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# The suppressive potential of a gene drive in populations of invasive social wasps is currently limited

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1 **Social insects are very successful invasive species, and the con-**  
2 **tinued increase of global trade and transportation has exacer-**  
3 **bated this problem. The yellow-legged hornet, *Vespa velutina***  
4 ***nigrithorax* (henceforth Asian hornet), is drastically expanding**  
5 **its range in Western Europe. As an apex insect predator, this**  
6 **hornet poses a serious threat to the honey bee industry and en-**  
7 **demict pollinators. Current suppression methods have proven**  
8 **too inefficient and expensive to limit its spread. Gene drives**  
9 **might be an effective tool to control this species, but their use has**  
10 **not yet been thoroughly investigated in social insects. Here, we**  
11 **built a model that matches the hornet's life history and modelled**  
12 **the effect of different gene drive scenarios on an established in-**  
13 **vasive population. To test the broader applicability and sensitiv-**  
14 **ity of the model, we also incorporated the invasive European pa-**  
15 **per wasp *Polistes dominula*. We find that although a gene drive**  
16 **can spread through a social wasp population, it can only do so**  
17 **under stringent gene drive-specific conditions. The main issue**  
18 **is that the large number of offspring that social wasp colonies**  
19 **produce guarantees that, even with very limited formation of**  
20 **resistance alleles, such alleles will quickly spread and rescue the**  
21 **population. Furthermore, we find that only a gene drive target-**  
22 **ing female fertility is promising for population control due to**  
23 **the haplodiploidy of social insects. Nevertheless, continued im-**  
24 **provements in gene drive technology may make it a promising**  
25 **method for the control of invasive social insects.**

26 **Gene drive | wasps | Modelling | Genetic biocontrol | *Vespa velutina* | *Polistes***  
27 ***dominula***

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## 29 Introduction

30 Invasive species represent a global issue that has worsened  
31 with increased global trade and transportation (1, 2). Sup-  
32 pression of these invasive species is often prohibitively ex-  
33 pensive, labour intensive, and largely ineffective (1). One  
34 such species currently invasive in Europe is the yellow-  
35 legged hornet *Vespa velutina nigrithorax*, hereafter called the  
36 Asian hornet. This insect was introduced to France from  
37 Southern China in 2004 (3, 4) and quickly spread to the whole  
38 of France, most of the Atlantic coast, Northern Italy, Bel-  
39 gium, parts of the United Kingdom, and parts of Germany,  
40 where the northernmost finding was made in 2020 (5, 6). This  
41 spread is in accordance with previous modelling of suitable  
42 environments (7, 8). Modelling also showed that there are  
43 many more areas in Europe suitable for the Asian hornet to

invade (8).

The Asian hornet likely has a serious impact on commercial  
bee colonies (9–11) and potentially on other pollinators such  
as wild bees and syrphids (5, 11). Up to two thirds of its diet  
consists of honey bees (11), and the annual loss for France's  
honey and pollination industry in 2015 was estimated at 53.3  
million euros (8). The invasion probably started with only a  
single fertilised queen (3), which underscores the great inva-  
sive potential of the Asian hornet. Indeed, one queen pro-  
duces on average 300 gynes that all have the potential to start  
a new nest the next year (12). On top of this great reproduc-  
tive potential, controlling the Asian hornet through conven-  
tional means is difficult; the nests are high up in trees, and  
thus hard to find, and they are also hazardous to approach.  
Bait trapping with food or chemicals is currently the most re-  
liable control method, though it is only partially effective and  
is not species-specific (13). These inadequacies highlight the  
need to find an effective strategy to control the Asian hornet  
before it spreads to other suitable regions.

Over the last decade, gene drives have emerged as a poten-  
tial tool to control invasive populations for which other mea-  
sures are ineffective (14–18). A gene drive is a genetic el-  
ement that spreads through a population over generations at  
a super-Mendelian rate. For population control, it is engi-  
neered to impose a fitness cost once it is prevalent. For ex-  
ample, a gene drive may disrupt a haplo-sufficient female fer-  
tility gene. Haplo-sufficient means that a single functioning  
copy of the gene is enough for a female to be fully fertile. At  
first, the gene drive is present mostly in a heterozygous state  
due to matings with wildtype individuals. Once it reaches  
a higher frequency, matings between gene drive individuals  
will occur more frequently and offspring will be homozygous  
for the gene drive, with female offspring thus being infertile.  
This way, population fecundity declines through the re-  
duced fertility of homozygous individuals (15). Gene drives  
have been demonstrated to work in yeast (19), fruit flies (20),  
mosquitoes (21, 22), and mice to a lesser extent (23, 24). The  
field has recently focused on improving safety and contain-  
ment which would make gene drives controlled enough for  
release in the wild (25). A range of gene drives have been de-  
signed to be less invasive by nature, or to mitigate risks to an  
extent. Some stop spreading after a certain number of gener-  
ations and are thus self-limiting (26–28), some require high

87 introduction frequencies (29–31), some can stop or remove a  
88 gene drive that is already present in a population (32, 33), and  
89 some target locally fixed alleles so that the gene drive cannot  
90 spread in non-target populations (34). With the advance of  
91 such containable gene drives, we can start to consider gene  
92 drive technology as a potential tool for controlling invasive  
93 social insects like the Asian hornet.

94 Creating a realistic life history model for a population is one  
95 of the first steps in determining if a gene drive might be an  
96 effective control agent (35). A previous study has modelled a  
97 gene drive causing male sterility in another haplodiploid social  
98 hymenopteran, the common wasp *Vespula vulgaris*, that  
99 is invasive in New Zealand (36). This type of gene drive  
100 was shown to be only mildly promising, because there was  
101 a trade-off between the spread and the impact of the gene  
102 drive. Namely, if the gene drive causes complete male sterility,  
103 it is unlikely to spread, whereas if the gene drive causes  
104 incomplete male sterility, it is unable to impact the fertility  
105 sufficiently for population control (36). Therefore, this  
106 specific gene drive design works similarly to sterile insect  
107 technology: a powerful, but only temporary method. Therefore,  
108 other gene drive designs are needed to control such  
109 populations more efficiently (37). For example, three recent  
110 modelling studies showed that gene drives can work in haplodiploid  
111 species under specific conditions (38–40).

112 In this study, we model several gene drive strategies to investigate  
113 the potential of gene drive technology to control Asian hornet  
114 populations. We look into both gene drive parameters and life  
115 history traits to find the most important factors that could affect  
116 the success of gene drives to control these invasive populations.  
117 We developed a model that can be easily adapted to other social  
118 haplodiploid insects, as the Asian hornet is not the only invasive  
119 social hymenopteran. Indeed, this group of insects, which is  
120 comprised of wasps, bees, and ants, contains many successful  
121 invasive species (41). We demonstrate the flexibility of the model  
122 by modelling a second invasive social hymenopteran, *Polistes dominula*,  
123 hereafter called the European paper wasp. This paper wasp is a  
124 widespread invasive species with a very different biology than the  
125 Asian hornet. It has much smaller colonies, and queens are almost  
126 exclusively monogamous (42). Modelling two species across the  
127 social wasp spectrum showed how life history influences gene  
128 drive efficiency. Our results show that gene drives can be used  
129 to contain an invasive population of either species, but only when  
130 the gene drive achieves extremely high efficiency. This is the case  
131 because high per-colony offspring numbers allow every possible  
132 resistance allele to subsist in the population once they arise,  
133 limiting the success of gene drives that generate resistance alleles.  
134 Consequently, species with lower numbers of offspring require a  
135 slightly less stringent gene drive efficiency. Therefore, we need  
136 significant advances in gene drive technology, especially lower  
137 rates of non-homologous end-joining and more efficient cutting  
138 rates, before this technology can control populations of invasive  
139 social wasps.

## 142 Material and Methods

143 The model is an individual-based, stochastic, year-by-year  
144 model with two main parts: 1) a realistic model of a social  
145 wasp population based on their life history and 2) the  
146 implementation of a gene drive (see figure 1). The model was  
147 built using R version 4.1.2 (43). We use AlphaSimR package  
148 version 1.0.1 (44). This package is designed for animal and  
149 plant breeding studies, but also serves as an excellent tool for  
150 modeling population genetics studies. The model can be found  
151 on GitHub at [https://github.com/HighlanderLab/yneiborg\\_hornet\\_gd](https://github.com/HighlanderLab/yneiborg_hornet_gd).  
152

153 **A. Model structure.** The structure of our model mimics the  
154 life cycle of a typical haplodiploid social wasp. Throughout  
155 the model, we only track female numbers and genotypes, as  
156 males only live for a short amount of time for mating  
157 purposes and little is known about their survival. We initiate  
158 the model with an equal number of females and males, of which  
159 the females (queens) represent the starting population size.  
160 Since we initiate the model with mated queens, each male is  
161 assigned as a mate for a queen. In the scenario of releasing  
162 females with gene drive, these are added as well. In the  
163 scenario of releasing males with a gene drive, these are added  
164 in the mating step in the first generation of the model. Depending  
165 on the chosen number of generations to model, the following  
166 steps are repeated:

167 1. **Offspring generation.** First, offspring are generated  
168 for each successfully mated queen. This is the point at which  
169 gene drive dynamics, such as homing or resistance allele  
170 formation, take place in the queen's germline as described in  
171 section B. Haploid male offspring are produced by the queen  
172 from unfertilised eggs, while diploid female offspring originate  
173 from fertilised eggs. For each female that has mated more than  
174 once, the total number of offspring is divided randomly over  
175 the multiple mates. We assume an equal number of female and  
176 male offspring. Previous findings report a 3:1 male to female  
177 ratio in invasive populations (45), but this is likely a result of  
178 overproducing infertile diploid males under inbreeding (46), as  
179 non-Fisherian sex ratios are unlikely to persist at a population  
180 level (47, 48). The number of female and male offspring are  
181 used as averages for a Poisson distribution for each sex so there  
182 is natural variation in the number of female and male offspring  
183 from each queen.

184 For Asian hornets, on average, one queen produces around 300  
185 females (12) and we assume the same number for males. European  
186 paper wasp nests are much less productive, with a single nest  
187 producing ~20 offspring of each sex (49).  
188

189 2. **Mating.** We have implemented random mating between  
190 males and females, except we impose the fitness costs of having  
191 a gene drive here. Both males and females with a gene drive in  
192 their genome have a certain probability of being removed from  
193 the mating pool. We assumed full dominance for the fitness cost,  
194  
195  
196

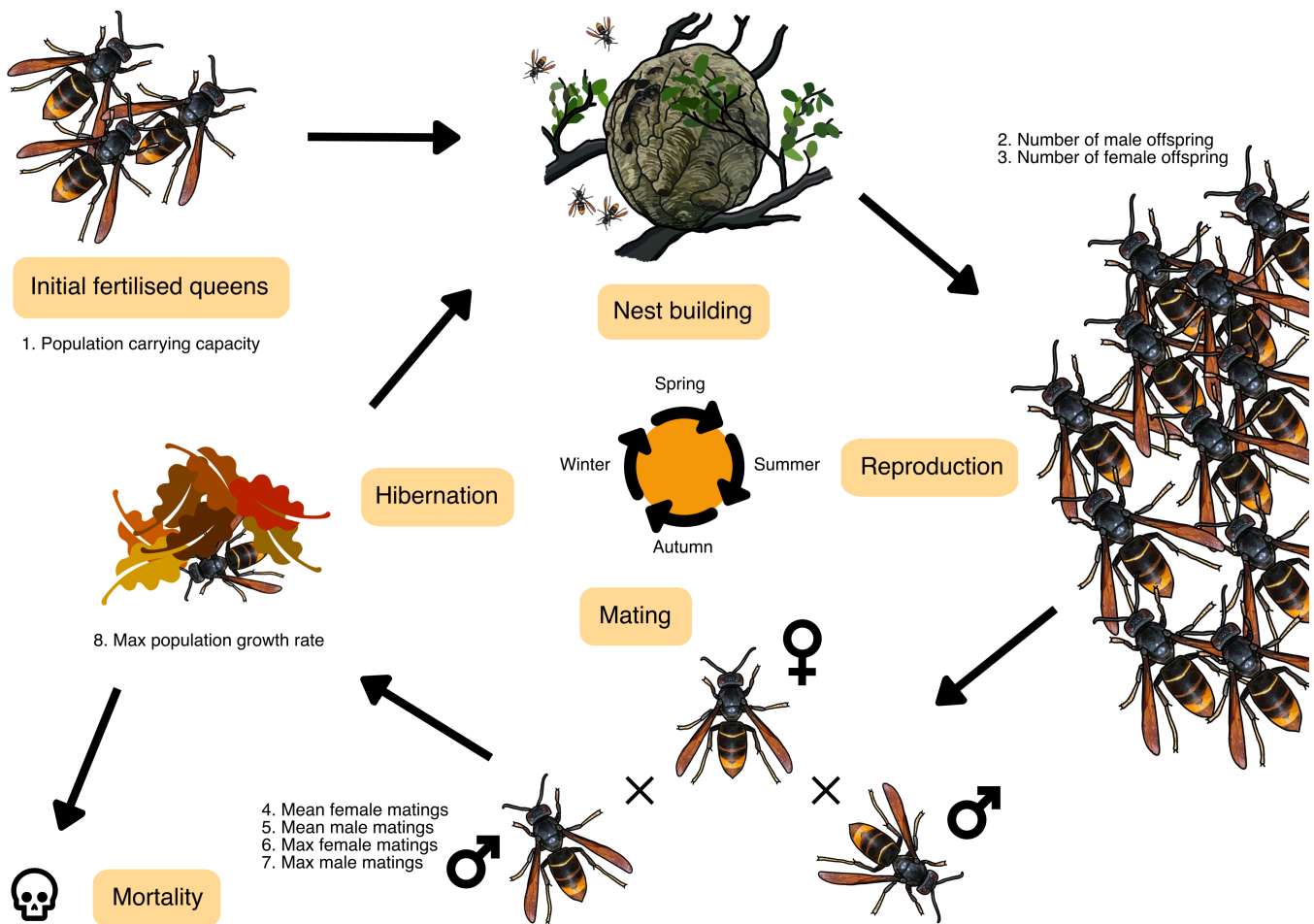


Fig. 1. Overview of the demographic model. For a specific explanation of the model, see the Material and Methods.

197 so both heterozygous or homozygous individuals are  
198 equally affected.

199 Next, as polyandry is shared by many social hy-  
200 menoptera (50, 51), we have included it in the model.  
201 For both females and males, the model takes the mean  
202 number of matings, the minimum number of matings,  
203 the maximum number of matings, and based on these  
204 values generates a random number of matings from a  
205 truncated Poisson distribution. For males, the mating  
206 frequencies from (52) include a high frequency of non-  
207 mating males, so we have not zero-truncated their mat-  
208 ing rate distribution.

209 The Asian hornet queen is polyandrous and is able to  
210 attract mates at great distances (53), so for mating rate  
211 we use a zero- and max-truncated Poisson distribution  
212 with a mean of 3.275 and a maximum of 4 (3). Male  
213 Asian hornet mating rates are unknown, so we used a  
214 max-truncated Poisson distribution with a mean of 0.9  
215 and a maximum of 2 based on mating frequencies for  
216 *Vespula maculifrons* (52). Mating rates for European  
217 paper wasp females are estimated to fall between 1 and  
218 1.1 (54, 55), and as such were modeled using a zero-  
219 and max-truncated Poisson distribution with a mean of  
220 0.2 and a maximum of 2. There is no accurate data that  
221 capture total male reproductive output in *P. dominula*

222 either, so we used the rates reported in *V. malicifrons*  
223 (52) instead.

224 After mates have been randomly selected this way, we  
225 remove pairings of which one or both individuals are  
226 infertile due to the gene drive. We thus assume that nei-  
227 ther female or male knows whether their mate is fertile  
228 until the offspring generation, at which point it is too  
229 late to find a new mate. This assumption is in line with  
230 the observation that hymenopteran females are largely  
231 unable to discriminate against infertile but otherwise  
232 healthy diploid males (46).

233 3. **Mortality.** Population size is regulated using a Pois-  
234 son distribution around a logistic function, which en-  
235 sures a maximum population growth rate and carrying  
236 capacity (56):

$$N_t = \text{Poisson} \left( \frac{K}{1 + \frac{K - N_{t-1}}{N_{t-1}} * r_{max}^{-1}} \right), \quad (1)$$

237 where  $N_t$  is the number of females in generation  $t$ ,  
238  $N_{t-1}$  the number of females in generation  $t-1$ ,  $K$   
239 is the carrying capacity, and  $r_{max}$  is the maximum  
240 growth rate. Note that the maximum growth rate  $r_{max}$   
241 is calculated using  $\frac{\ln(R_0)}{T}$  with  $R_0$  being the intrinsic

242 growth rate observed by (56),  $T$  being the generation  
243 time of 1 year.

244 Then, using the maximum possible population size in  
245 this generation and total number of female offspring,  
246 we calculate the mortality rate:

$$P_{mortality} = 1 - \frac{N_t}{\text{female offspring}}. \quad (2)$$

247 Each female thus has a probability of dying. The sur-  
248 viving females become queens and generate the off-  
249 spring for the next generation. Male population num-  
250 bers are not monitored, as they only live for a short  
251 amount of time and little is known about their survival.

252 **B. Gene drive implementation.** Although AlphaSimR  
253 was designed to model large numbers of loci for quantita-  
254 tive genetics in plant and animal breeding, the framework is  
255 perfect for tracking the single locus of a gene drive. Each  
256 individual is modelled with a single gene drive locus and in-  
257 heritance is random following Mendelian laws. We have im-  
258 plemented a basic homing gene drive which copies itself to  
259 the other chromosome in the germ line and has four potential  
260 alleles: wildtype (WT), gene drive (GD), resistance (RE), and  
261 non-functional (NF). We model diploid females and haploid  
262 males, so there is no gene drive activity in the male genome.  
263 Like Prowse et al. (2017) (37), we account for a probability  
264 of cutting ( $P_{cut}$ ) of 0.95, a probability of non-homologous  
265 end-joining ( $P_{NHEJ}$ ), and a probability that non-functional  
266 repair occurs ( $P_{NFR}$ ) of 0.67, which is the probability of  
267 a frame-shift occurring within the targeted gene. We evalu-  
268 ate the sensitivity of results to the default probability of cut-  
269 ting ( $P_{cut}$ ) and probability of non-homologous end-joining  
270 ( $P_{NHEJ}$ ). We also model a fitness cost of carrying the gene  
271 drive abstracted as a certain probability of mortality before  
272 mating ( $P_{mort}$ ). We conservatively assume that the fitness  
273 cost of carrying the gene drive has complete dominance, that  
274 is, it is equally deleterious for homo-, hemi-, and heterozy-  
275 gotes.

276 **C. Modelled scenarios.** To show two sides of the social  
277 wasp spectrum, we do all our modelling for two species of  
278 invasive social wasps that have distinct life histories. The  
279 first species we model is the Asian hornet, which is an ex-  
280 tremely successful invasive species, probably due to its abil-  
281 ity to produce many new queens each generation. Females of  
282 this species are also very polyandrous. The second species is  
283 the European paper wasp, which has a more modest number  
284 of offspring and females are less polyandrous.

285 We first focus on which type of homing gene drive might  
286 work best for social wasps. We test a neutral gene drive and  
287 gene drives that cause female, male, and both-sex infertility.  
288 We test all of these gene drives with or without polyandry  
289 in both species. In these scenarios, we model current stan-  
290 dard gene drive efficiencies:  $P_{cut} = 0.95$  and  $P_{NHEJ} = 0.02$ ,  
291 keeping  $P_{mort}$  at 0, as in (37).

292 Next, we vary the parameters of the gene drive to find the  
293 space in which a gene drive works in our species. First, we

294 vary  $P_{cut}$  and  $P_{NHEJ}$  together, second we vary  $P_{mort}$  and  
295  $P_{NHEJ}$  together, and third we vary  $P_{cut}$  and  $P_{mort}$  together.  
296 Finally, we vary life history parameters of the wasps using  
297 "optimal", "intermediate", and "realistic" gene drive param-  
298 eters, to evaluate how these parameters influence gene drive  
299 performance. The optimal gene drive scenario uses  $P_{cut} =$   
300  $1$ ,  $P_{NHEJ} = 0$ , and  $P_{mort} = 0$ . The intermediate gene drive  
301 scenario uses  $P_{cut} = 0.97$ ,  $P_{NHEJ} = 0$ , and  $P_{mort} = 0.1$ .  
302 The realistic gene drive scenario uses  $P_{cut} = 0.95$ ,  $P_{NHEJ}$   
303  $= 0.02$ , and  $P_{mort} = 0.1$ .

304 For each model, except figure 2 and S2, we ran 10 replicates  
305 to get an estimate of the variance of the results. For figures 2  
306 and S2, we ran 100 repetitions because the male gene drive  
307 release showed a lot of variation.

## 308 Results

309 The spread of the gene drive depends heavily on its design. In  
310 the following paragraph we describe the frequencies of wild-  
311 type and gene drive alleles shown in figure 2, while popula-  
312 tion sizes for the same scenarios are available in figure S1. A  
313 neutral gene drive spreads quickly through the female Asian  
314 hornet population, but does not reach complete fixation as re-  
315 sistance alleles and non-functional alleles appear (figure 2A).  
316 These resistance alleles and non-functional alleles are then  
317 subject to random drift. Female carriers are much more ef-  
318 fective in spreading the gene drive (figure 2A-top row) than  
319 male carriers (figure 2A-bottom row). More often than not,  
320 the gene drive introduced by males goes extinct (in 83 out  
321 of 100 replicates), particularly when coupled with male in-  
322 fertility (extinction in all 100 replicates). In the cases it does  
323 spread, the spread is slower and less consistent compared to  
324 an introduction through females.

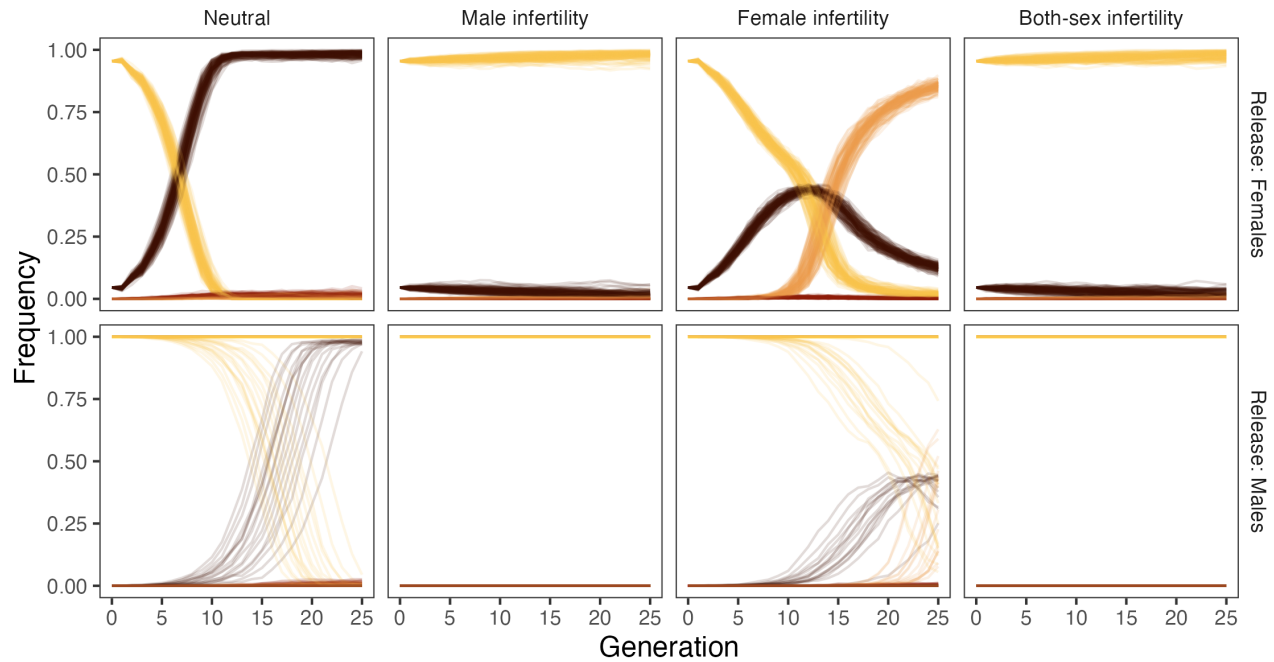
325 Gene drives designed for population suppression show simi-  
326 lar dynamics. When the gene drive targets fertility, we see  
327 that targeting male fertility prevented spread of the gene drive  
328 through the population. The spread stops immediately when  
329 the gene drive is introduced via males. This effect persists  
330 when targeting female fertility at the same time. A gene drive  
331 targeting female fertility spreads rapidly through the popula-  
332 tion, but also leads to a rapid increase of resistance alleles in  
333 the population, which overtake the gene drive.

334 The spread of the gene drives does not differ much between  
335 the European paper wasp (figure 2B) and the Asian hornet  
336 (figure 2A). As in the Asian hornet, targeting male fertility  
337 prevents the gene drive from spreading, including when cou-  
338 pled to female infertility. Targeting female fertility remains  
339 more effective. European paper wasp males are more suc-  
340 cessful at introducing a gene drive (11 out of 100 replicates  
341 failed to spread the gene drive) than the Asian hornet males,  
342 but females remain more effective nonetheless.

343 To untangle the effects of polyandry and reproduction rate  
344 on the spread of the gene drive, we modeled the Asian hor-  
345 net without polyandry, and the European paper wasp with  
346 polyandry (figure S2). In the latter case the female can mate  
347 with up to 4 males. Comparing figures 2 and S2 the effect  
348 can mostly be seen when males are used to release the gene  
349 drive. The top rows (female release) of figure 2A and B and

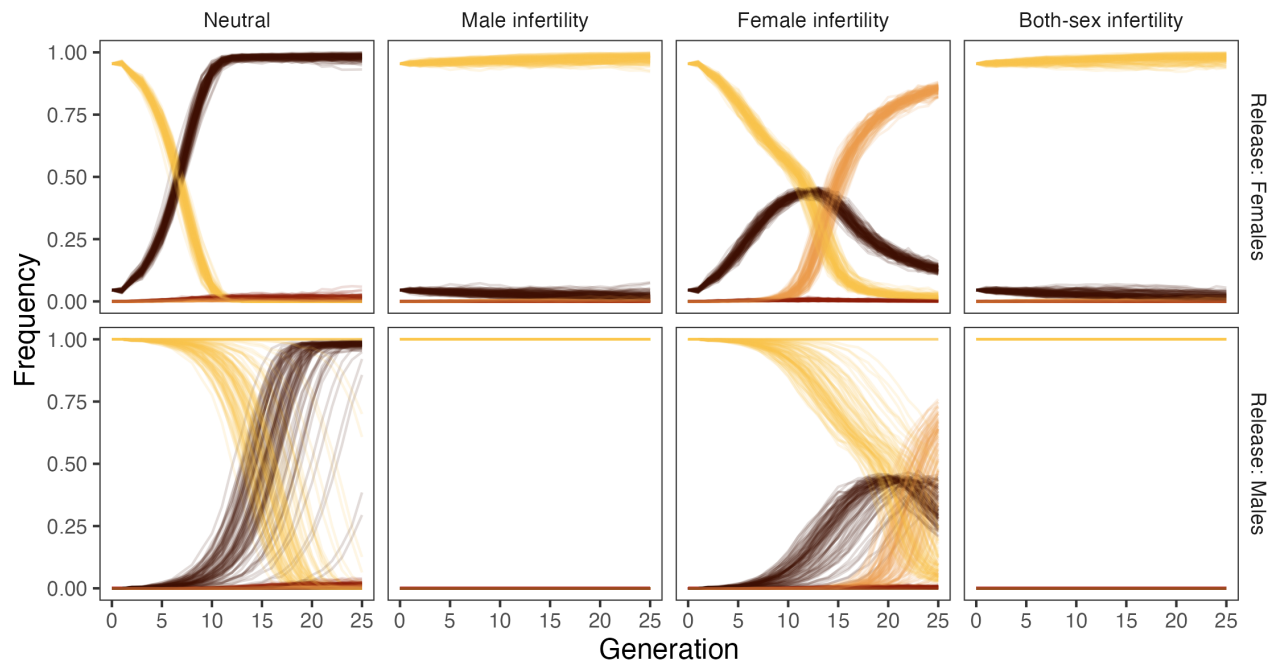
A

### Asian hornet



B

### European paper wasp



Allele — GD — NF — RE — WT

**Fig. 2.** Frequencies of wildtype (WT), gene drive (GD), resistance (RE), and non-functional (NF) alleles in a female Asian hornet population (A) and a female European paper wasp population (B) by gene drive strategy and release carriers (females or males). The different strategies (neutral, male infertility, female infertility, and both-sex infertility) determine how the gene drive operates. In the neutral strategy there is no fitness cost to having the gene drive, whereas in the infertility strategies, the designated sex cannot reproduce when homo- or hemizygous for the gene drive.

figure S2A and B do not differ in any discernible way. The bottom rows (male release) of figure 2A and B and figure S2A and B are different, for the neutral and female infertility gene drive. When polyandry is introduced in the European paper wasp (figure S3B), the gene drive spreads more reliably when released by male carriers. Conversely, the variability in the spread of the gene drive increases when polyandry is removed from the Asian hornet (figure S2A). However, although gene drive spread via male carriers becomes more reliable when species are polyandrous, release via female carriers clearly remains the more reliable option.

Non-neutral gene drives are not capable of fixing in any of the modelled populations (figure 2 and S2). This is because resistance alleles rapidly spread through the population due to the heavy selective pressure the gene drive introduces. This way, these resistance alleles outcompete the gene drive, and rescue the population. This is so much the case that non-neutral gene drive do not change the population sizes (figure S1). Resistance alleles are formed when the DNA strand is repaired with non-homologous end-joining after being cut by the Cas9 protein. This method is error-prone and can insert viable mutations which decrease the affinity of the gRNA for the target sequence. Probability of non-homologous end-joining ( $P_{NHEJ}$ ) is not the only parameter inherent to the gene drive that affects its efficiency. Different gRNA target sites can have different probabilities of cutting the opposite DNA ( $P_{cut}$ ). Gene drives have an inherent fitness cost when present in a genome, here called the probability of heterozygous mortality ( $P_{mort}$ ).

We varied gene drive parameters and estimated which parameters are critical and what values are required for a proper population suppression. In both the Asian hornet and the European paper wasp, only absence of non-homologous end-joining ( $P_{NHEJ} = 0$ ) will make gene drive work reliably (figure 3A-D). Nor will a cutting rate ( $P_{cut}$ ) below 1 make gene drive work reliably in the Asian hornet (figure 3A). In the European paper wasp, a cutting rate of 0.97 is the lowest workable value (figure 3B). Heterozygous mortality ( $P_{mort}$ ) affects both species nearly equally. Reliable suppression stops above a 0.275 (figure 3C and D) in both cases, although the drop in reliability is steeper in the Asian hornet. We also explored cutting rate against heterozygote mortality in a gene drive in the absence of non-homologous end-joining (figure 3E and 3F). The European paper wasp has a larger area of success than the Asian hornet. Estimates for the European paper wasp have more noise, which could be due to lower reproductive values. Based on these results we have chosen three different gene drive conditions for further analysis: optimal, intermediate, and realistic as shown on figure 3.

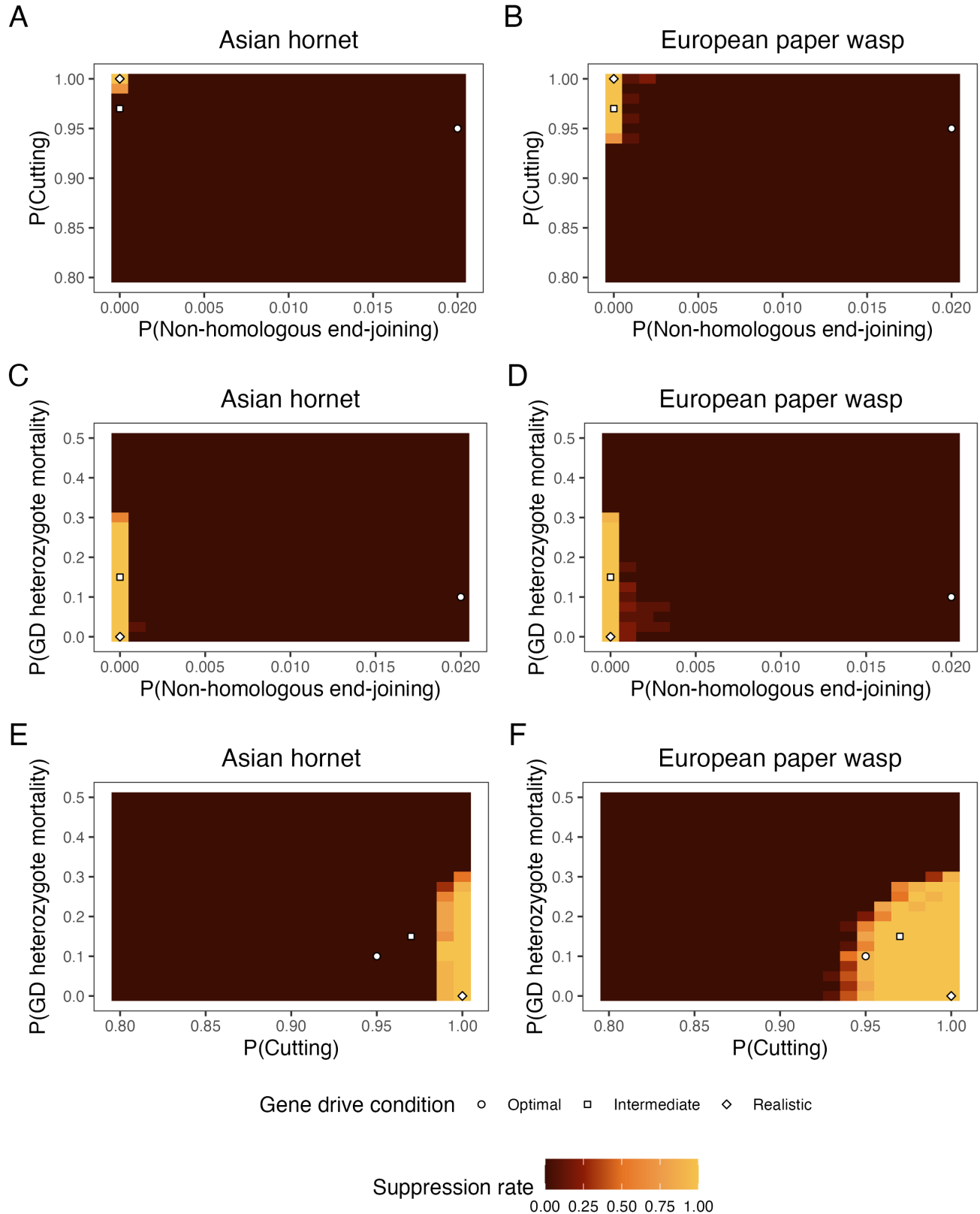
To test the sensitivity of our model and results to the used biological parameters, we performed a sensitivity analysis for both modeled species (figure S3 and S4) with the three different gene drive conditions: optimal, intermediate, and realistic. Under realistic conditions, there is only a visible effect in the European paper regarding the number of offspring parameter. Only an extremely low mean number of progeny affects

the spread of the gene drive (figure S4). The other parameters have no effect on the gene drive success in either species, which is in line with figure 2. Resistance alleles prevent the fixation of the gene drive and rescue the population. The intermediate condition was between the optimal and realistic conditions and showed that in the European paper wasp all the tested parameters influence gene drive success, particularly the mean number of progeny. In the Asian hornet, there is only a small effect visible for the mean number of progeny. The gene drive is unable to suppress the population in any of the other scenarios. Since this parameter differs the most between the two species and it is critical for the spread of alleles under drift, we evaluated a wide range of values in each species, well beyond the biological limits in the two species (figure S5). This sensitivity analysis showed a similar effect of the number of progeny on gene drive success in both species irrespective of their other biological parameter values (figure S3 and S4). This indicates that under the intermediate gene drive conditions the sheer number of progeny in Asian hornets is a limiting factor for the capacity of gene drives to suppress this invasive species. Under optimal conditions, the gene drive is always successful, regardless of the biological parameters.

## Discussion

Invasive social hymenopterans, such as the Asian hornet, can cause significant ecological and commercial damage in their invasive ranges. Difficulties in the application of conventional methods for the control of invasive social hymenopterans have led to a surge of interest in the possibility of using gene drive to suppress such invasive populations. In this paper we have modelled the efficacy of gene drives for population control of two invasive social wasps, the Asian hornet (*Vespa velutina nigrithorax*) and the European paper wasp (*Polistes dominula*) under a variety of gene drive and life history parameters. We find that the fecundity of social insect colonies represents a major limiting factor for the efficacy of gene drives. As a result, gene drives can only suppress invasive wasp populations when gene drives operate with extreme efficiency. Other life history traits that we examined were less impactful. We also find that a gene drive targeting fertility is only effective when targeting females. When a gene drive targeted male fertility or the fertility of both sexes, it could not spread. Overall, our results indicate that, despite the potential value of gene drive as a control agent for invasive social insects, the current efficiency of gene drives is insufficient to overcome the biological efficiency of social insect reproduction.

We found that selection resulted in the rapid fixation of alleles conferring resistance to drive, such that the gene drive was never able to reach fixation under currently-realistic parameters of gene drive efficiency. While there are proposals that improve gene drive efficiency (for example 57), the relatively high fecundity of female social insects raises the bar for required gene drive efficiency. Due to the reversal of longevity/fecundity trade-offs, reproductive females in social hymenopteran species may reach levels of fecundity mag-



**Fig. 3.** Heatmaps of the suppression rate in the Asian hornet (**A** & **C**) and the European paper wasp (**B** & **D**) using gene drives that have varying probabilities of non-homologous end-joining ( $P(\text{Non-homologous end-joining})$  or  $P_{NHEJ}$ ) and cutting ( $P(\text{Cutting})$  or  $P_{cut}$ ) or mortality of gene drive heterozygotes ( $P(\text{GD heterozygote mortality})$  or  $P_{mort}$ ). Note that the model was run for 50 generations because in many intermediate cases 25 generations was not sufficient for the gene drive to suppress the population.



463 nitudes higher than those possible for non-social organisms  
464 (58, 59). This fecundity reduces the effects of drift and there-  
465 fore the potential efficacy of gene drive: the more progeny  
466 each gene drive carrier female produces, the more likely that  
467 all possible allele combinations will be represented among  
468 those progeny, thereby reducing the likelihood that any given  
469 allele will be fixed by chance. For the same reason, the prob-  
470 ability that a novel resistance allele will be lost by drift before  
471 being spread by positive selection is reduced when female fe-  
472 cundity is higher.

473 Our comparison of two different social wasps with very dif-  
474 ferent numbers of progeny demonstrates the importance of  
475 fecundity. The parameter space in which the gene drive was  
476 able to effectively suppress a population was larger for the  
477 European paper wasp than for the Asian hornet. This differ-  
478 ence appears to have been driven by the lower mean progeny  
479 sizes in the paper wasp. Notably, when we varied mean  
480 progeny number for each species while keeping all other vari-  
481 ables equal, the rate of suppression was approximately equal  
482 for the two species for any given number of progeny, suggest-  
483 ing that it is fecundity rather than other factors that drove the  
484 difference in gene drive suppressing the population between  
485 the species.

486 Our results indicate that, in social wasps, a driving element  
487 that targets fertility can only successfully spread if its effects  
488 are female-specific. Gene drives targeting fertility either in  
489 males or in both sexes were never successful in our mod-  
490 elling, because haploid males are unable to act as asymp-  
491 tomatic carriers of the gene drive. Our results therefore in-  
492 dicate that any successful attempt to control invasive hap-  
493 lodiploid species using fitness-targeting gene drives will nec-  
494 essarily target females rather than males, in line with the  
495 findings of a previous modeling study (39). This fact may  
496 represent a significant impediment to the biological control  
497 of invasive haplodiploids using gene drives, since the rate of  
498 formation of resistance alleles is expected to be substantially  
499 higher in females than in males (60).

500 High fecundity and haplodiploidy represent two significant  
501 challenges to the potential efficacy of gene drive as a control  
502 agent for invasive social wasps. A third challenge is the risk  
503 that the gene drive could spread to other wasp species by hy-  
504 bridization: rates of inter-specific hybridization appear to be  
505 significantly higher among hymenopterans than other arthro-  
506 pods (61), and the introgression of a driving allele into na-  
507 tive wasp species is a meaningful risk given that social wasps  
508 perform important ecosystem services in their native ranges  
509 (62). Thus, even if the technical efficiency of drive can be  
510 optimised to the point that it is a viable option for the control  
511 of invasive wasps, gene drive's safety as a control agent may  
512 remain a significant concern.

513 We found that a neutral gene drive could spread much more  
514 reliably than one targeting fertility. In theory, a gene drive  
515 without any directly detrimental phenotypic effects can still  
516 contribute to biocontrol, if the gene drive leaves affected in-  
517 dividuals vulnerable to further control measures. For exam-  
518 ple, a gene drive that disrupts resistance to a specific pesti-  
519 cide could allow that pesticide to be used as a control mea-

sure once the gene drive has reached high frequency or be-  
come fixed (40). However, such an approach requires tar-  
geted management techniques, which are not currently avail-  
able for invasive social hymenopterans excepting a few ant  
species (63, 64). As such, direct targeting of female ferti-  
lity is likely to remain the most promising route for managing  
invasive social hymenopterans using gene drive.

Despite the challenges presented by haplodiploidy and high  
fecundity, we found that a gene drive targeting female fer-  
tility could spread to a significant frequency (~0.75) within  
social wasp populations before being negated by the spread  
of resistance alleles. Even at these high frequencies, however,  
we found no impact of gene drive on population size, because  
the high fecundity of individual reproductive females allowed  
the population to remain at carrying capacity even while the  
driving allele was present at high frequencies. Anything short  
of complete fixation of the gene drive was insufficient to sup-  
press an invasive population. Combined with the rapid gen-  
eration of resistance alleles in a short number of generations,  
this result indicates that a homing gene drive would be inef-  
fective at suppressing invasive social wasp populations over  
both long and short timescales.

Like any model, ours includes assumptions and simplifica-  
tions. Parameterisation of the model proved difficult due to a  
relative paucity of life history data for vespidae wasps, despite  
the ecological importance of this group (62). For example,  
we assume that female mating rates are zero-truncated, such  
that females never fail to find at least one male with whom  
to mate. This assumption may become unrealistic for very  
small population sizes, but empirical data that would allow  
us to accurately model this effect are lacking. For this rea-  
son, we instead used estimates from several closely related  
species as described in our methods. Other potential limita-  
tions of our model include the lack of any spatial component,  
including a complete lack of immigration and emigration, the  
assumption of perfect admixture without mate choice, and the  
high heterozygous mortality.

## 557 Conclusions

558 We have modeled the spread of a homing gene drive un-  
559 der a variety of conditions of life history and drive efficacy  
560 through populations of two invasive social wasps: the Asian  
561 hornet and the European paper wasp. We find that, due to  
562 large progeny numbers produced by reproductive females in  
563 these species, a homing allele can only reach fixation under  
564 extremely efficient drive conditions. These findings, together  
565 with limitations imposed by haplodiploidy and potential for  
566 inter-specific hybridization, highlight the difficulty of apply-  
567 ing genetic biocontrol measures to social hymenopterans. We  
568 conclude that until it is possible to develop gene drives with  
569 much higher efficiency of spread and much lower rates of re-  
570 sistance allele formation, more conventional approaches such  
571 as nest destruction and bait trapping will remain the best  
572 methods for the control of invasive social wasps.

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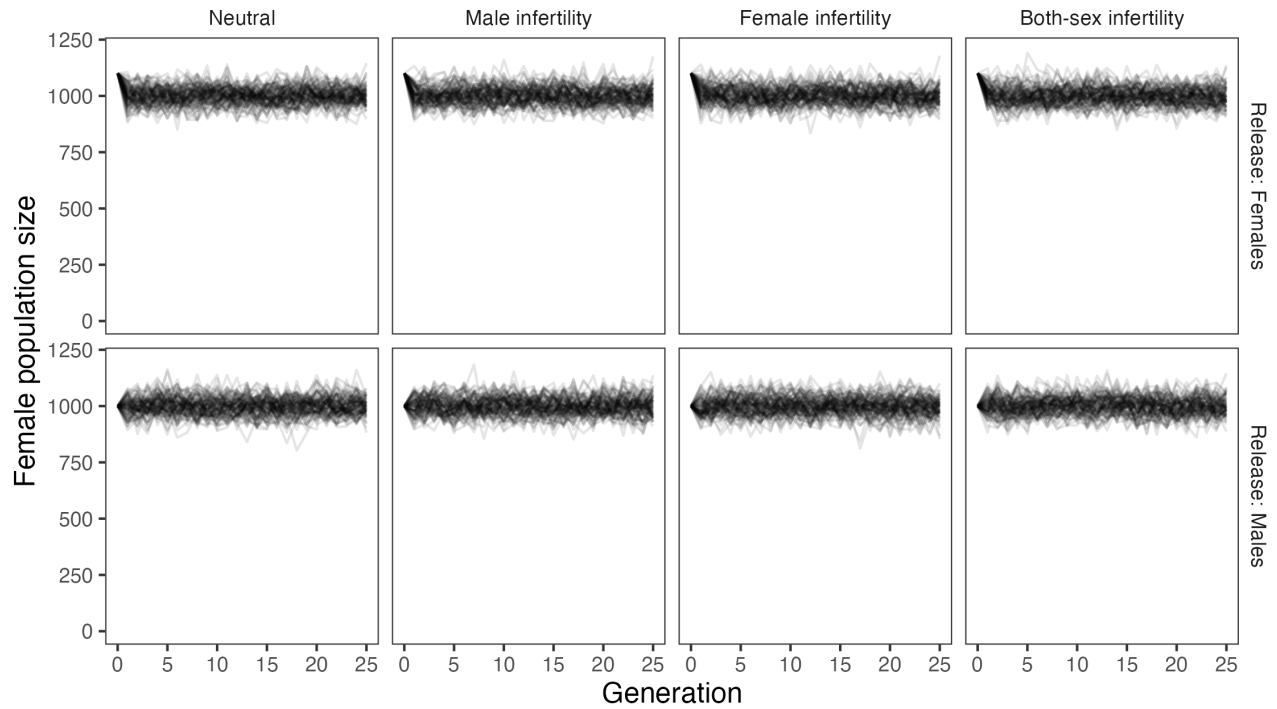
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## Supplementary Material

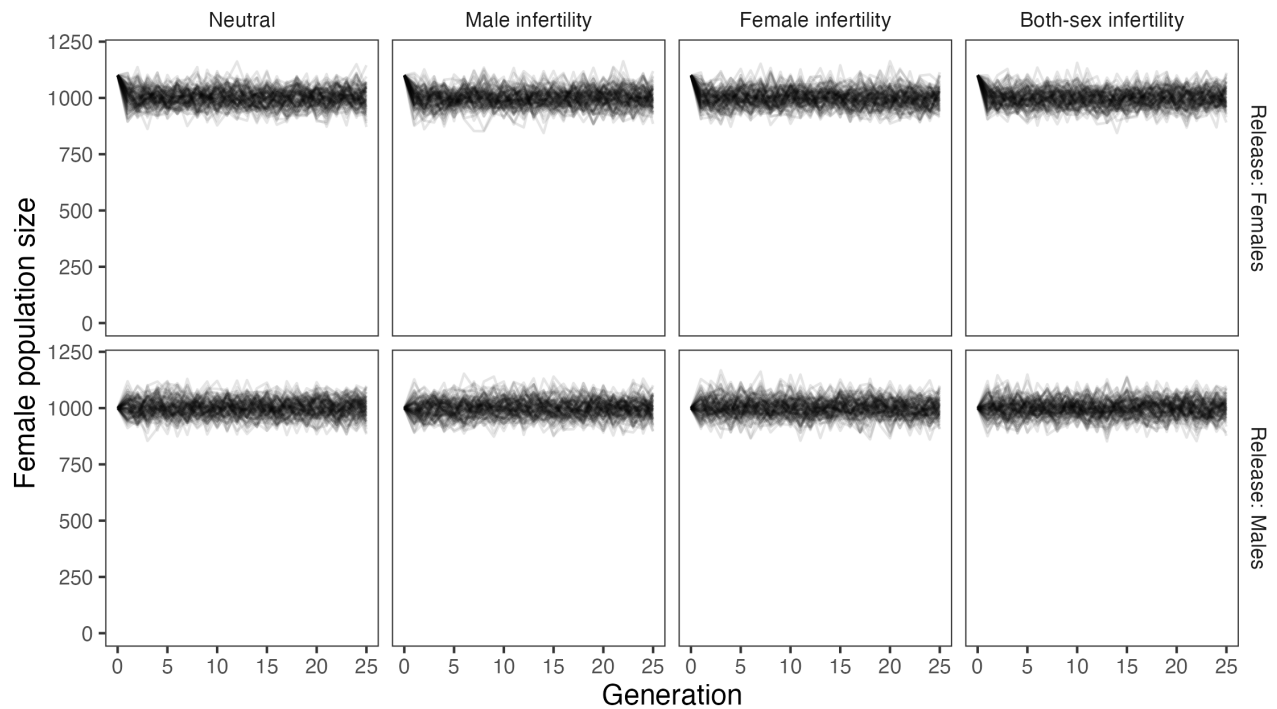
A

### Asian hornet



B

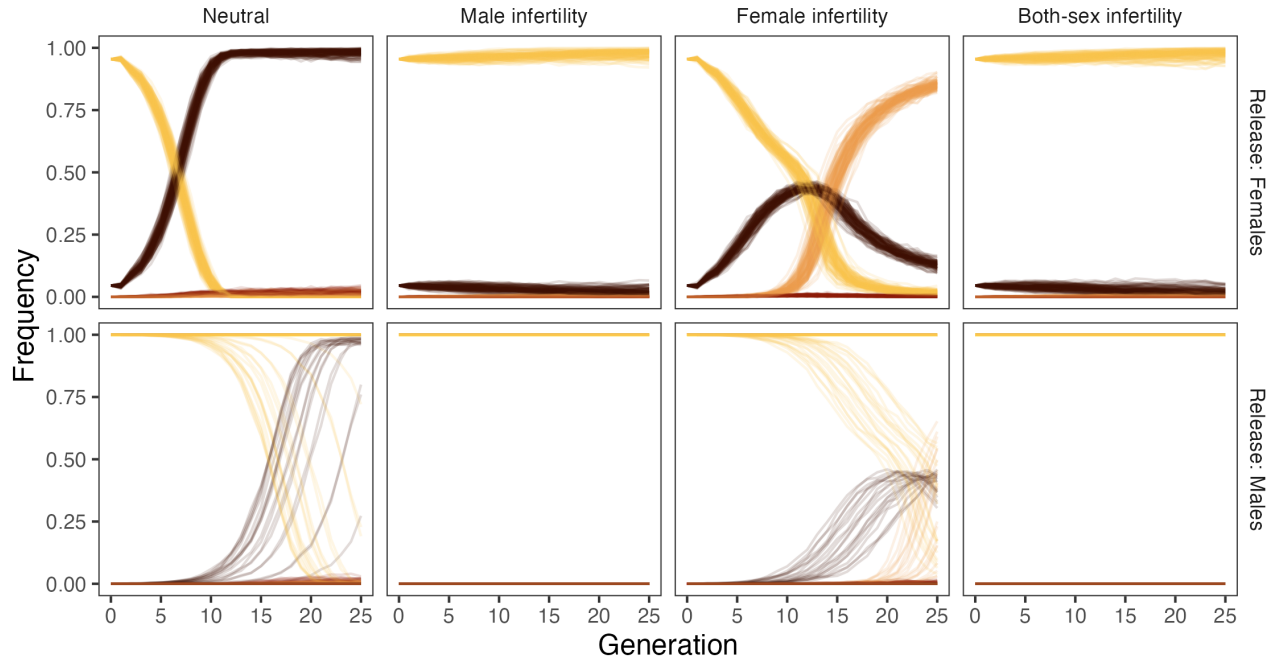
### European paper wasp



**Fig. S1.** Female population size for Asian hornet (A) and European paper wasp (B) by gene drive strategy and release carriers (females or males). The different strategies (neutral, male infertility, female infertility, and both-sex infertility) determine how the gene drive operates. In the neutral strategy there is no fitness cost to having the gene drive, whereas in the infertility strategies, the designated sex cannot reproduce when homo- or hemizygous for the gene drive.

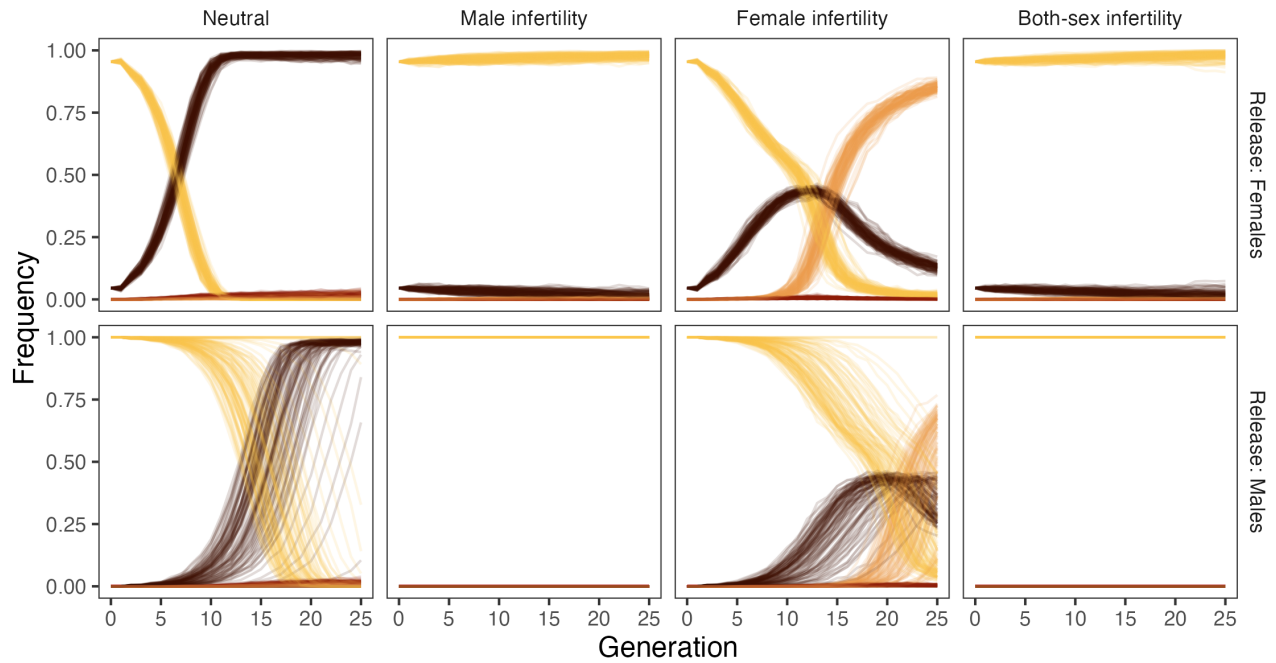
A

### Asian hornet



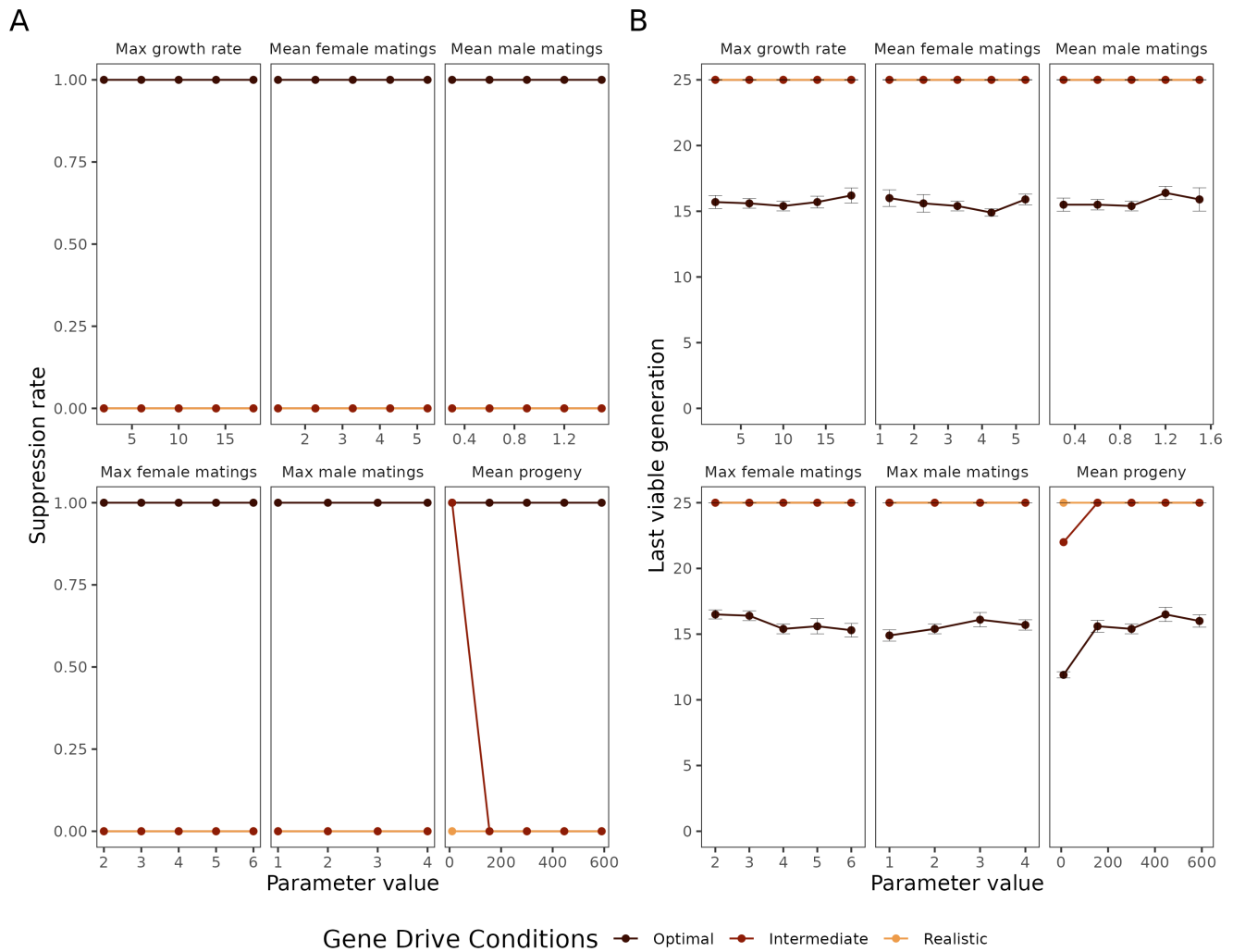
B

### European paper wasp

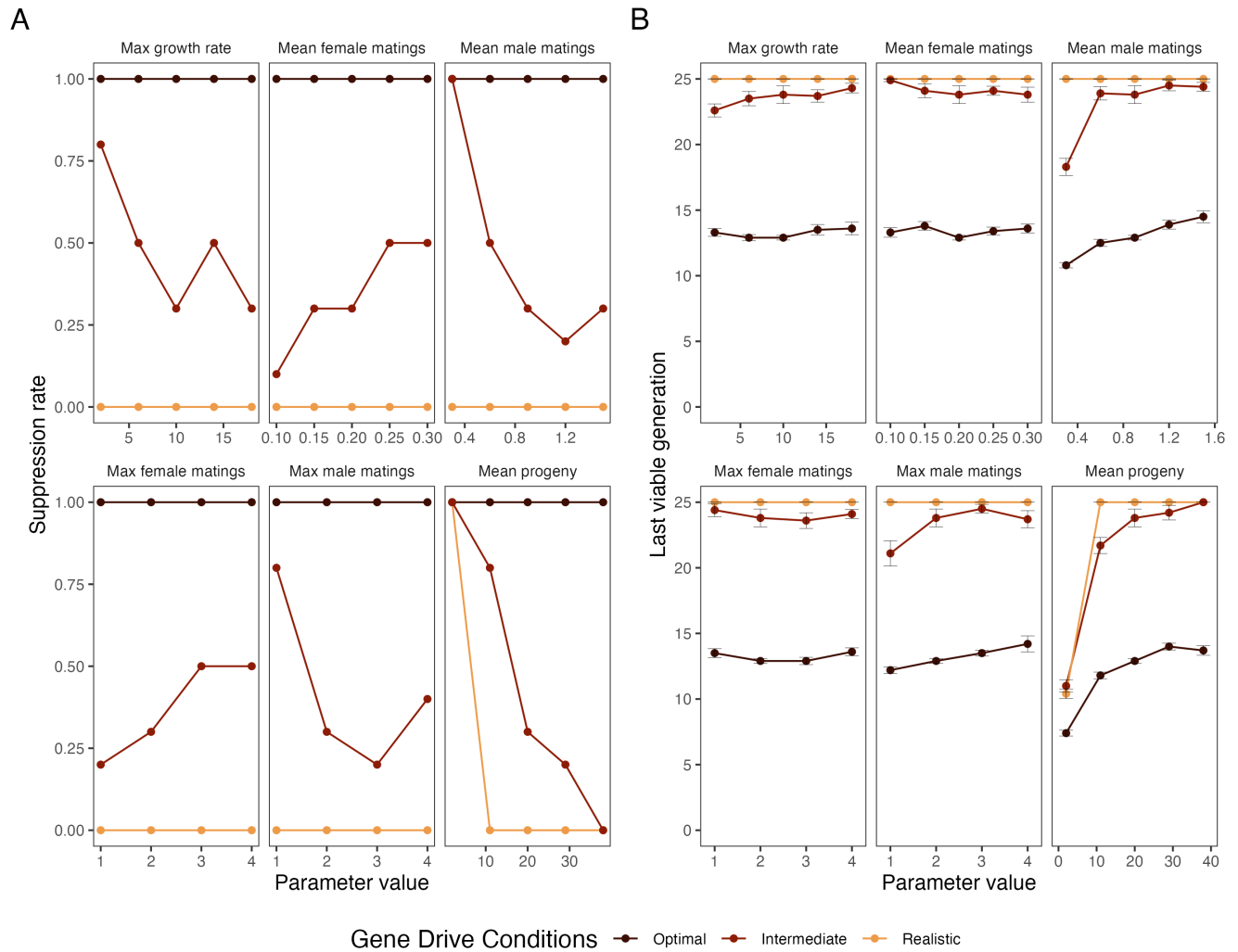


Allele — GD — NF — RE — WT

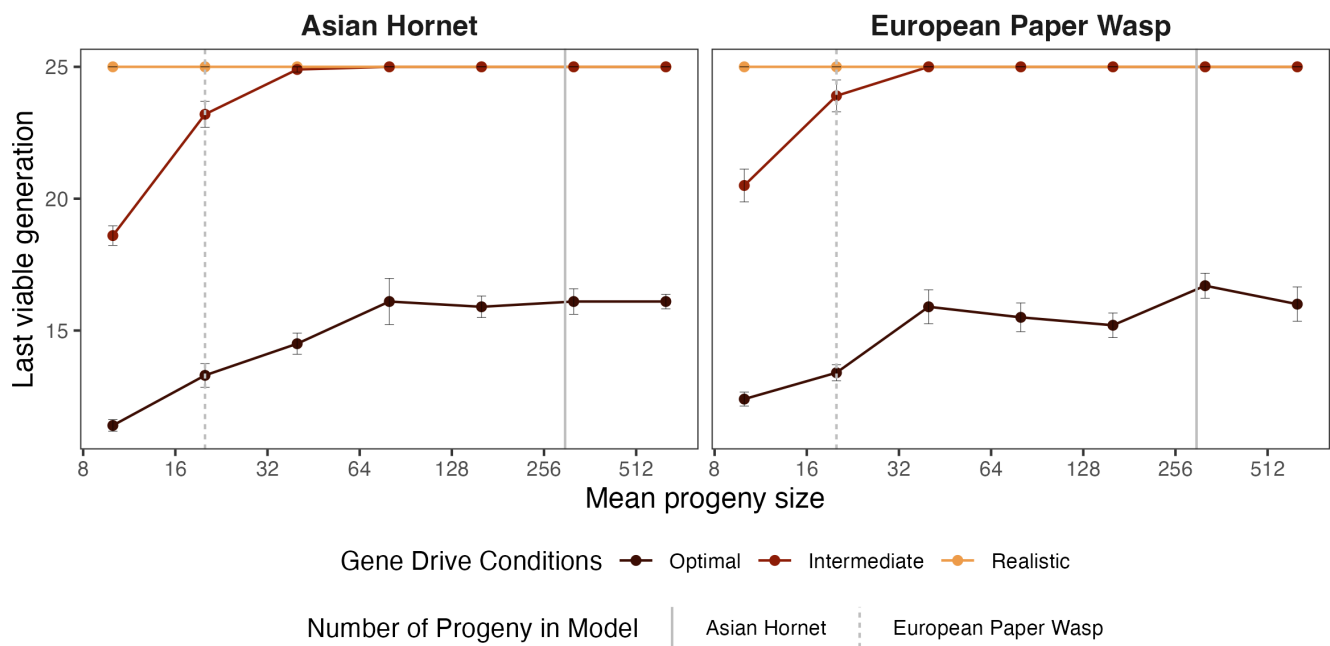
**Fig. S2.** Frequencies of wildtype (WT), gene drive (GD), resistance (RE), and non-functional (NF) alleles in a female Asian hornet population with no polyandry (**A**), and a female European paper wasp population with polyandry (**B**) by gene drive strategy and release carriers (females or males). The different strategies (neutral, male infertility, female infertility, and both-sex infertility) determine how the gene drive operates. In the neutral strategy there is no fitness cost to having the gene drive, whereas in the infertility strategies, the designated sex cannot reproduce when homo- or hemizygous for the gene drive.



**Fig. S3.** Sensitivity analysis for the biological parameters of the **Asian hornet**. **A** shows the suppression rate after the model has run for 25 generations. **B** shows the last viable generation over 25 years. The model was run under three different gene drive conditions: optimal, intermediate, and realistic. Under the realistic conditions the gene drive has a probability of non-homologous end-joining ( $P_{NHEJ}$ ) of 0.02, a cutting rate ( $P_{cut}$ ) of 0.95, and a heterozygous mortality ( $P_{mort}$ ) of 0.1. Under the optimal conditions these values are all 0. Under the intermediate conditions the gene drive has a probability of non-homologous end-joining ( $P_{NHEJ}$ ) of 0, a cutting rate ( $P_{cut}$ ) of 0.97, and a heterozygous mortality ( $P_{mort}$ ) of 0.15. Error bars represent the standard error of the mean.



**Fig. S4.** Sensitivity analysis for the biological parameters of the **European paper wasp**. **A** shows the suppression rate after the model has run for 25 generations. **B** shows the last viable generation over 25 years. The model was run under three different gene drive conditions: optimal, intermediate, and realistic. Under the realistic conditions the gene drive has a probability of non-homologous end-joining ( $P_{NHEJ}$ ) of 0.02, a cutting rate ( $P_{cut}$ ) of 0.95, and a heterozygous mortality ( $P_{mort}$ ) of 0.1. Under the optimal conditions these values are all 0. Under the intermediate conditions the gene drive has a probability of non-homologous end-joining ( $P_{NHEJ}$ ) of 0, a cutting rate ( $P_{cut}$ ) of 0.97, and a heterozygous mortality ( $P_{mort}$ ) of 0.15. Error bars represent the standard error of the mean.



**Fig. S5.** Last viable generation over 25 years for **A** The Asian hornet, and **B** the European paper wasp with different numbers of offspring. The grey lines indicate the values we used for each species. The model was run under three different gene drive conditions: optimal, intermediate, and realistic. Under the realistic conditions the gene drive has a probability of non-homologous end-joining ( $P_{NHEJ}$ ) of 0.02, a cutting rate ( $P_{cut}$ ) of 0.95, and a heterozygous mortality ( $P_{mort}$ ) of 0.1. Under the optimal conditions these values are all 0. Under the intermediate conditions the gene drive has a probability of non-homologous end-joining ( $P_{NHEJ}$ ) of 0, a cutting rate ( $P_{cut}$ ) of 0.97, and a heterozygous mortality ( $P_{mort}$ ) of 0.15. Error bars represent the standard error of the mean.