System dynamics to support targeted and climate-informed releases of *MB*-infected mosquitoes for malaria control in Kenya

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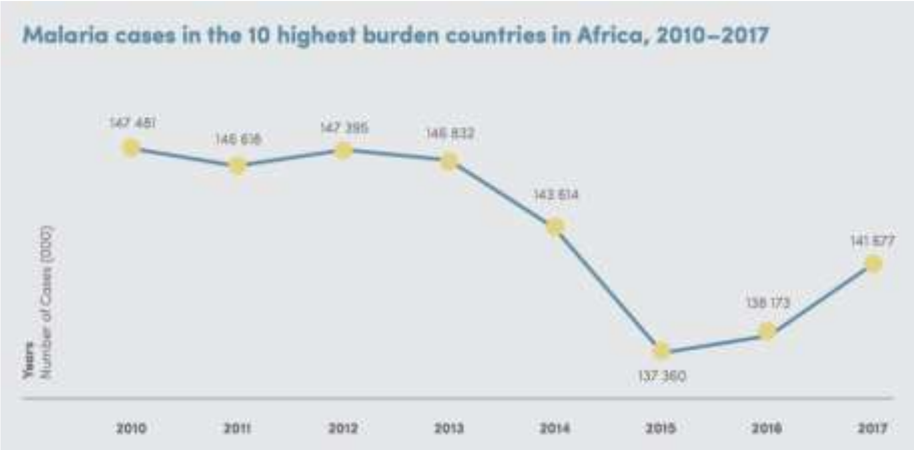
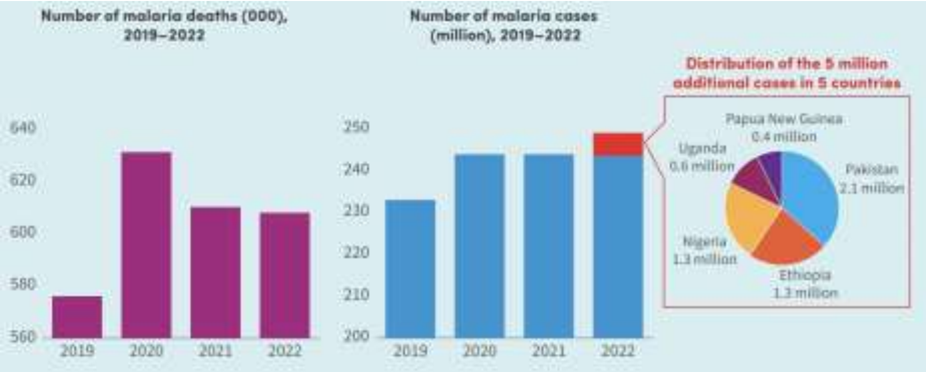
Malaria: Challenges in its control efforts

Trend in malaria

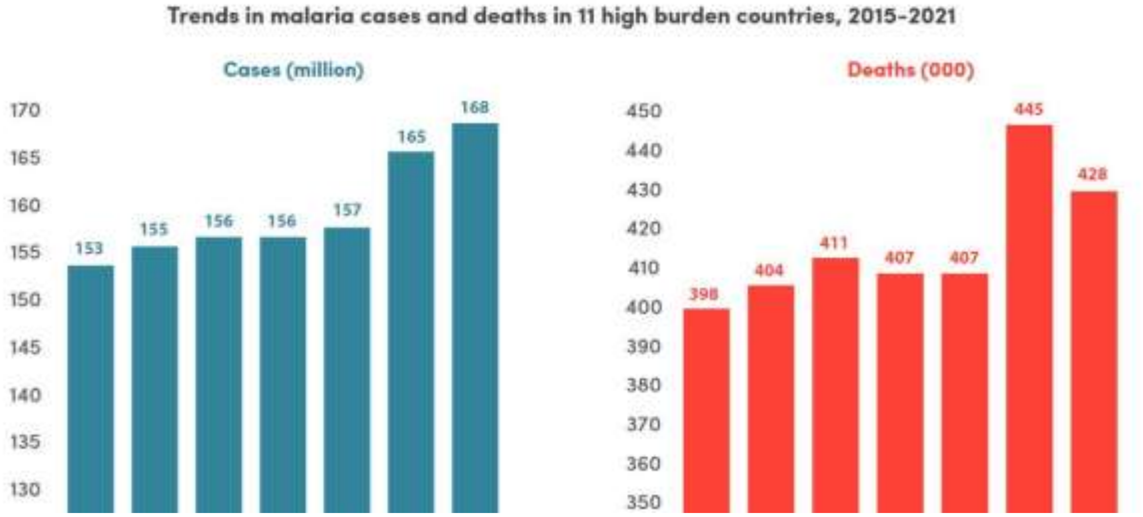
Since 2015, there is a resurgence in the number of malaria cases



WHO



MMV



World malaria report 2021

Implemented strategies

- Indoor Residual Spray
- Larvicides
- Insecticide Treated Nets
- Preventive drugs

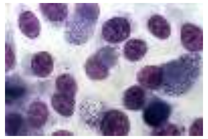
Challenges

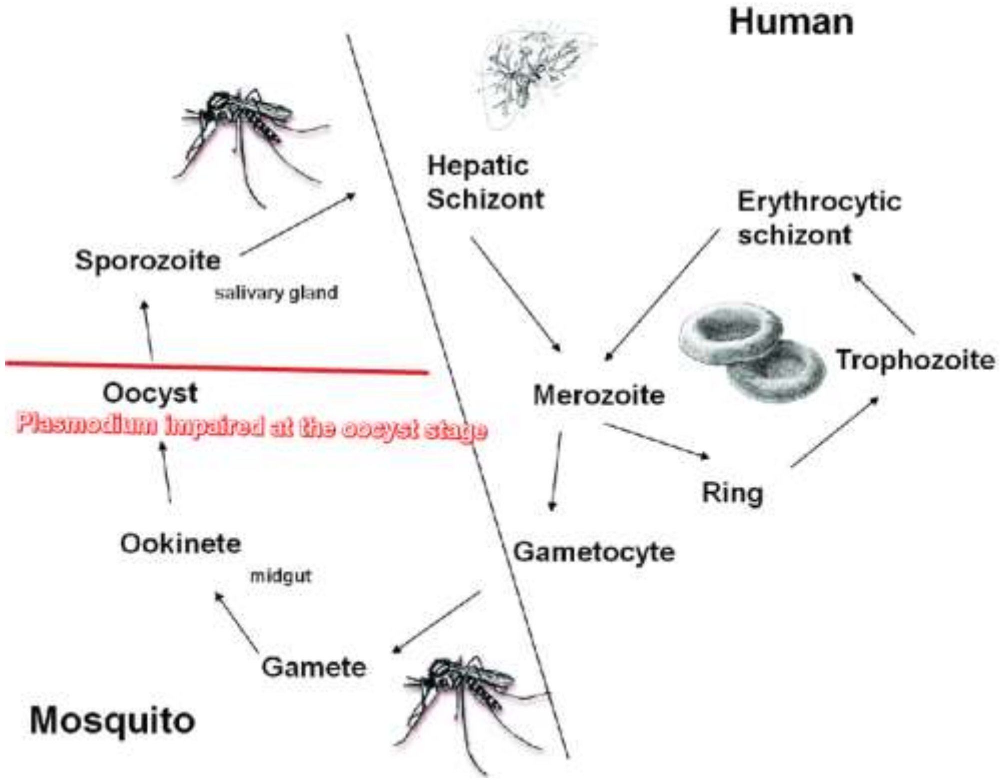
- Insecticide resistance
- Drug resistance

So..
There is need for innovative malaria control strategies

Microsporidia MB-mediated *Plasmodium* transmission blocking

Microsporidia MB, intracellular simple eukaryotes, classified within or as a sister group to fungi, impair the Plasmodium development at the oocyst stage.





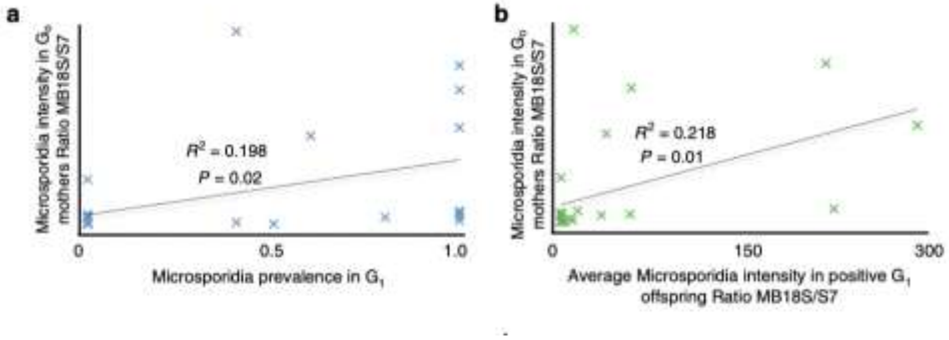
Microsporidia MB-properties

Vector hosts :

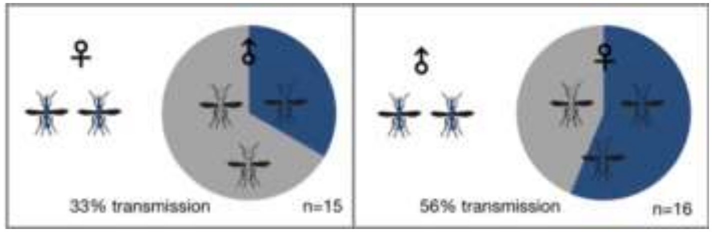
- Anopheles arabiensis
- Anopheles funestus
- Anopheles coluzzi

✓ No significant effect on fitness

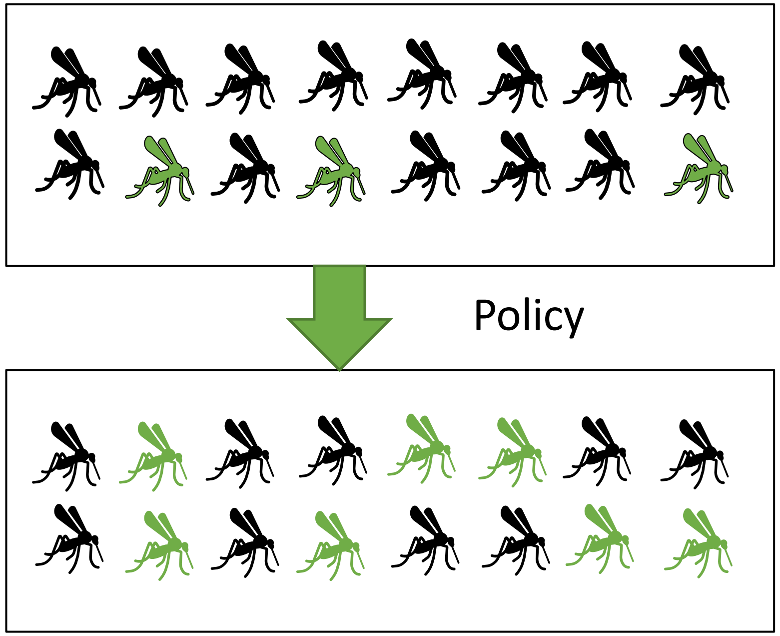
The *MB infection is transmitted to the next generation (G1) (vertical transmission) 45-100%*



The *MB infection is transmitted horizontally from female to male and female to male through mating*



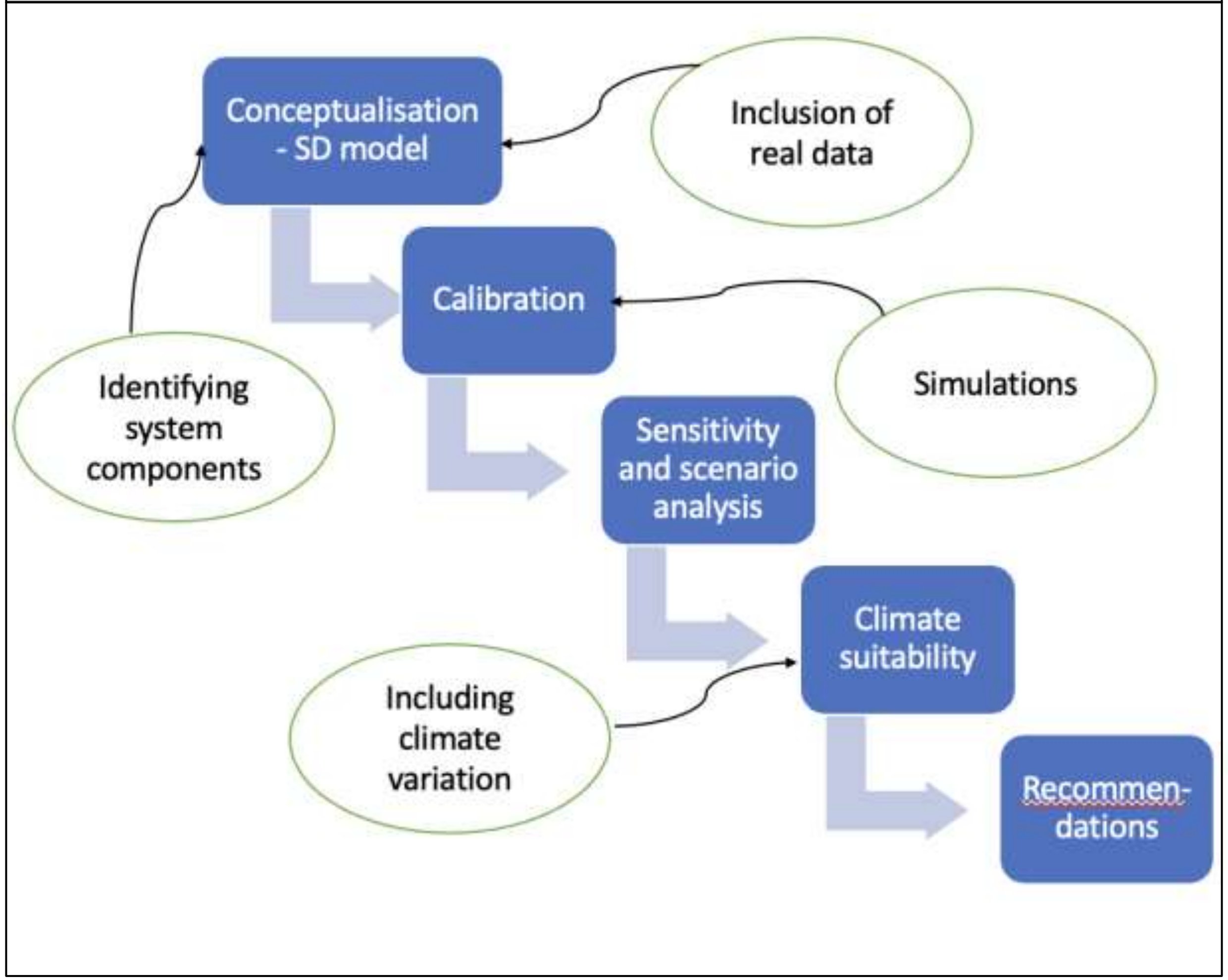
Investigating the control potential of MB



Goal

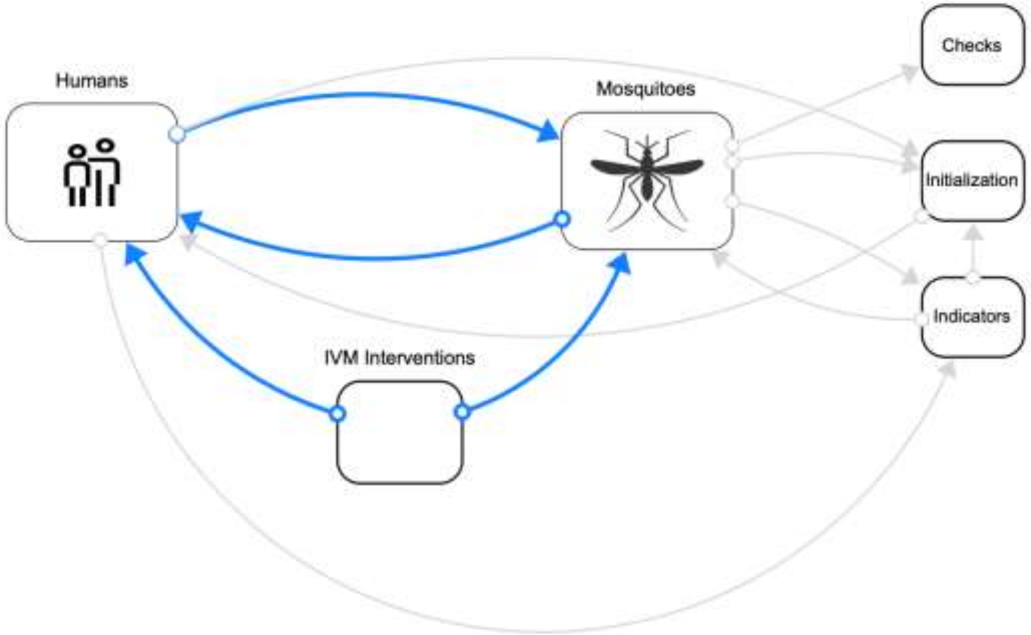
Supporting the analysis of how targeted *Microsporidia MB* release program can contribute to reducing malaria case burden.

Method : System dynamics model



Developing the System Dynamics model

Humans are distributed into :
- ✓ Susceptible
- ✓ Infected
- ✓ Recovered



Release policy is defined :
- ✓ Number of released mosquitoes (per capita per year) (How many)
- ✓ Release period and total duration. (How long)
- ✓ Release frequency (How often)

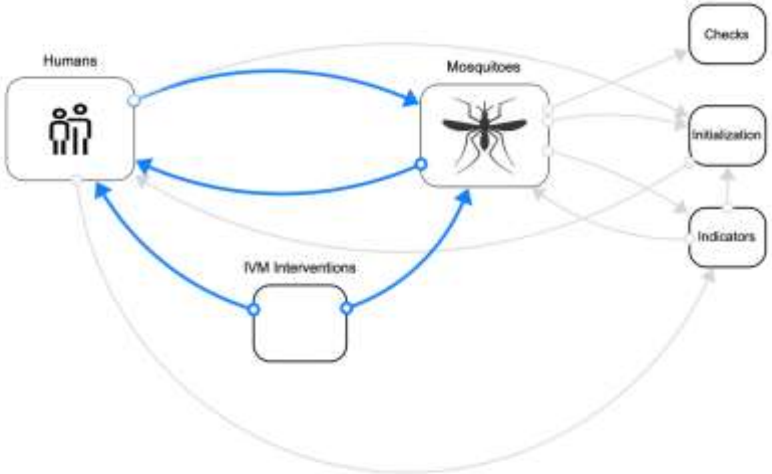
Environmental factors :
- ✓ Temperature
- ✓ Rainfall
- ✓ Humidity

Additional integrated strategies considers :
- ✓ Insecticide Treated Nets
- ✓ Indoor residual spray
- ✓ Environmental management measures

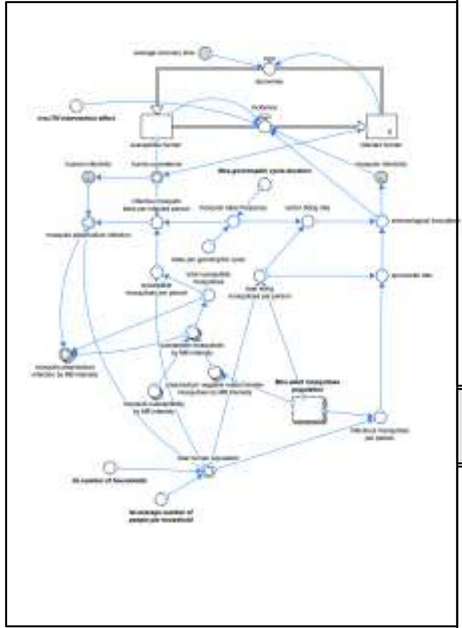
Mosquitoes are disaggregated by :
- ✓ Gender [2]: established at oviposition
- ✓ Age [41]: time-based, starting from pupation
- ✓ Mating [2]: tracks female only, age-based probability, mate only once
- ✓ MB Intensity [4]: negative, low, mid, high CT; progress is time-based
- ✓ Plasmodium [4]: negative; gametocytes, oocyst, sporozoites

Overview of the system dynamics model

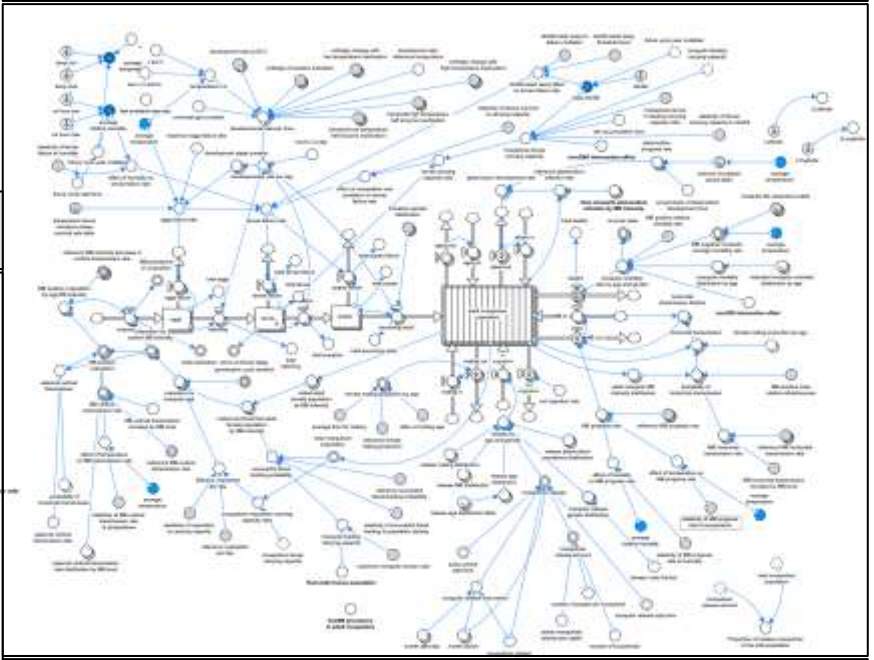
The *system dynamics model* proposed here is a highly aggregated mathematical model built using the software Stella Architect.



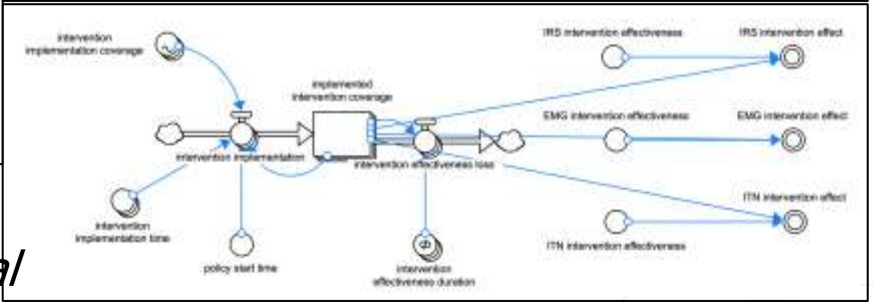
Human module



Mosquito module



Additional interventions : ITN, EMG, IRS



ITNs : Insecticide Treated Nets, EMG : Environmental Management Measures, IRS : Indoor Residual Spray

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Calibration using Ahero, Kenya data

Data in Ahero

- Mosquito data available from July 13, 2021 to December 27, 2023 (*Day 194 to Day 650*)
- Malaria data available from July 2021 to December 2023

Statistics of fit

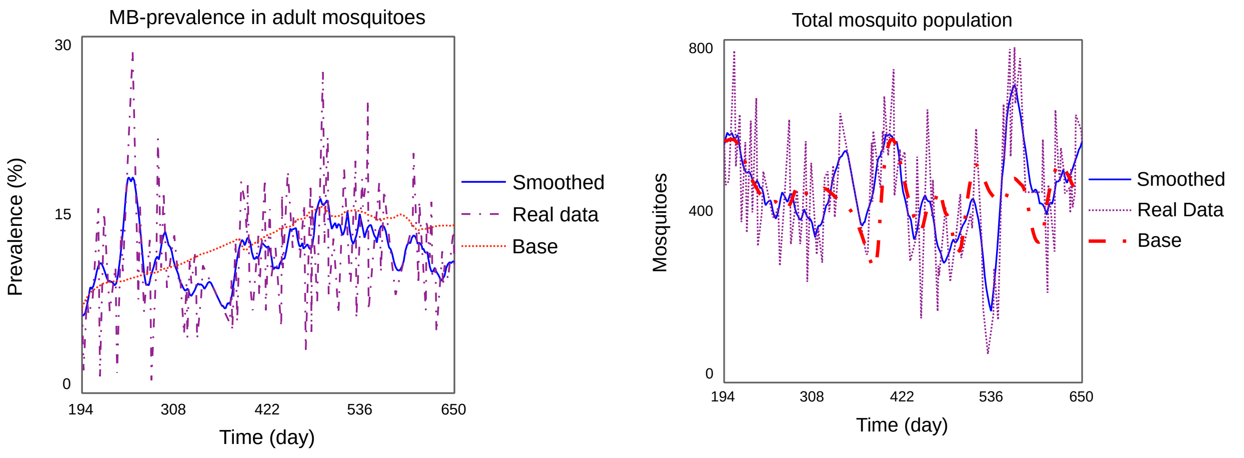
Metrics are RMSPE (Root Mean Square Percentage Error) and TBIAS (Mean Bias).

✓ $RMSPE = \sqrt{\frac{1}{n}\sum_{t=1}^{n}\left(\frac{y_t - \bar{y}_t}{y_t}\right)^2}$

✓ $TBIAS = \sqrt{\frac{1}{n}\sum_{t=1}^{n}(\bar{y}_t - y_t)}$

RMSPE (Root Mean Square Percentage Error) assesses accuracy relative to the magnitude of observed values while TBIAS (Mean Bias) highlights the average deviation between observed and predicted values.

RMSPE ≈ 1 *and* $TBIAS \approx 0.6\%$



RMSPE ≈ 0.2 *and* $TBIAS \approx 3.2\%$

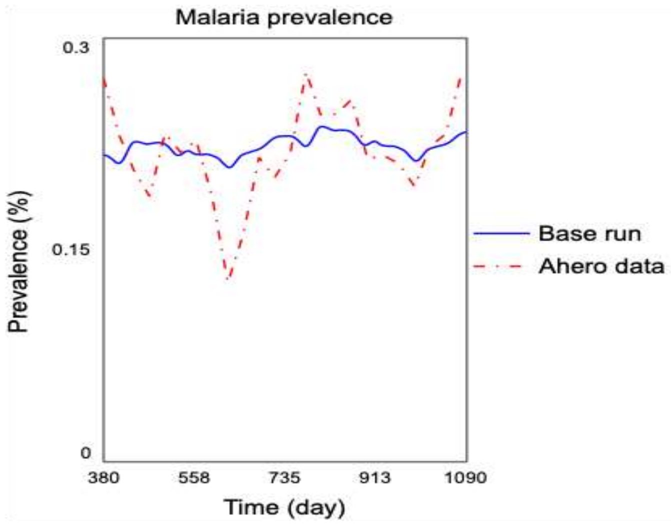
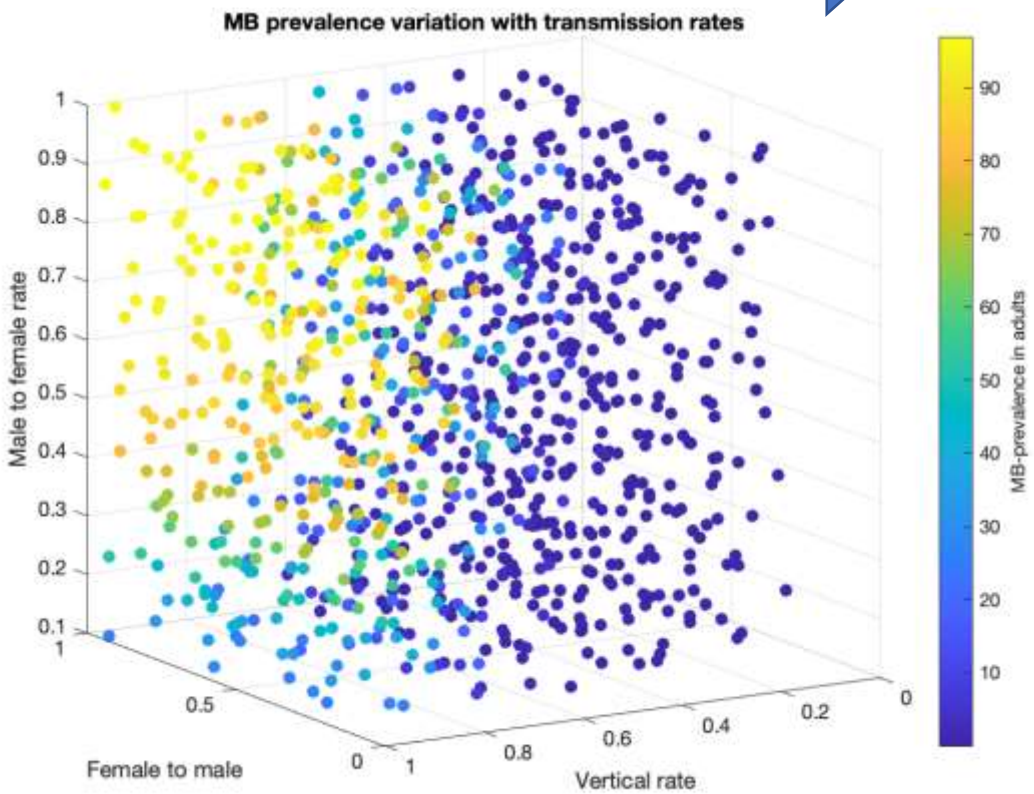


Figure 6. Malaria prevalence in the model calibrated to Ahero data.

So..
While the model cannot capture short terms fluctuations, it does appropriately capture the underlying trends

Importance of the strain of *MB*

Effect of MB transmission rates

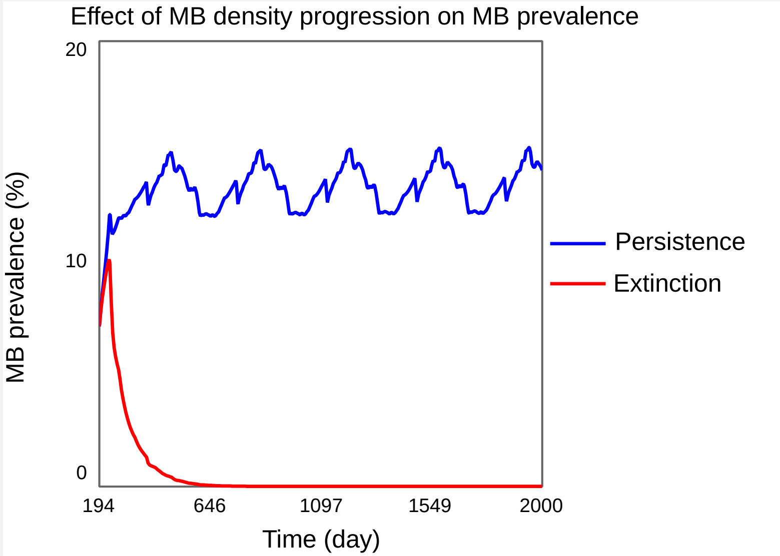


A sensitivity analysis of 1000 runs where the vertical transmission, male to female and female to male horizontal transmission rates are selected following a uniform distribution between 0.1 and 1.

A low prevalence of *MB*-infected mosquitoes (< 20%) in adults can be explained either by a low vertical transmission rate (< 0.5) or a high vertical transmission (> 0.6 & < 0.75) with a low male to female horizontal transmission rate (< 0.35).

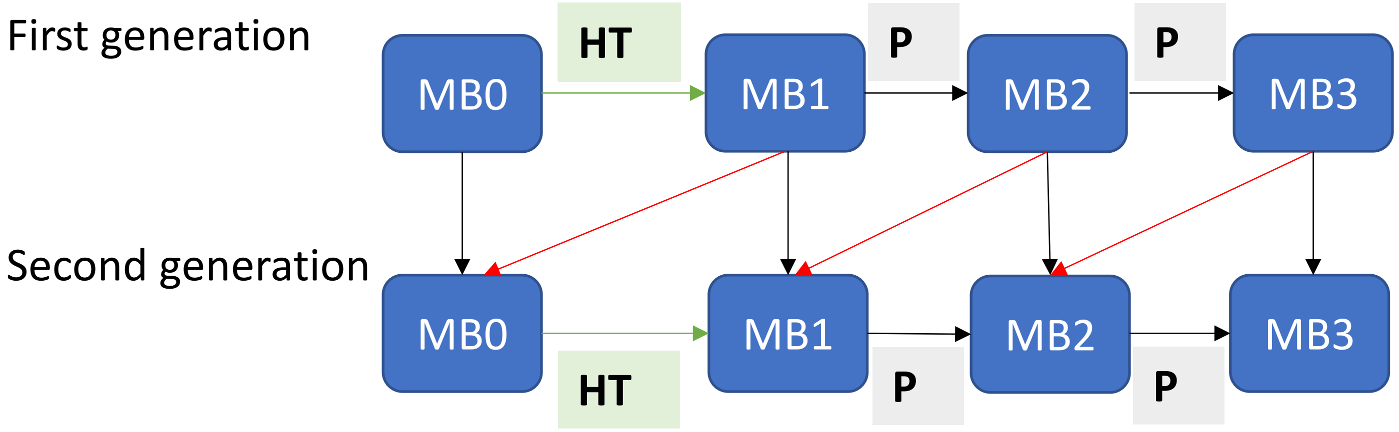
Importance of the *MB* density in the mosquito

Effect of MB progress rates



	Reference MB progress rate			
Persistence scenario	MB0	MB1	MB2	MB3
	0	0.3	0.2	0
Extinction scenario	MB0	MB1	MB2	MB3
	0	0.01	0.01	0

Assumption



HT Horizontal transmission

P Progress rate (time-based)

In the extinction case which might seem unexpected, the progress rate from *MB1* to *MB2* and from *MB2* to *MB3* is very low. Thus, most *MB*-infected mosquitoes have a low CT, which is lost from one generation to the next, this easily led to the extinction of *MB*-infected mosquitoes.

Predicted impact of MB on malaria prevalence

For various release frequency

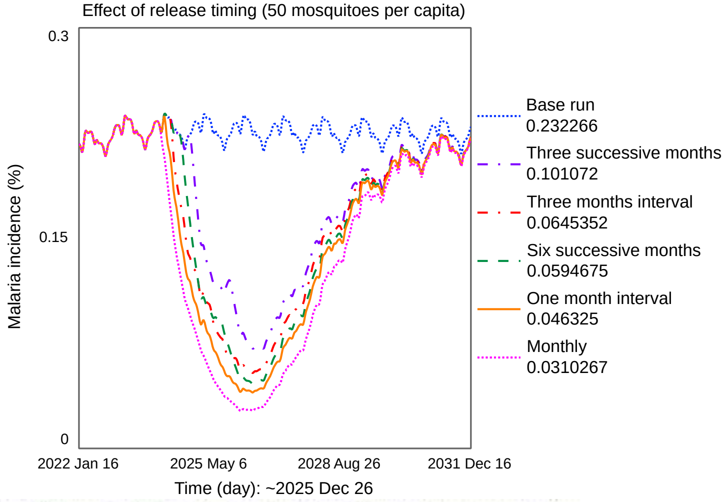


Table 2. Effectiveness of different release strategies (release timing) in reducing malaria incidence.

	Monthly	One month interval	Six successive months	Three months interval	Three successive months
Malaria incidence when release stop	3.10%	4.63%	5.94%	6.45%	0.93%
Time for the malaria incidence to reach 10%	2.03 year	1.83 year	1.76 year	1.56 year	1.19 year
Number of mosquitoes	250 per release	500 per release	500 per release	1000 per release	1000 per release

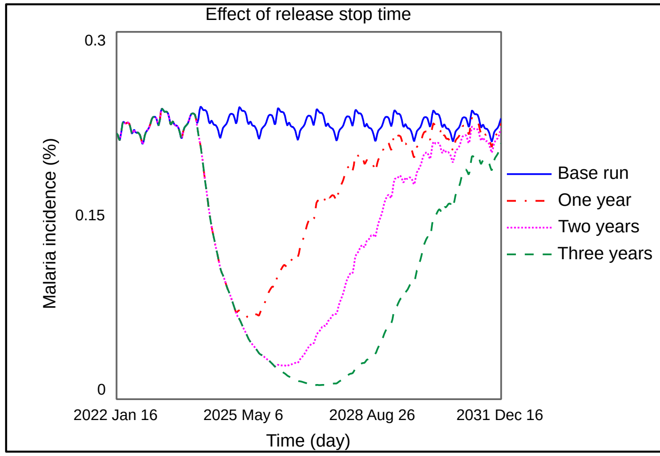


Table 4. Effectiveness of different release strategies (release stop time) in reducing malaria incidence.

	One year	Two years	Three years
Malaria incidence when release stop	7.9%	3.09%	1.23%
Time for the malaria incidence to reach 10%	1.19 year	2.02 years	2.76 years
Number of mosquitoes	250 per release Total released: 3000	250 per release Total released: 6000	250 per release Total released: 9000

For various release duration

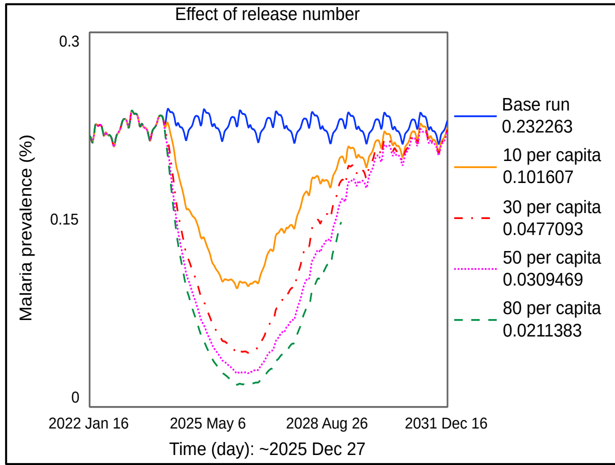


Table 3. Effectiveness of different release strategies (release amount) in reducing malaria incidence.

	10 per capita	30 per capita	50 per capita	80 per capita
Malaria incidence when release stop	10.16%	4.77%	3.09%	2.11%
Time for the malaria incidence to reach 10%	0.72 year	1.75 year	2.03 year	2.32 year
Number of mosquitoes	50 per release	150 per release	250 per release	400 per release

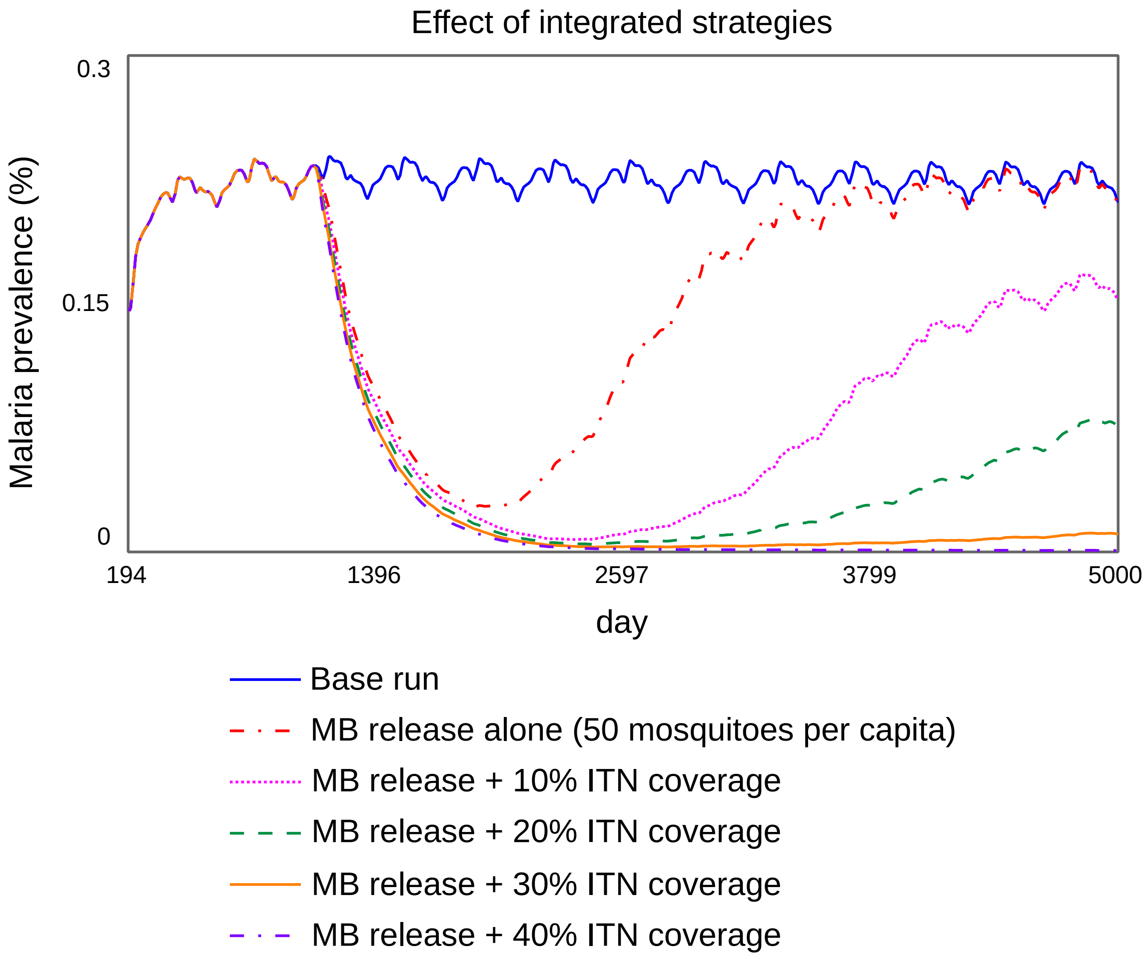
For various release number

So..

As expected, an increased prevalence of *MB*-infected mosquitoes contributes to malaria incidence reduction

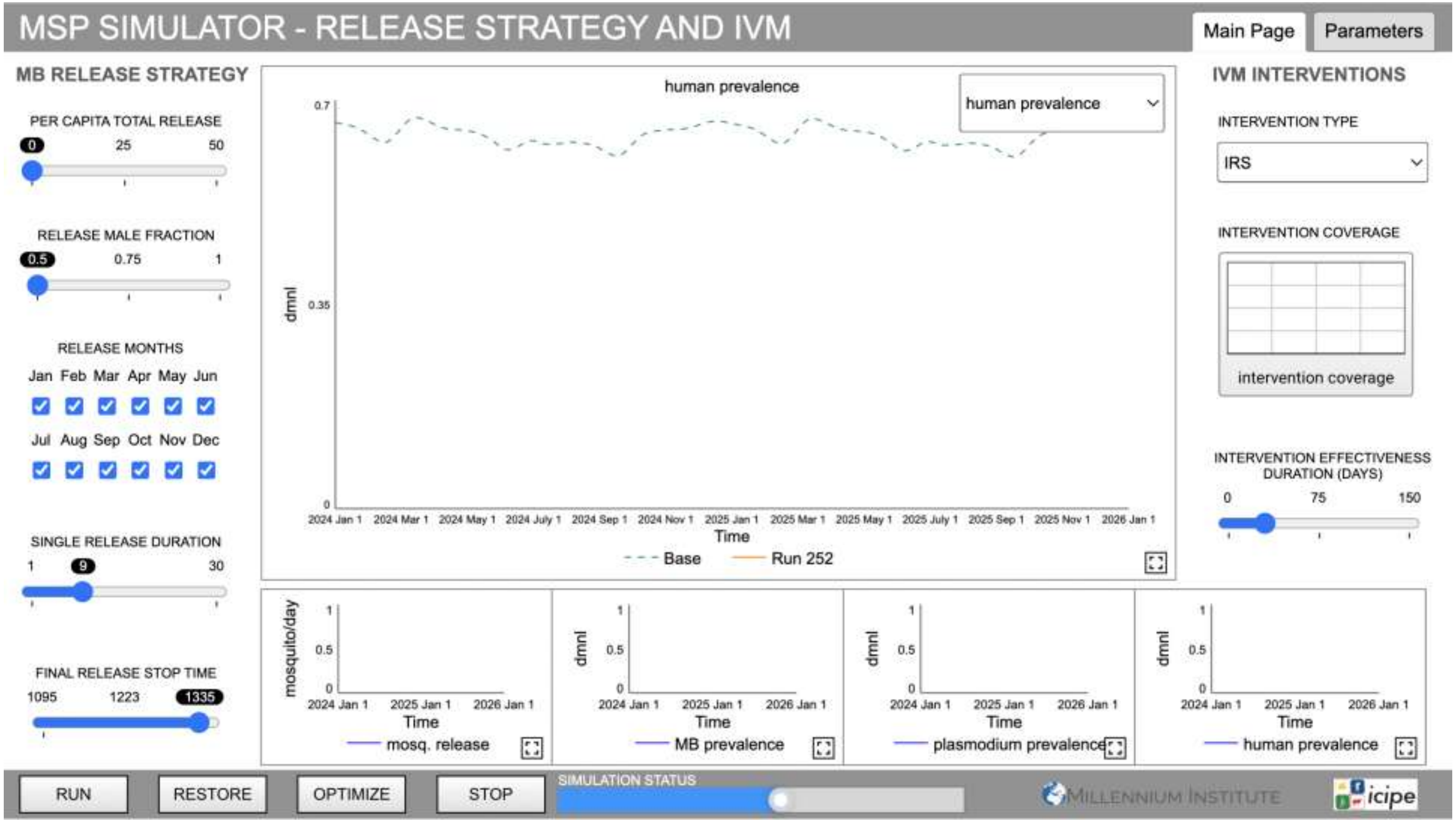
The shorter the interval time between the releases instants, the better the effects.

Combining MB with other control methods



We evaluate the combination of *MB*-based malaria control policy and effect of different ITNs coverage.

So..
Maintaining a higher ITN coverage can be pivotal in sustaining zero malaria prevalence.



Accessible simulation interface

https://exchange.iseesystems.com/public/millenniuminstitute/msp-35/index.html#page1

Target areas for MB-based interventions (ongoing)

0.1 degree grid over kenya

↓

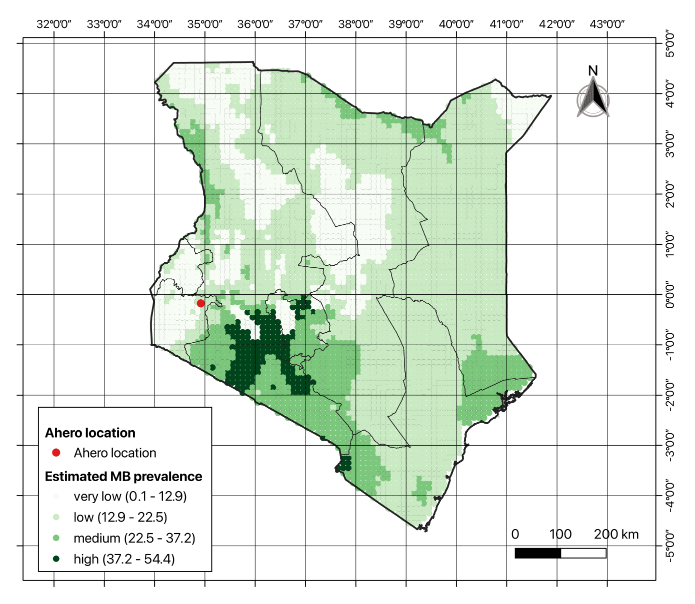
Centroid extracted and climatic variables from google earth engine

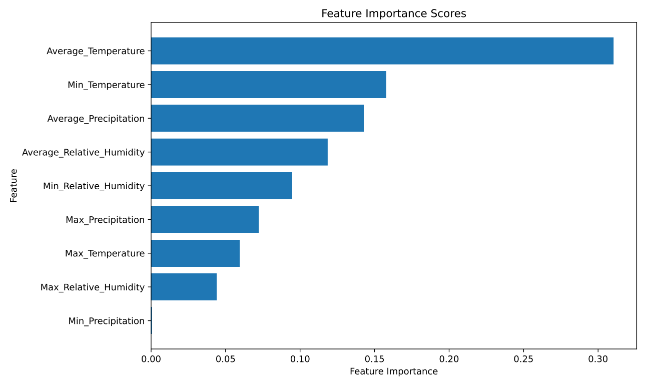
↓

Model run over each centroid

↓

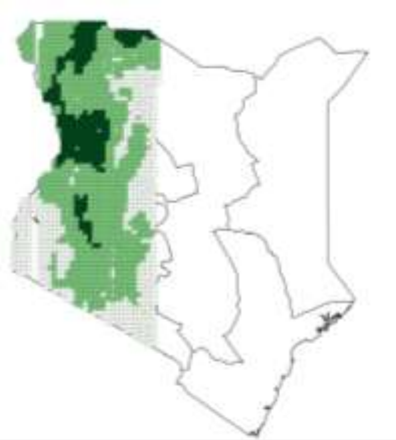
Mapping of the returned estimated prevalence



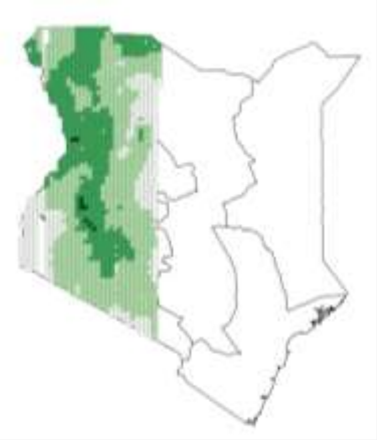


MB seems to easily propagate in areas of low mosquito abundance (importance of competition)

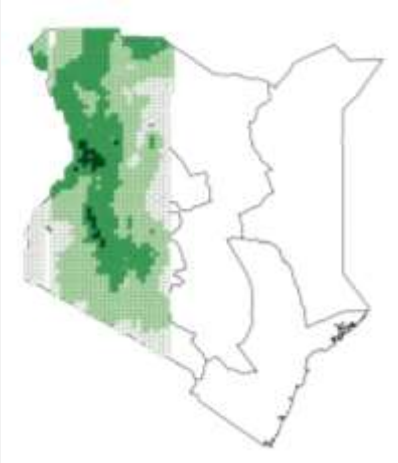
Jan 2023



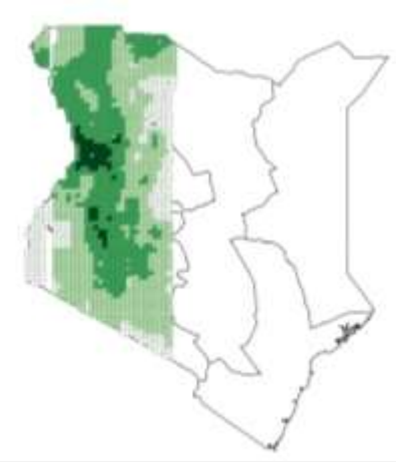
Avril 2023



Aout 2023



Nov 2023



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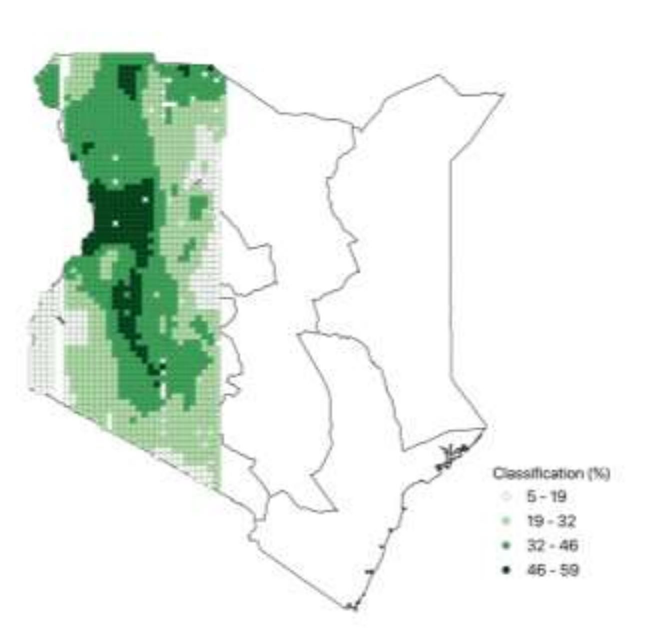

Need of additional data

Guiding malaria control policymakers

Summary

- A system dynamics model was built to analyse the interactive dynamics of MB, mosquitoes and humans.
- A web-interface was provided.
- Scenario analysis were performed

Key insights

- The strain is important as it defines the vertical and horizontal transmission rates
- The density is an important factor, which defines the extinction or persistence of the symbiont
- Climate has a strong effect on the outcome of spread of *MB*.
- Competition between wild and *MB*-infected mosquitoes is critical for the success of the intervention
- *MB* alone cannot sustain malaria elimination and multiple releases are necessary but a integrated strategies can sustain malaria elimination
- An increasae of *MB*-infected mosquitoes would contribute to malaria incidence reduction, but a cost-effectiveness analysis is necessary to identify the relevant target areas

Limitations

- Limited data
- Non-assessment of current implemented
- Web-interface calibrated to Ahero
- Spatial analysis only based on climatic variables
- Multiple vectors

Next

Cost-benefit analysis

Acknowledgement

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