Supporting Information Appendix: Impact of Mosquito Gene Drive on Malaria Elimination in a Computational Model with Explicit Spatial and Temporal Dynamics

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SI Appendix: Methods

The Namawala simulations presented use a single well-mixed patch, but this is insufficient to simulate the outcome for released gene-drive mosquitoes in a spatially-explicit time-varying landscape. The Garki District, site of well-known elimination experiments in the 1970s [1], is explicitly simulated with 1 km x 1 km grid cells. Baseline dynamics are fit using a larval habitat model that is a linear combination of a temporary rainfall driven and constant capacity models. The resulting overall larval habitat is fit to an EIR of 18 infectious bites per person per year, which is at the low end of that seen for a single species during the Garki Project (see Supplemental Figure 6). A release grid is constructed arranging 15 release sites on an approximately 10 km x 10 km grid (see Supplemental Figure 7).

The dispersion patterns of *Anopheles* mosquitoes is uncertain, and mark-release-recapture studies provide partial but incomplete data [2]. In the present simulations, female mosquitoes can move to any of up to eight adjacent grid cells. This motion is governed by a parameter determining the fraction of local mosquitoes that leave a 1 km x 1 km grid cell each day. The default is set to 0.15 (15 percent of female mosquitoes disperse out of a grid cell in any day), but this parameter is swept from 0 to 0.5 to determine its effects, if any. Male mosquitoes are assumed to stay within the grid cell from which they emerge, assuming that a supply of nectar and emerging females are near their original aquatic habitat.

Finally, the mechanisms to implement gene drive were added to the basic model. Each vector has a data structure that holds its properties, including gender, age (if vector age-specific dynamics are enabled), parity, a contained data structure for its genetics, and another contained data structure for females containing the genetics of its mate. Within this genetic data structure, there were slots for insecticide resistance and other traits, and a new genetic variable was added for the gene drive construct, with potential values of wildtype, half, or full (wildtype, heterozygous, homozygous).

In the case of dual germline homing, all the gametes of a wildtype vector are wildtype. For a modified gene-homozygous vector, its gametes each carry the driving gene. For a heterozygous vector, with one copy of the driving gene, **0.5 + 0.5(homing)** of the gametes carry the driving gene, while **0.5 – 0.5(homing)** of its gametes are wildtype. Gametes then probabilistically combine given their resulting relative proportions. An egg receives one gamete from the mother and one from the male mate; if it receives two copies of the driving gene, it is homozygous; if it receives one copy, it is heterozygous; if it receives no copies, it is wildtype. The associated fecundity reduction is applied to the egg batch size of homozygous females, but no fitness cost is applied to heterozygous or wildtype females.

In the case of driving-Y, all females are considered wildtype, while modified males carry a driving Y-chromosome. Females that mate with a male carrying this driving-Y will have as offspring wildtype females and males carrying the driving-Y. The fraction of offspring that are driving-Y males is then **0.5+0.5(Xshredding)**, and the fraction of offspring that are wildtype females is **0.5-0.5(Xshredding)**. The

total egg batch size is reduced by the parameter fecundity reduction for each female that mates with a modified male. Only females that mate with a driving-Y male have their fertility reduced. If it is desired to have 65% of the original egg batch size to be driving-Y male and 35% fertile female, then X-shredding should be 0.3 and fecundity reduction 0. If however, the desire is to have 65% of the original egg batch size be driving-Y male and no females, then X-shredding should be 1.0 and fecundity reduction should be 0.35. How these two parameters interplay can be seen above in the Results section.

For the case of non-homologous end-joining (NHEJ), a NHEJ rate **r** is defined as the fraction of homing events in which the target site is cleaved and changed from wildtype but the drive construct is not successfully copied during repair. Thus for dual germline homing, the fraction of wildtype gametes will remain **0.5 - 0.5(homing)**, the fraction carrying the drive construct **0.5 + 0.5(homing)(1-r)**, and the fraction with wildtype disrupted but without the drive construct **0.5 + 0.5(homing)r**. Both the case in which this disrupted gene remains as fertile as wildtype and the case in which the disrupted gene has the same fecundity reduction as the drive construct are studied. In either case, the allele is now resistant to further drive from the original construct.

SI Appendix: Figures

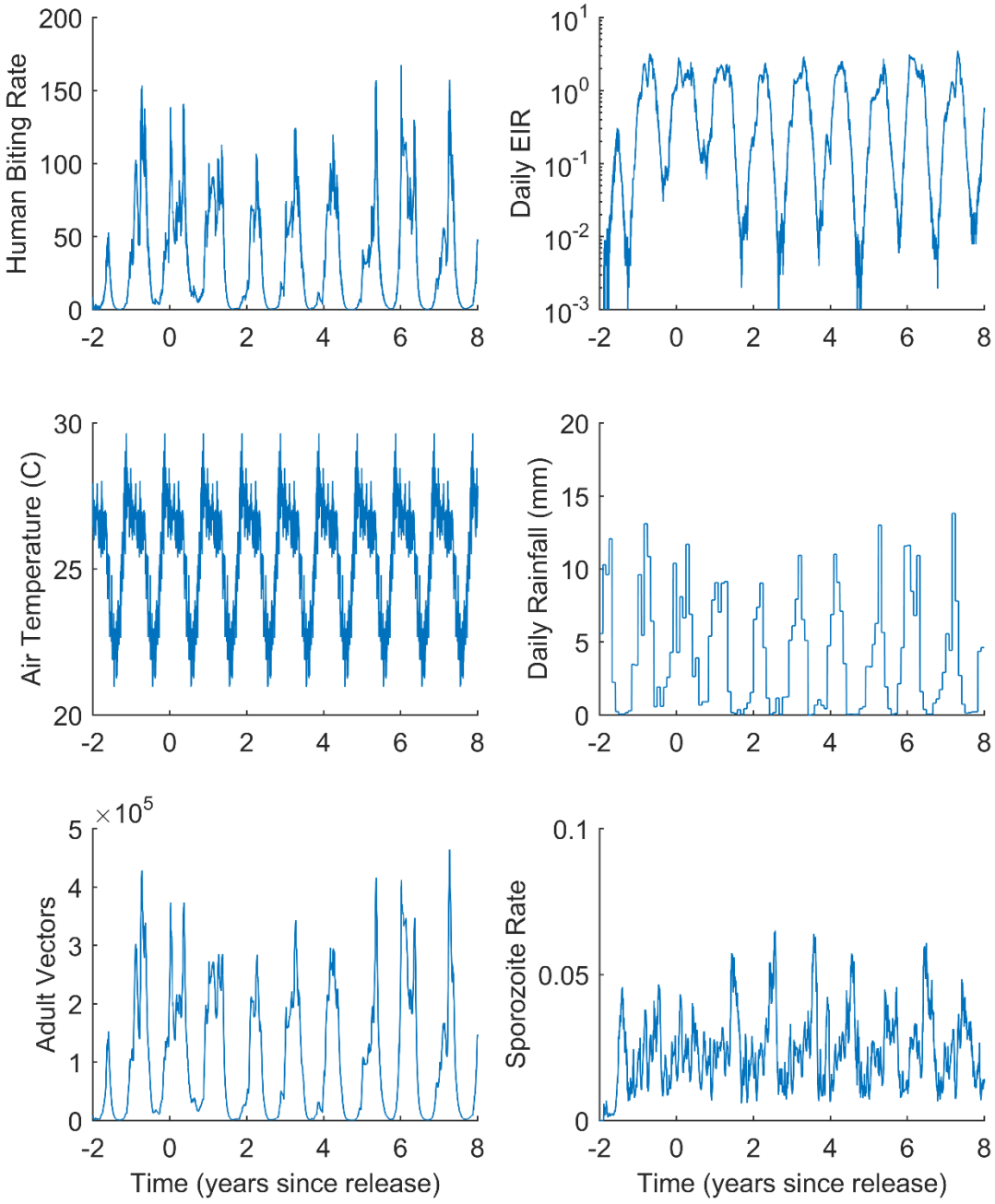

Figure S1: Namawala baseline dynamics. Note that the depth of the low season varies from year to year. Temperature is warm throughout the year, with average daily temperatures in the 20's. EIR in this setting is 300-350 per year.

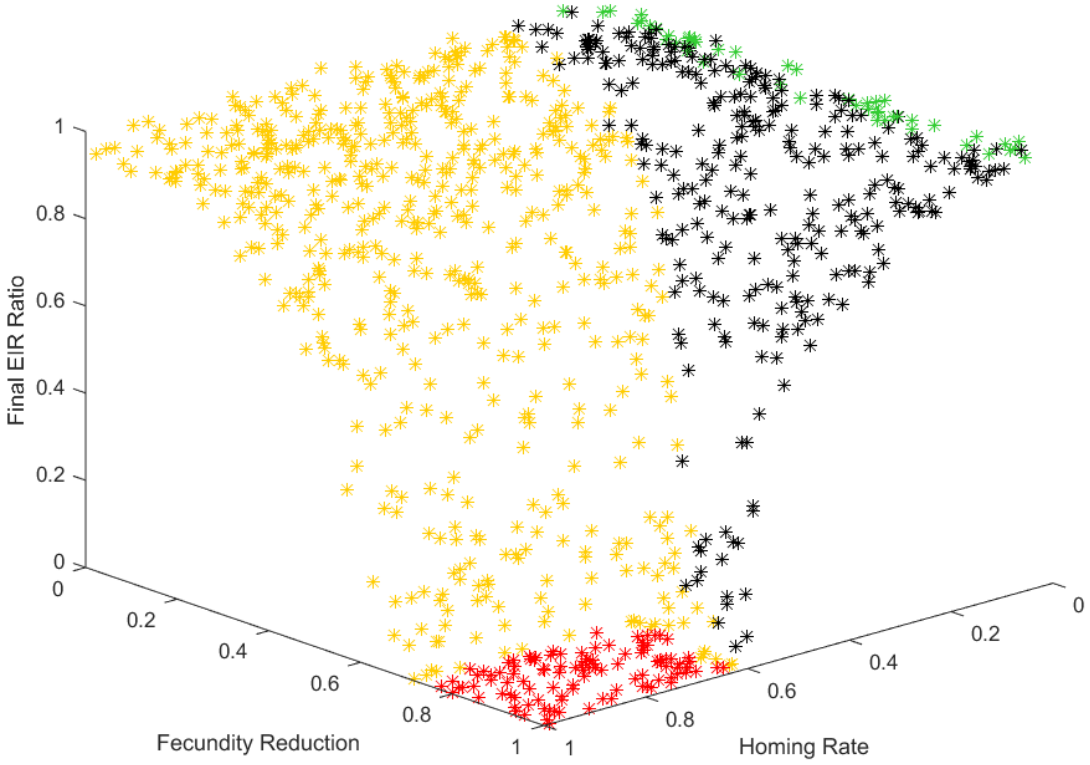

Figure S2: Reduction in annual EIR in the eighth year after release as a fraction of baseline, for the simulations mapped in Figure 1—Namawala seasonal dynamics with 500 Dual Germline homing males released. Note that substantial EIR reductions can be achieved without the population disappearing.

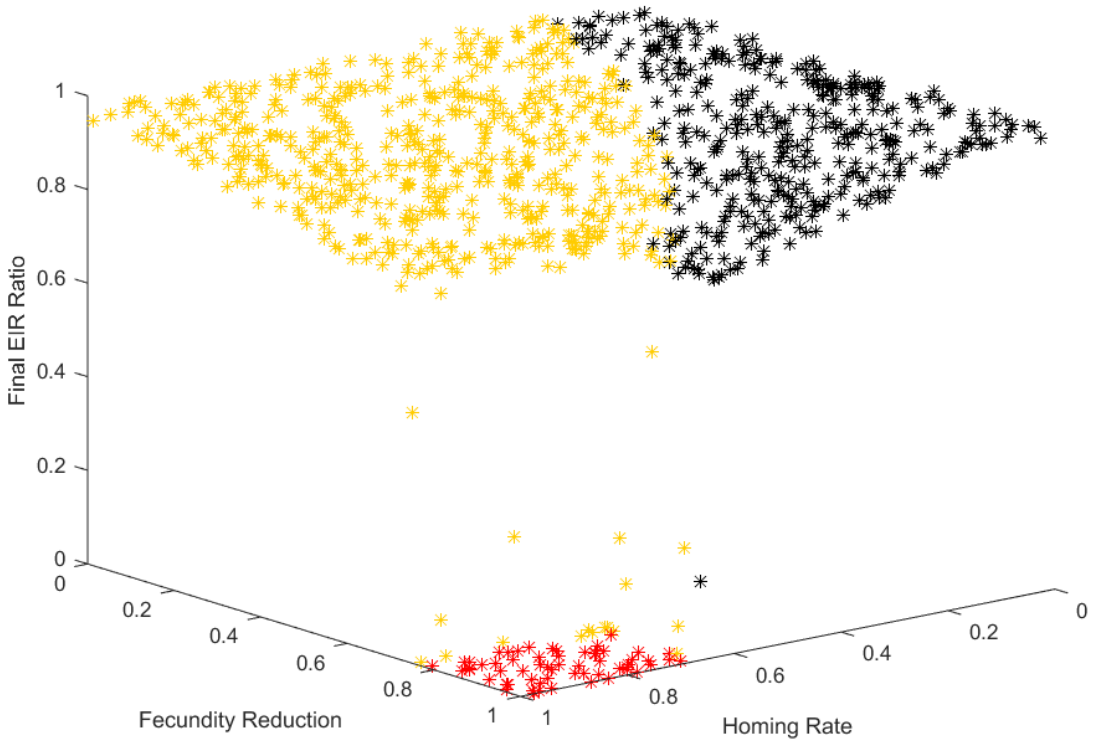

Figure S3: Reduction in annual EIR in the eighth year after release as a fraction of baseline, for the simulations mapped in Figure 2—Namawala constant weather dynamics with 500 Dual Germline homing males released. Note that the EIR reductions are less than in the seasonal case, because seasonal fluctuations are not available to reduce the population.

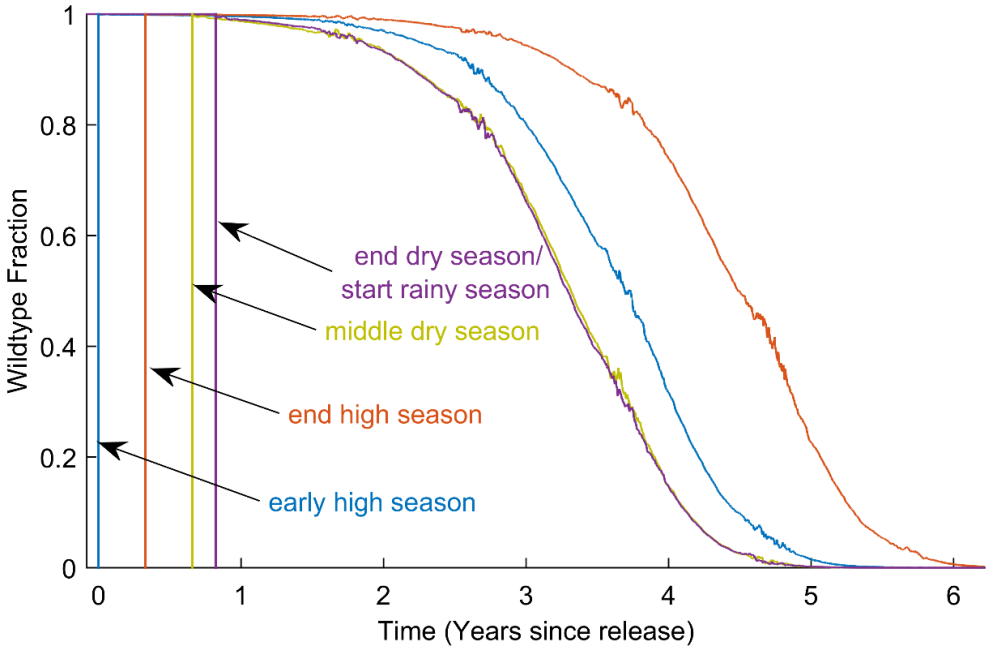

Figure S4: Effect of release timing for Namawala dual germline homing scenario, with homing of 0.2 and no fecundity reduction. Releasing at the start of the rains is most effective at taking over the population most rapidly, and releasing at the end of the high season is least effective.

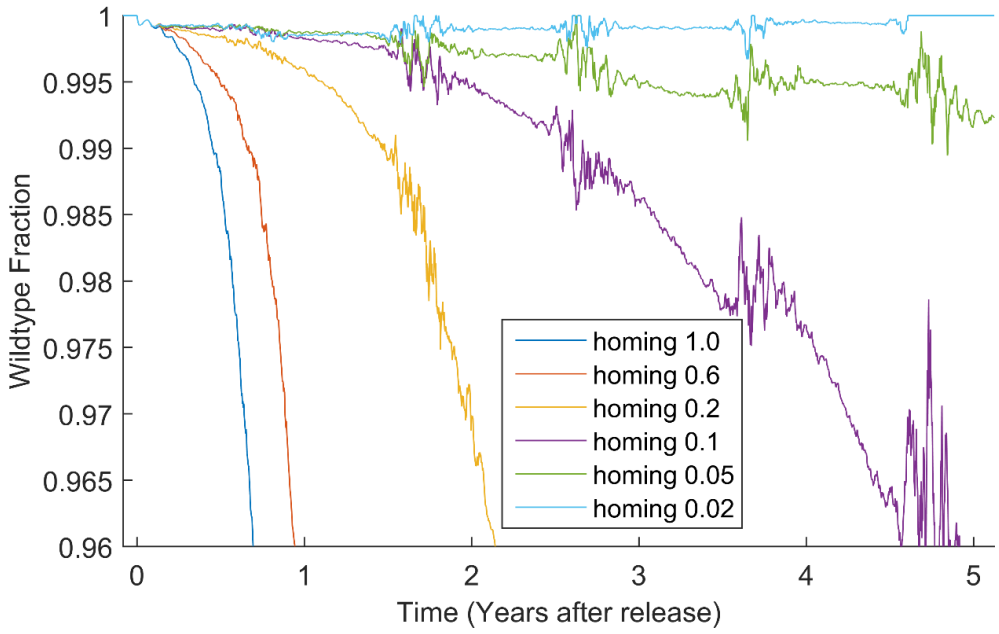

Figure S5: A zoomed in view of the wildtype fraction over time for simulations from Figure 1, showing increasing homing avoiding stochastic fadeout. 500 dual germline homing males are released at time 0, and for low homing, seasonally-driven fluctuations eventually result in loss of the construct. Stochastic noise in the wildtype fraction corresponds to the decline of the vector population at the end of the rainy season through the low population in the dry season.

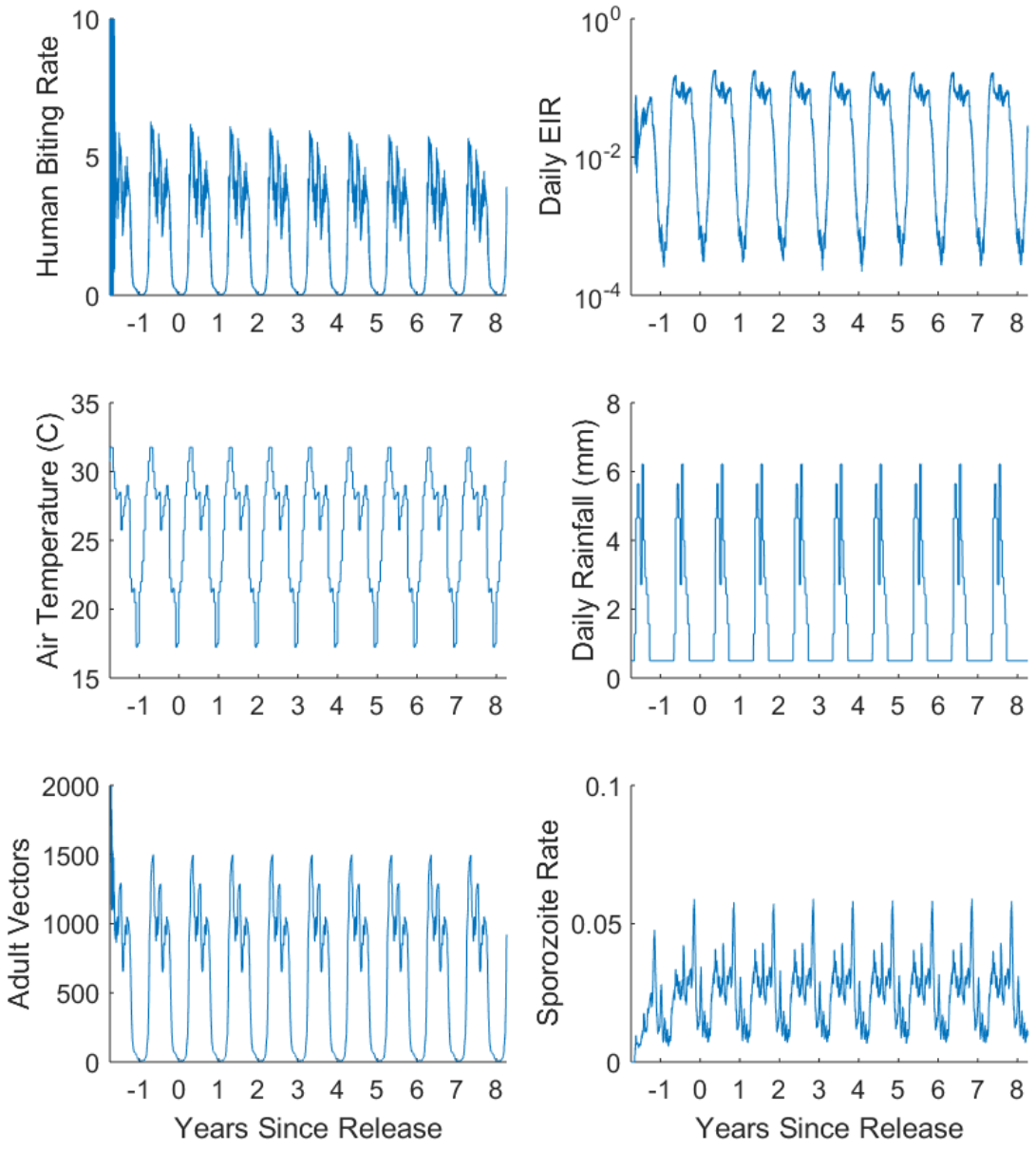

Figure S6: Garki baseline dynamics. Note the pronounced low season for multiple months in a row. EIR in this setting is approximately 18 per year, roughly what was measured for the *Anopheles gambiae* complex for Rafin Marke. This low EIR corresponds to lower population mixing across the landscape and makes it more difficult for an introduced construct to take over the population.

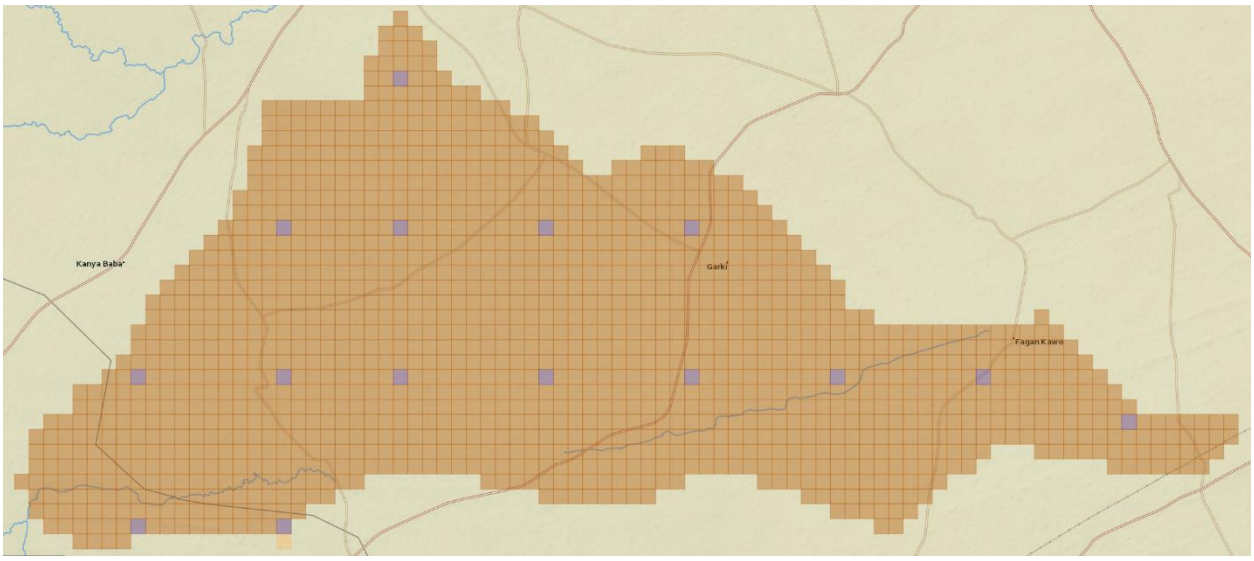

Figure S7: Garki release grid. Each cell is a 1-km cell in the simulation. The purple squares are the 15 release sites, approximately on a 10 km grid. The denser grid used in some Driving-Y releases completes this grid in a face-centered cubic pattern, with a total of 30 release sites.

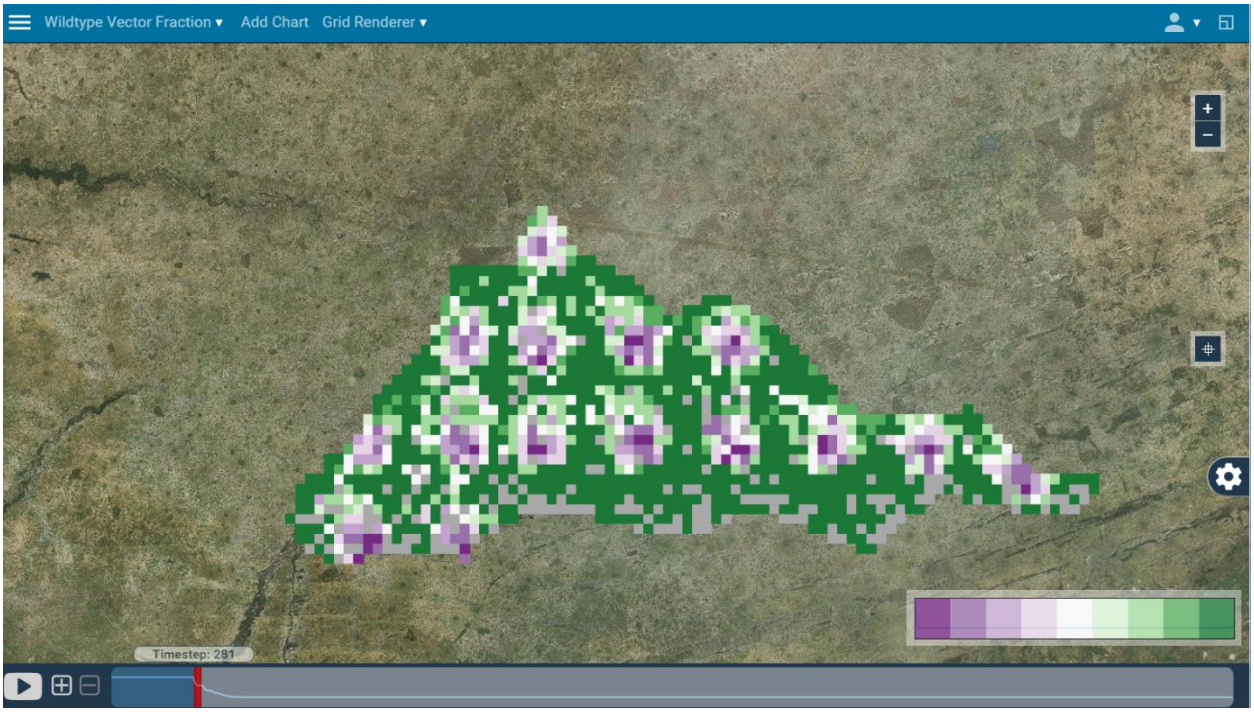

Figure S8: Screenshot of simulation animation of wildtype prevalence a few weeks following start of releases. Green corresponds to completely wildtype, purple very few wildtype, and gray a complete absence of homozygous wildtype, with intermediate colors a proportional fraction of homozygous wildtype.

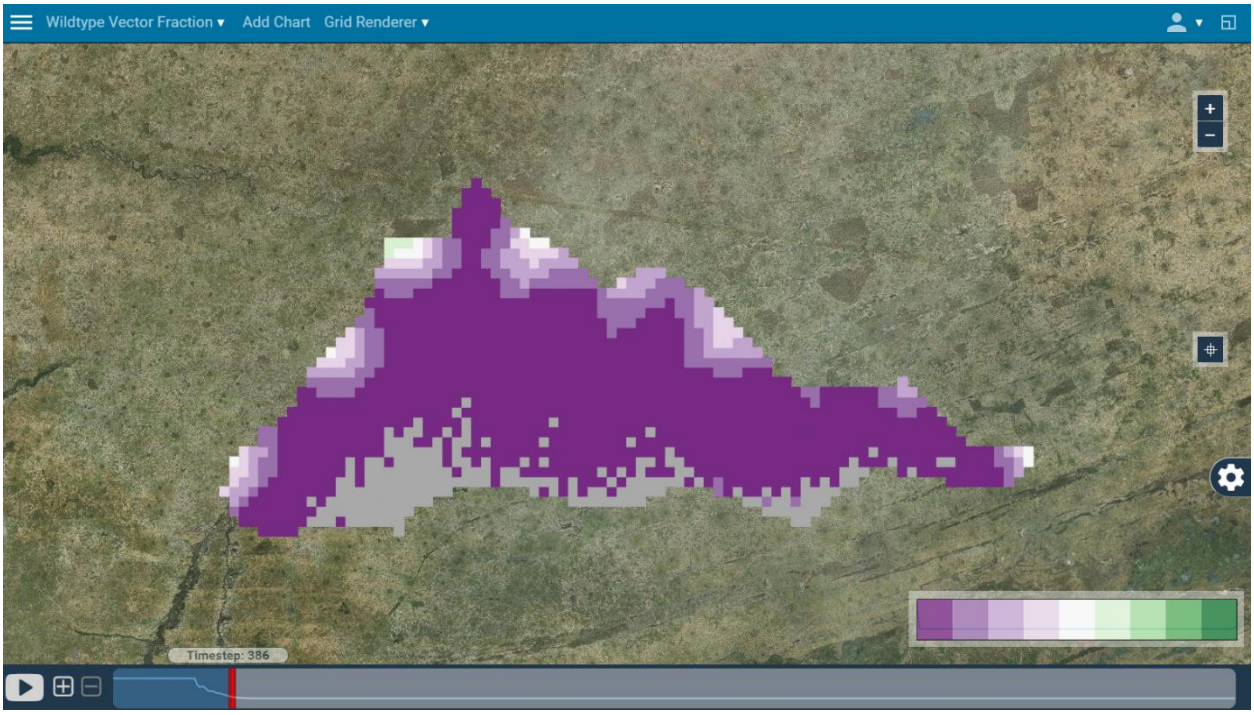

Figure S9: Screenshot of successful Garki simulation near the end, as gene drive mosquitos have reached every patch and wildtype fraction is decreasing to zero.

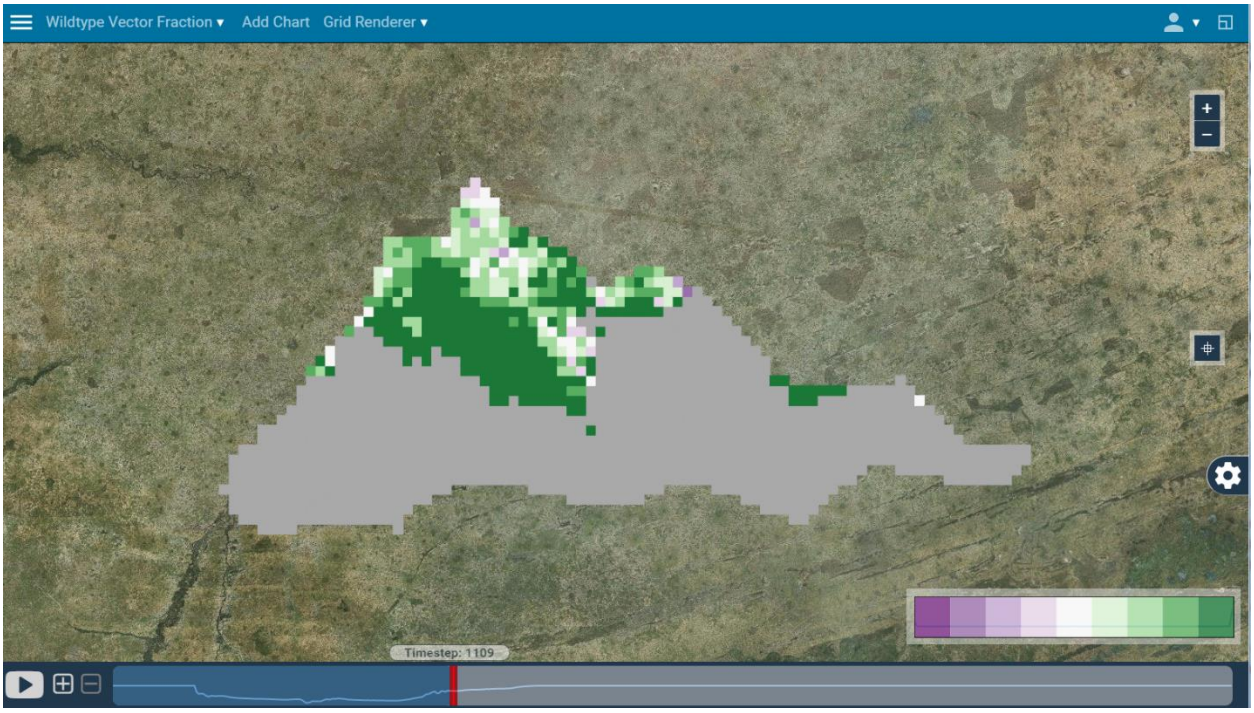

Figure S10: Screenshot of a failed Garki mosquito release, when most patches have seen the vector population collapse, but small pockets of wildtype mosquitoes survive to re-colonize the landscape.

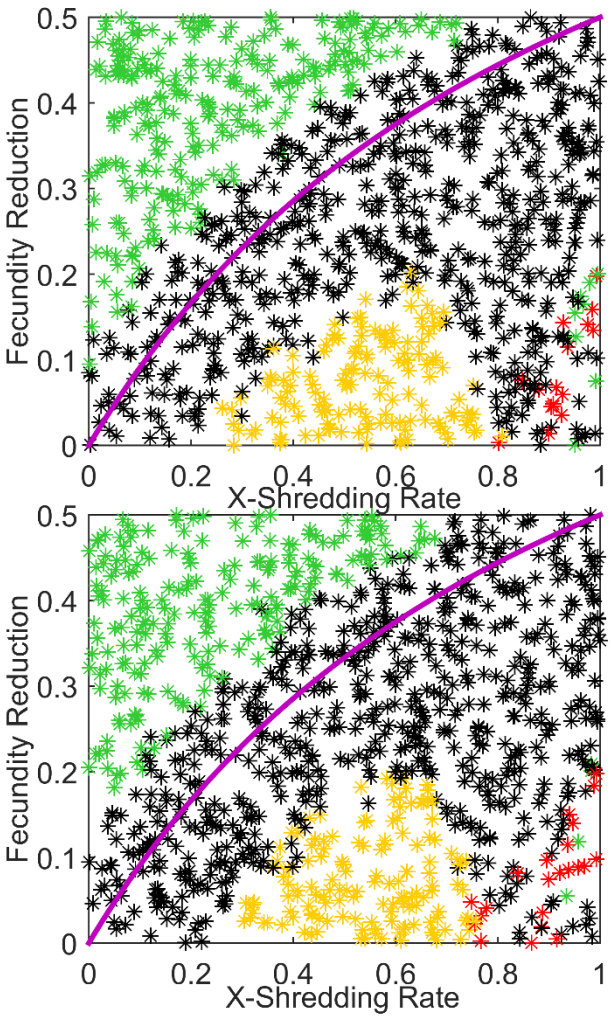

Figure S11: Driving-Y chromosome introduced into Garki District simulation with full seasonality, releasing 500 driving-Y males from each of 30 sites every week for 1 year, varying X-shredding rate versus fecundity reduction. (bottom) Continuing the 30 site weekly releases for 2 years, varying X-shredding rate and fecundity reduction.

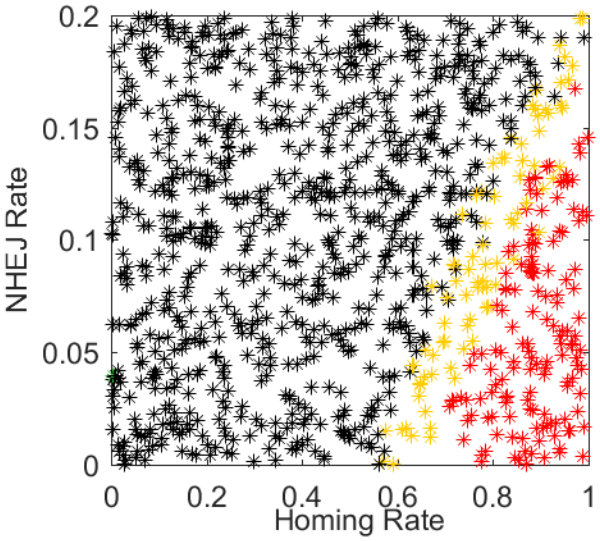

Figure S12: A dual germline homing construct with fecundity reduction of 0.8 is released in Namawala, repeating the NHEJ experiment of Figure 8 (top), but now with constant weather. The cross-section for zero NHEJ Rate matches the fecundity reduction of 0.8 line in Figure 2, and NHEJ alleles have fecundity disrupted to the same extent as those carrying the gene drive construct.

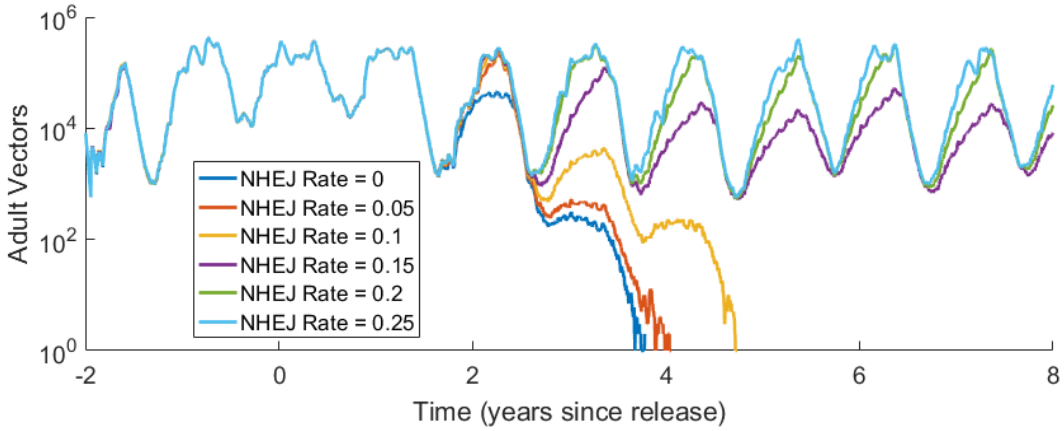

Figure S13: Traces of the adult vector population for the seasonal Namawala results in Figure 8 (top), in which a dual germline homing gene drive construct with fecundity reduction of 0.8 is released with varying rates of non-homologous end-joining. The NHEJ alleles are assumed to have fertility reduced by the same 0.8 fraction, but no further drive occurs from that allele and the allele is now resistant to further drive. For NHEJ Rates above 0.1, the vector population has a high probability of persistance, and the higher the NHEJ Rate below that, the longer it takes to suppress the population.

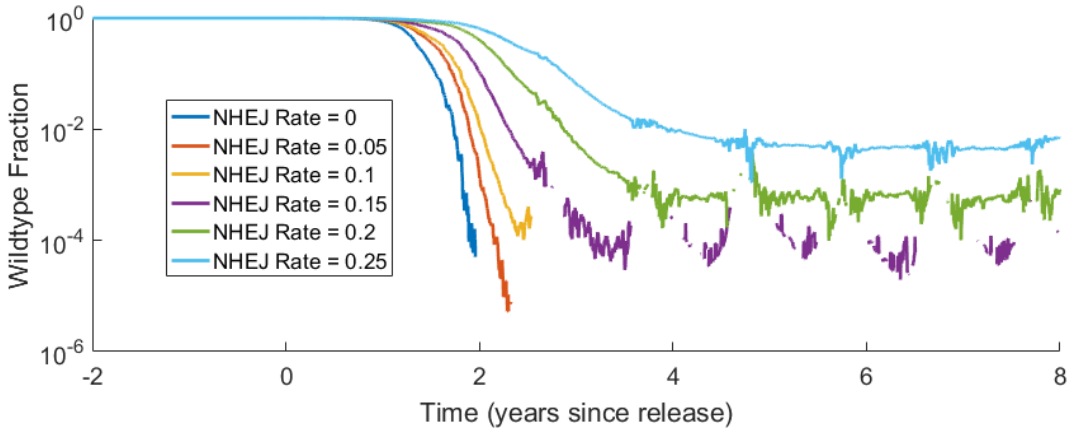

Figure S14: The fraction of homozygous wildtype mosquitoes for the six simulations shown in Supplemental Figure 13. For low NHEJ rates, the wildtype is eliminated, but for higher NHEJ rates, the wildtype allele persists. This wildtype allele maintains overall population fertility, and its fraction can be estimated from the homozygous wildtype fraction in the traces above.

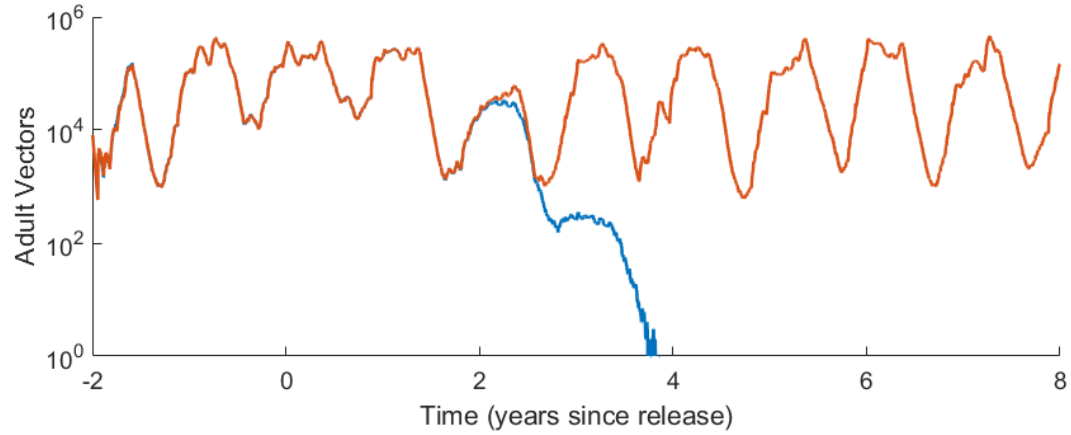

Figure S15: A dual germline homing gene drive construct with homing = 0.8, fecundity reduction = 0.8, and NHEJ rate = 0 is released into the seasonal Namawala setting. The blue trace shows the result for a single wildtype that is susceptible to the drive construct, and the red trace shows the same setting, but with 0.005 of the population refractory to the drive construct due to genetic variation at the target. The second year after release looks similar in terms of the suppression in the population, but instead of continuing to full population suppression, the resistant allele originally in the population rescues the local population and returns to full population dynamics the following year, but now with the whole population carrying the resistant allele and the originally-dominant wildtype gone.

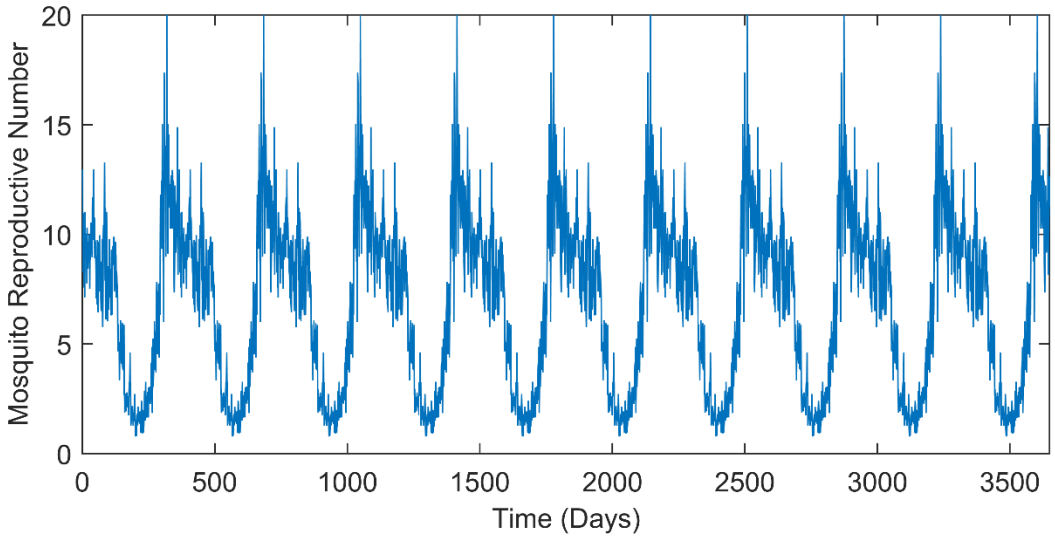

Figure S16: The time course of the mosquito reproductive number R_m in Namawala.

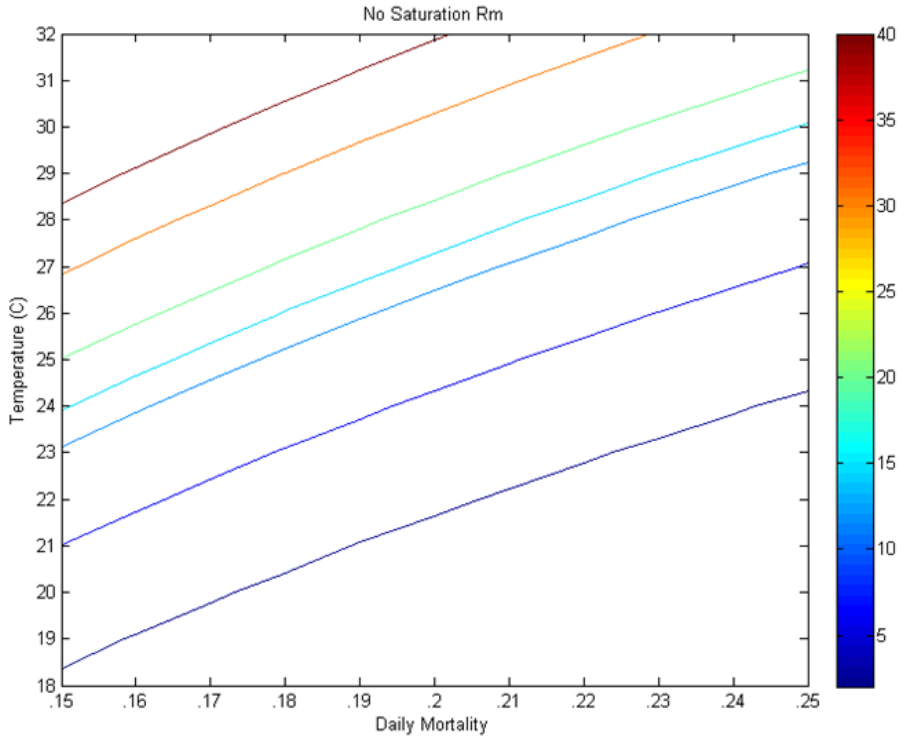

Figure S17: R_m versus weather and larval parameters. Isoclines correspond to R_m of 40, 30, 20, 15, 12, 6, and 2. Simulations in this manuscript use a larval daily mortality of 0.22, so R_m varies over the course of the year from under 2 to over 15.

References

1. Molineaux, L. and G. Gramiccia, *The Garki Project: Research on the Epidemiology and Control of Malaria in the Sudan Savanna of West Africa*. 1980, Geneva: World Health Organization.
2. Guerra, C., et al., *A global assembly of adult female mosquito mark-release-recapture data to inform the control of mosquito-borne pathogens.* Parasites & Vectors, 2014. **7**(1): p. 276.