Evolutionary simulations of Z-linked suppression gene drives

Luke Holman*
**luke.holman@unimelb.edu.au*

Abstract

My abstract text.

Keywords: *W*- and *X*-shredders, Lepidopteran pests, meiotic drive, population control, schistosomiasis, selfish genes.

*School of BioSciences, The University of Melbourne, Victoria, Australia.

Introduction

Developments in biotechnology will soon make it feasible to control or eliminate populations of disease vectors, pathogens, agricultural pests, and invasive species using 'gene drives' [1–6]. Gene drives assist the propagation of engineered genes through populations using a range of mechanisms including gene conversion, poison-antidote systems, segregation distortion, and genetic incompatibility [7,8]. For example, the CRISPR-Cas9 gene editing system can be used to create a transgenic insertion that is transmitted to almost 100% of the offspring of heterozygous individuals instead of the usual 50%, because the wild type allele is cut and then repaired using the transgene as a template. Gene drives are often categorised into two types, both of which can be created using CRISPR-Cas9. 'Replacement drives' aim to propagate a human-beneficial allele through the population, e.g. an allele that interferes with the tranmission of malaria by mosquitoes [1,9]. Conversely, 'suppression drives' aim to cause extinction (or at least a reduction in population size), for example by propagating an allele that causes lethality or sterility (MORE HERE [2,5]), or which skews the population sex ratio – typically towards males MORE HERE [10–12].

Many recent theoretical papers have investigated the feasibility, efficacy, and potential negative consequencies of emerging gene drive technologies. For example, Noble et al. [6] used models to show that the most basic implementation of a CRISPR gene drive might be highly invasive and could rapidly spread to fixation across whole meta-populations, which will often be undesirable. Conversely, other models [13,14] have concluded that alleles that are resistant to being cut and replaced by CRISPR gene drives could prevent them from spreading and acheiving their aims. The issue of resistance is compounded because the standard implementation of CRISPR drives (but see [4,5,14]) tends to create its own resistance alleles as a by-product, through a process called non-homologous end joining (NHEJ; [1,14,15]). Given the potential safety, ethical, and sociopolitical concerns surrounding gene drives, some theoretical papers have focused on gene drives that would go extinct once their job is done [11,16], would stay confined to particular populations [17], and/or could be reversed once they have spread [18].

Here, I focus on the evolutionary dynamics of a Z-linked suppression gene drive. The simulation is inspired by proposals for various types of CRISPR-Cas9 Z-linked gene drives that have been proposed by Kevin Esvelt and colleagues (see www.sculptingevolution.org/genedrives/current/schistosomiasis; at the time of writing, these ideas have not been published in a journal or pre-print archive). Various Z-linked suppression drives proposed by Esvelt and colleagues are shown schematically in Figure 1. The gene drive would enjoy a transmission advantage in ZW females, and optionally also in ZZ males. Esvelt et al. propose that Z-linked drives could be used to control the trematode parasites (*Schistosoma* spp.) responsible for the deadly disease schistosomiasis, though Z-linked drives could theoretically be used to control any organism with female-heterogametic sex determination (such as Lepidopteran pests or invasive birds).

A Z-linked gene drive could suppress populations by biasing gametogenesis in females, for example by cutting unique sequences on the W chromosome in order to destroy it; such a gene drive would be a 'W-shredder', similar to the X-shredders that are being developed to control

XY species [12,19,20]. Females carrying the gene drive would thus produce relatively few W-bearing eggs, and therefore produce mainly drive-carrying sons. Esvelt et al. point out that the total number of offspring produced by these drive-carrying females will depend on multiple factors, such as the timing of the drive mechanism, the strength of individual-level fitness costs to drive carriers, and the ecology of the target species, with attendant consequences for the evolutionary dynamics of the drive. For example, for some W-shredders, drive females might produce roughly the same number of (mostly-male) offspring as a wild-type female because the W chromosome is destroyed at an early enough stage in oogenesis that the number of mature eggs is not affected (Figure 1, 1A). Alternatively, drive-carrying females might produce half (or less than half) the number of offspring, e.g. if the drive works by destroying all ova or offspring that inherit a W chromosome, and females cannot compensate by producing more. As an alternative to W-shredders, Esvelt et al. also proposed that one could suppress populations using a Z-linked locus that caused sterility or lethality in females. If this female-harming gene was capable of gene drive in males (see below), it could perhaps reach high enough frequencies to suppress the population.

Esvelt and colleagues also note that if the Z-linked locus caused gene drive in *males* in addition to females, it would probably spread through the population faster and be more likely to result in extinction. Male gene drive could be accomplished using 'standard' CRISPR-Cas9 gene conversion (REF), whereby the driving Z locus would convert the wild type locus using homing endonuclease activity followed by DNA repair inside males carrying one driving Z and one wild-type Z, leading these males to produce mostly drive-carrying sperm and offspring.

Here, I present an evolutionary simulation that can accommodate all of these hypothesised types of Z-linked drives. I aimed to test which properties of the gene drive and the ecology of the target species are critical to determining the likelihood and speed with which the gene drive causes extinction. For example, the gene drive will presumably spread faster if it can bias transmission in both sexes, but perhaps a female-only gene drive (which might be easier to engineer) would be perfectly adequate. Also, since the population will become more male-biased as the gene drive invades, there will be eco-evo feedback (REF) that might affect the evolutionary outcome in non-intuitive ways. For example, the altered sex ratio might intensify the fitness advantage accruing to any resistant W chromosomes or autosomal modifiers that prevent W-shredding (due to Fisherian selection for an even sex ratio; [21]), relative to that observed in earlier models focusing on gene drives carried on autosomes [13,14]. Moreover, the change in sex ratio could affect the demographics of the population, particularly if males and females contribute differentially to density-dependent population growth [22], or have different dispersal rates [23]. The model incorporates the possibility that Z-linked resistance alleles are sometimes formed through NHEJ in males that are heterozygous for the drive allele [1,14,15]. It is not clear *a priori* whether the creation of resistant Z-linked alleles by NHEJ is a equally problematic for a Z-linked gene drive as it is for an autosomal drive, because it would only hinder gene conversion in males, assuming that NHEJ does not occur in response to W-shredding (which is likely, because the W-shredder could be designed to target many repetitive regions of the W chromosome).

Table 1: List of variables, and their corresponding parameter(s) in the model, which were varied in order to study their effects on the likelihood of population extinction.

Variable	Parameter(s)	Outcome
Strength of gene drive in females (e.g. W-shredding)	p_{shred}	1.00
Strength of gene drive in males (e.g. gene conversion)	p_{conv}	1.00
Cost of gene drive allele to female fecundity	c_f	1.00
Cost of gene drive allele to male mating success	c_m	1.00
Frequency of W-linked resistance mutations	μ_W	1.00
Frequency of Z-linked resistance mutations and NHEJ	μ_Z and p_{nhej}	1.00
Frequency of autosomal resistance alleles	μ_A and μ_B	1.00
Patchiness of the population	k	1.00
Dispersal rate of males and females	x_m and x_f	1.00
Global versus local density-dependence of female fecundity	ψ	1.00
Contribution of males relative to females in density-dependence	δ	1.00
Number of gene drive carrier males released	$n_{release}$	1.00
Release strategy: all in one patch, or global	-	1.00
Fecundity of females at low population densities	r	1.00
Shape of density dependence	α	1.00

Methods

Overview

We model a finite population of dioecious diploids with ZW sex determination, living in j discrete habitat patches that are arranged linearly in a ring (preventing complications due to 'edge effects'). The model considers the demography and evolution of a population into which $n_{release}$ males carrying the Z-linked gene drive are released. The drive allele is capable of gene drive in females (e.g. through W-shredding) and optionally also gene drive in males (e.g. via gene consersion). The life cycle consists of discrete generations, each composed of the following phases: birth, dispersal between patches, breeding with patches, and death of the parental generation. The species has 3 loci with 2 or 3 alleles each, some of which potentially show non-Mendelian inheritance. The equilibrium population size was roughly 10,000 in all simulations prior to the release of the gene drive. The model is a stochastic individual-based simulation written in R 3.4.0 and was run on `Spartan`, a computer cluster at the University of Melbourne. An accompanying website presents the R scripts (with annotations) used to run the model and generate the figures (link).

Loci and alleles

Each male in the simulation carries one Z-linked locus and two autosomal loci, each with two alleles. Each female carries a single allele at the Z-linked locus plus a W chromosome, as well as two alleles at both of the autosomal loci.

There are three possible Z-linked alleles: a gene drive allele (denoted Z^*), a wild-type allele ($Z+$) which is vulnerable to gene drive in Z^*Z+ males, and a resistant allele (Zr)

that is immune to gene drive in *Z*Zr* males. Similarly, there are two possible types of *W* chromosomes: a wild-type *W* chromosome (*W+*) that is vulnerable to gene drive by the *Z** allele, and a resistant *W* chromosome (*Wr*) that is immune to gene drive.

The two autosomal loci, denoted *A/a* and *B/b*, control immunity to *W*-shredding and gene conversion respectively. *A/a* and *B/b* could be called 'trans-acting' resistance loci, since they are at a different locus (indeed, a different chromosome) to the gene drive allele, in contrast to the 'cis-acting' resistance conferred by the *Zr* and *Wr* alleles. The *A* allele is dominant to *a* and confers immunity to *Z*-linked gene drive (e.g. *W*-shredding) in females. The *B* allele is dominant to *b* and confers immunity to *Z*-linked gene drive (e.g. gene conversion) in males.

Calculating female and male fitness

We assume that wild-type individuals (i.e. those lacking any drive or resistance alleles) have a fitness (w) of 1, while other genotypes have $0 \leq w \leq 1$. The fecundity of females carrying the gene drive is reduced by a factor $1 - C_f$, where a small C_f implies minimal costs (e.g. because the *W*-shredding occurs early enough that lost ova/offspring can be replaced), $C_f = 0.5$ could represent the case where all daughters die and are not replaced, and $C_f = 1$ means that gene drive females are completely sterile (which is useful for modelling a female-sterilising *Z*-linked suppression drive as opposed to a *W*-shredder). Similarly, the fitness of males carrying the gene drive is reduced by a factor $1 - C_m$; male fitness is used in the calculation of mating success (see below). Furthermore, the resistant chromosomes *Wr* and *Zr* are assumed to reduce fitness by a factor $1 - C_w$ and $1 - C_z$ respectively. All costs are multiplicative; for example, a *Z*Zr* male would have fitness $(1-C_m)(1-C_z)$. Additionally, all costs are assumed to be dominant, meaning that having one drive or resistance allele is equally costly as having two.

AUTOSOMES?

Gamete production and gene drive

We assume that the *A/a* and *B/b* loci segregate independently during meiosis and display standard Mendelian inheritance. Inheritance of the sex chromosomes is also Mendelian, except for certain genotypes carrying one copy of *Z**.

Firstly, *Z*W+aaBB*, *Z*W+aaBb*, and *Z*W+aabb* females produce a fraction $\frac{1}{2}(1 + p_{shred})$ of *Z*-bearing gametes and $\frac{1}{2}(1 - p_{shred})$ *W*-bearing gametes. Therefore, these three female genotypes produce >50% sons when $p_{shred} > 0$, due to the shortage of *W* chromosomes in their gametes. Note that the gamete frequencies of *Z*Wr females*, or of females carrying at least one *A* allele, conform to the standard Mendelian expectations due to resistance.

Secondly, *Z*Z+AAbb*, *Z*Z+Aabb*, and *Z*Z+aabb* males produce a fraction $\frac{1}{2}(1 + p_{conv} - p_{conv}p_{nhej})$ of gametes carrying the *Z** allele, $\frac{1}{2}(1 - p_{conv})$ gametes carrying the *Z+* allele, and $\frac{1}{2}(p_{conv}p_{nhej}))$ gametes carrying the *Zr* allele. Thus, gene conversion occurs in males if $p_{conv} > 0$, meaning that the *Z** allele is over-represented in the gametes of these three

male genotypes. The parameter p_{nhej} represents non-homologous end joining, in which an endonuclease-based gene drive fails to copy itself to the homologous chromosome, and instead deletes its target site and thereby creates a resistant allele. The gamete frequencies of *Z*Zr* males, or of males carrying at least one *B* allele, conform to the standard Mendelian expectations due to resistance.

Calculating female fecundity

In the breeding phase of the lifecycle, we first determine the number of offspring produced by each female in the population. We first calculate the expected fecundity of each female, which is affected by three factors: the female's genotype, the density of males and females in the local patch and/or in the full population, and some global parameters in the model.

Specifically, the expected fecundity of female i (F_i) is calculated as

$$F_i = (1 + w_i r(1 - (D_i/K)^{\alpha}))$$

where D_i is the 'density' experienced by female i, w_i is her fitness ($0 \leq w_i \leq 1$), K is the carrying capacity, and r and α are constants that scale the maximum possible fecundity and the shape of density-dependence, respectively. Thus, we assume that offspring production is density-dependent following a Richards model [24].

To ensure that the simulation captures various possible types of life history and ecology, we calculate the density D_i in various ways across different simulation runs. First, we define the 'global density' d_g, which acts equally on every female in every patch, as

$$d_g = \sum_{i=1}^{N_f} w_i + \delta N_m$$

where N_f and N_m are the numbers of females and males across all patches, the first term is the summed fitnesses of all these females, and δ is a constant (range: $0 - \infty$) that scales the effect of each male on d_g relative to a female with fitness $w_i = 1$. This formulation means that females with high relative fitness (i.e. fecundity) have a stronger effect on the global density than do low-fitness females. We also assume that each male contributes a fixed amount to the global density, irrespective of his genotype/fitness (male fitness only affects male mating success; see below). The parameter δ represents sex differences in ecological niche use and behaviours that affect female fecundity. For example, we might expect $\delta < 1$ in species where males and females utilise very different environmental niches, or $\delta > 1$ in species with strong inter-locus sexual conflict.

Second, we define the 'local density' d_j, which is experienced by every female in patch j, as

$$d_j = \sum_{i=1}^{n_{f,j}} w_i + \delta n_{m,j}$$

where $n_{f,j}$ and $n_{m,j}$ are the numbers of females and males in patch j. As before, this formulation means that d_j depends on the fitnesses of the females in the patch, as well as the number of males (scaled by the constant δ).

Finally, the overall density experienced by female i in patch j (D_i) is a composite of the global and local densities given by $D_i = \psi d_g + (1 - \psi)d_j$. The parameter ψ scales the importance of global and local density to female fecundity. When $\psi = 0$, only local density matters and selection on females is entirely "soft", while when $\psi = 1$ only global density matters and selection on females is completely "hard" (REFERENCE). Intermediate values of ψ produce a mixture of hard and soft selection on females, and the growth rate of population depends on density at both scales.

Once we have calculated the expected fecundity of each female (F_i), we generate the realised fecundity of the female by randomly sampling from a Poisson distribution with $\lambda = F_i$ (allowing for stochastic variation in fecundity between females with equal F_i). If the resulting number of offspring exceeds the global carrying capacity K, we randomly cull the offspring until K are left.

Competition between males

After determining how many offspring each female produces, we determine the fathers of each of these offspring. We assume that all breeding occurs within patches, such that males only compete for matings/fertilisations with males in the same patch. If the patch contains k different male genotypes and there are $n_1, n_2, ...n_k$ males of each genotype, the probability that a male of genotype k is the father of any given offspring is

$$p_j = \frac{n_k w_k}{\sum_{i=1}^{k} n_i w_i}$$

such that relatively common and/or high-fitness male genotypes are more likely to sire offspring. This formulation means that we assume that both sexes potentially reproduce with multiple partners.

Reproduction, mutation and dispersal

After picking the parents, we randomly generate each offspring's genotype based on the gamete (and thus zygote) frequencies that are expected from the parental genotypes. Offspring are born in the same patch as their parents, and the parental generation is replaced by the offspring generation (i.e. we assume discrete, non-overlapping generations).

When an offspring is created, each *Z+* allele it carries has a chance μ_Z to mutate to a *Zr* allele, and *vice versa* (i.e. mutation in both directions is equally probable). Similarly, each *W+* allele has a chance μ_W to mutate to a *Wr* allele, and *vice versa*.

Female and male offspring disperse to another patch with probabilities x_f and x_m respectively. We model two types of dispersal, in separate simulations: local dispersal, in which offspring move to one of the two neighbouring patches with equal probability (recalling that the patches are arranged in a ring), or global dispersal, in which dispersing offspring can land in any of the other patches.

One compete run of the simulation

We first initialised a population of 10,000 individuals (i.e. the carrying capacity, K) with low or zero frequencies of *Zr*, *Wr*, *A* and *B* alleles, higher frequencies of the wild type *Z+*, *W+*, *a*, and *b* alleles, and zero *Z** gene drive alleles. We then iterated the population for 50 generations of burn-in, to allow the population to approach demographic and genotypic equilibrium. We then introduced $n_{release}$ males with the genotype *Z*Z*aabb*, which represents the release into the wild of a laboratory-reared strain homozygous for the driving *Z* and for autosomal factors conferring susceptibility to drive. Males are released after density-dependent regulation of female fecundity, but before picking fathers for the offspring. In some simulations, all the *Z*Z*aabb* males were released in a single patch, while in others the $n_{release}$ males were randomly and evenly divided across all k patches. We continued to cycle through the lifecycle (birth, migration, breeding, death) until either A) the driving *Z** allele went extinct, B) the population went extinct, C) the *Wr* chromosome went to fixation (making population suppression impossible), D) the *Z** allele fixed, but failed to cause population extinction, or E) 900 generations had elapsed. We recorded which of these five outcomes occurred, as well as the allele frequencies, population size, and sex ratio at each generation.

Investigating the parameter space

For each of the parameters in Table 1, we selected two or more possible parameter values (e.g. high versus low rates of *W*-shredding p_{shred}; many versus few patches k). We then ran the model once for all possible combinations of these parameter values (n = XXX model runs). The aim was to measure the 'main effect' of each parameter across a background of assumptions for the other parameters, as well as to investigate all the possible 2-way interactions between the parameters (e.g. to test if the effect of p_{shred} depends on k and *vice versa*).

Results

Three illustrative simulation runs

Blah blah

Main effects of each parameter

Figure 2 shows the main effects of each of the parameters in the model, arranged in order of their effect on the probability of extinction (recall that we ran the simulation for all possible combinations of values shown along the x-axis of Figure 2). By far the most important parameters were the strength of gene drive in females (i.e the propensity to produce sons over daughters, p_{shred}), and the cost the Z* allele to females (c_f). These results were expected: the gene drive will not cause extinction unless Z*-carrying females produce a strongly male-biased sex ratio (e.g. due to efficient W-shredding), and extinction is more likely when Z*-carrying females produce larger numbers of Z*-carrying sons. The strength of the gene drive in males (p_{conv}) had a smaller but still noticeable effect on the extinction probability, and the model confirmed our intuition that it is helpful but non-essential that the Z* allele drives in males (e.g. through gene conversion) in addition to shredding the W chromosome.

When we modelled a Z-linked allele that causes total sterility in females ($c_f = 1$) and is capable of gene drive in males, extinction occured in a few simulation runs, though not nearly as many as for a W-shredding Z chromosome. This results indicates that gene drives which work by killing or sterilising females that carry them are less likely to cause extinction than drives which work by 'hijacking' these females to produce more drive-carrying males. Female-killing or -sterilising gene drives may still be very useful for some cases, but they may need larger releases in order to be effective. Also, because we modelled a Z-linked drive, it is not possible for the fitness costs of the drive to be recessive in females; other models have shown that autosomal or X-linked female-harming drives can be effective, particualrly if their costs are recessive (such that the driver reaches a high frequency before beginning to kill its carriers).

As expected, extinction was less likely to occur when some individuals show resistance to W-shredding, due to either W-linked or autosomal alleles. The presence of alleles conferring resistance to gene drive in males (either on the Z chromomsome or an autosome) also had an effect on the extinction rate. However, the gene drive was still perfectly capable of causing extinction rate even when resistance to the male-acting part of the gene drive was ubiquitous (e.g. when the gene drive created a resistant allele 10% of the time). This represents further evidence that it may not be necessary to ensure that Z-linked, W-shredding gene drives also work in males.

Interestingly, the Z* allele was still able to spread and to cause extinction when it had a strong negative effect on male reproductive success (e.g. $c_m = 0.2$, meaning that a drive male is only 80% as likely to father offspring as is a wild-type male in the same patch). ...

Several of the ecological variables examined also affected the extinction probability. Chief among these was the shape parameter of the Richards density-dependence function, α. For $\alpha < 1$, fecundity declines at a decelerating rate as density increases, such that most of the population is depleted before per-female fecundity reaches very high values, making extinction more likely. Conversely for $\alpha > 1$, fecundity declines at an accelerating rate with increasing density, making extinction less likely because per-female fecundity increases rapidly once the population starts to shrink due to the spread of the gene drive. We also found

the unsuprising result that populations in which females can reach high fecundity at low population densities (captured by the parameter r) are more difficult to drive extinct. Also, we found that extinction was slightly more probable when female fecundity depends mostly on the local density (as opposed to global density; ψ in Figure 2). This is because local density can still be high as the global density declines due to the spread of the Z* allele in other patches.

We also found increasing rates of extinction with δ, which scales how male density affects female fecundity. When δ is high, extinction is more probable because female fecundity does not increase as much once the drive has begun to spread, due to the ever-increasing numbers of males. Conversely, lower values of δ mean that male numbers are relatively unimportant in determining female fecundity, making extinction less likely since the removal of females by the gene drive lessens competition on the remaining females. This result highlights that it is important to consider the ecology of the target species.

Populations that are split into many semi-isolated patches were more difficult to drive extinct that those that comapratively free of spatial struction, though the effect on extinction rate was small (k in Figure 2). The likely reason is that a highly-structured population can contain refugia where the drive allele is absent, as well as empty patches created by local extinctions that can be re-colonised by the wild type allele. The frequency and mode of migration was relatively unimportant, though there was a slight tendency for higher dispersal rates to stave off extinction, presumably because dispersal allows the re-colonisation of patches in which local extinction has occurred. In a similar vein, we found that extinction was slightly less likely to occur when dispersal could carry individuals to any patch, as opposed to neighbouring patches only. Finally, we found essentially no effect of the release strategy, suggesting that it may not be necessary to release a *W*-shredding gene drive across the species' entire range provided that there exists gene flow between patches.

Discussion

- schistos have large males, small females
- birds often have sex-biased dispersal
- females may be more demographically limiting leps, since it is them that lays the eggs
- dominant costs assumption

Acknowledgements

I thank the organisers, funding bodies (European Society for Evolutionary Biology; Swiss National Science Foundation), and attendees of ESEB's 2018 *Progress Meetings in Evolutionary Biology* for sparking my interest in gene drives. I also thank Kevin Esvelt for outlining ongoing research on his website; without his openness, this paper would not have been written.

References

1. Gantz VM, Jasinskiene N, Tatarenkova O, Fazekas A, Macias VM, Bier E, James AA. 2015 Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*. *Proceedings of the National Academy of Sciences* **112**, E6736–E6743.

2. Hammond A *et al.* 2016 A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*. *Nature Biotechnology* **34**, 78.

3. Wang Z, Pan Q, Gendron P, Zhu W, Guo F, Cen S, Wainberg MA, Liang C. 2016 CRISPR/Cas9-derived mutations both inhibit HIV-1 replication and accelerate viral escape. *Cell Reports* **15**, 481–489.

4. Prowse TA, Cassey P, Ross JV, Pfitzner C, Wittmann TA, Thomas P. 2017 Dodging silver bullets: good CRISPR gene-drive design is critical for eradicating exotic vertebrates. *Proc. Roy. Soc. B* **284**, 20170799.

5. Kyrou K, Hammond AM, Galizi R, Kranjc N, Burt A, Beaghton AK, Nolan T, Crisanti A. 2018 A CRISPR–Cas9 gene drive targeting *doublesex* causes complete population suppression in caged *Anopheles gambiae* mosquitoes. *Nature Biotechnology*

6. Noble C, Adlam B, Church GM, Esvelt KM, Nowak MA. 2018 Current CRISPR gene drive systems are likely to be highly invasive in wild populations. *eLife* **7**, e33423.

7. Lindholm AK *et al.* 2016 The ecology and evolutionary dynamics of meiotic drive. *Trends in Ecology & Evolution* **31**, 315–326.

8. Champer J, Buchman A, Akbari OS. 2016 Cheating evolution: Engineering gene drives to manipulate the fate of wild populations. *Nature Reviews Genetics* **17**, 146.

9. Marshall JM, Akbari OS. 2015 Gene drive strategies for population replacement. In *Genetic control of malaria and dengue*, pp. 169–200. Elsevier.

10. Beaghton A, Beaghton PJ, Burt A. 2017 Vector control with driving Y chromosomes: modelling the evolution of resistance. *Malaria Journal* **16**, 286.

11. Burt A, Deredec A. 2018 Self-limiting population genetic control with sex-linked genome editors. *Proc. Roy. Soc. B* **285**, 20180776.

12. Papathanos PA, Windbichler N. 2018 Redkmer: An assembly-free pipeline for the identification of abundant and specific x-chromosome target sequences for x-shredding by crispr endonucleases. *The CRISPR Journal* **1**, 88–98.

13. Drury DW, Dapper AL, Siniard DJ, Zentner GE, Wade MJ. 2017 CRISPR/Cas9 gene drives in genetically variable and nonrandomly mating wild populations. *Science Advances* **3**, e1601910.

14. Unckless RL, Clark AG, Messer PW. 2017 Evolution of resistance against CRISPR/Cas9 gene drive. *Genetics* **205**, 827–841.

15. Gantz VM, Bier E. 2015 The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. *Science*, aaa5945.

16. Min J, Noble C, Najjar D, Esvelt KM. 2017 Daisyfield gene drive systems harness repeated genomic elements as a generational clock to limit spread. *BioRxiv*, 104877.

17. Maselko M, Heinsch SC, Das S, Smanski MJ. 2018 Genetic incompatibility combined with female-lethality is effective and robust in simulations of *Aedes aegypti* population control. *bioRxiv*, 316406.

18. Vella MR, Gunning CE, Lloyd AL, Gould F. 2017 Evaluating strategies for reversing CRISPR-Cas9 gene drives. *Scientific Reports* **7**, 11038.

19. North A, Burt A, Godfray HCJ. 2013 Modelling the spatial spread of a homing endonuclease gene in a mosquito population. *Journal of Applied Ecology* **50**, 1216–1225.

20. Galizi R, Doyle LA, Menichelli M, Bernardini F, Deredec A, Burt A, Stoddard BL, Windbichler N, Crisanti A. 2014 A synthetic sex ratio distortion system for the control of the human malaria mosquito. *Nature Communications* **5**, 3977.

21. Holman L, Price TA, Wedell N, Kokko H. 2015 Coevolutionary dynamics of polyandry and sex-linked meiotic drive. *Evolution* **69**, 709–720.

22. Rankin DJ, Kokko H. 2007 Do males matter? The role of males in population dynamics. *Oikos* **116**, 335–348.

23. Li X-Y, Kokko H. 2019 Sex-biased dispersal: A review of the theory. *Biological Reviews* **in press**.

24. Fowler CW. 1981 Density dependence as related to life history strategy. *Ecology* **62**, 602–610.

Supporting information