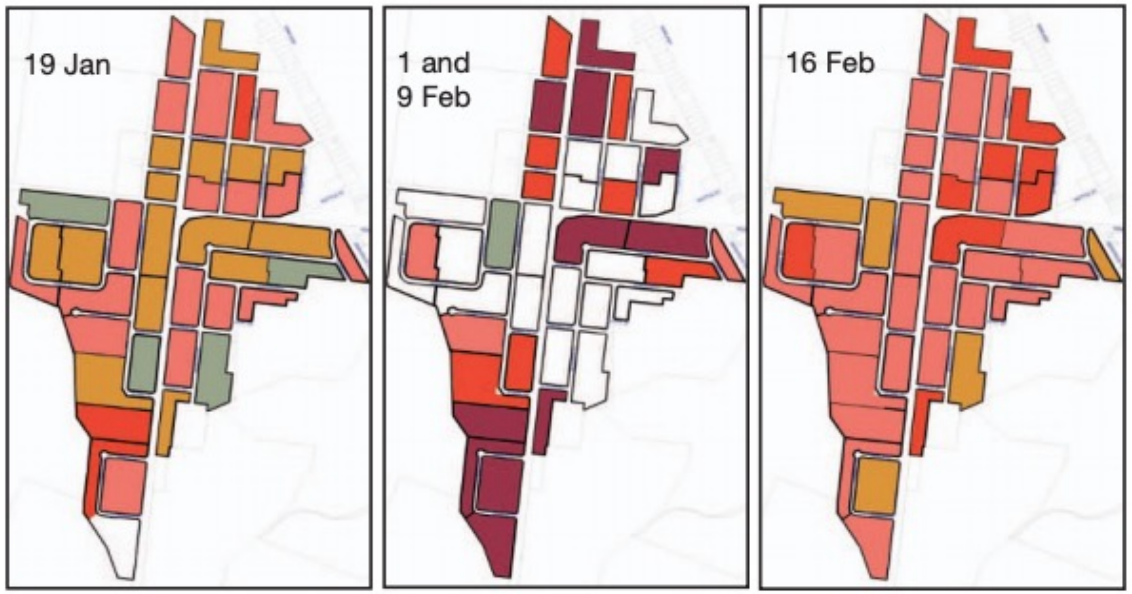
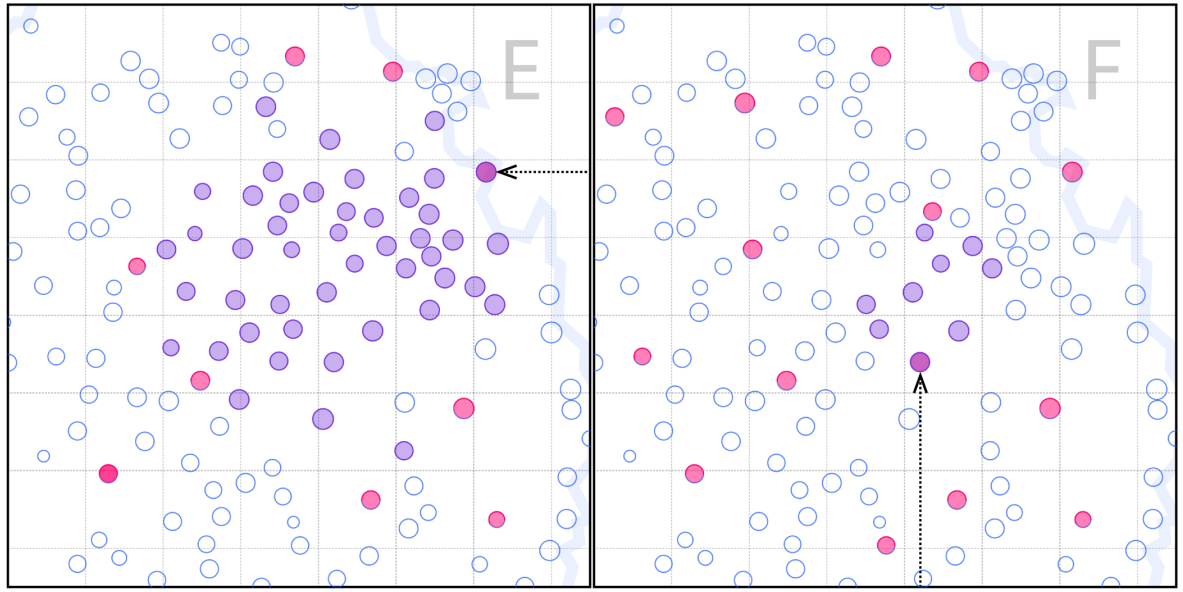
A roadmap for monitoring gene drive release scenarios over time + the role of models

John M. Marshall, Gordana Rašić, Neil F. Lobo, Eileen H. Jeffrey Gutiérrez, Héctor M. Sánchez C.





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Overview

1. Pre-release monitoring:
   - Understand temporal dynamics of local mosquito populations
   - Inform release strategies
   - Provide baseline data to assess intervention impact
2. Monitoring during a release:
   - Monitor release impact (changes in genotype frequencies & population size / malaria incidence)
   - Assess biosafety (e.g., confinement)
3. Post-release monitoring:
   - Monitor continued persistence & effectiveness of intervention
   - Assess extent of spatial spread
4. Modeling & statistical tools:
   - Distribution of traps & required sampling effort
   - Adaptive releases

frontiers in Genetics

Monitoring Needs for Gene Drive Mosquito Projects: Lessons From Vector Control Field Trials and Invasive Species

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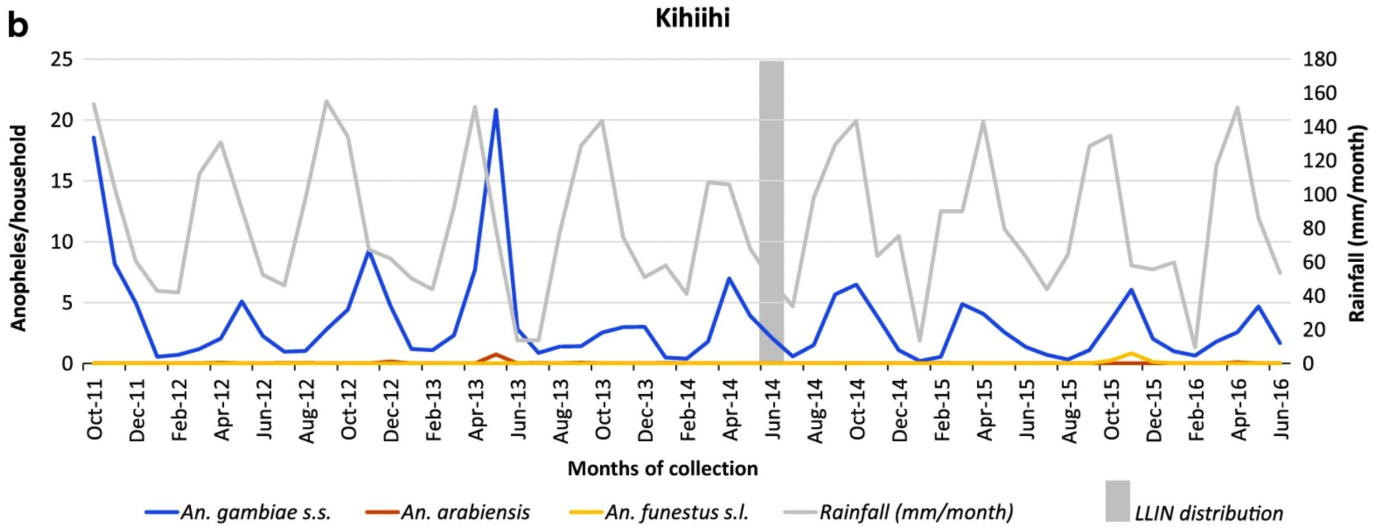
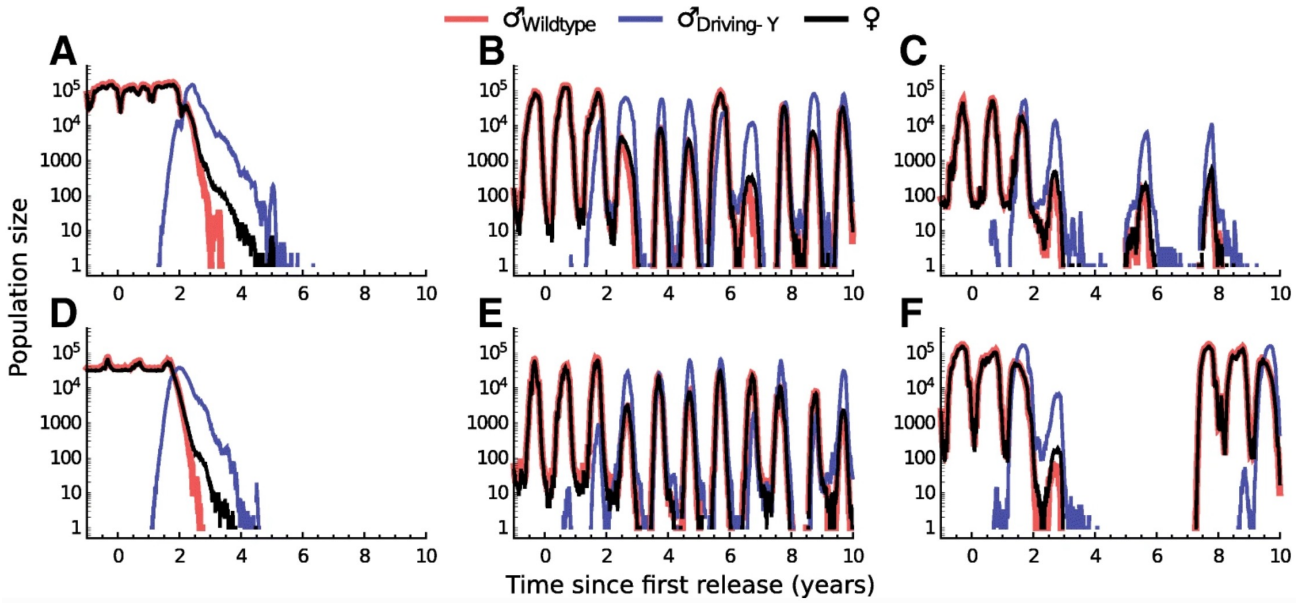
As gene drive mosquito projects advance from contained laboratory testing to semi-field testing and small-scale field trials, there is a need to assess monitoring requirements to: i) assist with the effective introduction of the gene drive system at field sites, and ii) detect unintended spread of gene drive mosquitoes beyond trial sites, or resistance mechanisms and non-functional effector genes that spread within trial and intervention sites. This is of particular importance for non-localized gene drive projects, as the potential scale of intervention means that monitoring is expected to be more costly than research, development and deployment. Regarding monitoring needs for population replacement systems, lessons may be learned from experiences with *Wolbachia*-infected mosquitoes, and for population suppression systems, from experiences with releases of genetically sterile male mosquitoes. For population suppression systems, assessing monitoring requirements for tracking population size and detecting rare resistant alleles are priorities, while for population replacement systems, allele frequencies must be tracked, and pressing concerns include detection of gene drive alleles with non-functional effector genes, and resistance of pathogens to functional effector genes. For spread to unintended areas, open questions relate to the optimal density and placement of traps and frequency of sampling in order to detect gene drive alleles, drive-resistant alleles or non-functional effector genes while they can still be effectively managed. Invasive species management programs face similar questions, and lessons may be learned from these experiences. We explore these monitoring needs for gene drive mosquito projects progressing through the phases of pre-release, release and post-release.

Keywords: population replacement, population suppression, *Wolbachia*, RIDL, invasive species, resistant alleles, gene drive, monitoring

Pre-release monitoring: Seasonal patterns





- Temporal measure of relative mosquito population size.
- Alongside environmental data (temperature, rainfall, etc.)
- Evaluation of sampling devices that accurately represent local mosquito densities.

- Modeling studies suggest seasonality can have a large influence on control program outcome.
- Optimal timing of releases is as the populations begin to grow.

- Mawejje HD, Kilama M *et al.* (2021) Malaria J
- North AR, Burt A, Godfray HCJ (2019) BMC Biology

Pre-release monitoring: Non-target species

Other local malaria vectors:

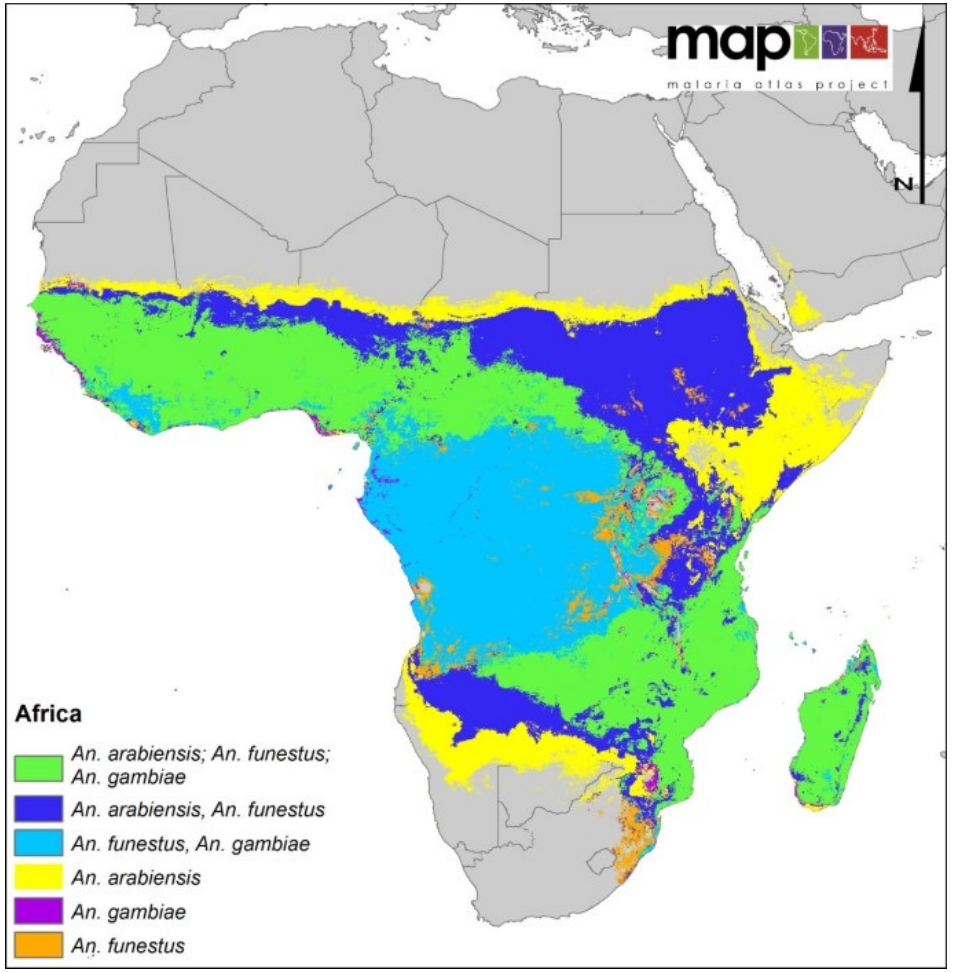
- To understand proportion of malaria transmission attributed to target species.

Species between which there is some gene flow:

- Could result in between-species spread of construct.

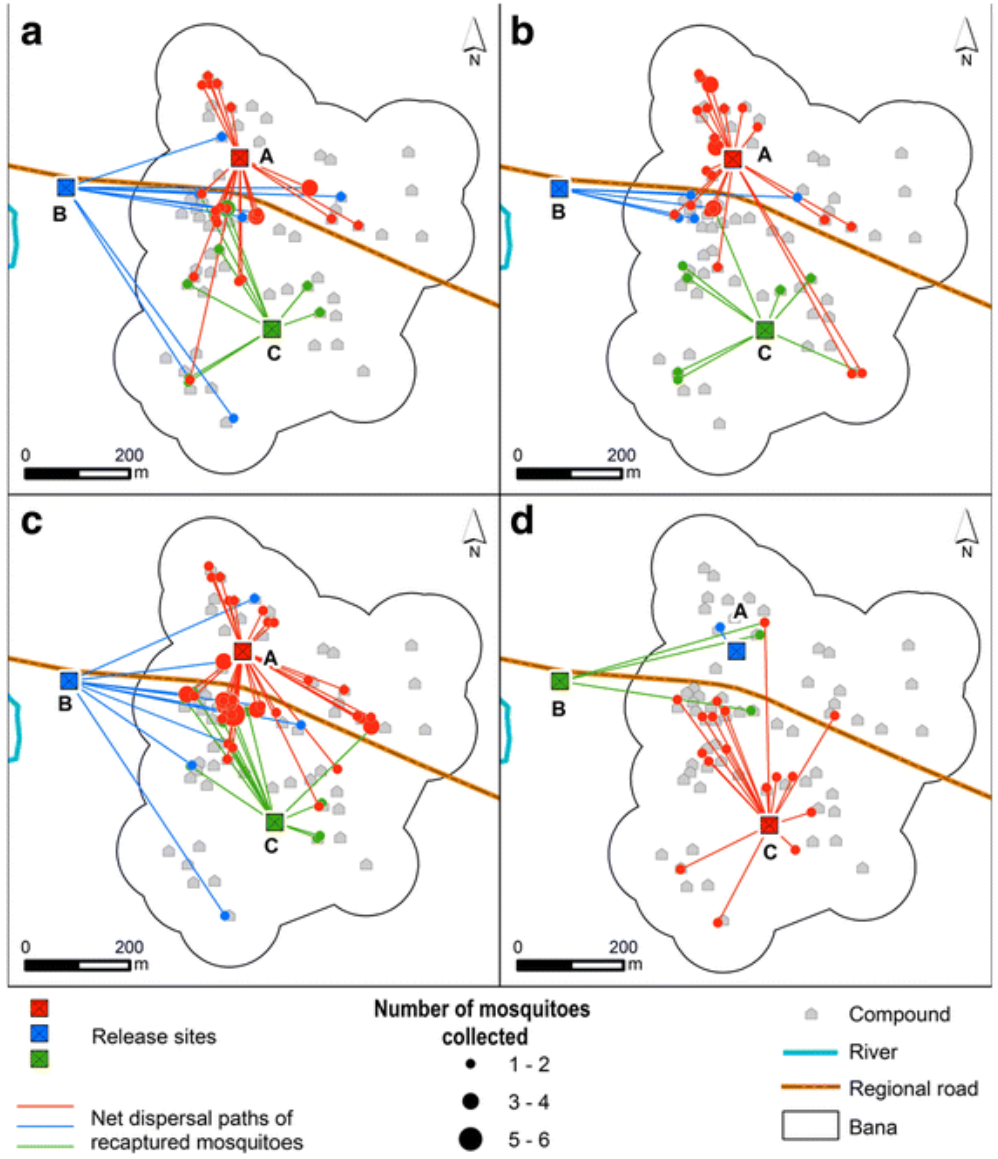
Species that may compete for a similar niche:

- To assess niche replacement risk for population suppression strategies.

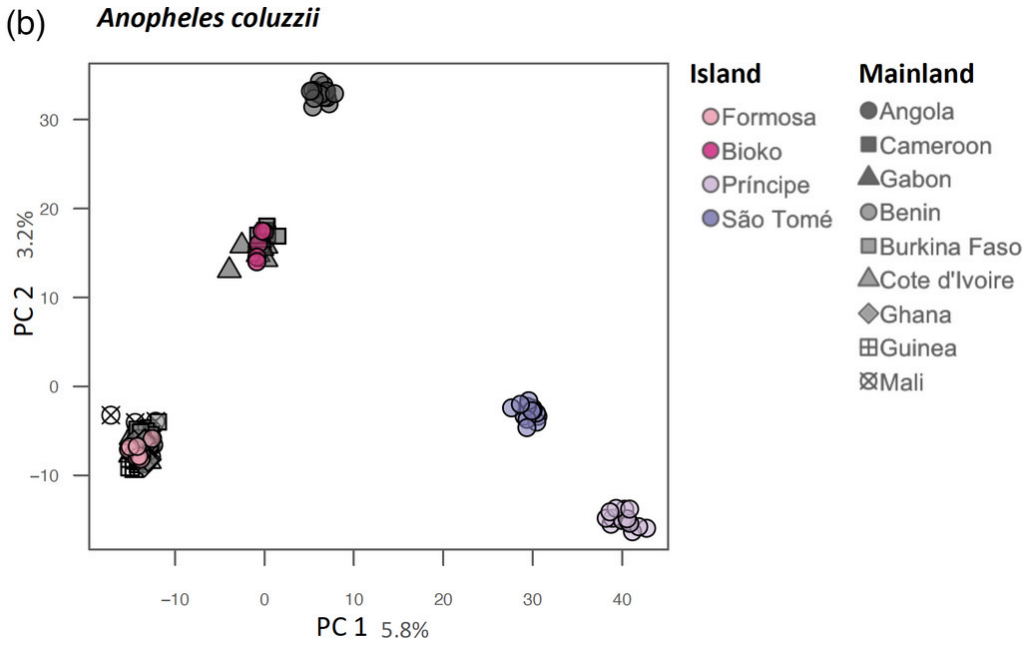


- Sinka ME, Bangs MJ, Manguin S, Rubio-Palis Y *et al.* (2012) Parasites & Vectors

Pre-release monitoring: Movement patterns



- MRR experiments can be used to estimate dispersal, population size & daily survival.
- Population genetics methods can be used to infer intermediate to large-scale movement.
- Important to assess: i) spatial scale of release, & ii) risk of escape.

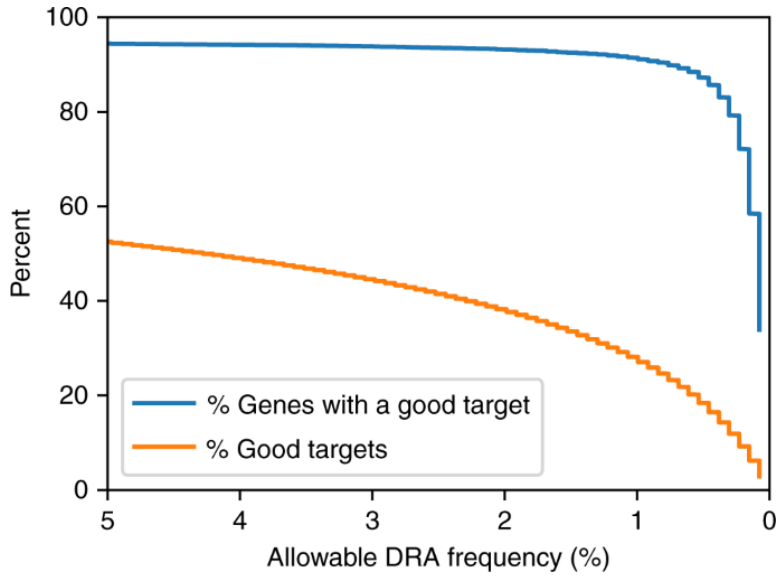


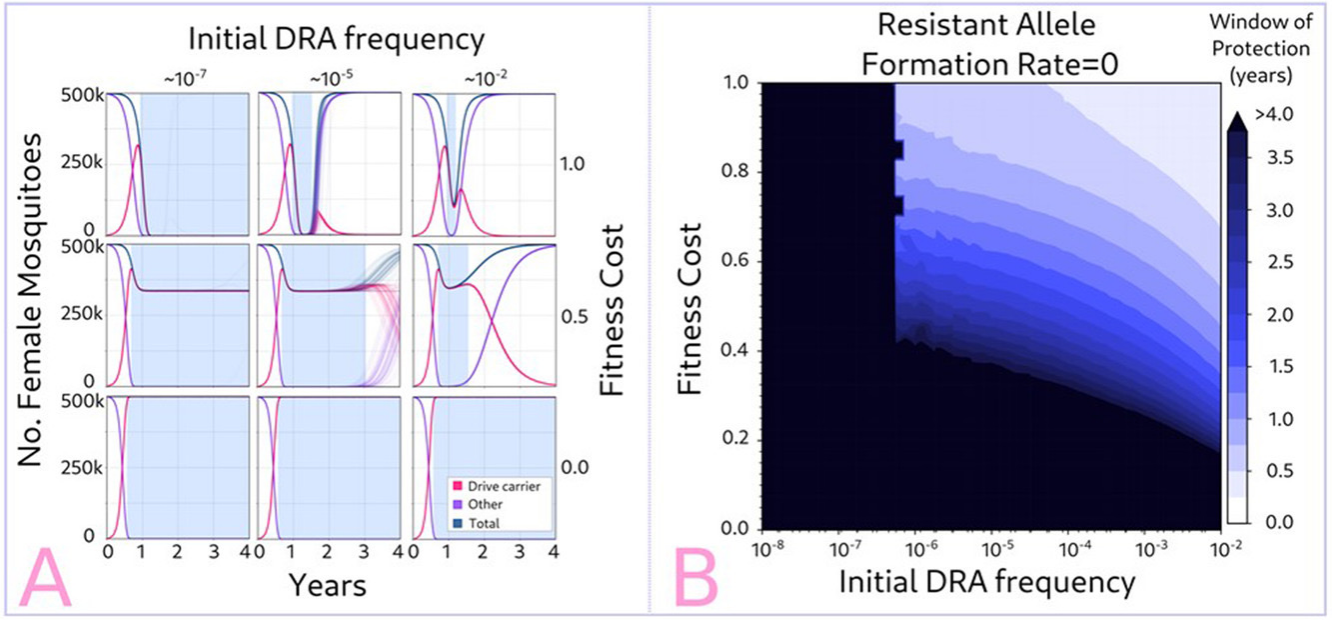
- Epopa PS, Millogo AA, Collins CM *et al.* (2017) Parasites & Vectors
- Lanzaro GC, Campos M, Crepeau M, Cornel A *et al.* (2021) Evol App

Pre-release monitoring: DNA polymorphisms

- Look for DNA sequence polymorphisms at target site.
- Some may confer a drive-resistant phenotype.

- For population suppression, must be extremely rare.
- For population replacement, fitness relative to drive allele is relevant; but frequencies <1% should be tolerable.



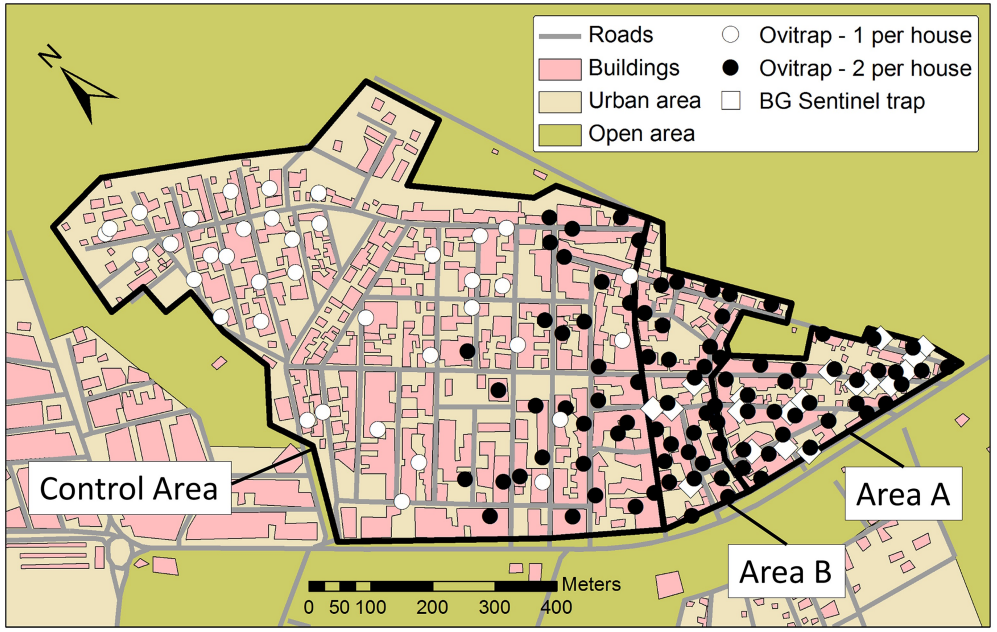


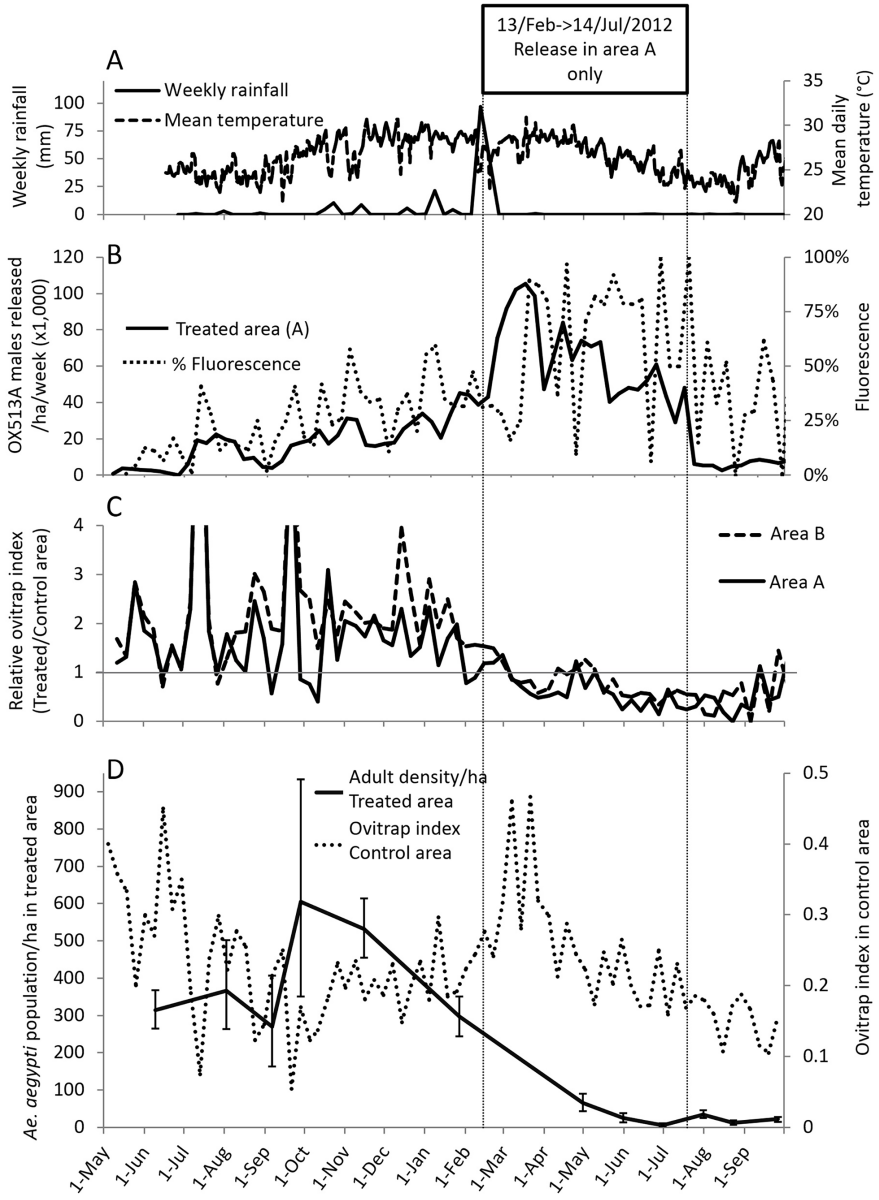
- Schmidt H, Collier TC, Hanemaaijer MJ, Houston PD *et al.* (2020) Nat Comm
- Lanzaro GC, Sánchez C. HM, Collier TC, Marshall JM *et al.* (2021) Bioessays

Monitoring during a release: RIDL

Aedes aegypti RIDL releases in Juazeiro:

- Grid of ovitraps spanning treated & control areas
- Larvae scored for transgene based on fluorescent marker
- Non-fluorescent larvae reared to adults to check for non-target species
- Mating competitiveness estimated during “rangefinder” phase
- Release density modified accordingly





- Carvalho DO, McKemey AR, Garziera L, Lacroix R *et al.* (2015) PLoS Negl Trop Dis

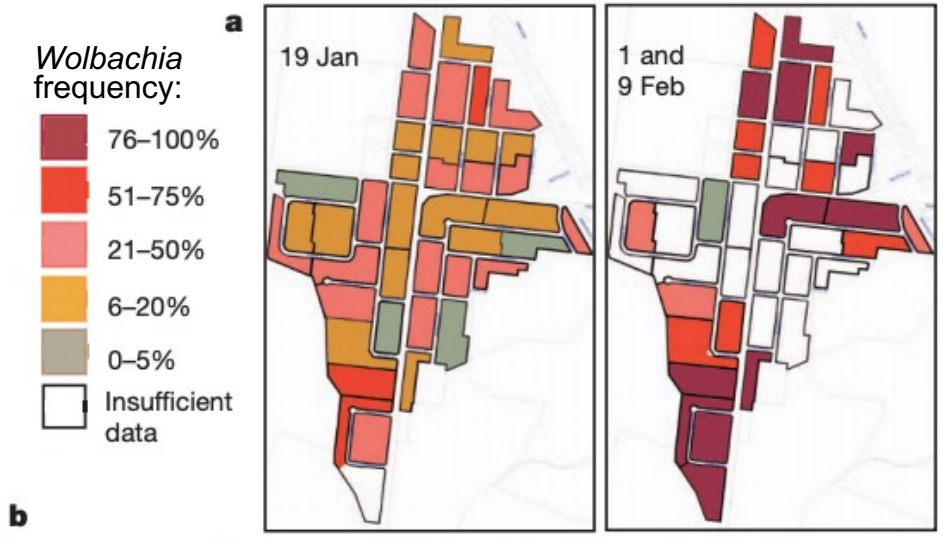
Monitoring during a release: Replacement

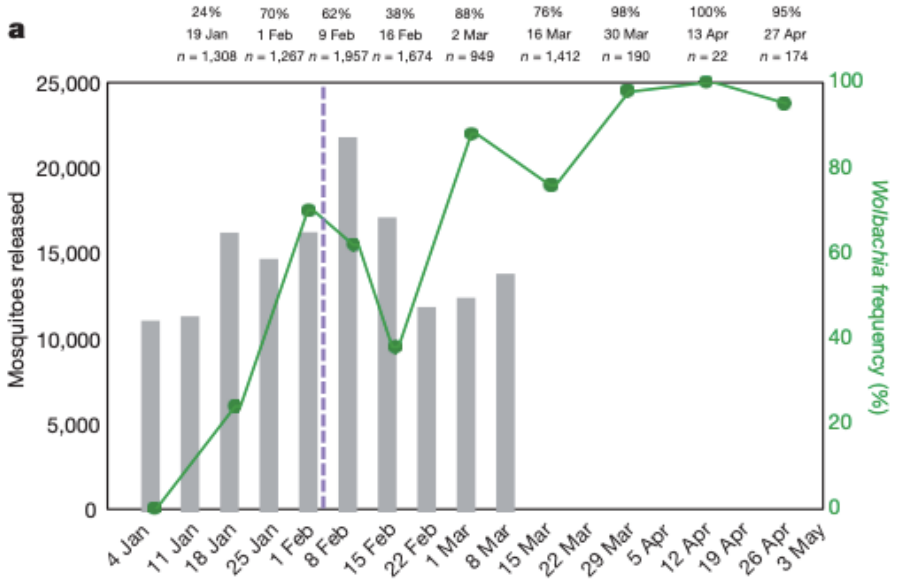
Wolbachia-infected *Aedes aegypti* releases in Queensland provide an excellent case study:

- Network of ovitraps (~1 per 2 houses)
- BG Sentinel traps (~1 per 30-45 houses)
- PCR assay to determine species & *Wolbachia* status
- Fitness costs were estimated during the trial
- Modeling ensured that releases would exceed the threshold frequency

Replacement gene drive releases may require additional assays:

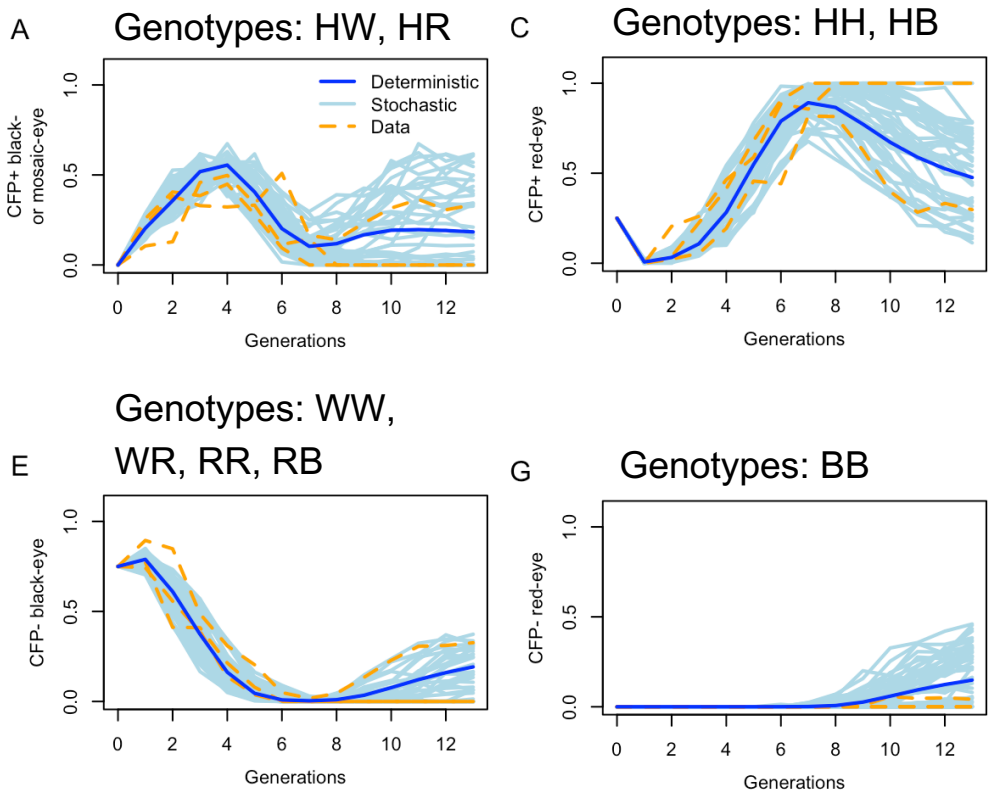
- Intact drive allele
- Alternative alleles (esp. drive-resistant alleles)
- Presence of drive allele in non-target species
- Ongoing model fitting can refine parameter estimates (esp. fitness of intact drive & alternative alleles) to ensure targets are met

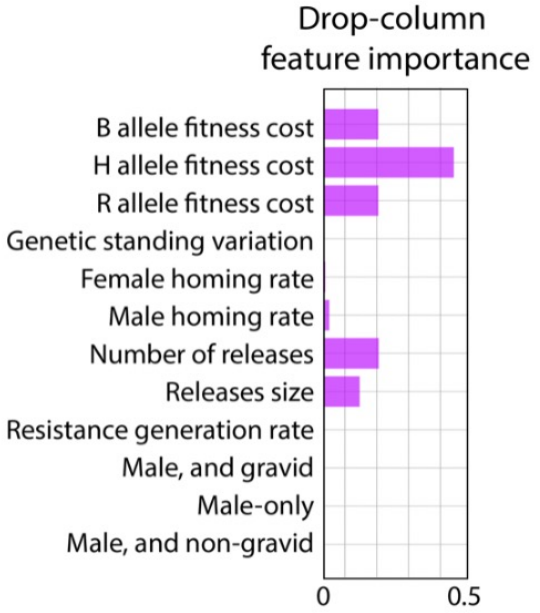


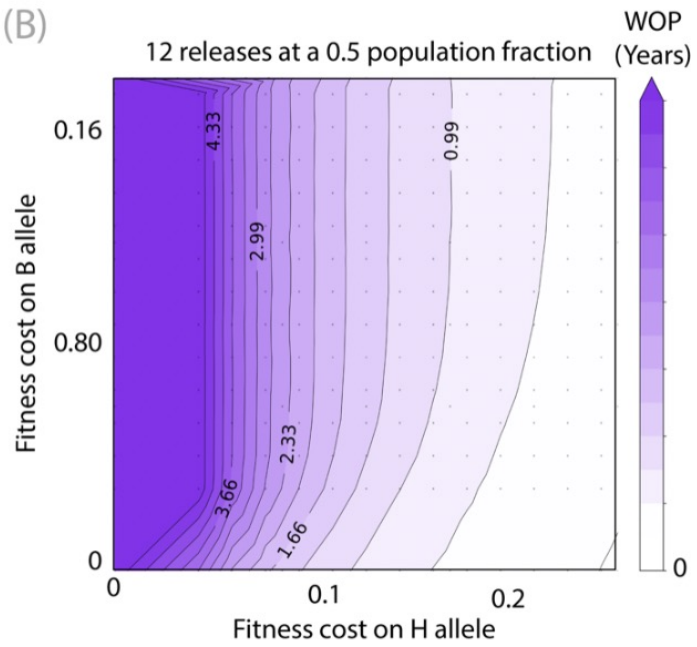


- Hoffmann AA, Montgomery BL, Popovici J, Iturbe-Ormaetxe *et al.* (2011) Nature

Monitoring during a release: Resistance alleles







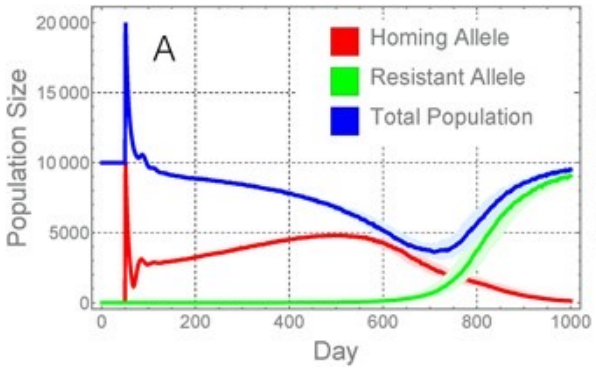
- In lab studies, the trajectories of marker phenotypes corresponding to genotypes allow us to estimate fitness costs associated with homing (H) and resistance (R, B) alleles.

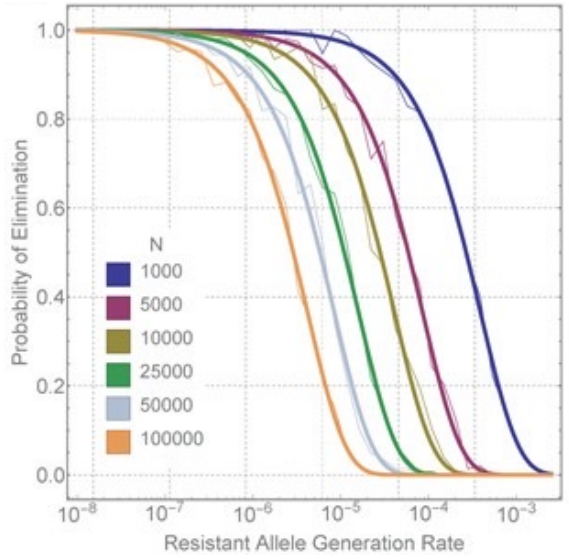
- Modeling studies suggest that the window of protection (period of time that the H allele exceeds, e.g., 90% in the population) is most sensitive to fitness costs of H, R & B.
- There is therefore great value in monitoring H, R & B phenotypes and/or assaying / sequencing.

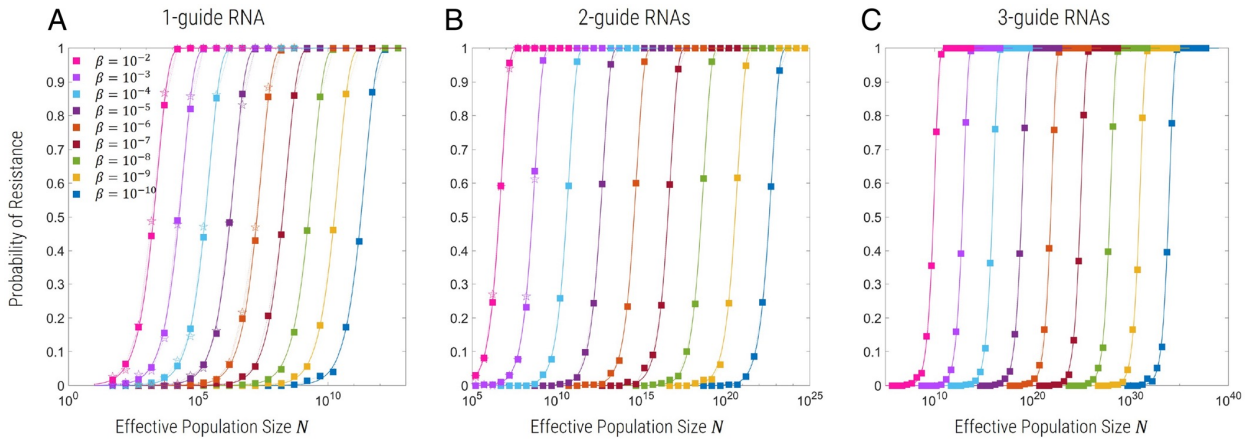
Monitoring during a release: Suppression

Suppression gene drive releases should monitor:

- Reduction in mosquito density
- Drive-resistant alleles
- Stability of suppression phenotype (e.g., fecundity reduction, sex ratio bias)
- Ongoing model fitting to refine parameter estimates & ensure targets are met
- Check for non-target species (esp. niche replacement by another vector species)

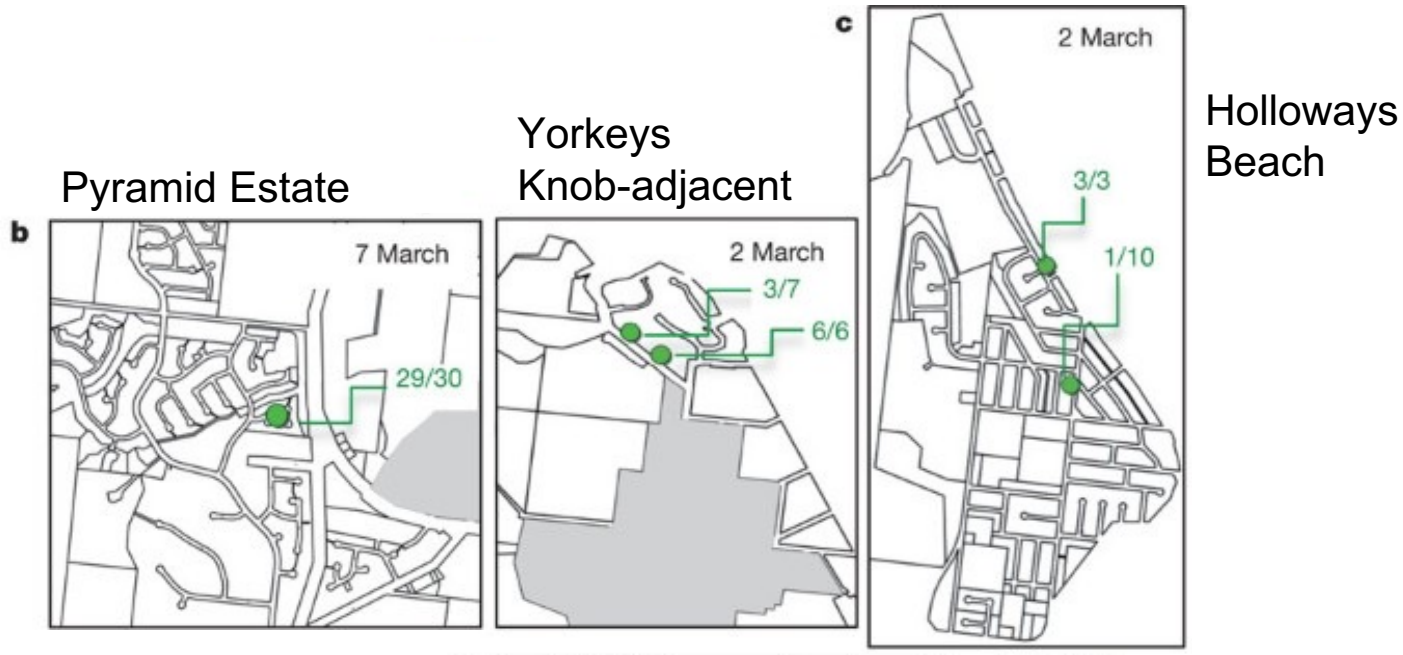






- Marshall JM, Buchman A *et al.* (2017) Sci Rep
- Khatri BS, Burt A (2022) Proc Natl Acad Sci USA

Monitoring during a release: Confinement

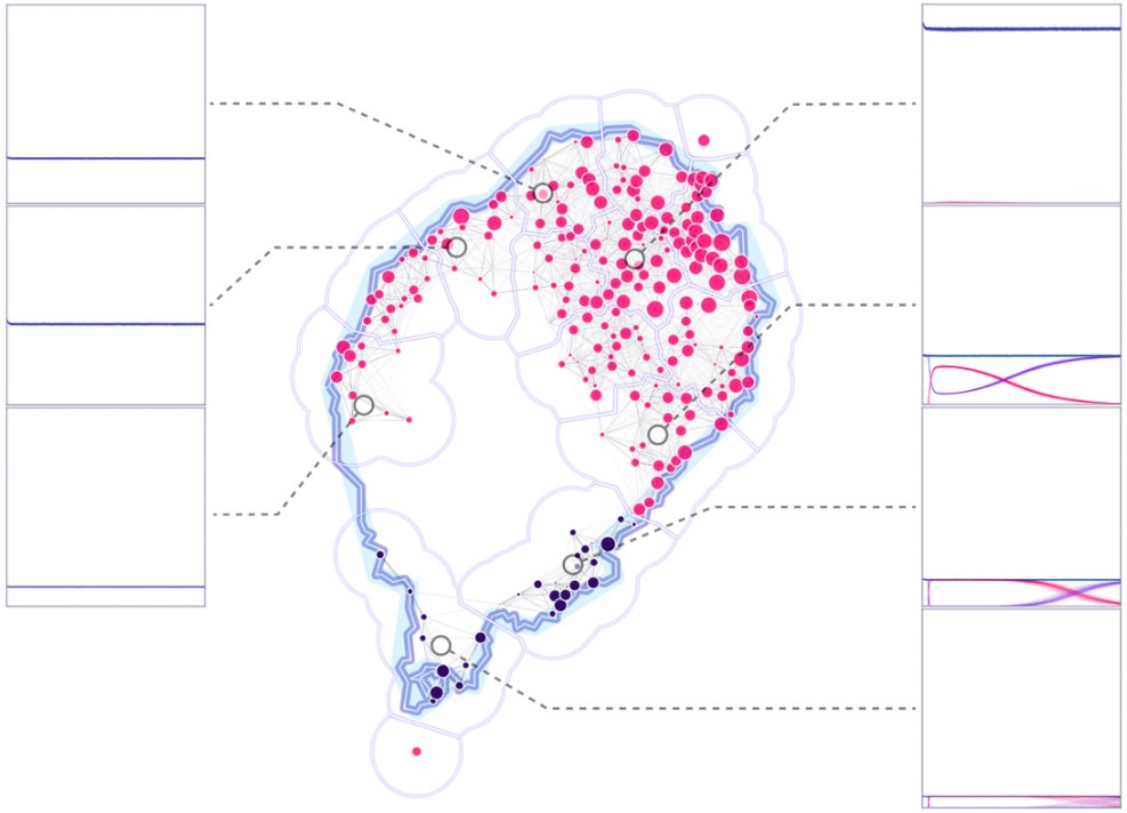


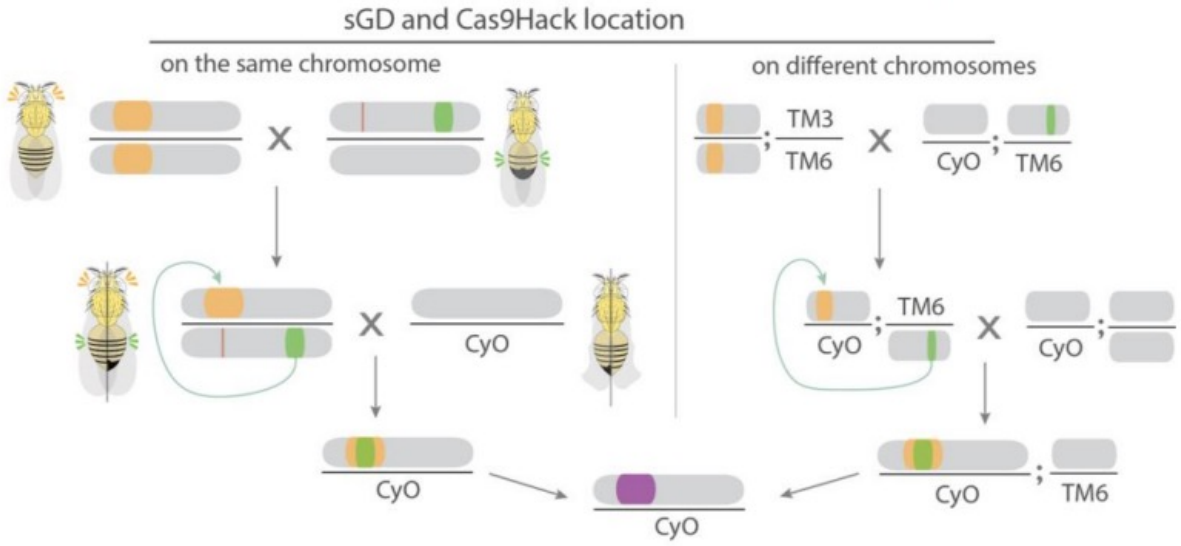
- The *Wolbachia* study in Queensland monitored areas near release sites for *Wolbachia*-infected mosquitoes.
- *Wolbachia* was sporadically detected in these areas, suggesting human-mediated movement.

- *Anopheles* can autonomously disperse further than *Aedes* mosquitoes.
- Therefore need rigorous monitoring of non-target populations during trials & interventions, including at nearby sea & airports.

- Hoffmann AA, Montgomery BL, Popovici J, Iturbe-Ormaetxe *et al.* (2011) Nature

Monitoring during a release: Split-drive





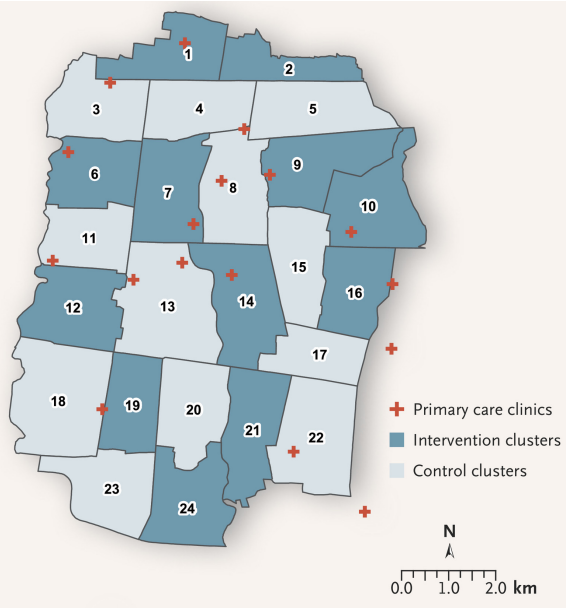
- Depending on priorities of local communities & governments (confinement vs. earlier release), a confinable split-drive release could precede a full-drive release with potential for wider spread.

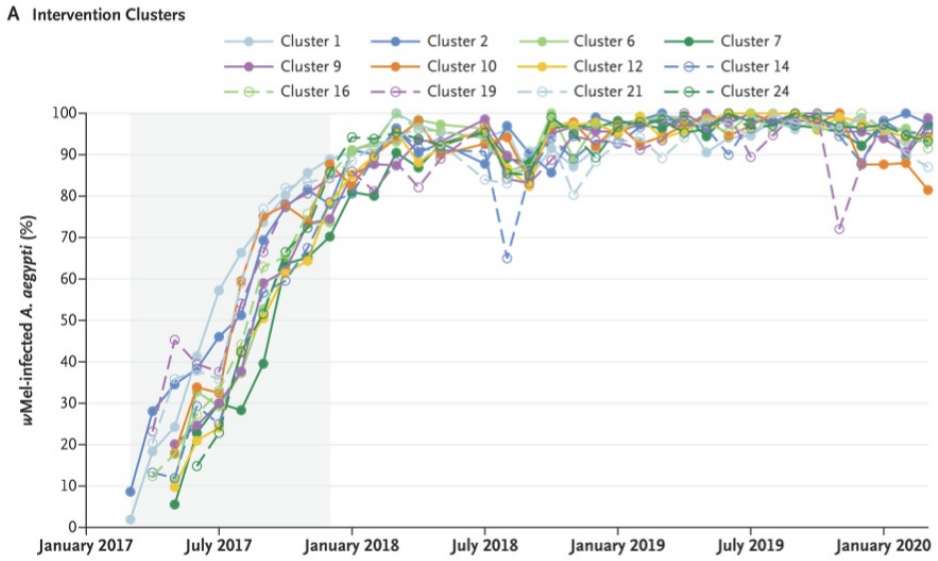
- Split-drive systems have been developed in the Bier Lab that can be converted into full-drive systems through a series of crosses.
- Homing & resistance rates appear conserved between designs, although fitness may differ.

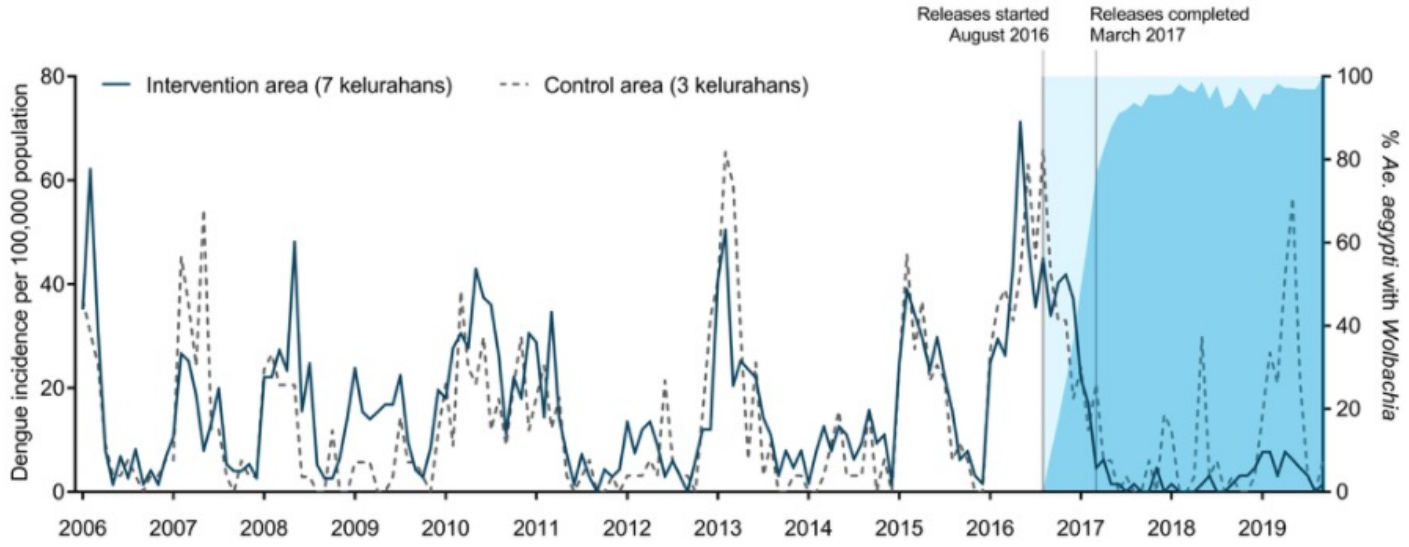
- Terradas G, Bennett JB, Li Z, Marshall JM, Bier E (2021) bioRxiv

Monitoring during a release: Epidemiology

- The *Wolbachia* RCT in Yogyakarta, Indonesia showed that epidemiological impact can be demonstrated through passive case monitoring.
- But need to consider other factors that could explain epidemiological outcomes too.
- E.g., monitor other local vector species.
- E.g., monitor insecticide resistance alleles if present in released mosquitoes.

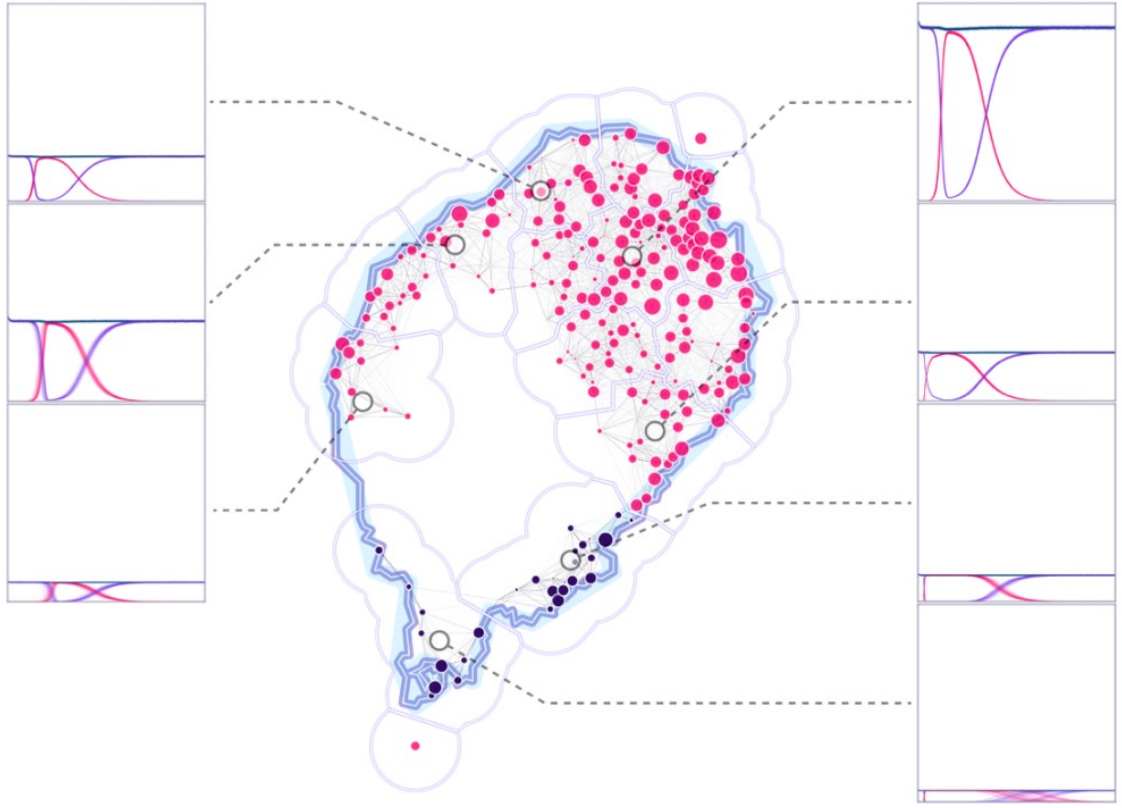




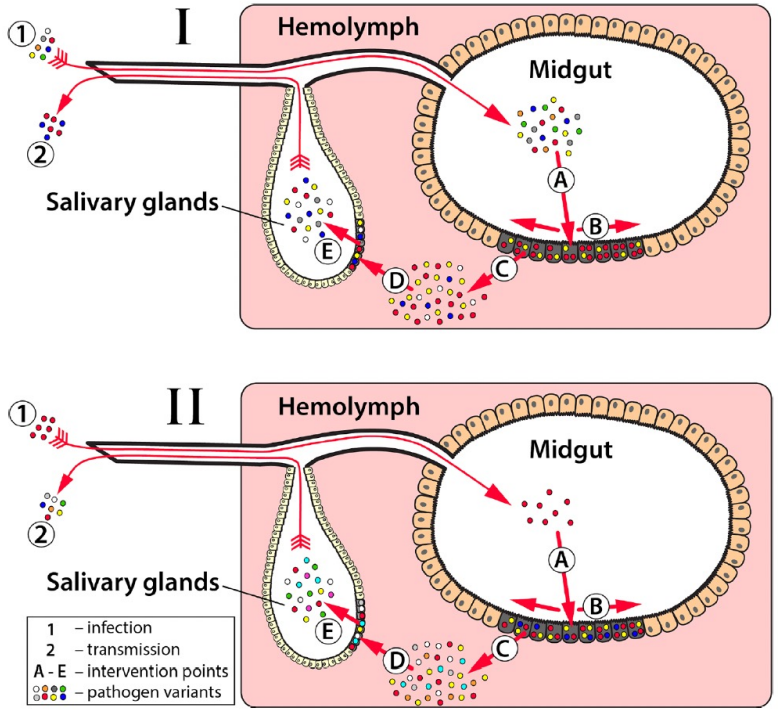


- Utarini A, Indiani C, Ahmad RA, Tantowiyojo W *et al.* (2021) New England J Medicine

Post-release monitoring: Replacement



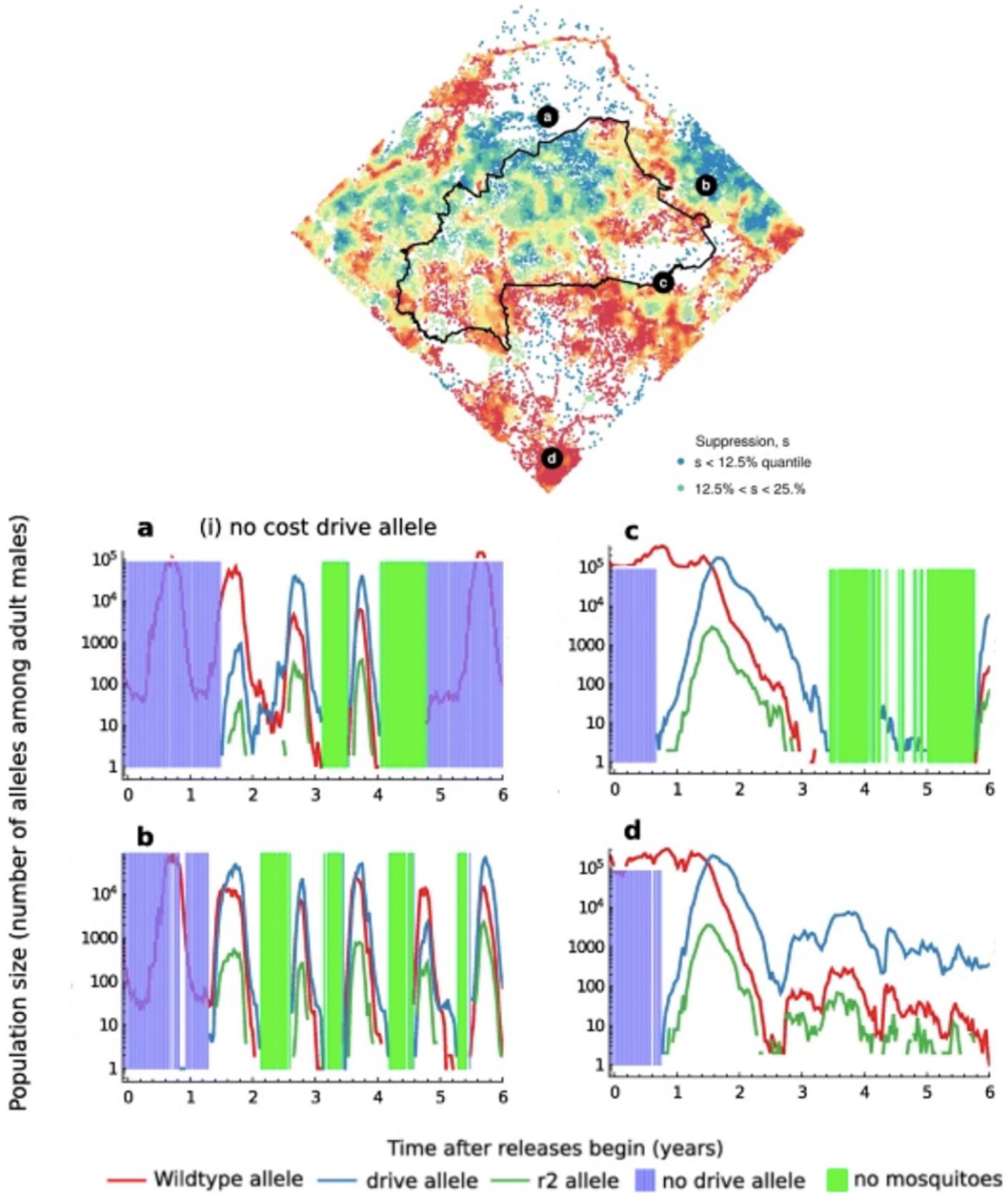
- Monitor for: i) persistence of drive (H) allele, & ii) prevalence of drive-resistant (R) alleles.
- R alleles that are less costly than H alleles may replace the H alleles when few cleavable wild-type (W) alleles remain.



- Monitor for continued function of effector gene.
- This may be lost due to: i) loss-of-function mutations in the effector, or ii) evolution of effector-resistant pathogen strains.

- Marshall JM, Raban RR, Kandul NP *et al.* (2019) Frontiers in Genetics

Post-release monitoring: Suppression



Post-release, suppression gene drive releases should monitor:

- Population size
- Drive-resistant alleles (early detection may help control their spread)
- Persistence of intact drive alleles / extinction-recolonization dynamics
- Check for non-target species (niche replacement by another vector species)
- Malaria incidence (may help to signal suppression failure)

- North AR, Burt A, Godfray HCJ (2020) BMC Biology

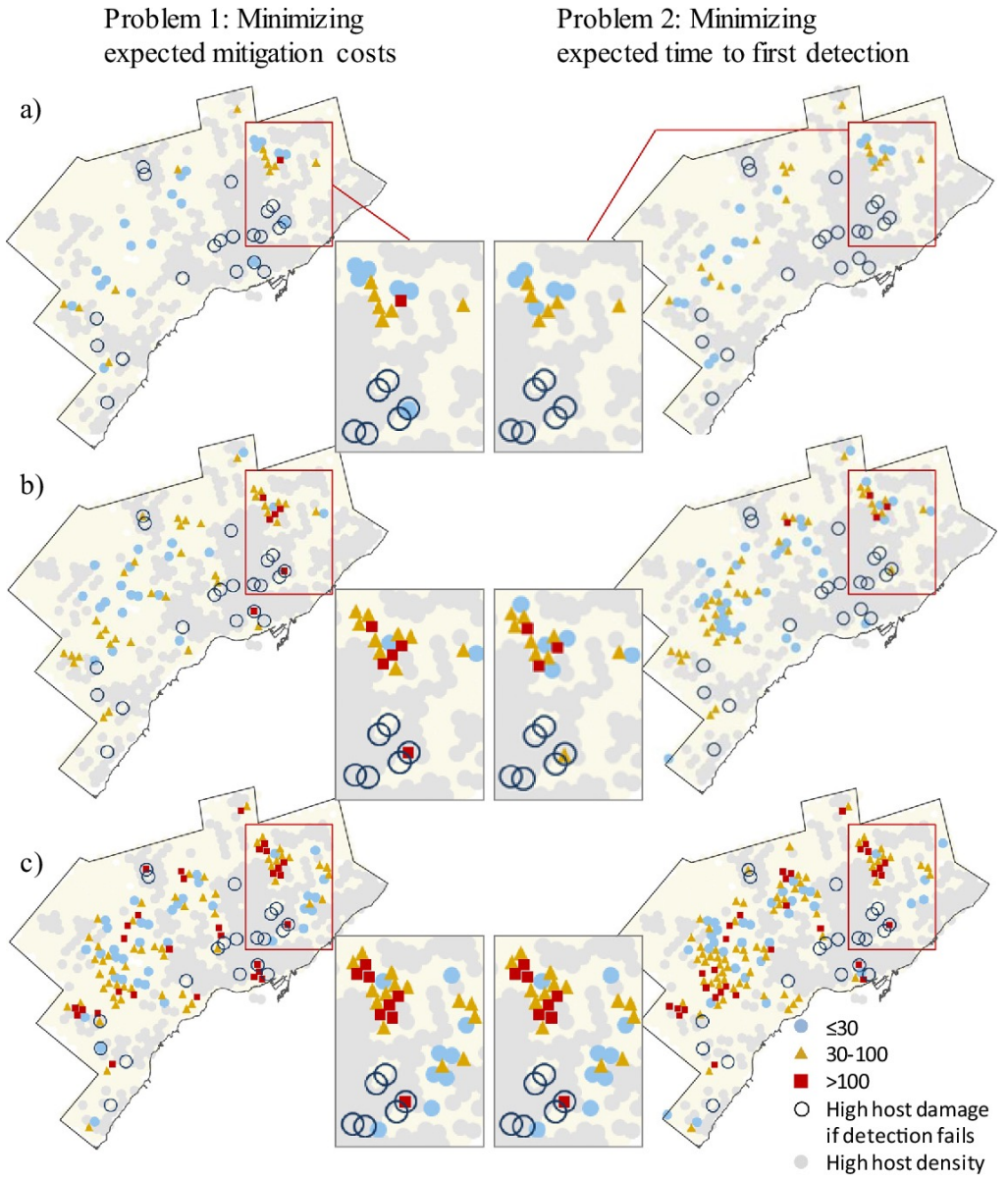
Post-release monitoring: Invasive species

Wide-scaler monitoring needs for gene drive:

- Spatial spread of drive allele when it is only intended to spread locally
- Emergence & spread of alternative alleles - drive-resistant alleles, non-functional effector genes
- Consider: scale, cost, expected effectiveness

Precedent from invasive species monitoring:

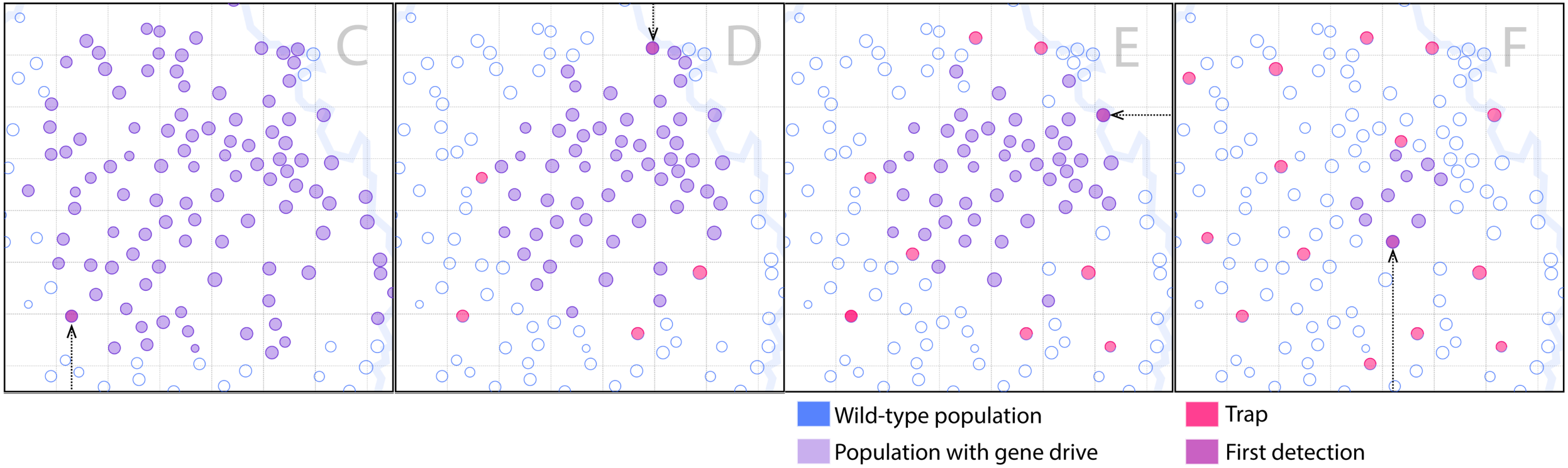
- Account for: life history, geographical distribution, expected pattern of spread, monitoring costs
- Model multiple scenarios
- Determine most cost-effective option
- Early detection is key to minimizing invasion impact



- Yeshamanov R, Haight R, Koch F, Venette R *et al.* (2019) Ecological Economics

Post-release monitoring: Wide-scale spread

- Explore optimal density & placement of traps & frequency of sampling to detect drive alleles, drive-resistant alleles or non-functional effector genes early enough to be managed.
- Expected to be a major cost driver.



- Rašić G, Lobo NF, Jeffrey Gutiérrez EH, Sánchez C. HM, Marshall JM (2022) Frontiers in Genetics

Modeling: Optimal trap placement to minimize time to first detection

MGSurvE 0.7.2.0

Latest version

`pip install MGSurvE`

Released: Aug 11, 2022

MGSurvE

Navigation

- Project description
- Release history
- Download files

Project links

- Homepage

Statistics

GitHub statistics:

- Stars: 0
- Forks: 1
- Open issues/PRs: 0

View statistics for this project via Libraries.io, or by using our public dataset on Google BigQuery

Project description

MGSurvE: Mosquito Gene SurveillancE

MGSurvE is a project that optimizes mosquito traps' placement in complex heterogeneous landscapes in an effort to minimize the time to detection of genetic variants of interest.

Please have a look at the documentation for more info and our pypi package for detailed installation instructions, and tutorials.

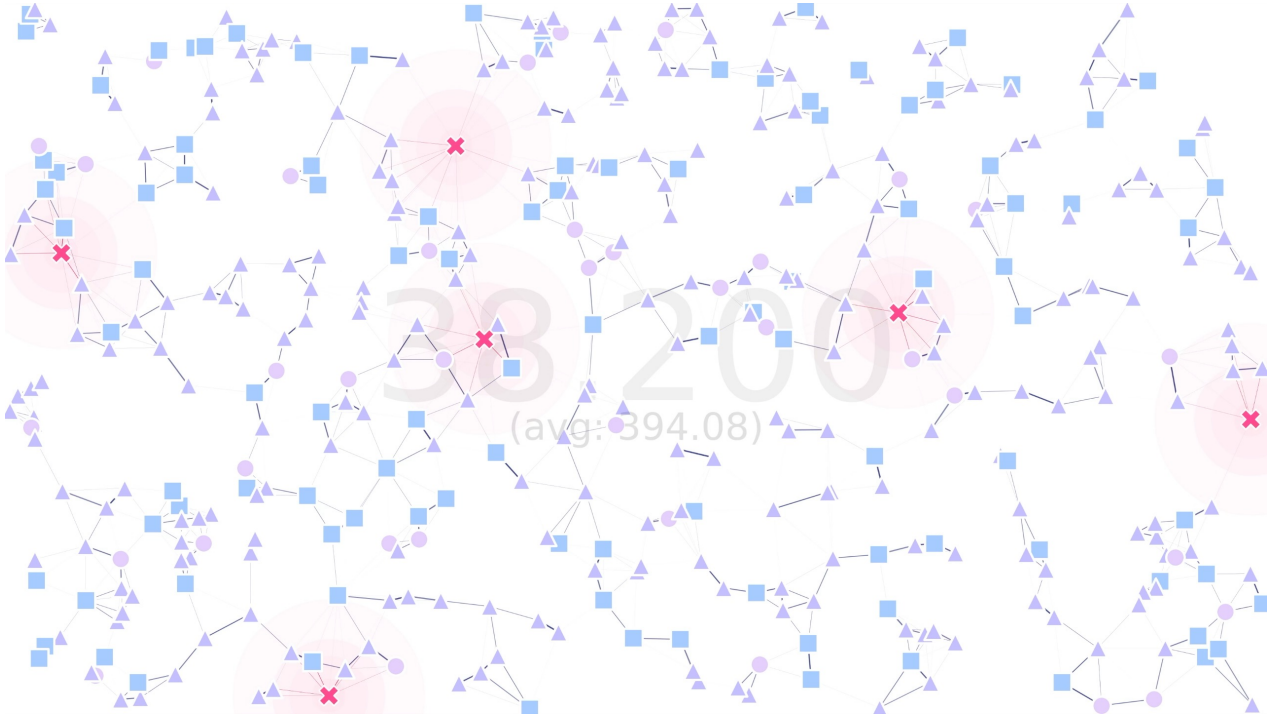
python 3.9 | 3.10 | pypi package 0.7.2.0 | docker img v0.7.2.0 | PyTests passing | Flake8 passing | CondaEnv passing | License GPLv3 | Open Source ? Yes!

To install the package's latest stable version run (usage of anaconda for environment management is strongly recommended):

```
pip install MGSurvE
```

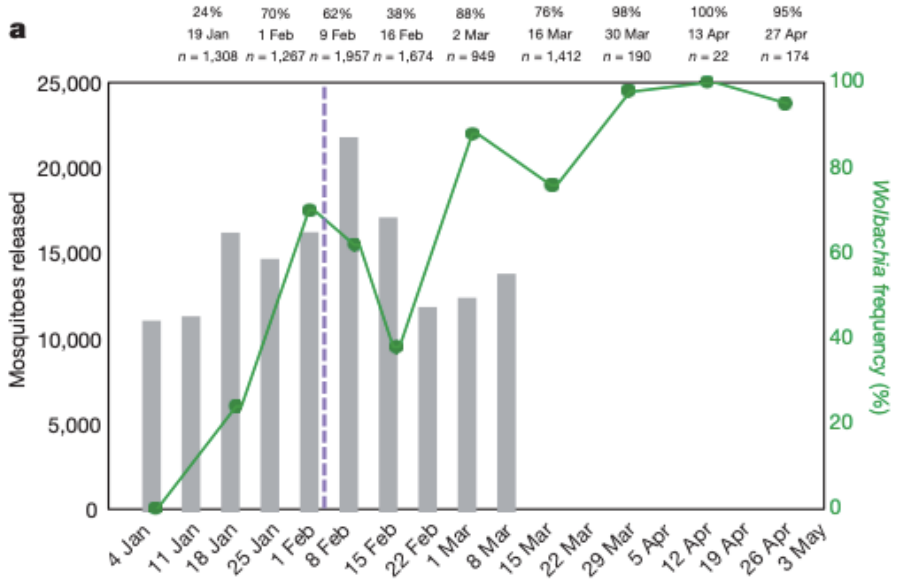
MGSurvE requires the installation of the DEAP optimization package, which should be installed automatically with our previous `pip` command. This package can also be installed with `conda install deap`, if needed; or by having a look at DEAP's documentation for additional methods. Please have a look at our installation instructions for common issues with some of the dependencies. Alternatively, pre-build images from our Dockerhub can be pulled and used to avoid dependencies issues.

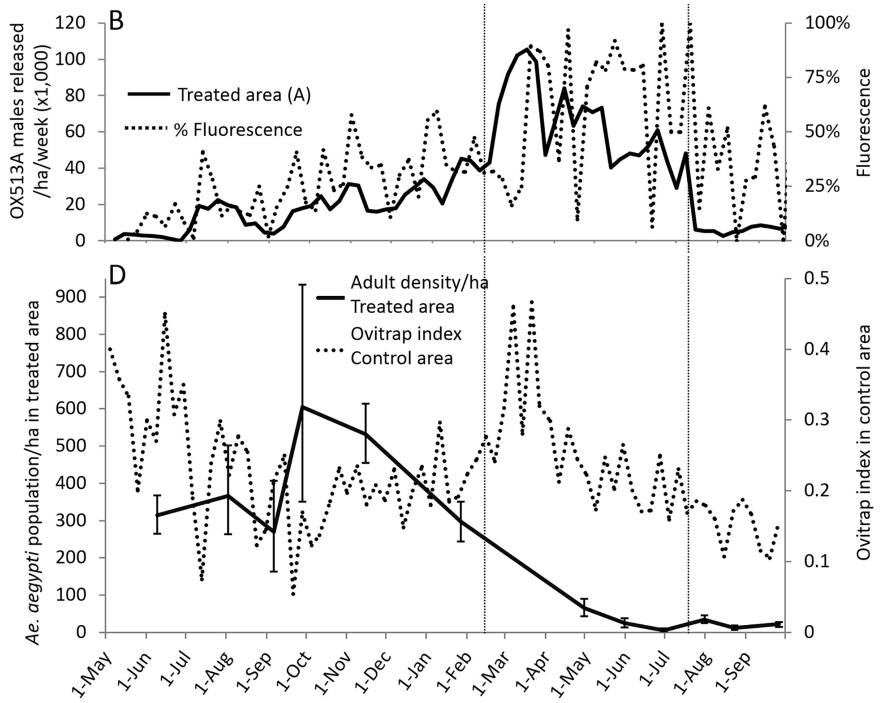
- MGSurvE can inform trap numbers & distribution to detect unwanted spread of H or R alleles within a desired timeframe.



- Sánchez C. HM, Smith DL, Marshall JM (2022) https://pypi.org/project/MGSurvE/

Modeling: Informing adaptive releases

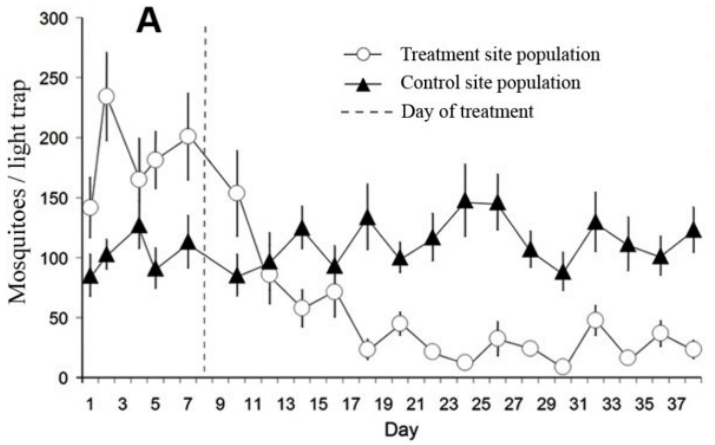


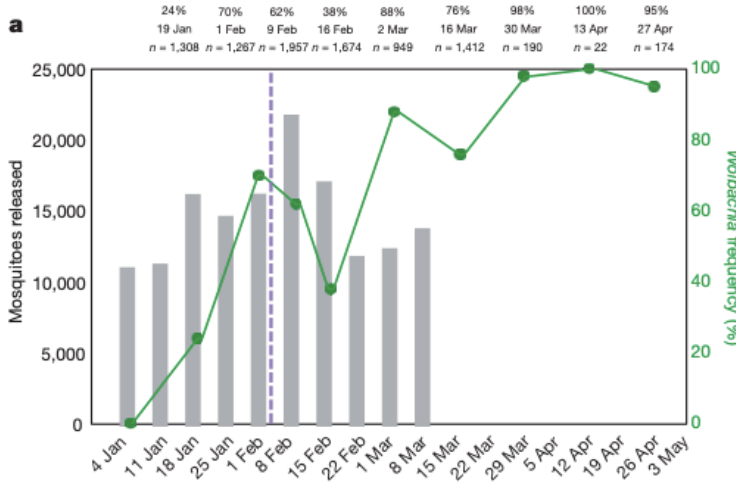


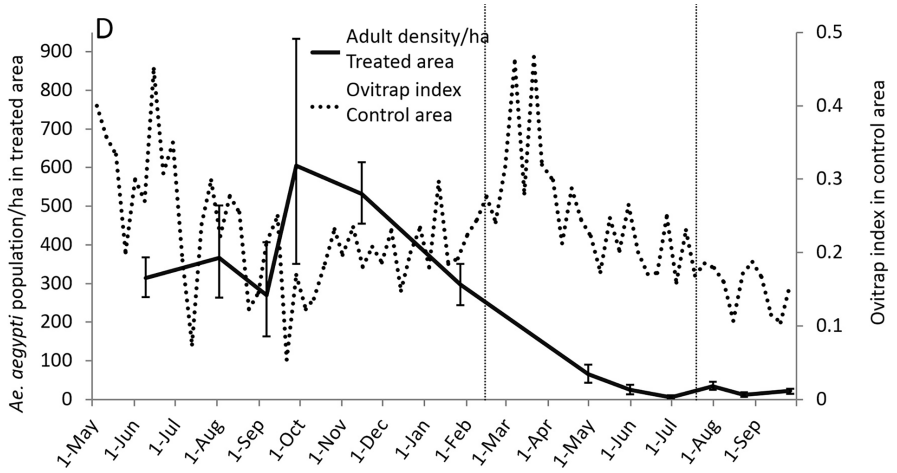
- The *Wolbachia* & RIDL trials used field estimates of fitness to validate or adapt their release program.
- Gene drive systems are described by more parameters. Which parameters should we aim to estimate from trajectories of spread?
- What would the monitoring requirements be to estimate these parameters?

- Hoffmann AA, Montgomery BL, Popovici J *et al.* (2011) Nature
- Carvalho DO, McKemey AR, Garziera L *et al.* (2015) PLoS Negl Trop Dis

Modeling: Desired outcome, required sample size





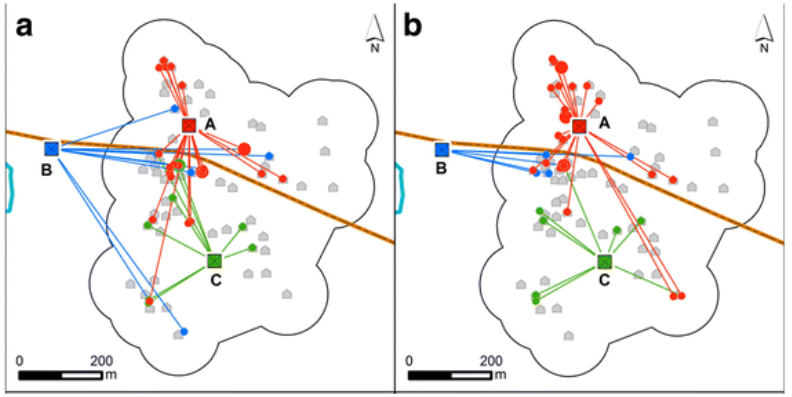


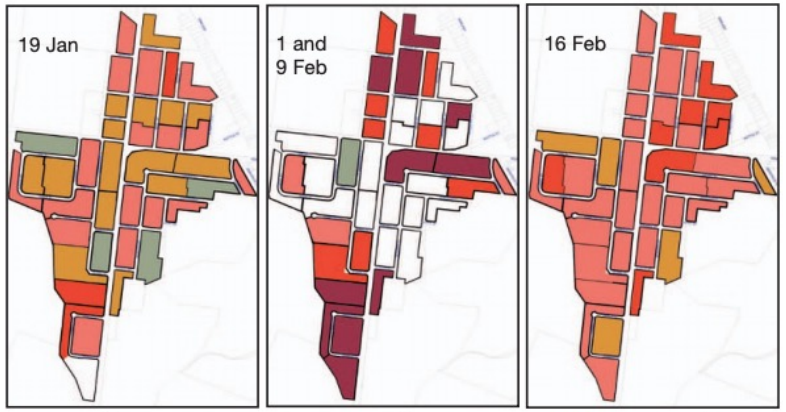
- What are the outcome(s) we would want to demonstrate from a first field trial?
- E.g., effector gene present in >80% / 90% of target species for 1 / 2 years? (replacement)
- E.g., population of target species suppressed by >80% / 90% for 1 / 2 years? (suppression)
- Result achieved within reasonable timeframe for a trial: e.g., 1 year?
- No alternative alleles of concern for wide-scale intervention?
- Infer sample size by ensuring trial is sufficiently powered to measure impact.

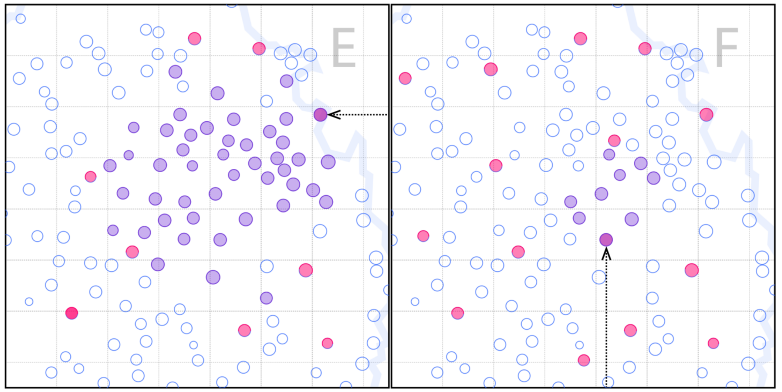
- Müller GC, Beier JC, Traore SF, Toure MB *et al.* (2010) Malaria J
- Hoffmann AA, Montgomery BL, Popovici J *et al.* (2011) Nature
- Carvalho DO, McKemey AR, Garziera L *et al.* (2015) PLoS Negl Trop Dis

Recap

1. Pre-release monitoring:
   - Seasonal & movement patterns
   - DNA sequence polymorphisms at target site
   - Non-target species
2. Monitoring during a release:
   - Assay for drive, resistance alleles are very important
   - Refine parameter estimates, including fitness
   - Consider passively collected epidemiological data
   - Monitor spread to non-target populations (e.g., ports)
3. Post-release monitoring:
   - Consider loss of effector gene function (replacement)
   - Explore causes for loss of population suppression
   - Lessons from invasive species for wide-scale spread
4. Modeling & statistical tools:
   - Optimal number & distribution of mosquito traps
   - Informing adaptive releases
   - Statistical significance to infer impact







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