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## Evolutionary simulations of Z-linked suppression gene drives

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## 1. Introduction

Developments in biotechnology will soon make it feasible to alter or eliminate populations of disease vectors, pathogens, agricultural pests, and invasive species using ‘gene drives’ [1–6]. Gene drives cause particular alleles (usually transgenes) to propagate through populations via a range of mechanisms including gene conversion, poison-antidote systems, segregation distortion, and genetic incompatibility [7–9]. For example, CRISPR-Cas9 gene editing 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%; this type of gene drive functions by inducing a double-strand break in the wild type allele, which is then repaired using the transgene as a template. Gene drives are often categorised into two types, both of which can be created with homing endonucleases like CRISPR-Cas9. ‘Replacement drives’ aim to propagate a human-beneficial allele that would not otherwise spread through the population, e.g. a mosquito allele that interferes with the transmission of malaria [1,10]. 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 [2,5,11], or which skews the offspring sex ratio – typically towards males [12–16].

Recent theoretical papers have investigated the feasibility, efficacy, and potential negative consequences of emerging gene drive technologies. For example, Noble et al. [6] used models to show that the basic version of a CRISPR gene drive might be highly invasive and could rapidly spread to fixation across whole meta-populations and species, which will sometimes be undesirable. Conversely, other models have concluded that alleles conferring resistance to the gene drive can prevent it from spreading and achieving its aims [17,18]. The issue of resistance is compounded because the standard implementation of CRISPR-Cas9 gene drive (but perhaps not updated versions; [4,5,18,19]) tends to create its own resistance alleles, e.g. when the double-stranded break induced by Cas9 is repaired using non-homologous end joining (NHEJ) instead of homology-directed repair [1–3,18,20]. Given the potential safety, ethical, and sociopolitical concerns surrounding gene drives, some models have focused on gene drives that would go extinct after a time [15,21,22], would stay confined to particular populations [11,22], and/or could be reversed once they have spread [23].

Here, I focus on the evolutionary dynamics of Z-linked suppression gene drives. The simulation is inspired by proposals for various types of Z-linked gene drives by Kevin Esvelt and colleagues, as well as their ongoing efforts to develop these Z drives (see [www.sculptingevolution.org/genedrives/current/schistosomiasis](http://www.sculptingevolution.org/genedrives/current/schistosomiasis); at the time of writing, these ideas have not been published in a journal or preprint). Various Z-linked suppression drives proposed by Esvelt and colleagues are shown schematically in Figure XX. 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 crop pests or even invasive populations of birds.

A Z-linked gene drive could suppress populations by biasing gametogenesis in females, for example by inducing double-stranded DNA breaks in the W chromosome in order to destroy it; such a gene drive would be a ‘W-shredder’, similar to the X- and Y-shredders under development for XY species [12,13,15,16,24,25]. Females carrying the gene drive would thus produce relatively few viable W-bearing eggs, and therefore produce mainly drive-carrying sons. Esvelt et al. point out that the evolutionary dynamics of the drive will depend on the fitness of drive carriers relative to wild types, the timing of W-shredding (e.g. in pre-meiotic cells vs mature ova or zygotes), and the ecology of the target species. For example, some W-shredder designs might allow drive females to produce roughly the same number of (mostly-male) offspring as a wild-type female provided that the W chromosome is destroyed early enough in oogenesis/development that the lost daughters can be replaced by sons (Figure XX). Alternatively, drive-carrying females

53 might produce half the number of offspring (or less), e.g. if the drive works by destroying all  
54 ova or offspring that carry a *W* chromosome, and this loss is not compensated by reduced  
55 competition on the surviving offspring. As an alternative to *W*-shredders, Esvelt et al. also  
56 proposed that one could suppress populations using a *Z*-linked locus that caused sterility or  
57 lethality in females. If this female-harming allele were capable of gene drive in males (see below),  
58 it could perhaps reach high enough frequencies to suppress the population. Esvelt et al. suggest  
59 that a *W*-shredder would also benefit from undergoing gene drive in males, though they suggest  
60 it might not be necessary. Male gene drive could be accomplished using 'standard' CRISPR-Cas9  
61 gene conversion, whereby the driving *Z* allele would convert the wild type locus using homing  
62 endonuclease activity followed by homology-directed repair, causing heterozygous males to  
63 produce mostly drive-carrying sperm and offspring.

64 Here, I present an evolutionary simulation that can accommodate all of these hypothesised  
65 types of *Z*-linked drives. I aimed to test which properties of the gene drive and the ecology  
66 of the target species are critical to determining the likelihood and speed with which the gene  
67 drive causes extinction. For example, the gene drive will presumably spread faster if it can  
68 bias transmission in both sexes, but perhaps a female-only gene drive (which might be easier  
69 to engineer) would be perfectly adequate. Also, since the population will become more male-  
70 biased as the gene drive invades, there will be eco-evo feedback that might affect the evolutionary  
71 outcome in non-intuitive ways that would be missed without a formal model. For example, the  
72 altered sex ratio might intensify the fitness advantage accruing to any resistant *W* chromosomes or  
73 autosomal modifiers that prevent *W*-shredding (due to Fisherian selection for an even sex ratio;  
74 [26]), relative to that observed in earlier models focusing on gene drives carried on autosomes  
75 [17,18]. Moreover, the change in sex ratio could affect the demographics of the population,  
76 particularly if males and females contribute differentially to density-dependent population  
77 growth [27,28], or have different dispersal rates [29]. The model incorporates the possibility that  
78 *Z*-linked resistant-to-drive alleles are sometimes created by NHEJ in heterozygote males, and tests  
79 whether these alleles are equally problematic as for autosomal drives [1–3,18,20].

## 80 2. Methods

### 81 (a) Overview

82 I model a finite population of dioecious diploids with *ZW* sex determination, living in  $j$  discrete  
83 habitat patches that are arranged linearly in a ring. The model considers the demography and  
84 evolution of a population into which  $n_{release}$  males carrying a *Z*-linked gene drive are released.  
85 The drive allele causes either *W*-shredding or sterility in females, and optionally also causes gene  
86 drive in heterozygous males (e.g. via gene conversion of the non-driving *Z*). The generations are  
87 non-overlapping and each one proceeds as follows: birth, dispersal between patches, breeding  
88 with patches, and death of the parental generation. The species has 3 loci with 2–3 alleles each,  
89 some of which potentially show non-Mendelian inheritance. The equilibrium population size  
90 was roughly 10,000 in all simulations upon release of the gene drive. The model is a stochastic  
91 individual-based simulation written in R 3.4.0 and was run on the Spartan computer cluster at  
92 the University of Melbourne.

### 93 (b) Loci and alleles

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

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

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

102 The two autosomal loci, denoted  $A/a$  and  $B/b$ , control immunity to  $W$ -shredding and gene  
 103 conversion respectively.  $A/a$  and  $B/b$  are ‘trans-acting’ resistance loci, since they are at a different  
 104 locus (indeed, a different chromosome) to the gene drive allele, in contrast to the ‘cis-acting’  
 105 resistance conferred by the  $Z^r$  and  $W^r$  alleles. The  $A$  allele is dominant to  $a$  and confers immunity  
 106 to  $Z$ -linked gene drive (e.g.  $W$ -shredding) in females. The  $B$  allele is dominant to  $b$  and confers  
 107 immunity to  $Z$ -linked gene drive (e.g. gene conversion) in males.

### 108 (c) Calculating female and male fitness

109 I assume that wild-type individuals (i.e. those lacking drive or resistance alleles) have fitness  $w$   
 110 = 1, while other genotypes have  $0 \leq w \leq 1$ . The fecundity of females carrying the gene drive is  
 111 reduced by a factor  $1 - c_f$ . Small  $c_f$  implies minimal costs (e.g. because lost gametes/offspring  
 112 are easily replaced),  $c_f = 0.5$  could represent the case where all daughters die and are not  
 113 replaced, and  $c_f = 1$  means that females carrying  $Z^*$  are completely sterile (setting  $c_f = 1$  allows  
 114 us to model a female-sterilising  $Z$ -linked drive rather than a  $W$ -shredder). Similarly, the fitness  
 115 of males carrying the gene drive is reduced by a factor  $1 - c_m$ ; male fitness determines mating  
 116 success (see below). Furthermore, the resistant chromosomes  $W^r$  and  $Z^r$  are assumed to reduce  
 117 fitness by factors of  $1 - c_w$  and  $1 - c_z$  respectively. For brevity, I assume that the autosomal  
 118 resistance alleles  $A$  and  $B$  are cost-free. All costs are multiplicative; for example, a  $Z^*Z^r$  male  
 119 would have fitness  $(1 - c_m)(1 - c_z)$ . Additionally, all costs are assumed to be dominant, meaning  
 120 that having one drive or resistance allele is equally costly as having two (note that this is only  
 121 relevant in males because of female heterogamety).

### 122 (d) Gamete production and gene drive

123 I assume that the  $A/a$  and  $B/b$  loci segregate independently during meiosis and display standard  
 124 Mendelian inheritance. Inheritance of the sex chromosomes is also Mendelian, except for certain  
 125 genotypes carrying one  $Z^*$  allele.

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

131 Secondly,  $Z^*Z+AAbb$ ,  $Z^*Z+Aabb$ , and  $Z^*Z+aabb$  males produce a fraction  $\frac{1}{2}(1 + p_{conv} -$   
 132  $p_{conv}p_{nhej})$  of gametes carrying the  $Z^*$  allele,  $\frac{1}{2}(1 - p_{conv})$  gametes carrying the  $Z^+$  allele, and  
 133  $\frac{1}{2}(p_{conv}p_{nhej})$  gametes carrying the  $Z^r$  allele. Thus, gene conversion occurs in males if  $p_{conv} > 0$ ,  
 134 meaning that the  $Z^*$  allele is over-represented in the gametes of these three male genotypes. The  
 135 parameter  $p_{nhej}$  represents non-homologous end joining, in which an endonuclease-based gene  
 136 drive fails to copy itself to the homologous chromosome, and instead deletes its target site and  
 137 thereby creates a resistant allele. The gamete frequencies of  $Z^*Z^r$  males, or of males carrying at  
 138 least one  $B$  allele, conform to the standard Mendelian expectations due to resistance.

### 139 (e) Calculating female fecundity

140 In the breeding phase of the lifecycle, the model first determines the number of offspring  
 141 produced by each female. The expected fecundity of female  $i$  ( $F_i$ ) is affected by three factors:  
 142 the female’s genotype, the density of males and females in the local patch and/or in the full  
 143 population, and some global parameters in the model, as follows:

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

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  $\alpha$  are constants that control the maximum possible fecundity and the shape of density-dependence, respectively (function inspired by [30]).

To ensure that the simulation captures various possible types of life history and ecology, I calculated density  $D_i$  in various ways in different simulation runs. First, I 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  $\delta$  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. I also assume that each male contributes a fixed amount to the global density, irrespective of his genotype/fitness (since I assume that male fitness only affects male mating success; see below). The parameter  $\delta$  represents sex differences in ecological niche use and behaviour. For example, we might expect  $\delta < 1$  in species where males and females utilise very different environmental niches, or  $\delta > 1$  in species where males are harmful to females.

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  $\delta$ ).

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  $\psi$  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” (similar to the model in [31]). Intermediate values of  $\psi$  produce a mixture of hard and soft selection on females, and the growth rate of population depends on density at both scales.

After calculating 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 exceeded the global carrying capacity  $K$ , the model randomly selects  $K$  surviving offspring.

## (f) 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  $n_1, n_2, \dots, n_k$  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 both sexes potentially reproduce with multiple partners.

### 183 (g) Reproduction, mutation and dispersal

184 After picking the parents, the model randomly generates each offspring's genotype based on the  
 185 expected gamete (and thus zygote) frequencies. Offspring are born in the same patch as their  
 186 parents, and the parental generation is replaced by the offspring generation.

187 When an offspring is created, each  $Z^+$  allele it carries has a chance  $\mu_Z$  to mutate to a  $Z^r$  allele,  
 188 and *vice versa* (i.e. mutation in both directions is equally probable). Similarly, each  $W^+$  allele has a  
 189 chance  $\mu_W$  to mutate to a  $W^r$  allele, and *vice versa*.

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

### 195 (h) One compete run of the simulation

196 The model first initialises a population of 10,000 individuals (the carrying capacity,  $K$ ) with  
 197 low or zero frequencies of  $Z^r$ ,  $W^r$ ,  $A$  and  $B$  alleles, higher frequencies of the wild type  $Z^+$ ,  
 198  $W^+$ ,  $a$ , and  $b$  alleles, and zero  $Z^*$  gene drive alleles. It then runs 50 generations of burn-in to  
 199 allow the population to reach demographic and genotypic equilibrium. Next,  $n_{release}$  males with  
 200 the genotype  $Z^*Z^*aabb$  are added to the population just before fathers are selected, representing  
 201 the release into the wild of a laboratory-reared strain homozygous for the driving  $Z$ . In some  
 202 simulations, all the  $Z^*Z^*aabb$  males were released in a single patch, while in others the  $n_{release}$   
 203 males were randomly and evenly divided across all  $k$  patches. The model continued until either  
 204 A) the driving  $Z^*$  allele went extinct, B) the population went extinct, C) the  $W^r$  chromosome  
 205 went to fixation (making population suppression impossible), D) the  $Z^*$  allele fixed, but failed  
 206 to cause population extinction, or E) 900 generations had elapsed. The model recorded which of  
 207 these five outcomes occurred, as well as the allele frequencies, population size, and sex ratio at  
 208 each generation.

### 209 (i) Investigating the parameter space

210 For each of the parameters in Table 1, I selected two or more possible parameter values (e.g. high  
 211 versus low rates of  $W$ -shredding  $p_{shred}$ ; many versus few patches  $k$ ). I then ran the model once  
 212 for all possible combinations of these parameter values ( $n = 6,000,000$  model runs). The aim  
 213 was to measure the effect of each parameter across a background of assumptions for the other  
 214 parameters, as well as to investigate all possible 2-way interactions between the parameters.

## 215 3. Results

### 216 (a) Three illustrative simulation runs

217 Figure 1 shows three contrasting evolutionary outcomes, illustrating some representative  
 218 evolutionary dynamics from among the 6,000,000 simulation runs. Tables S1-S2 give the relative  
 219 frequencies of the various possible outcomes (e.g. extinction occurred in 28% of simulations  
 220 involving  $W$ -shredders).

221 In Figure 1A, the release of 20  $Z^*Z^*$  males at generation 50 (c. 0.2% of the population)  
 222 was followed by the rapid invasion of the  $Z^*$  allele, which caused population extinction by  
 223 reducing the number of females. Figure 1A assumes that the  $Z^*$  alleles causes perfect  $W$ -shredding  
 224 ( $p_{shred} = 1$ ), that  $Z^*$  has minimal fitness costs, and there is no resistance to  $W$ -shredding (Table  
 225 S3).

226 In Figure 1B,  $Z^*$  invaded but failed to cause extinction, even though it was assumed that  
 227  $p_{shred} = 1$  and there is no resistance to  $W$ -shredding. However, the simulation in Figure 1B

assumed the presence of heavy fitness costs to individuals carrying at least one  $Z^*$  allele ( $c_f = 0.5$  and  $c_m = 0.2$ ), and that there was no gene drive in males ( $p_{conv} = 0$ ). The assumptions  $p_{shred} = 1$  and  $c_f = 0.5$  could imply that the  $W$ -bearing eggs/offspring of  $Z^*W+$  females are destroyed but not replaced, such that  $W$ -shredding increases the proportion but not the absolute number of offspring that inherit the  $Z^*$  allele. Essentially  $Z^*$  spreads via ‘spite’ [32], in that it removes  $W$  chromosomes from the local population and thereby makes room for more  $Z^*$  alleles, creating indirect fitness benefits. However, the net fitness returns of the  $Z^*$  allele’s ‘strategy’ (i.e. sacrificing 20% fitness in males in order to remove  $W$  chromosomes in females) decline as the  $W$  chromosome becomes rarer, allowing the cost in males to greatly slow the spread of  $Z^*$ .

Lastly, Figure 1C shows a case where the invasion of  $Z^*$  was halted and then reversed by the evolution of autosomal and  $Z$ -linked resistance alleles. Following the introduction of the  $Z^*$  allele, resistant  $Z^r$  mutants were created via non-homologous end joining, and then  $Z^r$  spread to fixation due to its immunity to gene conversion in males. The autosomal resistance allele  $A$  also spread;  $A$  confers resistance to  $W$ -shredding and was initially present in the population at 5% frequency. The spread of  $A$  caused the sex ratio to revert to normal, preventing extinction, and  $Z^*$  went extinct due to its direct fitness costs no longer being outweighed by the benefits of  $W$ -shredding and gene conversion. Incidentally, the resistant allele  $A$  was favoured over  $a$  because the male-biased population sex ratio created by  $Z^*$  favours the production of daughters, and  $AA$  and  $Aa$  females produce more daughters than  $aa$  females in populations where  $Z^*$  is present.

### (b) Effects of each parameter on the evolution of a $W$ -shredder

Figure 2 shows the main effects of each model parameter, for models of a  $Z$ -linked  $W$ -shredder that potentially also benefits from gene drive in  $Z^*Z$  males. Figure S1 is similar to Figure 2, but instead shows the number of generations until extinction on the  $y$ -axis. Under favourable assumptions, extinction occurred around 20 generations after introduction of the gene drive, though it was often longer (Figure S1).

In Figure 2, the parameters are arranged in approximate order of their importance to extinction probability. By far the most important predictors of extinction were the efficiency of  $W$ -shredding in females ( $p_{shred}$ ) and the existence of resistance against  $W$ -shredding: extinction never occurred unless  $p_{shred}$  was high and autosomal alleles conferring resistance to  $W$ -shredding (allele  $A$  in the model) were absent. This makes sense, because a  $W$ -shredder cannot cause extinction unless  $Z^*$ -carrying females produce a strongly male-biased sex ratio, and resistance to  $W$ -shredding cannot readily evolve. Extinction also occurred a little more quickly when  $p_{shred}$  was 1 rather than 0.95 (Figure S1).

The strength of gene drive in  $Z^*Z$  males ( $p_{conv}$ ; colours in Figure 2) also predicted extinction probability. However,  $p_{conv}$  was not as important as was the strength of  $W$ -shredding, and the  $W$ -shredder frequently caused extinction even if it did not drive in males, or if resistance to male gene drive was common. The benefit to extinction probability provided by male gene drive depended on other factors in the model (see plots of interactions; Figures XX); for example, male gene drive was at its most beneficial when resistance to it could not evolve (either through natural genetic variation, or the creation of resistant  $Z^r$  alleles through NHEJ). Although it did not strongly determine the probability of extinction probability, male gene drive did considerably speed up extinction (Figure S1). For example, assuming perfect  $W$ -shredding, adding male gene drive with  $p_{conv} = 0.95$  reduced the expected time to extinction from around 75 to 22 generations.

The cost of the  $Z^*$  allele to female fitness also affected extinction probability, and its effect interacted with the strength of gene drive in  $Z^*Z$  males. Specifically, assuming that the  $Z^*$  allele halves female fitness ( $c_f = 0.5$ ) cancels out the fitness benefits of segregation distortion for the  $Z^*$  allele, and so extinction could only occur when  $c_f = 0.5$  if there was gene drive in males. Reassuringly, increasing  $c_f$  from 0.01 or 0.1 had almost no effect on the likelihood of extinction, meaning that  $W$  shredders might be an effective means of population control even if females carrying the gene drive suffer a 10% fitness cost. Similarly, assuming that  $Z^*$  was costly to male carriers also had little effect on extinction probability: extinction occurred almost as frequently

when the reduction in male mating success was 20% rather than 1%. Both  $c_f$  and  $c_m$  were positively correlated with the time to extinction, particularly when there was no gene drive in males (Figure S1).

Several of the ecological variables examined also affected the extinction probability. Chief among these was the shape parameter,  $\alpha$ , of the density-dependence function.  $\alpha < 1$  means that female fecundity declines at a decelerating rate as density increases, such that per-female fecundity only approaches its maximum value when the population is heavily depleted, making extinction more likely. Conversely for  $\alpha > 1$ , fecundity declines at an accelerating rate with increasing density, making extinction less likely due to the immediate increases in per-female fecundity that manifest once the population begins to shrink due to the spread of the gene drive. Unsurprisingly, I also found that populations in which females have a higher maximum possible fecundity ( $r$ ) are somewhat more difficult to drive extinct, though the model confirmed that *W*-shredders can, in principle, drive extinct highly fecund species. Also, extinction was slightly more probable when female fecundity was determined more by local density than global density ( $\psi$  in Figure 2). This is because local density can remain high (and thus, per-female fecundity can remain low) even in meta-populations that are declining due to the spread of the  $Z^*$  allele in some of their sub-populations.

Extinction probability also increased with  $\delta$ , the parameter that determines how male density affects female fecundity. When  $\delta$  is high, female fecundity is constrained from increasing as the drive allele spreads by the ever-increasing proportion of males, contributing to extinction. Conversely, lower values of  $\delta$  mean that male numbers are relatively unimportant in determining female fecundity, making extinction less likely because the shortage of females created by the gene drive alleviates competition on the remaining females. This result highlights that it is important to consider the ecology and population dynamics of target species when designing gene drives that work by eliminating one sex.

Populations that are split into many semi-isolated patches were more difficult to drive extinct than those that are comparatively free of spatial structure, though the effect on extinction rate was small (Figure 2). The likely reason is that a highly-structured population allows for refugia that lack the gene drive allele. The frequency and sex bias in dispersal was relatively unimportant to extinction probability, though there was a slight tendency for higher dispersal rates to stave off extinction, presumably because dispersal allows recolonisation of patches that were cleared by the gene drive. Similarly, it did not matter whether dispersal carried individuals to any patch, or only to neighbouring patches. Finally, there was no effect of the release strategy, suggesting that it may be unnecessary to release a *W*-shredding gene drive across the species' entire range provided that there is gene flow between patches. An additional implication of this result is that we cannot expect *Z*-linked gene drives to remain confined to their release sites, as previously found for autosomal drives [6].

The *W*-shredder was able to fail for two principal reasons: it reached fixation without causing extinction, or it went extinct (Table S1). The former happened only if resistance to *W* shredding could evolve (either via resistant *W* chromosomes, or the *A* allele), while the latter happened whenever the fitness benefits of gene drive were overwhelmed by the fitness costs imposed on drive carriers.

### (c) Effects of each parameter on a female-sterilising *Z* drive

I also used the model to examine the evolution of a *Z*-linked allele that causes gene drive in males and also causes total sterility in females ( $c_f = 1$ ; Figure S2). This alternative type of gene drive was also effective at causing extinction, but only under the assumption that the population has little or no resistance to gene drive in males. For example, extinction never occurred if even 1% of the progeny of  $Z^*Z$  males inherited a resistant  $Z'$  allele created by non-homologous end joining [c.f. 18]. Extinction also required that gene drive in males was strong (high  $p_{conv}$ ), and that there were no autosomal resistance alleles to male gene drive. The effects of the other parameters in the model were similar as for a *W*-shredder (Figure S2), and extinction (when it occurred) took a

330 fairly similar number of generations (around 25-30; Figure S3). As before, the  $Z^*$  allele sometimes  
331 went extinct, typically because the strength of gene drive in males was not sufficiently strong to  
332 overcome the fitness costs to drive carriers (Table S2).

## 333 4. Discussion

334 The model indicates that  $W$ -shredders are, in principle, a very effective method for eliminating  
335 populations, especially if  $Z^*W$  females produce no daughters and resistance to  $W$ -shredding  
336 cannot readily evolve. The results of the model have implications for the design of  $Z$ -linked  
337  $W$ -shredders and female-sterilising suppression drives.

338 One design consideration is whether to engineer  $W$ -shredders that are also capable of gene  
339 drive in males, e.g. by including guide RNAs in the gene drive cassette that target the  $Z$   
340 as well as the  $W$  chromosome. In the model,  $W$ -shredders very often caused extinction even  
341 without male gene drive (i.e. when  $p_{conv} = 0$ ), provided that females carrying the  $W$ -shredder  
342 had comparable fecundity to wild type females, and that carrier females produce very few  
343 daughters. Conversely if  $W$ -shredder females had low fecundity (around half that of a wild type,  
344 or below) or produced some daughters, male gene drive was essential for the  $W$ -shredder to  
345 cause extinction, or at least for extinction to occur quickly enough to be useful. Although male  
346 gene drive was not always essential to extinction, it did reduce the number of generations until  
347 extinction occurred, sometimes substantially. Therefore, I conclude that it would almost certainly  
348 be worth the effort to incorporate a male-acting gene drive if developing a  $W$ -shredder for species  
349 with long generation times, such as invasive birds. However the rate of population decline may be  
350 adequate even without male gene drive for species that have multiple generations per year, such  
351 as Lepidopteran pests and *Schistosoma* parasites. This could simplify the design of  $W$ -shredders  
352 since they would only need to target the  $W$ , particularly because male-acting CRISPR-based  
353 drives have proved more challenging to develop in at least some taxa (due to sex differences  
354 in DNA repair; [33]). Conversely, strong male gene drive is essential to extinction for female-  
355 sterilising suppression drives.  $Z$ -linked alleles that drive in males and sterilise females were  
356 effective at causing extinction, but were very vulnerable to the evolution of resistance to male  
357 gene drive (e.g. because drive-resistant alleles are created via NHEJ; [18]).

358 Another aim when designing  $W$ -shredders should be to ensure that female carriers produce  
359 as few daughters as possible (ideally none), while producing a large number of drive-carrying  
360 sons (ideally as many as the total offspring produced by non-carriers). This implies that one  
361 should ideally design a construct that cleaves the  $W$  chromosome early in gametogenesis or  
362 development, to increase the chance that the number of surviving progeny produced by each  
363 female is unaffected. For some species, this may mean placing the  $W$ -shredder under the control of  
364 a promoter that is active in the female germ line [perhaps *nanos*; 34,35], such that females are able  
365 to replace lost  $W$ -bearing oocytes before they are provisioned with limiting maternal resources.  
366 For other species, it may be possible to shred the  $W$  chromosome in  $W$ -bearing ova or embryos  
367 using maternally-derived Cas9 and guide RNAs deposited in the egg after being synthesised  
368 by the  $Z^*$  allele [somewhat like *Medea*; 36]. In Lepidoptera, juvenile density is often strongly  
369 negatively correlated with survival, and there are maternally-transmitted endosymbionts that  
370 are able to drive through populations by killing males to lessen competition on their infected  
371 sisters [e.g. 37,38]; these observations suggest that  $W$ -shredder alleles would invade Lepidopteran  
372 populations even if  $Z^*W$  females produced half as many viable eggs.

373 The  $W$ -shredding mechanism should also be designed in a way that makes it difficult for  $W$ -  
374 linked or *trans*-acting resistance to shredding to evolve. One way to do this would be to use  
375 a single guide RNA that targets  $W$ -specific sequences that have high copy number, or to use  
376 multiple guide RNAs that target multiple  $W$ -linked sequences [34]. This way, multiple changes  
377 to the reference sequence would be required for a  $W$  chromosome to acquire resistance to  
378 cleavage by the  $W$ -shredder. To ensure that the targets of cleavage do not become resistant as  
379 a result of indels induced by non-homologous end joining (NHEJ), one can ensure that the guide  
380 RNA's target lies within an essential gene where an indel would be selectively disadvantageous,

381 preventing resistant alleles from accumulating in the population. This may not be necessary if the  
382 W-shredder targets many W-linked loci, but it is an important design consideration for any male  
383 component of the gene drive, because the evolution of Z-linked resistance completely nullifies the  
384 usefulness of male gene drive (echoing e.g. [18]). Recent work suggests that it is possible to create  
385 arrays containing many guide RNAs separated by spacers [39]; advances like this suggest that it  
386 may soon be easier to create gene drives that utilise multiple guide RNAs.

387 The model also indicated that extinction does not require the release of large numbers of  
388 individuals: releasing 20  $Z^*Z^*$  males was often enough to eliminate a spatially-structured  
389 metapopulation of 10,000 individuals within a few generations. On the one hand, this is an  
390 advantageous property because W-shredders would be cheap and easy to deploy once they are  
391 developed, and they are likely to extirpate whole metapopulations even if gene flow between  
392 subpopulations is weak. However, such high invasiveness will rarely be desirable, because it  
393 makes the gene drive more difficult to restrict to a particular area, country, or population. This  
394 could limit the usefulness of W-shredders to control species like Lepidoptera and birds, where  
395 one may wish to eradicate only invasive or agriculturally damaging populations, while leaving  
396 other populations untouched. Modifications to gene drive design – such as the self-limiting ‘daisy  
397 drive’ system – are being developed to address this important concern [21,22].

398 The model further showed that W-shredders can fail to cause extinction if carrier individuals  
399 have low fitness, although extinction was frequently observed even when these fitness costs were  
400 substantial. Populations in which females can become highly fecund as the population shrinks  
401 (i.e. low  $\alpha$  and high  $r$ ) are also harder to drive extinct, though this could likely be solved by  
402 continually releasing more drive males. The model also highlighted that W-shredders, and indeed  
403 any gene drive that skews the sex ratio towards males, are most effective in suppressing species  
404 in which the density of males is an important determinant of population growth, e.g. because  
405 males use resources that females need [28]. By contrast if male density is not very important  
406 to population growth (e.g. because females are limited by a resource that is not consumed by  
407 males), female fecundity increases as females become rarer, slowing the decline in population size  
408 caused by the W-shredder and potentially staving off extinction. Interestingly, the sexes are very  
409 different in the *Schistosoma* trematodes which cause schistosomiasis, which have been proposed  
410 as candidates for control using a W-shredder by Kevin Esvelt and colleagues. Female *Schistosoma*  
411 live inside the body of the much larger male, who feeds on the host’s blood and passes some of  
412 it to the female. Presumably, this means that the number of males (not females) is the primary  
413 determinant of whether a host/population is saturated, making *Schistosoma* a good candidate for  
414 control with W-shredders. In Lepidoptera and birds – two other ZW taxa that could potentially be  
415 controlled with W-shredders – males and females generally have very similar ecological niches,  
416 such that W-shredders should be effective. Other ecological parameters like the patchiness of the  
417 population ( $k$ ), the frequency and sex bias of dispersal ( $x_f$  and  $x_m$ ), and the scale of competition  
418 ( $\psi$ ) had relatively little effect on the probability of extinction.

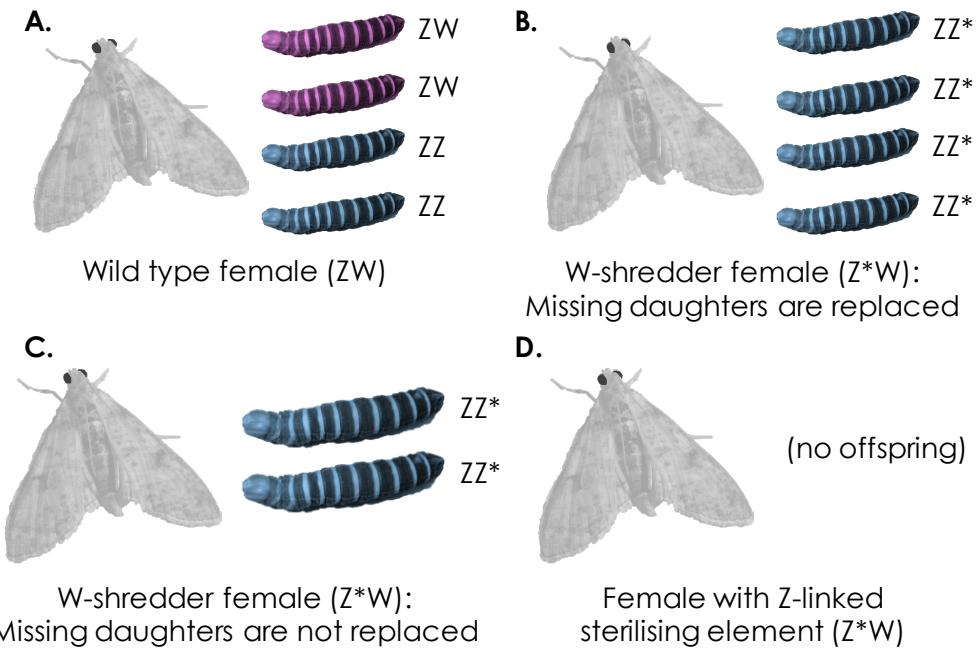
419 Finally, I note that W-shredders might tend to be easier to develop than X-shredders. Initial  
420 efforts to develop an X-shredder in *Anopheles* mosquitos were hindered because the I-PpoI protein  
421 that cleaves the X was paternally transmitted to the embryo inside both sperm, causing all  
422 embryos to die (not just daughters) due to cleavage of the maternally-inherited X. Although this  
423 technical issue was later addressed by modifying I-PpoI [13], such intergenerational effects would  
424 not be a problem for a W-shredder since the W chromosome is unique to females. Additionally,  
425 W-shredders might sometimes be easier to develop than gene drives that work by deleting genes  
426 that are essential to female (but not male) fitness [e.g. 15]. This is because one could design a  
427 prototype W-shredder based only on sequence data from the sex chromosomes, while identifying  
428 genes with female-specific fitness effects requires more detailed data (e.g. expression profiling or  
429 knockout studies) that is not always readily available.

## 430 5. Tables

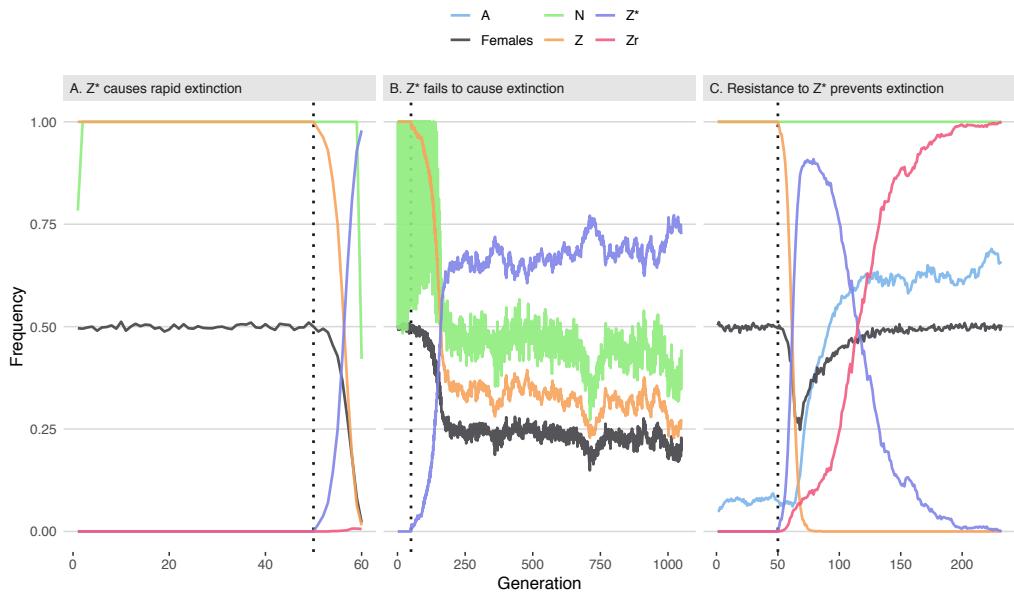
431 **Table 1:** List of variables, and their corresponding parameter(s) in the model, which were varied  
 432 in order to study their effects on the likelihood of population extinction.

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

<sup>433</sup> 6. Figures



**Figure 1.** Some hypothetical  $Z$ -linked suppression drives considered in the model. Panel A illustrates normal inheritance of sex chromosomes in a wild type female (assumed to be mated to a wild type male; not shown): the offspring sex ratio is even. In panel B, the female carries a  $W$ -shredder that kills gametes or offspring early enough that missing daughters are replaced with more  $Z^*$ -bearing sons. In panel C, the lost daughters are not replaced, though their absence increases the survival probability of the sons (show by their larger size), assisting the propagation of the  $Z^*$  allele. Lastly, panel D shows a  $Z$ -linked female-sterilising allele; since it is never passed on, such an allele would go extinct unless it is benefits from gene drive in heterozygous males.



**Figure 2.** Three illustrative runs of the simulation, showing evolution in response to the introduction of 20 males carrying a  $W$ -shredder at Generation 50 (marked by dotted line). In panel A, the driving  $Z^*$  allele fixed very quickly, causing population extinction through a shortage of females. In panel B, the  $Z^*$  allele spread until its fitness costs began to negate its transmission advantage, causing the population to persist at a reduced size. In panel C, the  $Z^*$  allele invaded, which selected for the resistance alleles  $A$  and  $Z^r$  and caused  $Z^*$  to go extinct. The population size  $N$  is shown as a fraction of its maximum value of 10,000. Table S3 gives the parameter spaces used for these three runs.

434 Data Accessibility. A website presenting and describing all scripts used to run the data can be found at  
435 XXX. Data underlying all figures can be downloaded from XXX.

436 Authors' Contributions. LH performed the analyses and wrote the manuscript.

437 Competing Interests. The author declares no conflict of interest.

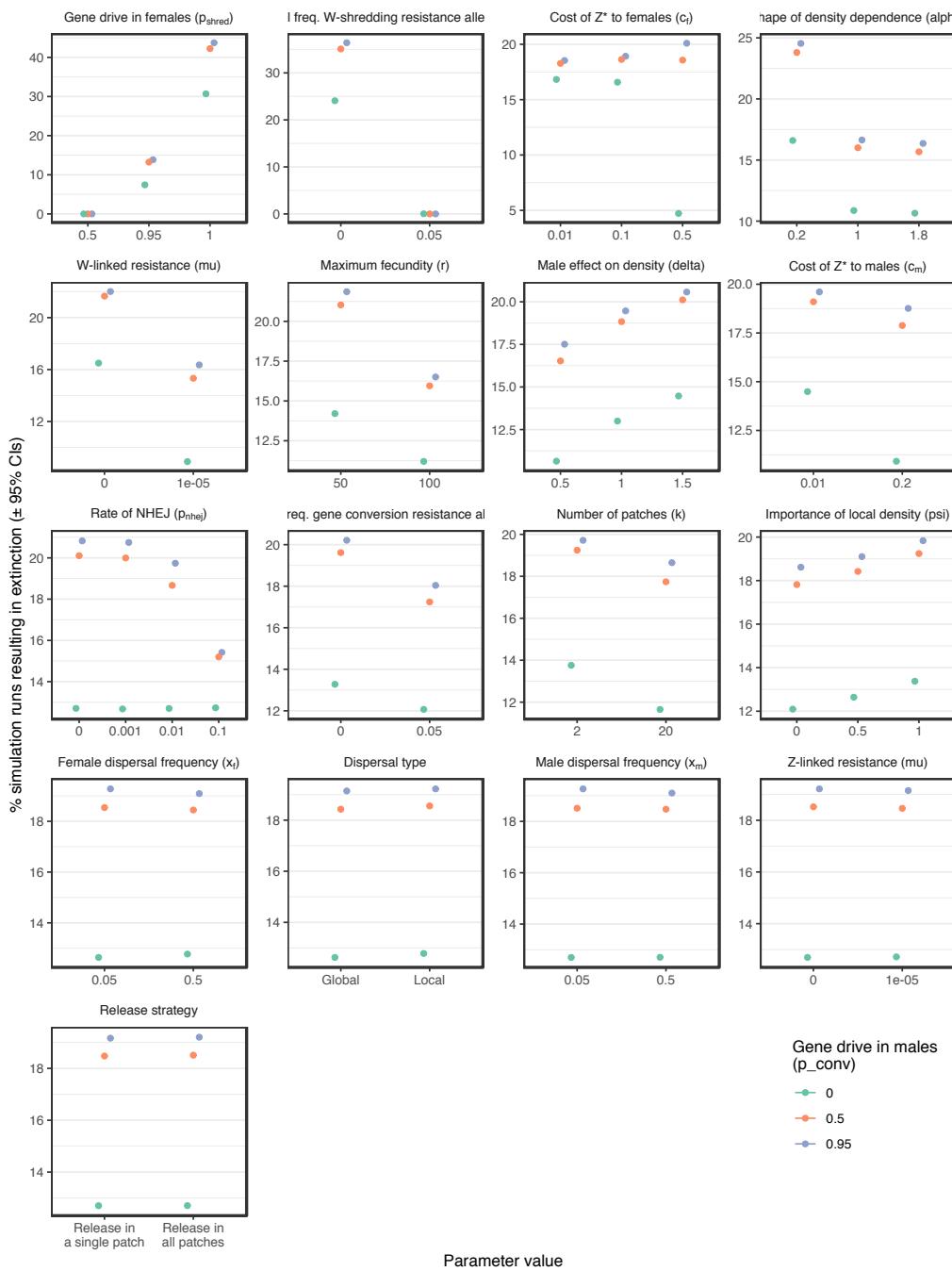
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445 paper.

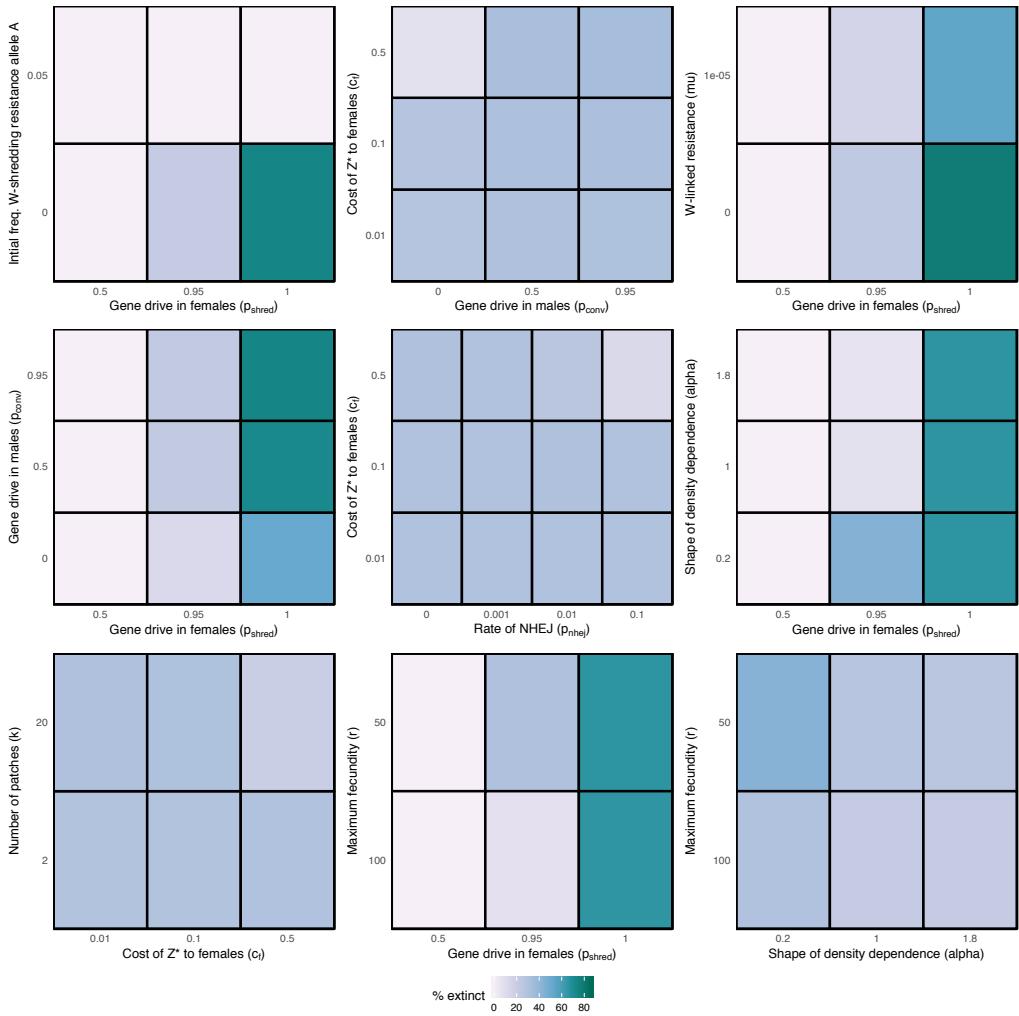
## 446 References

- 447 1. Gantz VM, Jasinskiene N, Tatarenkova O, Fazekas A, Macias VM, Bier E, James AA. 2015  
448 Highly efficient Cas9-mediated gene drive for population modification of the malaria vector  
449 mosquito *Anopheles stephensi*. *PNAS* **112**, E6736–E6743.
- 450 2. Hammond A, Galizi R, Kyrou K, Simoni A, Siniscalchi C, Katsanos D, Gribble M, Baker  
451 D, Marois E, Russell S et al.. 2016 A CRISPR-Cas9 gene drive system targeting female  
452 reproduction in the malaria mosquito vector *Anopheles gambiae*. *Nature Biotechnology* **34**, 78.
- 453 3. Wang Z, Pan Q, Gendron P, Zhu W, Guo F, Cen S, Wainberg MA, Liang C. 2016 CRISPR/Cas9-  
454 derived mutations both inhibit HIV-1 replication and accelerate viral escape. *Cell Reports* **15**,  
455 481–489.
- 456 4. Prowse TA, Cassey P, Ross JV, Pfitzner C, Wittmann TA, Thomas P. 2017 Dodging silver  
457 bullets: good CRISPR gene-drive design is critical for eradicating exotic vertebrates. *Proc. Roy.  
458 Soc. B* **284**, 20170799.
- 459 5. Kyrou K, Hammond AM, Galizi R, Kranjc N, Burt A, Beaghton AK, Nolan T, Crisanti A. 2018  
460 A CRISPR-Cas9 gene drive targeting *doublesex* causes complete population suppression in  
461 caged *Anopheles gambiae* mosquitoes. *Nature Biotechnology*.
- 462 6. Noble C, Adlam B, Church GM, Esvelt KM, Nowak MA. 2018 Current CRISPR gene drive  
463 systems are likely to be highly invasive in wild populations. *eLife* **7**, e33423.
- 464 7. Lindholm AK, Dyer KA, Firman RC, Fishman L, Forstmeier W, Holman L, Johannesson  
465 H, Knief U, Kokko H, Larracuente AM, Manser A, Montchamp-Moreau C, Petrosyan VG,  
466 Pomiąkowski A, Presgraves DC, Safranova LD, Sutter A, Unckless RL, Price TAR. 2016 The  
467 ecology and evolutionary dynamics of meiotic drive. *Trends in Ecology & Evolution* **31**, 315–326.
- 468 8. Champer J, Buchman A, Akbari OS. 2016 Cheating evolution: engineering gene drives to  
469 manipulate the fate of wild populations. *Nature Reviews Genetics* **17**, 146.
- 470 9. Oberhofer G, Ivy T, Hay BA. 2019 Cleave and Rescue, a novel selfish genetic element and  
471 general strategy for gene drive. *PNAS* **116**, 6250–6259.
- 472 10. Marshall JM, Akbari OS. 2015 Gene drive strategies for population replacement. In *Genetic  
473 Control of Malaria and Dengue*, pp. 169–200.
- 474 11. Maselko M, Heinsch SC, Das S, Smanski MJ. 2018 Genetic incompatibility combined with  
475 female-lethality is effective and robust in simulations of *Aedes aegypti* population control.  
476 *bioRxiv* p. 316406.
- 477 12. Windbichler N, Papathanos PA, Crisanti A. 2008 Targeting the X chromosome during  
478 spermatogenesis induces Y chromosome transmission ratio distortion and early dominant  
479 embryo lethality in *Anopheles gambiae*. *PLoS Genetics* **4**, e1000291.
- 480 13. Galizi R, Doyle LA, Menichelli M, Bernardini F, Deredec A, Burt A, Stoddard BL, Windbichler  
481 N, Crisanti A. 2014 A synthetic sex ratio distortion system for the control of the human malaria  
482 mosquito. *Nature Communications* **5**, 3977.

- 483 14. Beaghton A, Beaghton PJ, Burt A. 2017 Vector control with driving Y chromosomes: modelling  
484 the evolution of resistance. *Malaria Journal* **16**, 286.
- 485 15. Burt A, Derec A. 2018 Self-limiting population genetic control with sex-linked genome  
486 editors. *Proc. Roy. Soc. B* **285**, 20180776.
- 487 16. Papathanos PA, Windbichler N. 2018 Redkmer: An assembly-free pipeline for the  
488 identification of abundant and specific X-chromosome target sequences for X-shredding by  
489 CRISPR endonucleases. *The CRISPR Journal* **1**, 88–98.
- 490 17. Drury DW, Dapper AL, Siniard DJ, Zentner GE, Wade MJ. 2017 CRISPR/Cas9 gene drives in  
491 genetically variable and nonrandomly mating wild populations. *Science Advances* **3**, e1601910.
- 492 18. Unckless RL, Clark AG, Messer PW. 2017 Evolution of resistance against CRISPR/Cas9 gene  
493 drive. *Genetics* **205**, 827–841.
- 494 19. Esveld KM, Smidler AL, Catteruccia F, Church GM. 2014 Emerging technology: concerning  
495 RNA-guided gene drives for the alteration of wild populations. *eLife* **3**, e03401.
- 496 20. Gantz VM, Bier E. 2015 The mutagenic chain reaction: a method for converting heterozygous  
497 to homozygous mutations. *Science* p. aaa5945.
- 498 21. Min J, Noble C, Najjar D, Esveld KM. 2017 Daisyfield gene drive systems harness repeated  
499 genomic elements as a generational clock to limit spread. *BioRxiv* p. 104877.
- 500 22. Noble C, Min J, Olejarz J, Buchthal J, Chavez A, Smidler AL, DeBenedictis EA, Church GM,  
501 Nowak MA, Esveld KM. 2019 Daisy-chain gene drives for the alteration of local populations.  
502 *PNAS* p. 201716358.
- 503 23. Vella MR, Gunning CE, Lloyd AL, Gould F. 2017 Evaluating strategies for reversing CRISPR-  
504 Cas9 gene drives. *Scientific Reports* **7**, 11038.
- 505 24. North A, Burt A, Godfray HCJ. 2013 Modelling the spatial spread of a homing endonuclease  
506 gene in a mosquito population. *Journal of Applied Ecology* **50**, 1216–1225.
- 507 25. Prowse TA, Adikusuma F, Cassey P, Thomas P, Ross JV. 2019 A Y-chromosome shredding gene  
508 drive for controlling pest vertebrate populations. *eLife* **8**, e41873.
- 509 26. Holman L, Price TA, Wedell N, Kokko H. 2015 Coevolutionary dynamics of polyandry and  
510 sex-linked meiotic drive. *Evolution* **69**, 709–720.
- 511 27. Rankin DJ, Kokko H. 2007 Do males matter? The role of males in population dynamics. *Oikos*  
512 **116**, 335–348.
- 513 28. Li XY, Kokko H. 2019a Intersexual resource competition and the evolution of sex-biased  
514 dispersal. *Frontiers in Ecology and Evolution* **7**, 111.
- 515 29. Li XY, Kokko H. 2019b Sex-biased dispersal: a review of the theory. *Biological Reviews* **in press**.
- 516 30. Fowler CW. 1981 Density dependence as related to life history strategy. *Ecology* **62**, 602–610.
- 517 31. Li XY, Holman L. 2018 Evolution of female choice under intralocus sexual conflict  
518 and genotype-by-environment interactions. *Philosophical Transactions of the Royal Society B:  
519 Biological Sciences* **373**, 20170425.
- 520 32. Gardner A, West SA. 2006 Spite. *Current Biology* **16**, R662–R664.
- 521 33. Grunwald HA, Gantz VM, Poplawski G, Xu XrS, Bier E, Cooper KL. 2019 Super-Mendelian  
522 inheritance mediated by CRISPR–Cas9 in the female mouse germline. *Nature* **566**, 105.
- 523 34. Champer J, Liu J, Oh SY, Reeves R, Luthra A, Oakes N, Clark AG, Messer PW. 2018 Reducing  
524 resistance allele formation in CRISPR gene drive. *PNAS* **115**, 5522–5527.
- 525 35. Zhang Z, Niu B, Ji D, Li M, Li K, James AA, Tan A, Huang Y. 2018 Silkworm genetic sexing  
526 through W chromosome-linked, targeted gene integration. *Proceedings of the National Academy  
527 of Sciences* **115**, 8752–8756.
- 528 36. Hay BA, Chen CH, Ward CM, Huang H, Su JT, Guo M. 2010 Engineering the genomes of wild  
529 insect populations: challenges, and opportunities provided by synthetic Medea selfish genetic  
530 elements. *Journal of Insect Physiology* **56**, 1402–1413.
- 531 37. Jiggins F, Hurst G, Jiggins C, vd Schulenburg J, Majerus M. 2000 The butterfly *Danaus  
532 chrysippus* is infected by a male-killing *Spiroplasma* bacterium. *Parasitology* **120**, 439–446.
- 533 38. Jiggins FM. 2003 Male-killing *Wolbachia* and mitochondrial DNA: selective sweeps, hybrid  
534 introgression and parasite population dynamics. *Genetics* **164**, 5–12.
- 535 39. Kurata M, Wolf NK, Lahr WS, Weg MT, Kluesner MG, Lee S, Hui K, Shiraiwa M, Webber  
536 BR, Moriarity BS. 2018 Highly multiplexed genome engineering using CRISPR/Cas9 gRNA  
537 arrays. *PloS one* **13**, e0198714.



**Figure 3.** The percentage of simulations of a *W*-shredder that ended in extinction, for all runs with a particular value (shown on the *x*-axis) for a given parameter (shown in the panels). For example, there were no extinctions in any of the thousands of runs for which  $p_{shred} = 0.5$ , while 60% of runs where  $p_{shred} = 1$  resulted in extinction. The panels are ordered by the range of the *x*-axis, which indicates the relative importance of each variable to extinction probability. Figure SXXX gives a similar plot for simulations of a female-sterilising  $Z^*$  allele.



**Figure 4.** Heatmap showing the nine strongest interactions between pairs of parameters in the model, as determined by the GLM plotted in Figure SXXX.