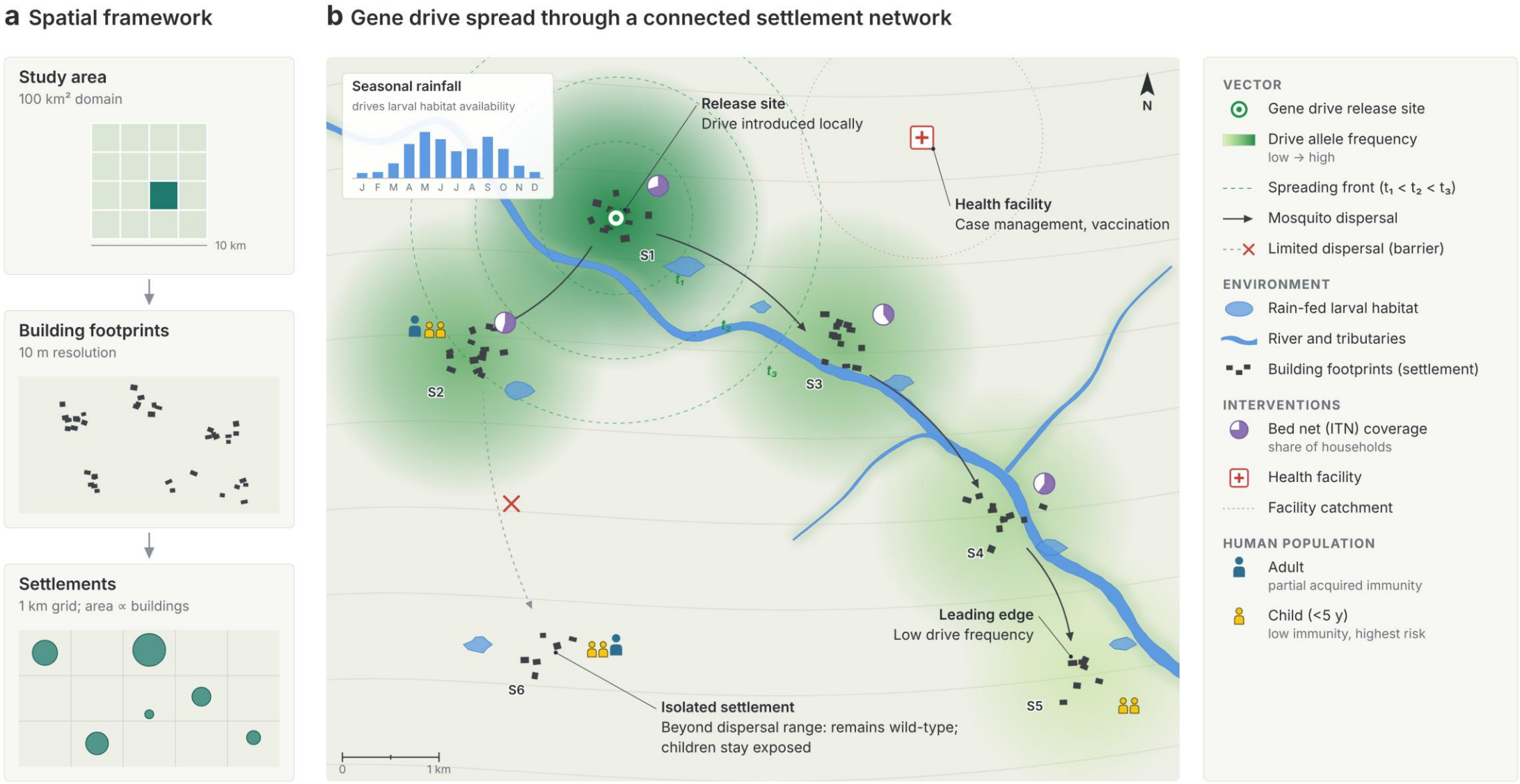
TARGET MALARIA

A Vector Control Research Alliance

Modelling field trials of gene drive releases for malaria vector population suppression

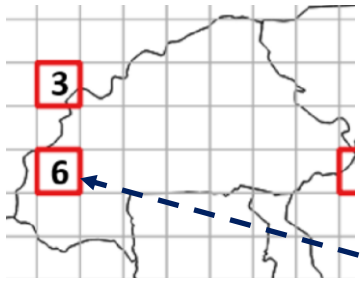
Penelope Hancock & Ace North

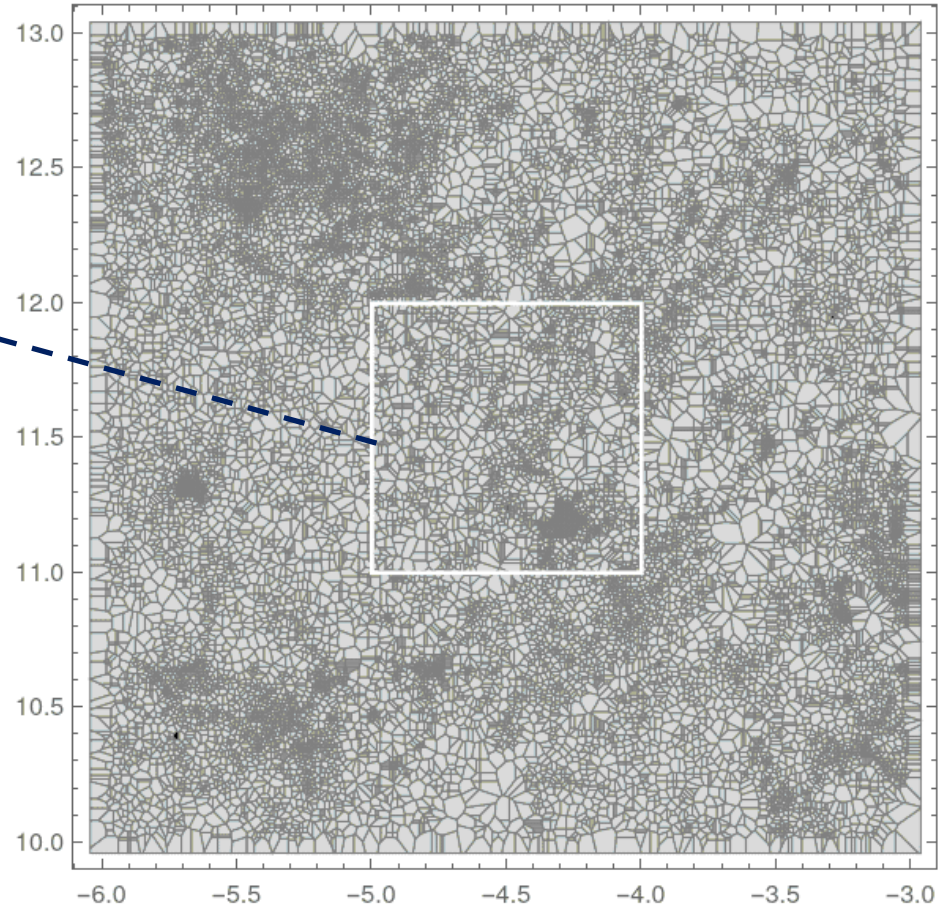
Models for real-world environments

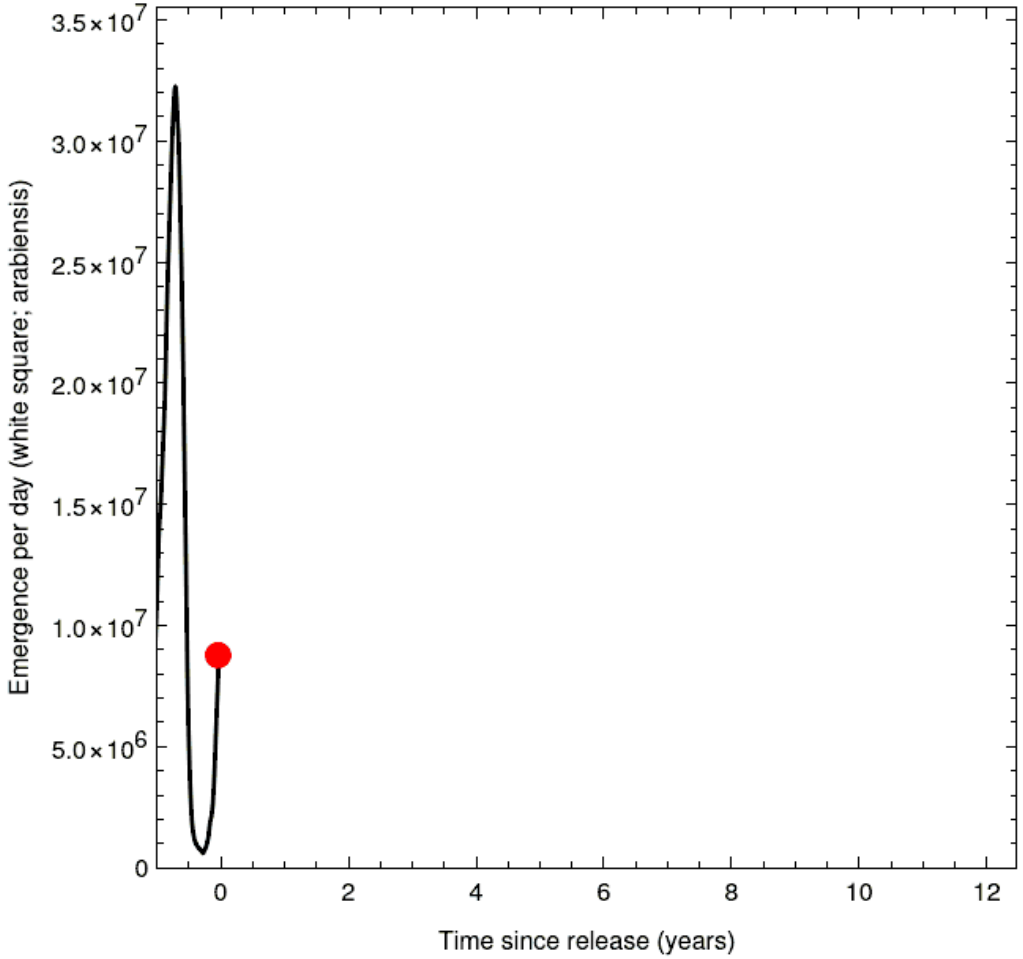


A spatial metapopulation model of gene drive in *Anopheles* species

Example :
Western Burkina Faso







Hancock P.A., North, A. et al.
(2024) *Nature Communications*

Gene drive frequency f

No mosquitoes | 0< f < 0.001 | 0.001< f < 0.01 | 0.01< f < 0.1 | 0.1< f < 0.2 | 0.2< f < 0.5 | f >0.5

More than one model is needed

A hierarchy of modelling approaches:

Simpler mathematical models → **Detailed agent-based simulation models**

increasing detail, realism & computational demand

Simpler mathematical models

Pros	Cons
• Easier to interpret	• Omits biological detail
• Easier to solve and validate	• Spatial representations are difficult to analyse
• Faster run time	
• More robust	

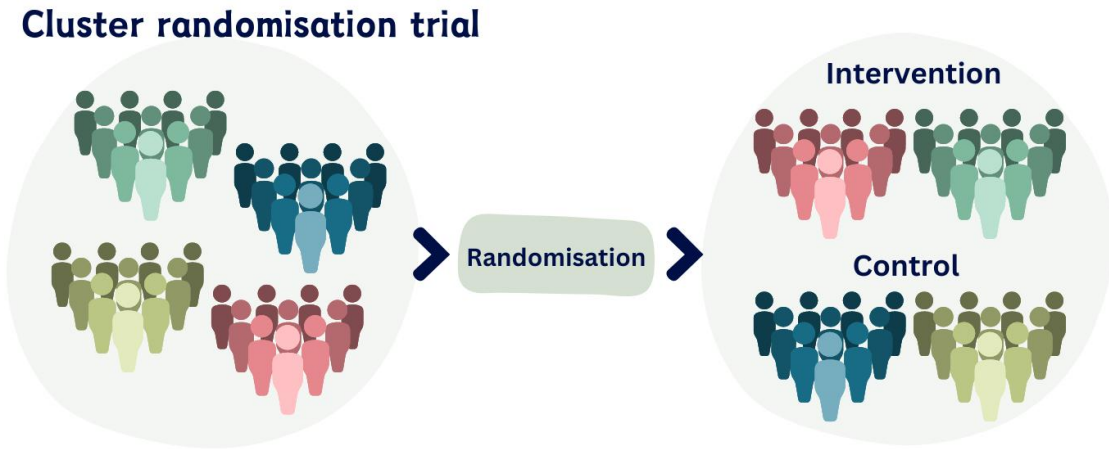
Detailed agent-based simulation models

Pros	Cons
• Greater realism	• More difficult to interpret
• Represent spatial processes	• More likely to contain errors
• Link ecological and epidemiological processes	• More difficult to check/validate
	• Long time to run
	• Requires a lot of computational resources

Modelling to inform gene drive field trials

Cluster Randomised Controlled Trials

- **Gold standard method to assess intervention epidemiological efficacy.**
- Instead of randomising individuals, whole groups (clusters) such as schools, clinics, or communities are randomised.
- Everyone in the selected cluster receives the same intervention.
- Useful when individual randomisation is impractical or risks contamination (people within a group influencing each other).
- Outcomes are compared between clusters to evaluate the intervention's effect.



Challenges for trial design for gene drives

Uncertainty in impact/efficacy

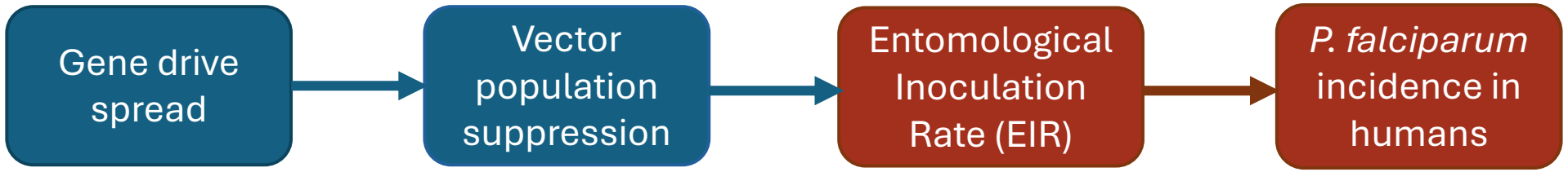
Space-time spread of the gene drive

- Uncertain rate of spatial spread
- Time-varying impact/efficacy
- ‘Spillover’ from intervention to control sites
- Non-reversible and spreads continually

Need for adaptive trial designs

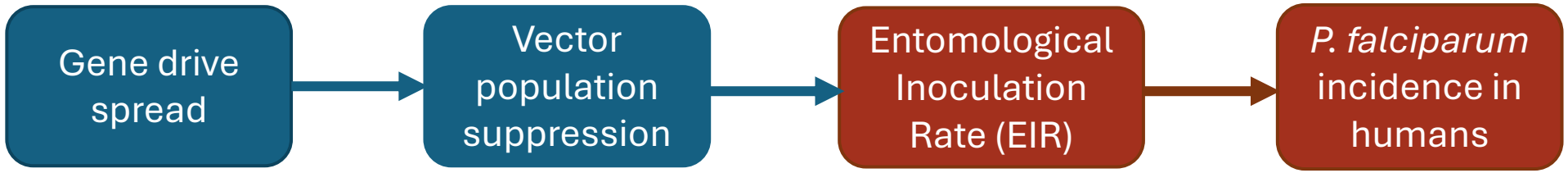
Modelling trial designs

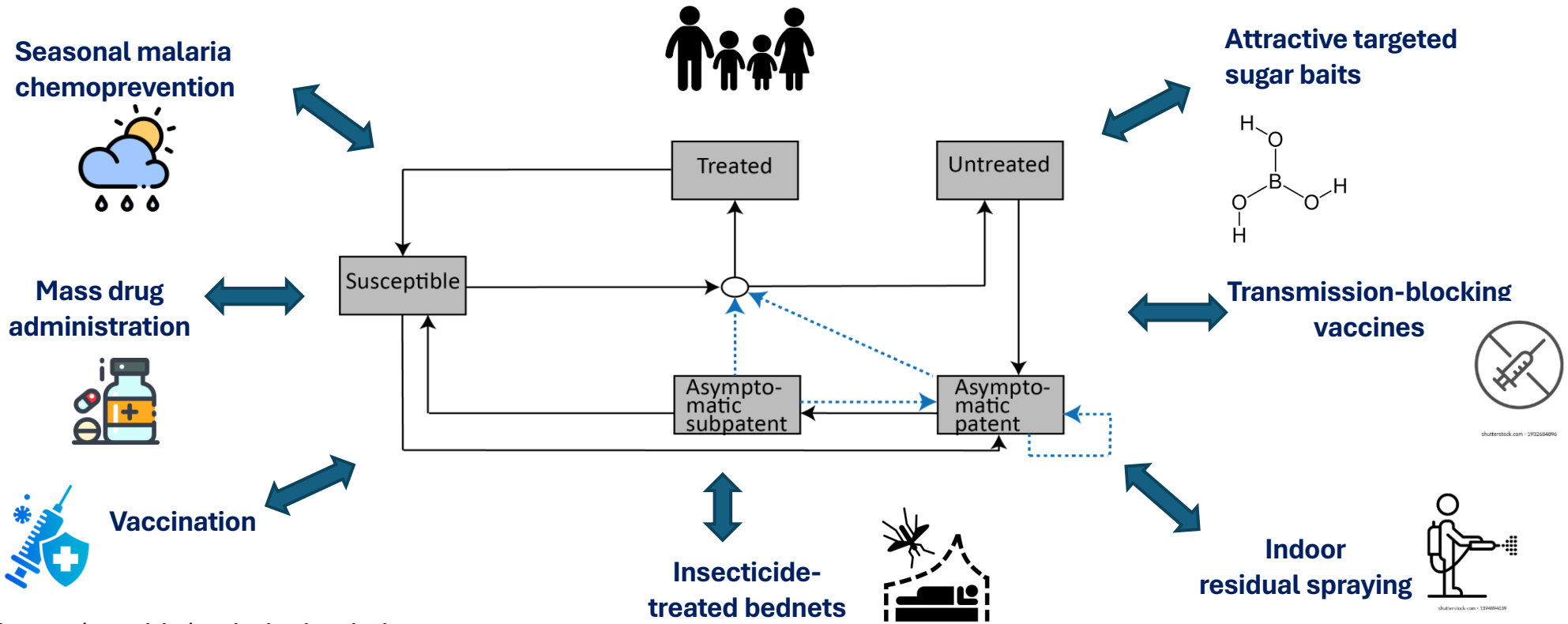
Combined entomological and epidemiological model:



Modelling trial designs

Combined entomological and epidemiological model:



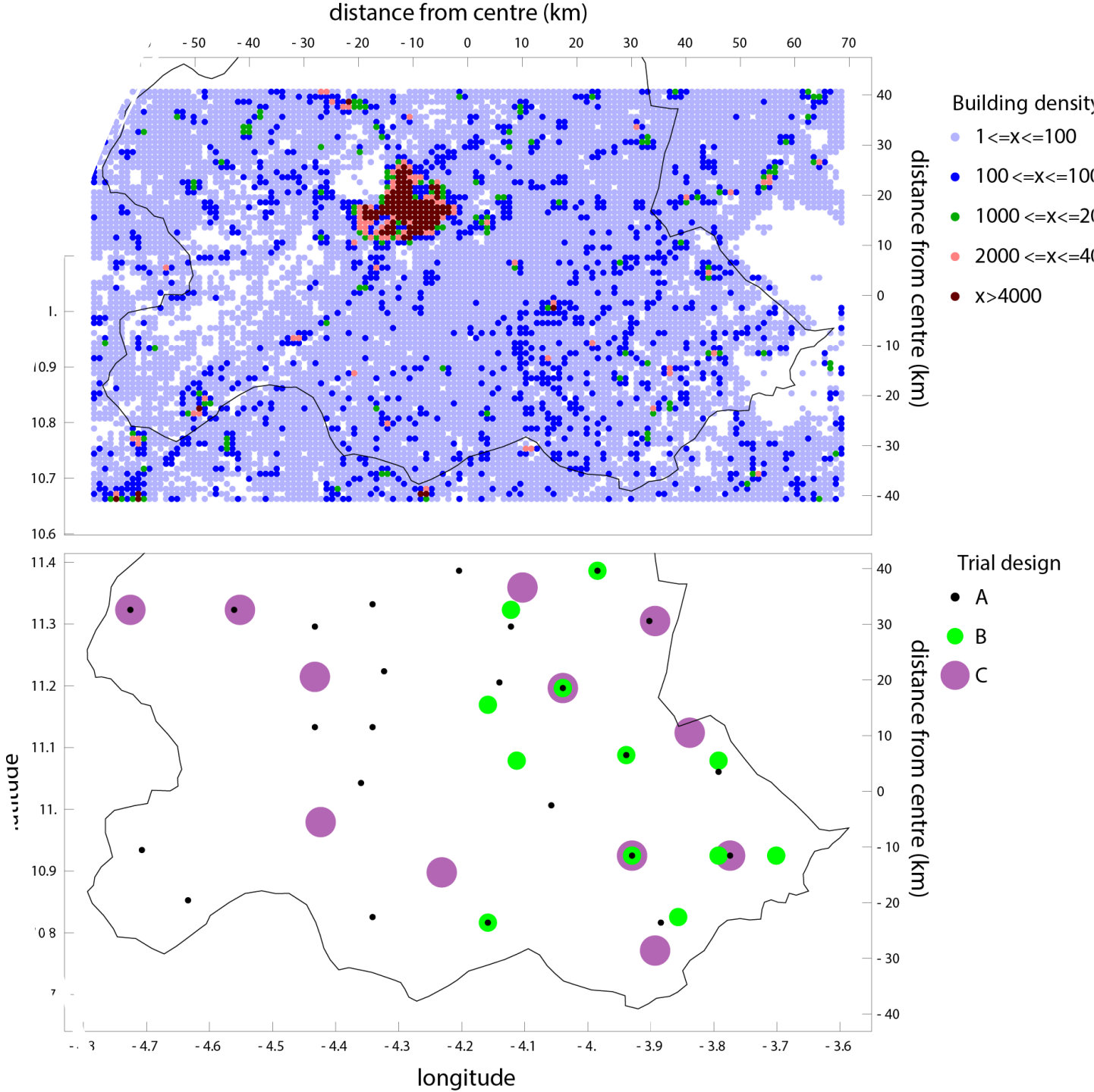


https://github.com/mrc-ide/malariasimulation

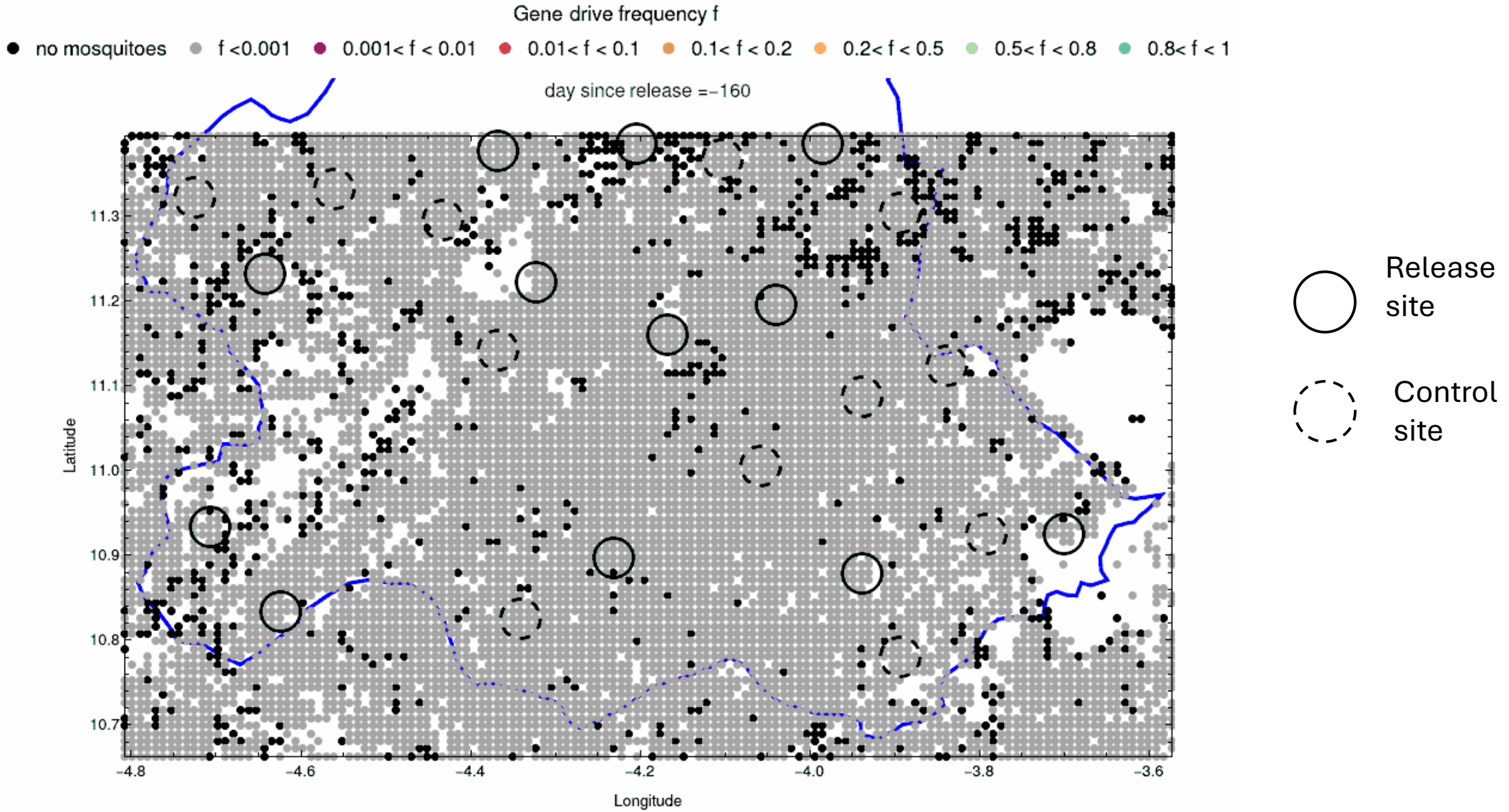
Modelling CRCTs

Three designs:

- **Design A:**
  - 24 clusters
  - minimum separation distance 10km
- **Design B:**
  - 12 clusters
  - minimum separation distance 10km
- **Design C:**
  - 12 clusters
  - minimum separation distance 15km

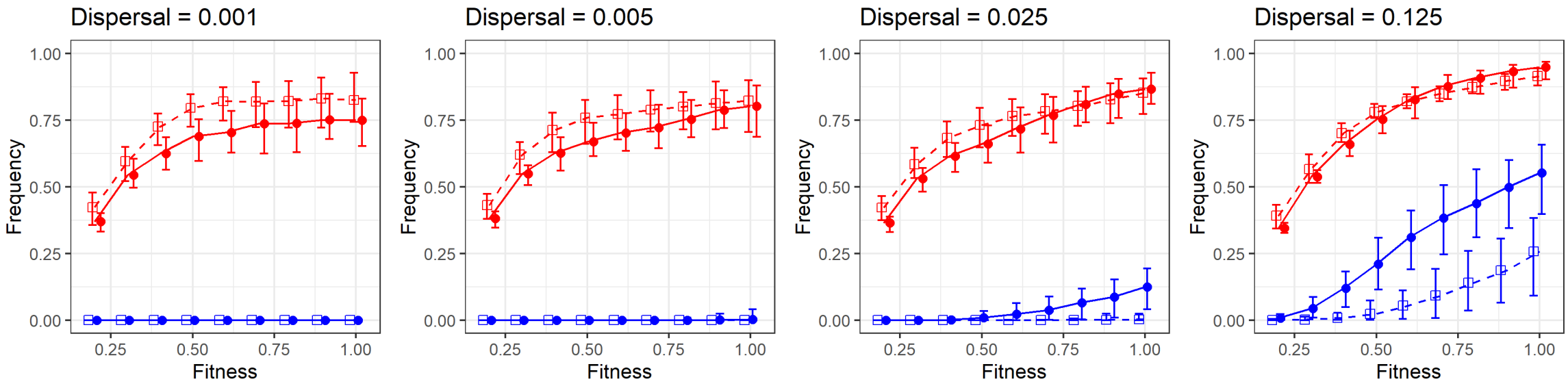


A spatial simulation model of a gene drive trial



Estimating spillover of gene drive into control sites

Design A:



Average gene drive frequency in release sites:

3-year trial

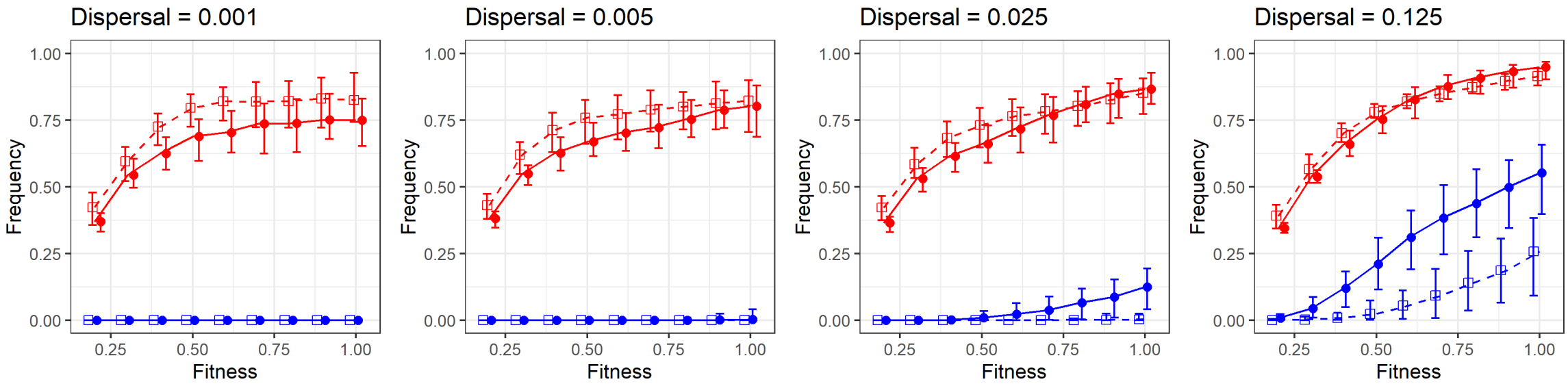
2-year trial

Average gene drive frequency in control sites:

3-year trial

2-year trial

Estimating spillover of gene drive into control sites



Spillover $S^{(j)}$: j=1 for 2-year trial
: j=2 for 3-year trial

$$S^{(j)} = \frac{\bar{f}_C^{(j)}}{\bar{f}_R^{(j)}}$$

Average frequency in control sites over j rainy seasons

Average frequency in release sites over j rainy seasons

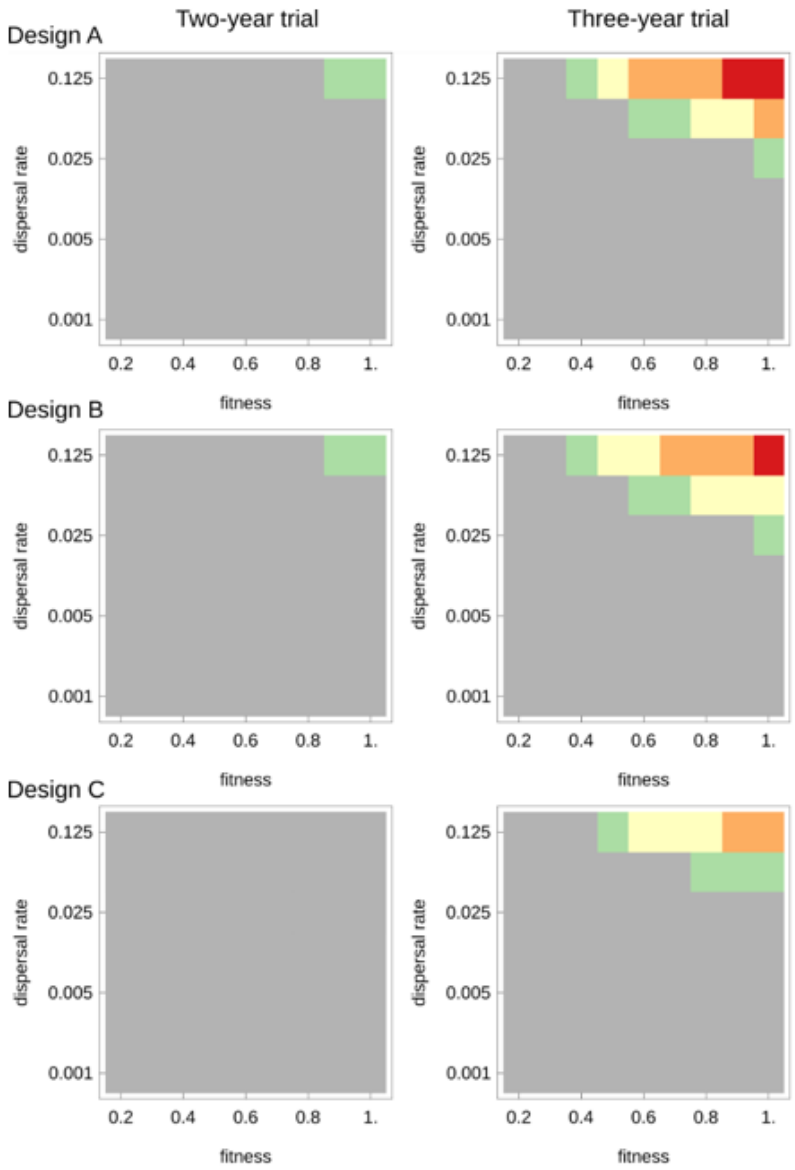
- $S^{(j)}$ ranges from 0 to 1

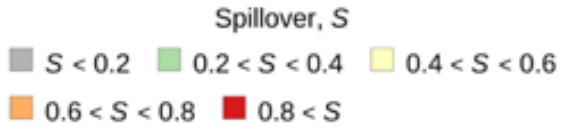
Estimating spillover of gene drive into control sites

Design A (24 clusters)

Design B (12 clusters)

Design C (12 clusters 15 kms apart)





- Spillover is low for a large part of the parameter space (*fitness of heterozygotes vs dispersal rate*)
- Spillover is higher for the Designs A and B compared to Design C
- Spillover is higher for the 3-year trial compared to the 2-year trial

Estimating epidemiological impacts

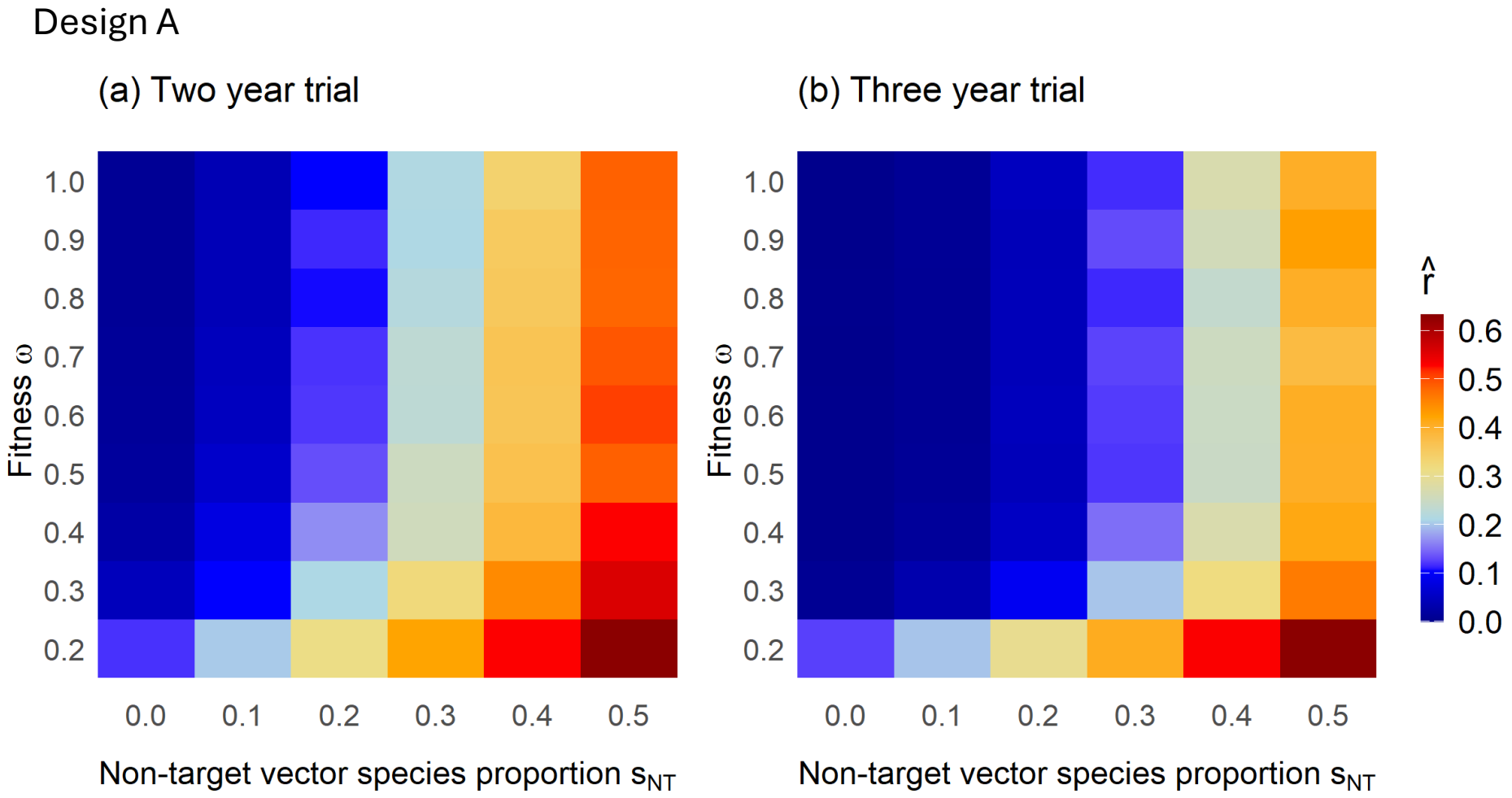
- The estimated epidemiological impact is the **rate ratio** $\hat{r}$

$$\boldsymbol{log}(\hat{\boldsymbol{r}}) = \bar{\boldsymbol{l}}_{\boldsymbol{i=1}} - \bar{\boldsymbol{l}}_{\boldsymbol{i=0}}$$

  - $\bar{\boldsymbol{l}}_{\boldsymbol{i=1}}$ is the log of the **mean malaria prevalence** in the release sites
  - $\bar{\boldsymbol{l}}_{\boldsymbol{i=0}}$ is the log of the **mean malaria prevalence** in the control sites

Estimating epidemiological impacts

- In the absence of spillover ($S^{(j)} < 0.01$) $\hat{r}$ is an unbiased estimator of r

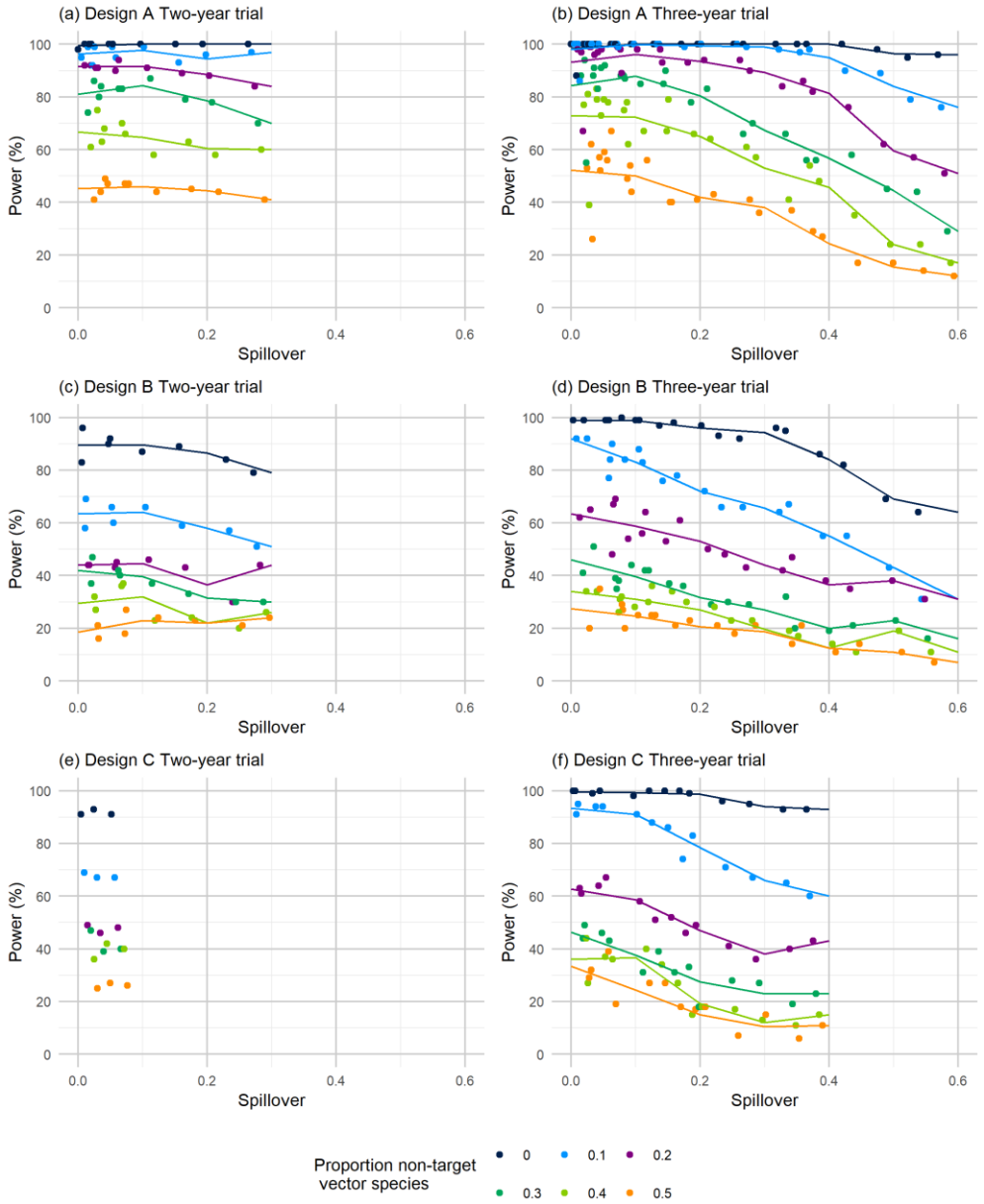


Effects of spillover on statistical power

Design A (24 clusters)

Design B (12 clusters)

Design C (12 clusters 15 kms apart)



- Trials with **smaller numbers of clusters** are more affected by spillover
- Power was **highest** for trials with more clusters despite greater spillover
- Power was **highest** for trials with longer durations despite greater spillover
- Trials have much higher power when **residual transmission by non-target** vector species is low

Summary

- Mechanistic models of spatial gene drive dynamics can identify tradeoffs between spillover, trial size, and trial duration in different epidemiological settings.
- Designs need to balance minimising spillover against achieving sufficient cluster numbers and long enough trial durations.
- Trials are much more efficient in areas where epidemiological impacts are greater due to low residual transmission by non-target vector species.
- Models to inform designs in specific settings need to be carefully calibrated using baseline data.

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Thank you

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