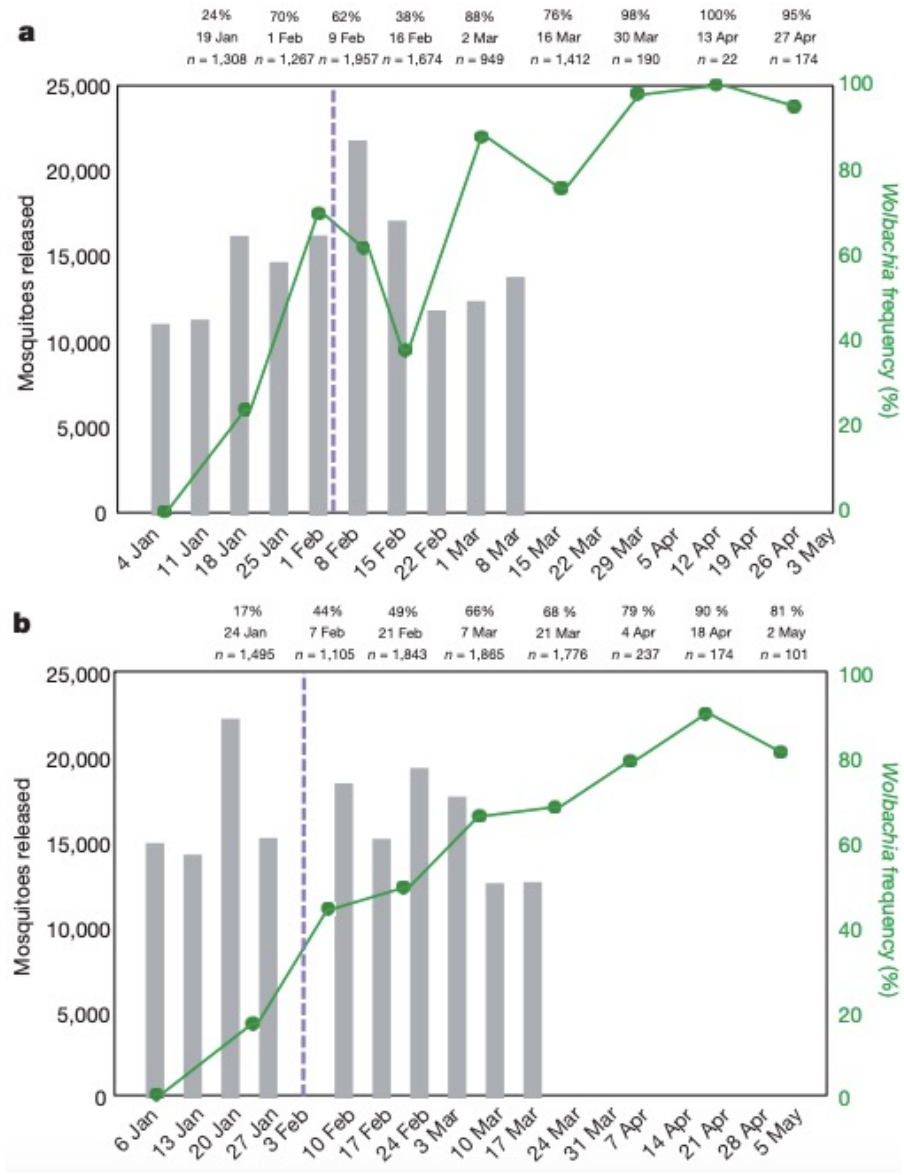
Field trial models: *Wolbachia* as a case study





- Utarini A, Indiani C, Ahmad RA, Tantowiyojo W *et al.* (2021) New England J Medicine

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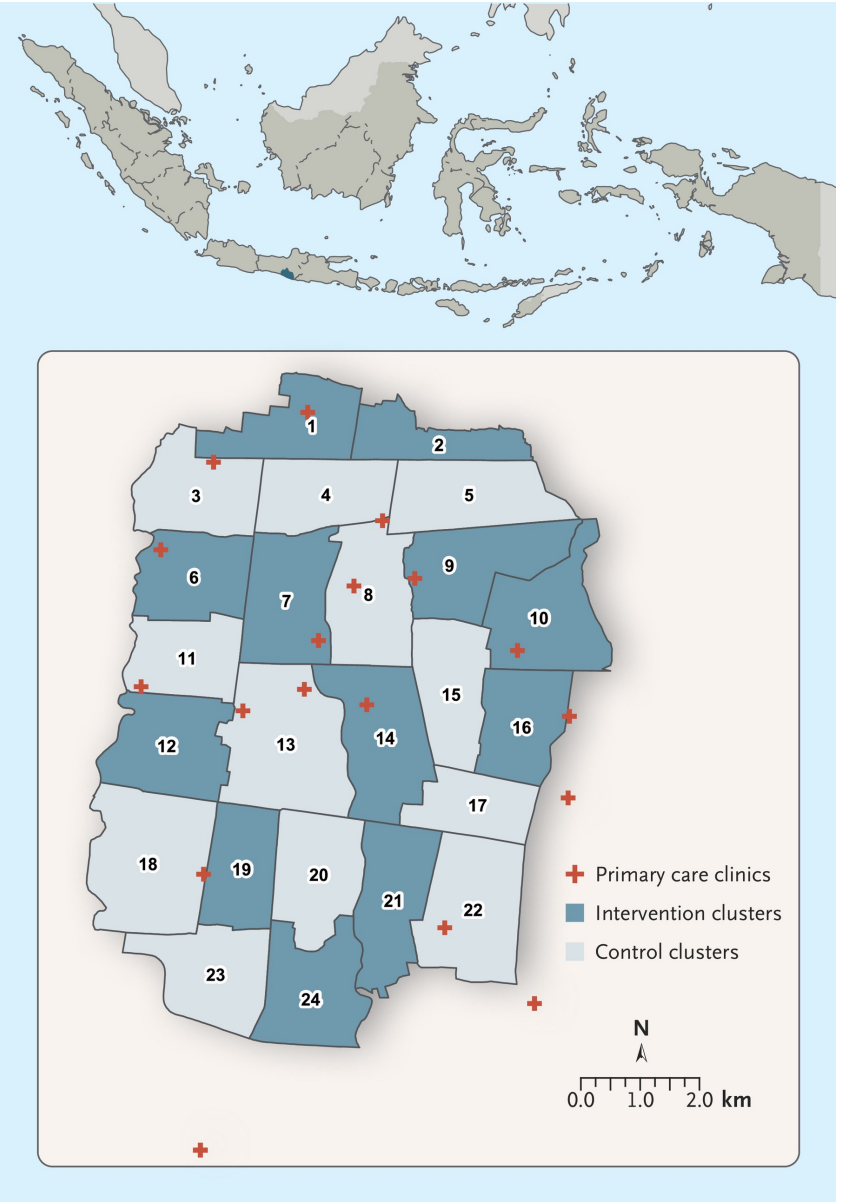

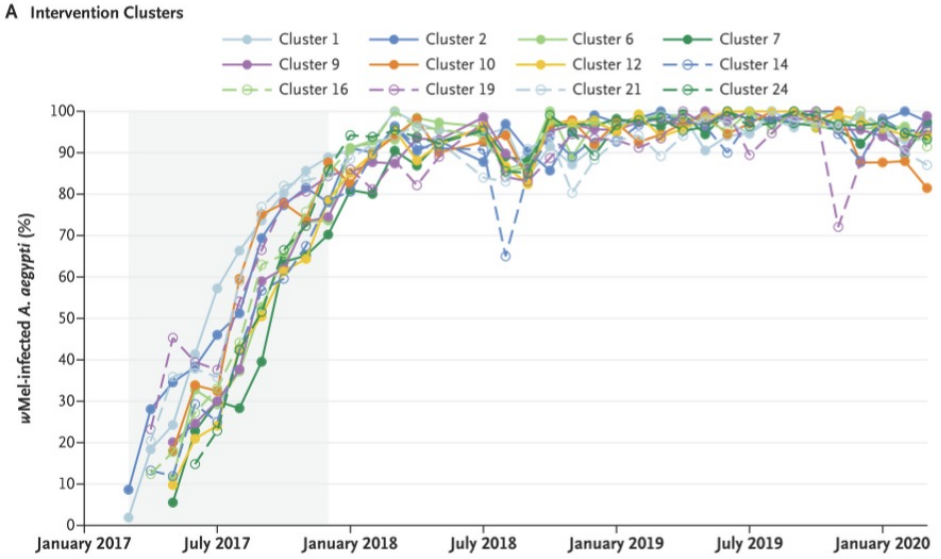

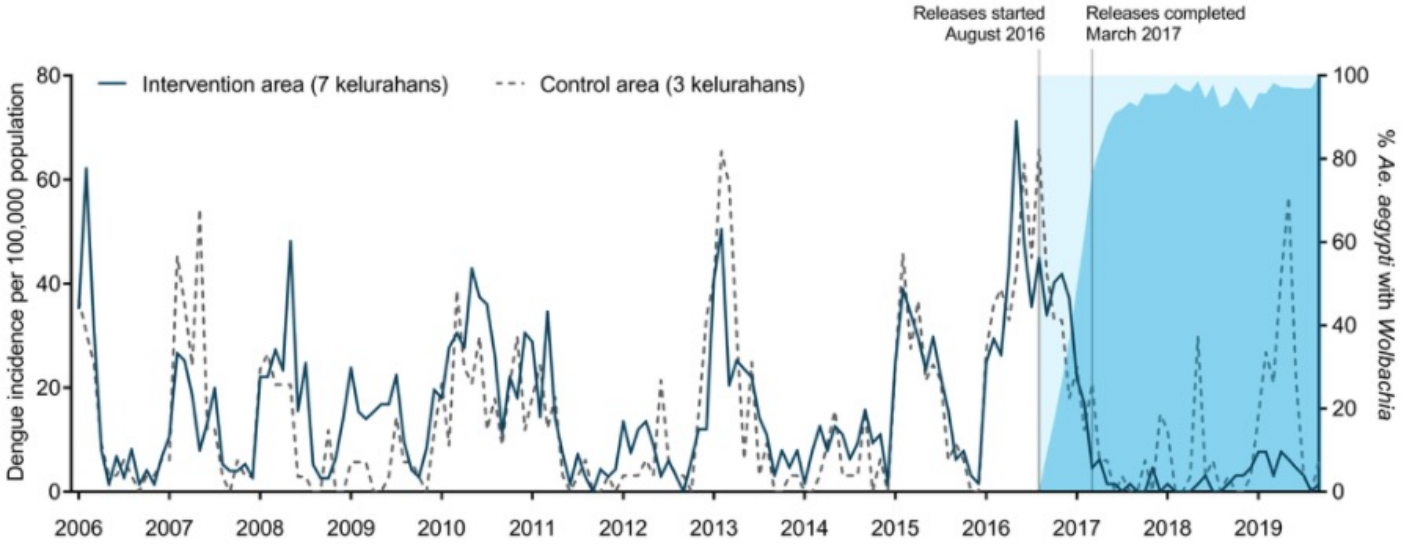

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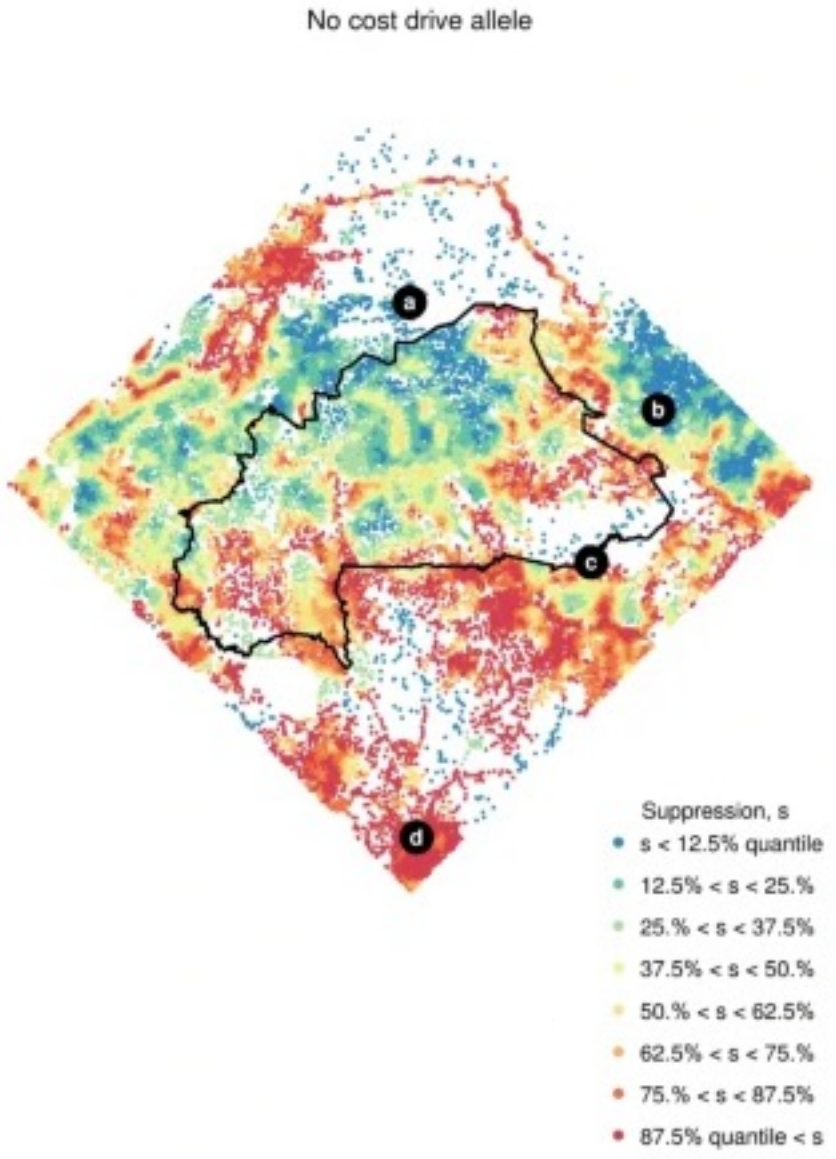
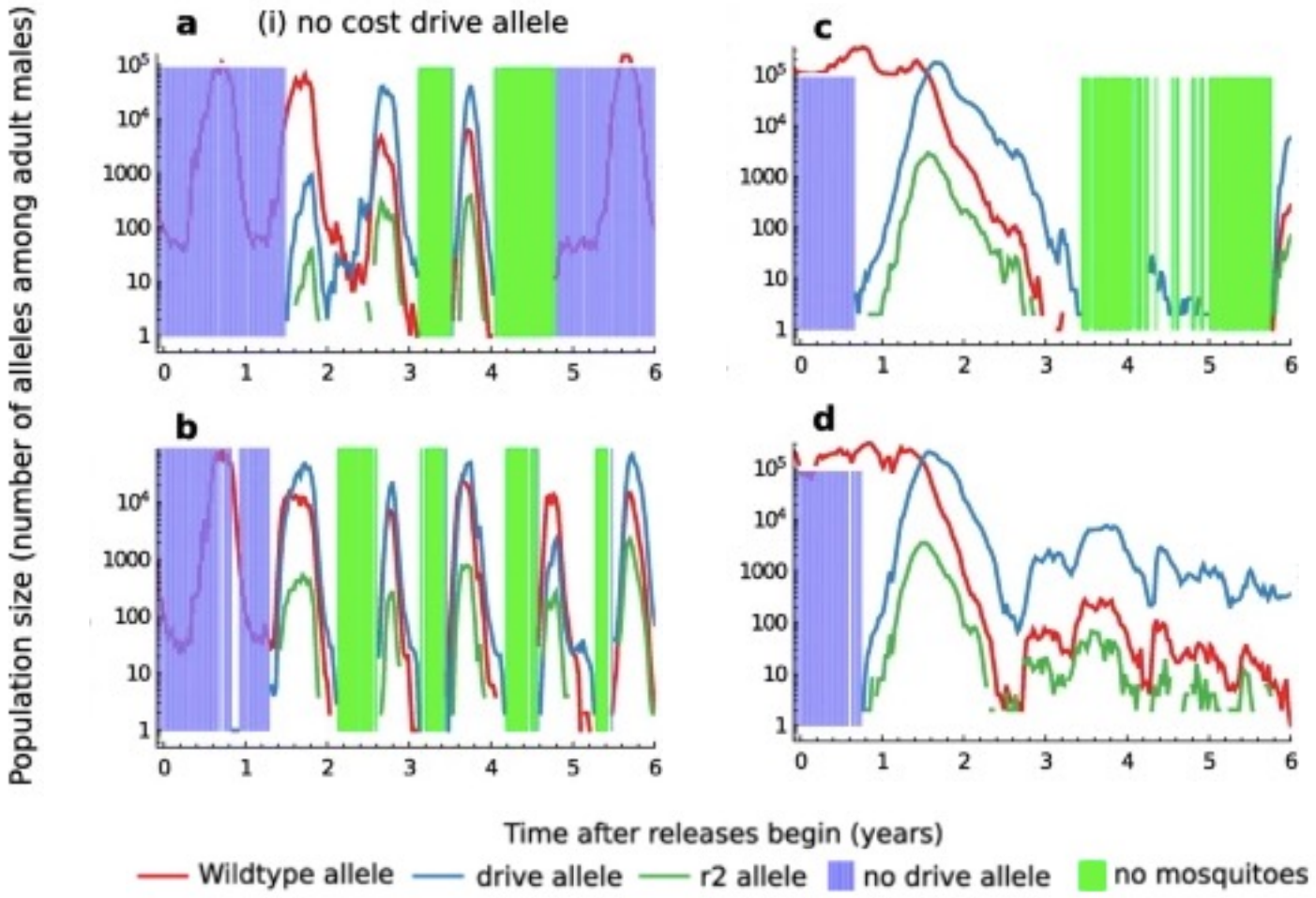
Intervention models: *dsx* drive in Burkina Faso





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Recap

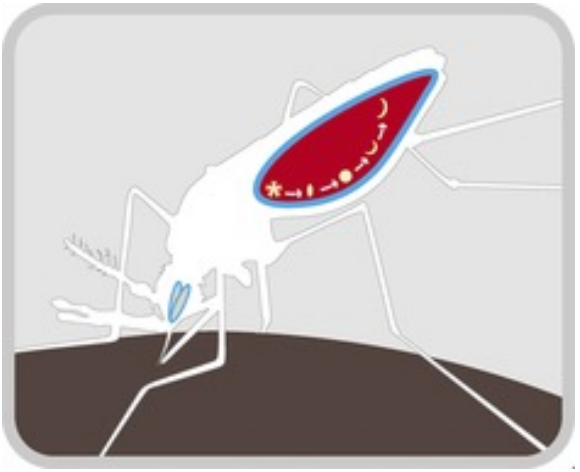
1. Modeling is expected to play a growing role as gene drive mosquito projects transition from lab to field

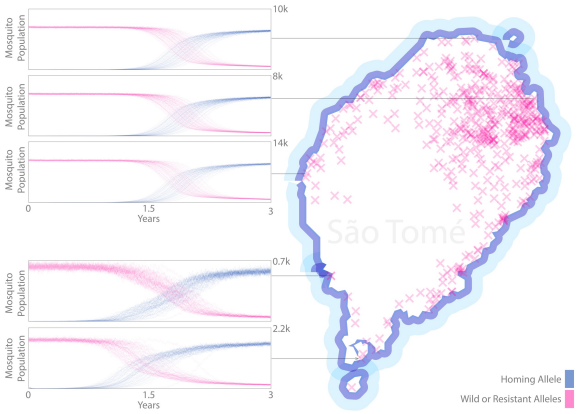
2. Data are required to refine models concerning mosquito density dependence, habitat distribution, movement patterns & resistance allele formation

3. Assessing alignment with a target product profile & risk assessment will be important prior to a release

4. Monitoring & surveillance are expected to be cost drivers & modeling can inform cost-efficiency

5. Modeling priorities will then progress from designing cage trials & field trials to wide-scale interventions





Acknowledgements

LAB MEMBERS:

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- Sean L. Wu
- Yogita Sharma
- Sanjay Lamba
- Gordana Rašić
- Darpa Anireddy
- Ashley Zhang
- Daniel López
- Priscilla Zhang
- Tomás León
- Jared B. Bennett
- Váleri Vásquez
- Agastya Mondal
- Francois Rerolle
- Natasha Harrison
- Hao Wang
- Ameek Bindra
- Chris De Leon

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- **Lanzaro Lab** @ UC Davis
- **James Lab** @ UC Irvine
- **Bier Lab** @ UCSD
- **Hay Lab** @ Caltech
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- **Dr Samson Kiware** @ Ifakara Health Institute
- **School of Public Health** @ UC Berkeley

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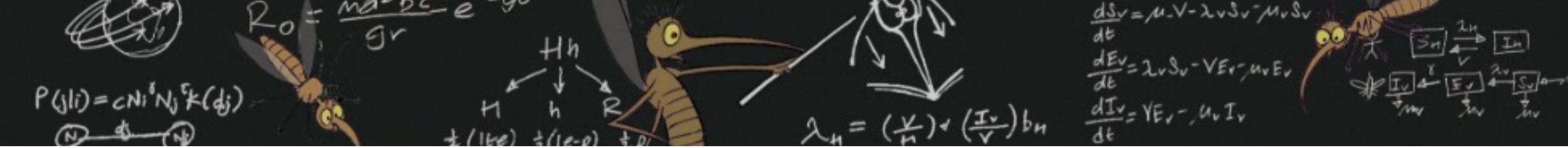

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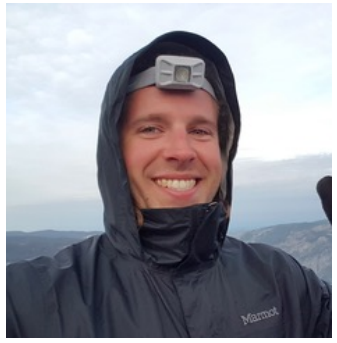

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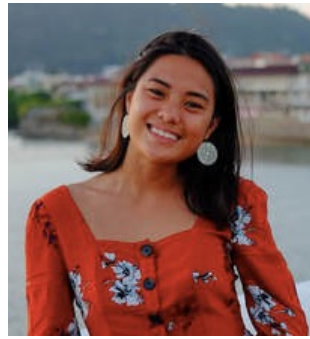

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