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Research Article

Evaluating the potential of a new murine gene drive for pre-emptive mouse plague control

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Abstract

Rodent outbreaks have significant ecological, agricultural and economic impacts around the world. Although they can occur with increasing frequency in some parts of the world, current management practices remain ineffective. Gene drives, which are genetic elements with positively biased transmission, have been theoretically shown to eradicate large populations of invasive mice on isolated islands and could potentially serve as pre-emptive tools against mouse plagues. Using a spatially explicit individual-based model, we investigated whether a recently developed murine gene drive, t_{CRISPR}, is effective in suppressing mouse populations within an open agricultural setting that experiences plague-like conditions with varying intensity and duration. We simulated various release strategies involving different temporal and spatial release efforts and measured the reduction in maximum plague population sizes relative to scenarios where no control was applied. Early releases allowed more time for the drive to spread before the onset of plagues, making it the most effective strategy to reduce the impact of plagues. Repeated and spatially extensive release efforts, which were initiated 3 years earlier and continued up to the onset of plagues, resulted in up to 90% reductions in the maximum population sizes compared to plagues without control. Effectiveness declined with later releases; those initiated at the onset of the plagues or later did not result in a decrease in population sizes. We tested whether the total release effort of the most effective strategy can be reduced by incorporating periods without any releases. We showed that pulsed releases with no-release gaps could be similarly effective; however, the timing of both releases was critical. Surprisingly, the lowest release effort, which was the one-time release of a single individual to the release sites, had almost no impact on the first plague, but had a substantial impact on subsequent recurring plagues that occurred 10 years later and reduced the maximum population sizes by ~80%. A newly-developed murine gene drive, t_{CRISPR}, could be an effective pre-emptive control tool for costly mice plagues. Early releases followed by supplementation could eliminate the need to predict or closely monitor their occurrence.

Key words: Agriculture, gene drive, genetic biocontrol, invasive species, *Mus musculus*, t_{CRISPR}

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Introduction

Rodent outbreaks occur throughout the world and often have significant ecological, agricultural and economic consequences (Jensen 1982; Leirs et al. 1996, 2010; Lima et al. 1999, 2003; Stenseth et al. 2003; Jacob and Tkadlec 2010; Paini et al. 2016; Andreassen et al. 2021). In Australia, the house mouse (*Mus musculus*) is an

invasive alien species whose populations can reach exceptionally high densities (≥ 2,000 mice per hectare) in grain growing regions (Singleton and Redhead 1990; Singleton et al. 2005). Plagues can affect large areas, spanning several hundred thousand square kilometres (White et al. 2024). Plagues occur approximately once every 7 years on a regional scale and once every 3 years nationwide (Singleton et al. 2005). However, the frequency of plagues appears to be increasing since the 1980s, driven by factors such as greater crop diversity and intensity, changes in farming practices, declines in sheep production and shifts in rainfall patterns due to climate change (Singleton et al. 2005). Plagues cause significant economic loss and social stress in rural communities in Australia (Brown and Singleton 2000). The estimated cost of the 1993/1994 plague in South Australia was US$60 million (Caughley et al. 1994), while the estimated cost of the 2020/2021 plague in New South Wales was US$600 million (White et al. 2024). The impact of mouse plagues extends beyond the damage to agricultural crops; impacting equipment, infrastructure and the environment, with adverse consequences for human health as well (Brown and Henry 2022; White et al. 2024).

Multiple factors influence the timing and severity of mouse plagues in Australia (Krebs et al. 1995b, 2004; Pech et al. 1999). Wet seasons lead to an abundance of seed crops and vegetation and, thus, more frequent litters in mice, which support rapid population growth. Mouse plagues are more likely to occur after several consecutive wet years, when food resources are abundant, allowing mouse populations to grow exponentially (Singleton et al. 2001; Mutze 2009). Rainfall during the winter months, which coincides with the grain growing season, also plays a crucial role in triggering these population surges (Brown and Singleton 1999). Increased soil moisture after rainfall also allows easier burrowing, which contributes to plagues by increasing survival rates (Newsome 1970). However, despite our increased understanding of plague dynamics, the timing and severity of these events remains difficult to predict (Kenney et al. 2003; Krebs et al. 2004).

Current plague management strategies are based on extensive monitoring (Caughley et al. 1998a, b; Brown et al. 2022), but are primarily reactive, implemented after farmers notice crop damage (Brown and Singleton 2000). These strategies include the use of rodenticides in and around farm buildings, as well as trapping around living areas to prevent accidental harm by rodenticides to humans and pets (Brown and Henry 2022). Alternative control methods that reduce mouse fertility are being considered to prevent population outbreaks (Singleton and Redhead 1990; Chambers et al. 1997; Singleton et al. 2024). Modified murine cytomegalovirus (MCVC), which is a herpes virus transmitted by close contact, has been proposed as an immunocontraceptive vector (Singleton et al. 2001; Davis et al. 2003). Disease-host models suggest that immunocontraception can have an impact on outbreaks provided that high levels of infertility can be achieved with MCVC and that the virus is highly transmissible in the field (Arthur et al. 2005). However, the transmissibility of this virus in the field remains unknown and factors such as multistrain competition and low levels of virus prevalence between outbreaks could reduce transmission (Arthur et al. 2005). Ensuring the effectiveness of this control strategy requires large-scale sterilisation of founders, as well as their subsequent generations and immigrants, a process that also presents a significant logistical challenge (Jacob et al. 2008).

Gene drives offer a potential strategy to prevent plagues. CRISPR-Cas9-based gene drives are "selfish" genetic elements that have the potential to modify or sup-

press a target population with increased transmission rates compared to Mendelian ratios. One of the most common gene drive configurations is a 'homing' drive in which Cas9 endonuclease and gRNA expression cassettes are inserted at the genomic site targeted by the gRNA. Activation during germline development results in the generation of a double-stranded DNA break on the homologous chromosome, repair of which by homologous recombination converts heterozygotes to homozygotes, ensuring gene drive transmission (Burt 2003; Windbichler et al. 2011; Gantz and Bier 2015). Incorporation of this 'homing' drive into a gene required for fertility or viability causes the gene to be non-functional, but if a single copy functional copy of a gene is enough to produce the wild type (i.e. haplosufficent), this can be used to drive populations to extinction (Deredec et al. 2008; Kyrou et al. 2018). Theoretical models have shown that 'homing' gene drives, which spread faulty female fertility genes, could eradicate large populations of mice (Prowse et al. 2017; Godwin et al. 2019; Champer et al. 2021; Birand et al. 2022a). However, to date, homing drives have been challenging to engineer in mice (Grunwald et al. 2019; Pfitzner et al. 2020; Weitzel et al. 2021). The homologous recombination repair mechanism that ensures biased transmission seems to be disfavoured compared to end-joining repair, particularly in the male germline. Non-homologous end joining (NHEJ) or microhomology-mediated end joining (MMEJ) often results in a small deletion or insertion mutation (indel) that renders the target site resistant to further cleavage, preventing the spread of the drive (Esvelt et al. 2014; Champer et al. 2017; Prowse et al. 2017; Unckless et al. 2017).

A recently developed gene drive in mice, t_{CRISPR}, circumvents the challenge of low homing rates by harnessing biased transmission of a naturally-occurring drive, the *t* haplotype (Gierus et al. 2022). The t^{w2} variant, which was used to engineer t_{CRISPR}, has ~95% transmission rates in male mice (Bruck 1957; Silver 1985). t_{CRISPR} has two additional components embedded within the natural t^{w2} drive: Cas9, expression of which is controlled by a male-specific promoter and a ubiquitously expressed gRNA targeting a haplosufficient female fertility gene (Gierus et al. 2022). With an extensive set of computer simulations and genetically engineered (i.e. transgenic) mouse data, Gierus et al. (2022) showed that the engineered t_{CRISPR} is predicted to spread female infertility genes effectively in a wild population and has robust eradication potential across a wide range of realistic parameter values related to gene drive efficiency and mouse life history. Typically, t_{CRISPR} spread throughout the landscape after its introduction and the frequency of the female fertility gene declined steadily within the first 10 years. Complete eradication of mice was achieved in ~20–25 years on the ~2, 000 ha island which initially had 200,000 mice. Although a high probability of loss of gene function (p_L) is required after a successful cut to prevent the evolution of functional resistant genotypes in the female fertility gene, in most cases, eradication was still achieved with t_{CRISPR} when loss of function was not guaranteed ($p_L < 1$) through homozygous male sterility (see fig. S2 in Gierus et al. (2022)).

Genetic biocontrol strategies show promise in controlling invasive species; however, their ability to rapidly spread genetic modifications through wild populations raises critical biosafety and ecological concerns (Esvelt et al. 2014; Champer et al. 2016). These include the risk of uncontrolled dispersal, off-target mutations, the evolution of resistance and impacts on ecosystems through unintended effects on food webs. In response, recent research, focusing on developing more controllable and reversible gene drive systems, emphasised the need for stepwise field trials

and long-term environmental monitoring (Marshall and Akbari 2018; Long et al. 2020; Combs et al. 2023). Addressing these challenges also requires internationally coordinated regulatory frameworks, comprehensive ecological risk assessments and meaningful public engagement to guide the responsible development and deployment of gene drive interventions (Oye et al. 2014; Long et al. 2020; Hartley et al. 2022; Yang 2024). Theoretical models offer essential insights into the efficacy and ecological impacts of this rapidly developing biotechnology, playing a critical role in supporting responsible evaluation and more informed risk assessment (Combs et al. 2023). Gierus et al. (2022) modelled the efficacy of t_{CRISPR} in an isolated island setting, but the performance of t_{CRISPR} in open, mainland populations under boom-bust dynamics has yet to be explored. To address this, we evaluate the potential impact of releasing t_{CRISPR} carrying individuals in an open agricultural landscape as a pre-emptive strategy against mouse plagues varying in intensity and duration. We find that t_{CRISPR} may provide a species-specific and humane tool to reduce the environmental and agricultural impact of mouse plagues in Australia.

In silico modelling

To investigate the efficacy of t_{CRISPR} in reducing the impact of mouse plagues, we used the spatially explicit individual-based model presented in Birand et al. (2022a, b). Individuals are diploid, with genetically controlled autosomal traits and sex chromosomes. Individuals occupy a rectangular array of patches that form a hypothetical land that is connected to the adjoining areas through immigration. Each patch can hold multiple individuals and individuals can utilise multiple patches within a single breeding cycle. Each breeding cycle is considered a model time step with the following events: 1) mate search within a predetermined distance from the individual's central patch; 2) mating, where all fertile females mate if they find a male during mate-search with the possibility of polyandrous mating; 3) density-dependent reproduction, where the number of offspring from each mated female is drawn from a Poisson distribution using discrete-time Beverton-Holt model (Kot 2001); 4) distance- and negative density- dependent natal dispersal; 5) survival of adults; 6) breeding dispersal of surviving adults as in step 4; 7) immigration of new individuals to the boundary patches from adjoining areas. The number of breeding cycles per year is given by n_c. Individuals that survive long enough pass through a number of breeding cycles until they reach a maximum age (age_m). Generations are overlapping (for more details, see Birand et al. (2022a, b); Gierus et al. (2022)).

Parameters related to life history traits (Table 1) are based on empirical data when available (Birand et al. 2022a; Gierus et al. 2022). If there are multiple males present in a female's breeding patch, she can mate with up to two males (n_m = 2) in a breeding cycle with probability p_m = 0.63 (Manser et al. 2020). The average number of offspring (b) produced by a female mouse in the absence of density-dependent regulation in each breeding cycle is six (Singleton et al. 2001; Murphy and Nathan 2021). The actual number of offspring a female produces during her lifetime depends on the number of breeding cycles she survives and the random number drawn from the Poisson distribution for each breeding cycle (Birand et al. 2022a, b). When the random number drawn is zero, which is often the case when the population size is near its carrying capacity, the female skips a breeding cycle without producing offspring. If the female mates with multiple males, the gene-drive carrying male's probability of siring an offspring is reduced by a sperm-dis-

Table 1. Parameters related to the life history of mice, gene drive efficiency, plague conditions and control effort. All parameters are specific to the time step (i.e. breeding cycle) in the model, except for the time gap between control initiation and plague onset (t_{gap}) and the plague duration *P*duration, which are in years. For sensitivity analyses (SA), parameter combinations are drawn from a uniform distribution (*U*) or uniform discrete distribution (U_d) using Latin hypercube sampling. For detailed sensitivity analysis of life history and gene drive parameters, see Birand et al. (2022a) and Gierus et al. (2022).

Parameter	Base value	SA
Life history:		
number of breeding cycles in a year (*nc*)	6	6
probability of multiple mating (p_m)	0.63	0.63
maximum number of males mated per breeding cycle (n_m)	2	2
sperm-disadvantage coefficient (d_s)	0.17	0.17
average number of offspring (*b*)	6	6
dispersal and mate-search distance (*D*)	5	U_d{5, 6}
dispersal coefficient (*a*)	1	1
density coefficient (*c*)	1	1
probability of adult survival (ω)	0.53	0.53
maximum age (age_m)	2	2
carrying capacity per patch (*K*)	1.5	1.5
immigration rate (c_{im})	0.05	*U*(0.01, 0.1)
Plague:		
carrying capacity per patch during plague (K_{plague})	15, 30	30
plague duration ($P_{duration}$)	1, 2	U_d{1, 2}
Control effort:		
time gap between control initiation and plague onset (t_{gap})	-0.5, 0, 1, 2, 3	*U*d{1, 2, 3}
total number of releases, with one release per breeding cycle (n_i)	1, 6, 12, 18, 21	*U*d{1, ..., 32}
number of release sites (n_p)	16, 64	*U*d{16, 36, 64}
number of gene-drive carrying individuals released (N_i)	10, 20, 30	*U*d{10, ..., 30}
Gene drive:		
transmission probability in heterozygous males (p_t)	0.95	0.95
probability of successful cut (p_C)	0.8	0.8
probability of loss of function after a successful cut (p_L)	1.0	1.0
drive fitness (ω_d)	1	1

advantage coefficient d_s compared to that of the wild-type male (Dean et al. 2006; Manser et al. 2017, 2020; Birand et al. 2022a; Gierus et al. 2022). The sex of each offspring is determined by the sex chromosomes inherited from its parents. The offspring produced are assumed to be adults in the next breeding cycle. The survival probability of adults per breeding cycle is ω = 0.53 and the maximum age (age_m) that they can reach is 2 years (Murphy and Nathan 2021), although the mean age they survive is < 1 years (Birand et al. 2022a). Based on observed intervals between litters, we assumed that the number of breeding cycles in a year (n_c) is six (Moro et al. 2018; Murphy and Nathan 2021). The immigration of individuals to each boundary patch is a Bernoulli trial with constant probability c_{im}. Since population recovery after traditional control methods is mostly through breeding with only limited re-colonisation from other places (Shilova and Tchabovsky 2009) and our initial simulations showed that immigration rates did not affect the impact of control during high-intensity plagues (Suppl. material 1: fig. S1), we assumed that the baseline immigration rate is c_{im} = 0.05.

Plague

During plagues, we assumed that the carrying capacities of the patches were elevated. Increasing carrying capacities increased both the fertility rates in females and the survival rates of the offspring produced (density-dependent reproduction in step 3 above). During a plague, mouse densities can reach up to 800–2000 mice/ha (Singleton et al. 2005; Brown et al. 2007). During non-outbreak years, the densities are typically less than 50 mice/ha (Singleton et al. 2001). We modelled plagues with varying intensity and duration to match these densities (see below). We also modelled recurring plagues that occur every five years.

Gene-drive strategy

We explored the efficacy of a recently developed gene drive t_{CRISPR} (Gierus et al. 2022), which leverages high transmission of the naturally occurring t haplotype (t^{w2}) and generates mutations deactivating the unlinked haplosufficient female fertility gene (Prl) that is highly conserved over an evolutionary timescale and, therefore, unlikely to develop further mutations without loss of function. As with t^{w2}, the inheritance of t_{CRISPR} is biased in males (with transmission probability p_t), but not in females; moreover, the males that are homozygous for the drive are sterile. Cas9 is only active in males and with a ubiquitously expressed gRNA, it disrupts a haplosufficient female fertility gene in the germline (with probability p_C); therefore, t_{CRISPR} males transmit the t_{CRISPR} transgene and a disrupted fertility gene to offspring. Females that inherit two copies of the non-functional fertility gene are sterile (see fig. 1 in Gierus et al. (2022)). The empirical values reported by Gierus et al. (2022) are used as base values for the gene drive parameters in all simulations (see Table 1).

Pre-emptive control effort

In the model, genetic biocontrol is used as a pre-emptive tool against mouse plagues. We modelled various scenarios with respect to the timing of the release relative to the onset of the plague (Fig. 1). The simulated control effort is generally initiated before the onset of the plague and the time gap (in years) between the initiation of control and the onset of the plague is denoted as t_{gap}. The release of t_{CRISPR} carrying males can continue during the plague; the total number of releases is given by n_i, with one release occurring in each breeding cycle. Since there is one release per breeding cycle, ni also represents the temporal release effort. For example, $n_i = 6$ corresponds to releases that last for one year, since $n_c = 6$. The control effort could also start at the onset of the plague or after. Depending on t_{gap} and n_i, release effort could continue during the plague. For example, when $t_{gap} = 1$ and $n_i = 12$, release starts one year before the plague and lasts for 2 years. Control effort is either continuous or pulsed. The former is a continuous release effort that lasts for multiple breeding cycles once initiated. The latter is carried out in two stages with a prolonged gap between the two pulses when releases are suspended. The release sites consist of predetermined patches distributed systematically across the landscape in a uniform checkerboard configuration. The number of sites (n_p) varies, along with the number of individuals released per site (N_i). The total number of individuals released throughout the entire release effort is $N_T = N_i n_p n_i$ (Suppl. material 1: table S2).

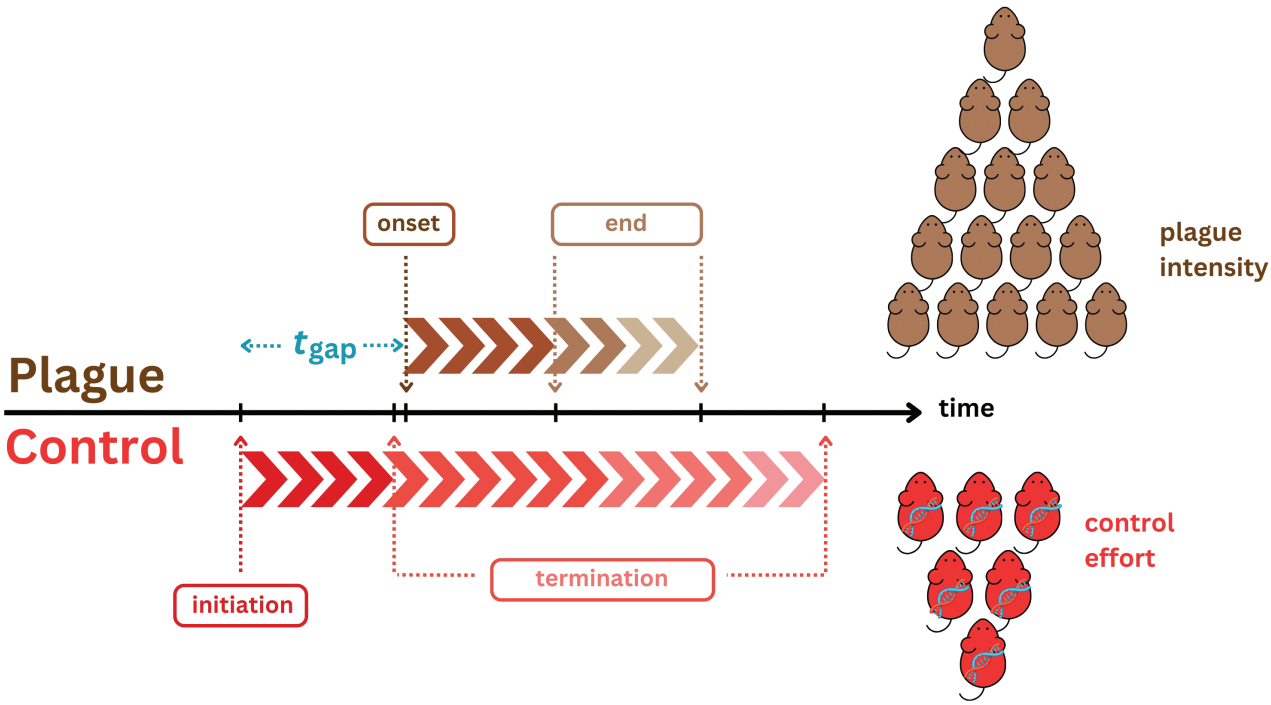

Figure 1. The timeline of genetic control releases and the plagues. The timing of the release efforts were variable, but were mostly initiated and terminated sometime before the onset of plagues as pre-emptive tools. The time gap between the control initiation and the plague onset is referred to as t_{gap}. Plague intensity and duration were also variable.

Simulated landscape and initial conditions

Our hypothetical agricultural land parcel is ~41ha (0.41 km^2) with ~2, 200 mice (based on density estimate: ~50 per ha, Singleton et al. (2001)). The simulated land is comprised of 32 × 32 = 1024 patches, each roughly corresponding to a 20 m × 20 m area and the dispersal distances D are adjusted accordingly (Krebs et al. 1995a; Birand et al. 2022a). Each patch is initiated with two individuals, the sexes of which are determined randomly. During plagues with varying intensity and duration, the resulting densities reached those reported in the literature (Suppl. material 1: table S1, Singleton et al. 2005; Brown et al. 2007). We ran simulations for a maximum of 200 breeding cycles and compared the maximum population sizes observed during plagues with various control efforts mentioned above with those without any control effort (for sample simulations, see Fig. 2).

Sensitivity analysis

We investigated the relative influence of control release parameters on the maximum population sizes observed during a high intensity plague with a global sensitivity analysis. We created 3,000 unique parameter combinations from the parameter ranges given in Table 1 using Latin hypercube sampling (randomLHS, R package *lhs*, Carnell (2020)) and carried out a single simulation for each parameter combination (Prowse et al. 2016). Finally, we examined the influence of parameter inputs using Boosted Regression Tree models (BRT; R package *dismo*, Hijmans et al. (2011)) that we fitted to the simulation outputs using the function gbm.step from the R package dismo (learning rate: 0.01; bag fraction: 0.75; tree complexity: 3; and 5-fold cross-validation, Elith et al. (2008)). We used a Gaussian error distribution for the maximum population size observed with control.

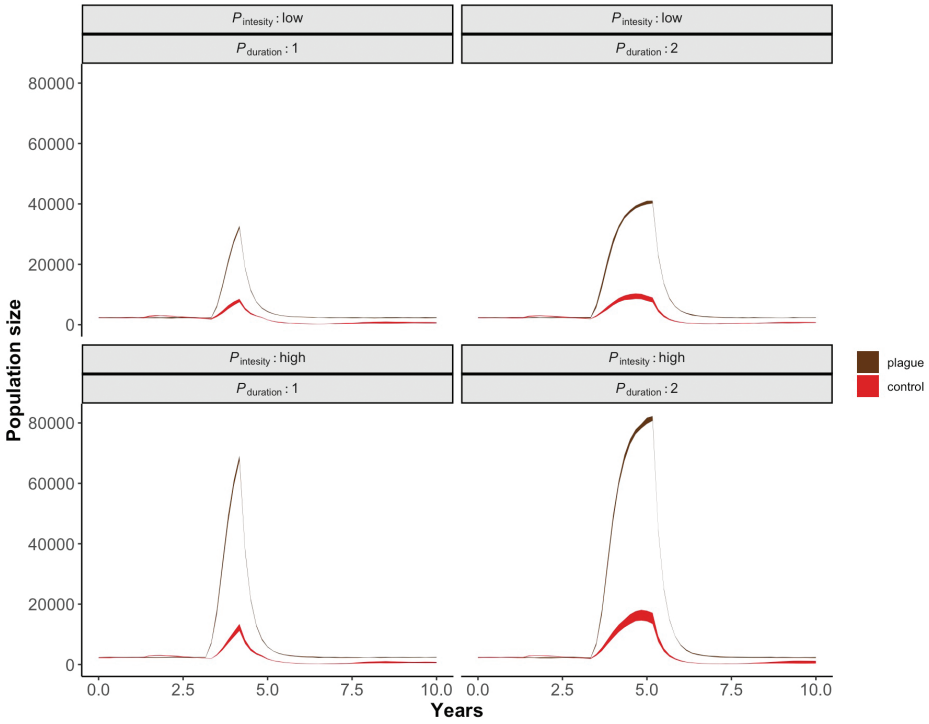

Figure 2. The population sizes through time during plagues with various intensity levels and duration without any control (brown) vs. when control (red) was initiated 2 years before plagues' onset. The width of the line represents the range (minimum and maximum) of population sizes seen in these sample simulations. Note that the population sizes remain low after the plague is over in simulations with control (based on 10 simulations for each parameter combination; other parameters were N_i = 30 individuals, n_i = 20 releases and n_p = 16 patches).

Results

The control releases had four components: (i) the time gap between the initiation of the control and the onset of plagues (t_{gap}); (ii) total number of releases with one release per breeding cycle (n_i); (iii) the number of release sites (n_p); and (iv) the number of individuals released per site (N_i). Release strategies based on various combinations of these four components varied significantly in suppressive power (Fig. 3).

The most significant difference in the effectiveness of the control was caused by t_{gap} (Fig. 3). The three-year time gap resulted in the greatest reductions in population sizes during the outbreak and the effectiveness of control declined when it was initiated closer to the outbreak. More than 90% reductions in the maximum population sizes were observed during plagues that lasted 1 year when the release was initiated 3 years before its onset and continued for 2 years ($n_i \geq 12$). Continuing the initiated releases after the onset of the plagues did not help reduce the population sizes further; maximum population size reductions were generally observed when the releases were stopped at the plagues' onset (vertical brown dashed lines in Fig. 3). Releases initiated at or after the plagues' onset ($t_{gap} \leq 0$) did not result in any measurable population reductions; moreover, in some cases, maximum population sizes exceeded those of the no control scenario due to the large number of introduced individuals (N_T). The time of release with respect to the onset of the plague was critical, because earlier releases allowed more time for the drive to spread in the population and were generally more successful. The frequency of fertile individuals

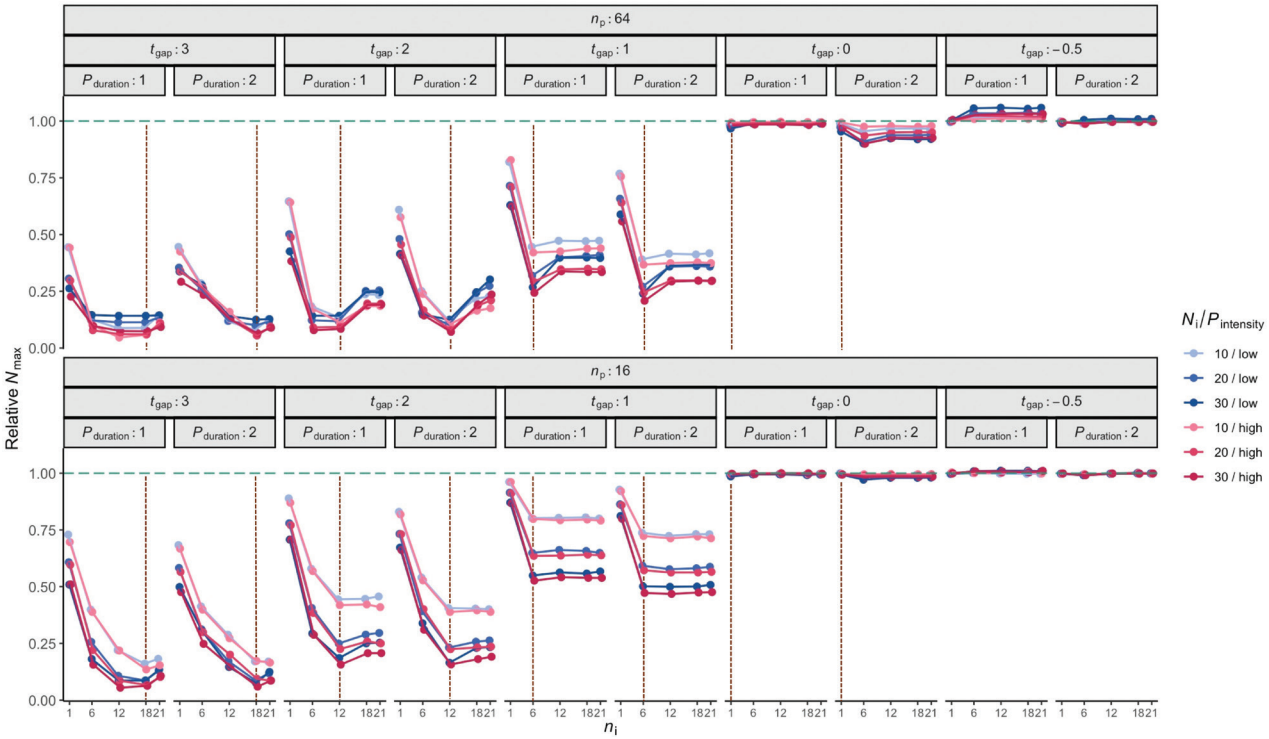

Figure 3. The average of maximum population sizes observed in response to various control release efforts relative to those during plagues with no control. The averages of maximum population sizes during the plague without control are given in Suppl. material 1: table S1. Vertical brown dotted lines show the releases that ended at time of plagues' onset; for example, when t_{gap} = 3 and n_i = 18, releases (to n_p sites with N_i individuals) were initiated 3 years before the plagues' onset and continued for 3 years (i.e. 18 breeding cycles). Note that there is no vertical line at t_{gap} = -0.5 since all the release efforts are initiated 0.5 years (3 breeding cycles) after the plagues' onset. Horizontal green dashed lines show when the relative N_{max} = 1, i.e. when there is no reduction in population sizes relative to those during plagues with no control (based on 20 simulations for each parameter combination; 12000 simulations in total).

with t_{CRISPR} at plagues' onset was higher in the release strategies that had a greater impact and resulted in greater suppression (Suppl. material 1: fig. S2).

Higher frequencies of t_{CRISPR} could also be achieved by releasing more transgenic individuals. As expected, the total number of transgenic individuals (N_T) released throughout the entire release effort strongly influenced the impact of the control (Suppl. material 1: fig. S3). However, there were diminishing returns; the addition of more transgenic individuals resulted in greater reductions in maximum population sizes up to a point, after which more releases did not further reduce population sizes. When releases were initiated at the time of plagues' onset (t_{gap} = 0), increasing the total release effort during each release by increasing the number of release sites n_p and the number of individuals released per site N_i had reduced the population sizes slightly, particularly during the plagues that lasted for 2 years. However, one-time releases (n_i = 1) were not as effective as multiple releases (n_i > 1) (Fig. 3) unless the release was spatially extensive (n_p = 64) and a large number of individuals were released in each patch (N_i = 30, i.e. one-time release of 1920 individuals had the same effect as multiple releases of 320 individuals and 160 individuals released at each breeding cycle over the course of one and two years, respectively (Suppl. material 1: fig. S4)). Indeed, multiple releases that lasted for a year or longer ($n_i \geq 6$) had a better impact on reducing maximum population sizes unless releases were delayed and could be more preferable since per breeding cycle release effort is much smaller (Suppl. material 1: fig. S5).

The spatial extent of the release effort also had an impact on the effectiveness of the control. Spatially extensive releases (n_p = 64) generally resulted in greater reductions in the maximum population sizes (Fig. 3). The difference was particularly pronounced if the releases were initiated 1 year before the onset of the plague (t_{gap} = 1). When spatial effort was sparse (n_p = 16) and releases were initiated 1–2 years before the onset of plagues, increasing the number of individuals released per site, N_i, improved the impact of controls. When spatial effort was extensive, adding more individuals per release site generally did not reduce the population sizes further. Lastly, the intensity of the plague did not affect the relative impact of the control, although the maximum population sizes observed during plagues with various intensity and duration were significantly different from each other (Fig. 2, Suppl. material 1: table S1, $P < 0.001$). Sensitivity analysis supported brute force simulations with similar results (Suppl. material 1: fig. S6): the timing of the release effort relative to the onset of the high-intensity plague (t_{gap}) had the greatest relative influence on maximum population sizes, followed by the number of releases (n_i), the number of patches (n_p) and the number of individuals released per patch (N_i). Other parameters had little or no influence.

Since control efforts with longer t_{gap} and higher numbers of releases (n_i) were more successful in reducing population sizes (Fig. 3 and compare subplots 1–5 in Fig. 4), we investigated whether the total number of gene-drive carrying individuals released could be reduced by introducing breaks between release efforts. Pulsed releases were carried out in two stages with a prolonged gap between them (plots 6–10 in Fig. 4). Note that the release strategies in subplots 3 (continuous) and 6 (pulsed) have the same control initiation and termination times; however, the latter have 33.3% fewer n_i, which can considerably reduce the total number of individuals released. Surprisingly, both releases (outlined in subplots 3 and 6) were similarly effective in reducing the impact of plagues. However, in the pulsed releases, the timing of both releases relative to the onset of plagues was critical. Increasing $t_{gap\text{-}1}$ for the first release for more than 3 years (compare subplots 6–8 in Fig. 4), reduced the control's impact; however, reducing $t_{gap\text{-}2}$ between the initiation of the second release and the onset of plagues, while keeping the timing of the first release constant (compare subplots 8–10 in Fig. 4), improved the impact of the control further and the maximum population sizes were reduced to similar levels as with the continuous control that was initiated 3 years earlier (plot 3 in Fig. 4). Note that the highest impact was achieved with the earliest first release and latest second release (compare subplots and 10 in Fig. 4). As before, the frequencies of fertile t_{CRISPR}-carrying individuals were higher in simulations that were more successful in suppression (Suppl. material 1: fig. S7).

The frequency of t_{CRISPR} continued to increase in the population despite the immigration of individuals from adjoining sites; therefore, the suppressive power of genetic control continued long after the plague ended (e.g. compare population sizes with and without control during non-outbreak years in Fig. 2). The least successful release effort was a single release strategy (n_i = 1) with N_i = 10 individuals without a spatially extensive release (n_p = 16, Fig. 3). The same one-time release strategy continued to have a substantial effect on plagues that occurred repeatedly every 5 years (Fig. 5) since the frequency of t_{CRISPR} continued to increase (Suppl. material 1: fig. S8). Reducing the overall release effort even further by releasing one individual per patch (N_i = 1) to n_p = 16 patches had a similar strong impact on plagues that occurred after > 10 years.

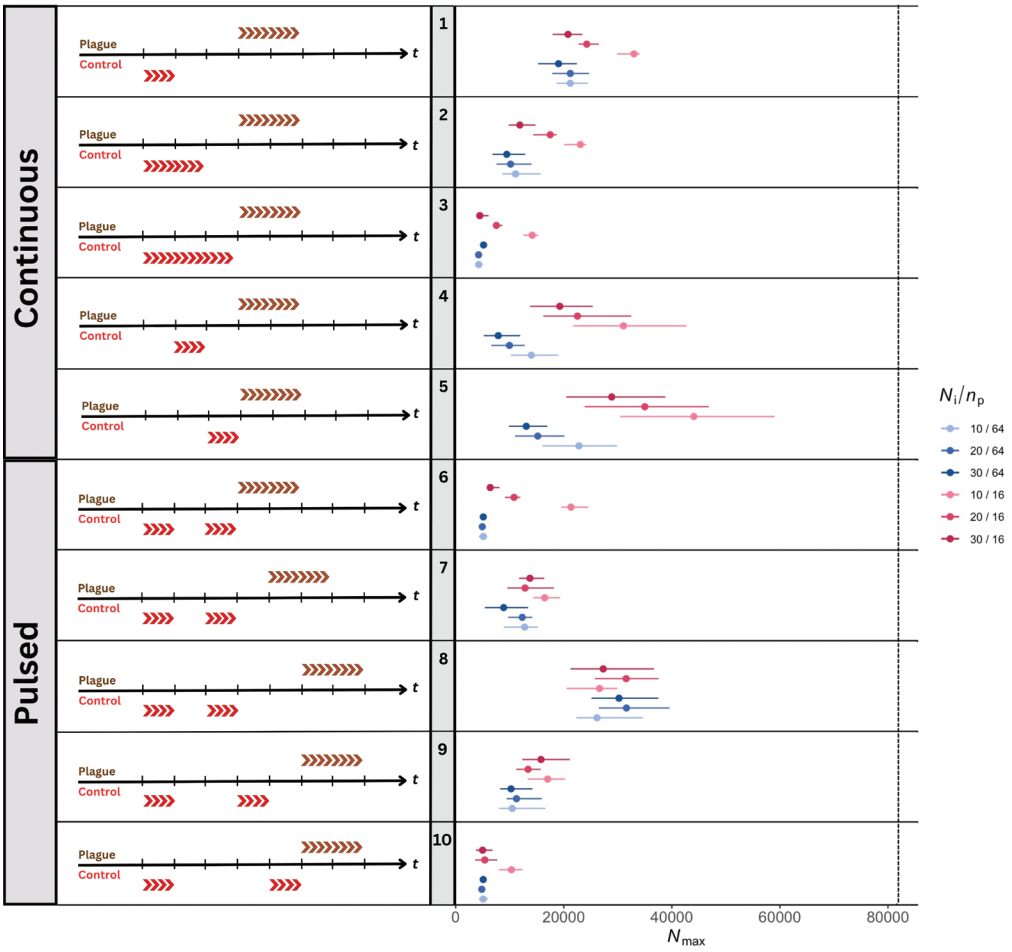

Figure 4. The median and the interquartile ranges for the maximum population sizes observed in response to various *continuous* (1–5) and *pulsed* releases (6–10) during high-intensity plagues that lasted for 2 years. The dashed line shows the median for the maximum population size during the plagues without control. The timeline of controls and plagues are outlined on the left of each subplot. Note that in 1–3, t_{gap} is constant, while number of releases, n_i is increasing; in 1, 4 and 5, t_{gap} is decreasing, while n_i is constant; in 6–10, n_i is constant; in 6–8, $t_{gap\text{-}1}$ is increasing; in 8–10, the timing of the first release is the same, whereas the timing of the second release is getting closer to the onset of the plague, i.e. $t_{gap\text{-}2}$ is decreasing (based on 20 simulations for each parameter combination).

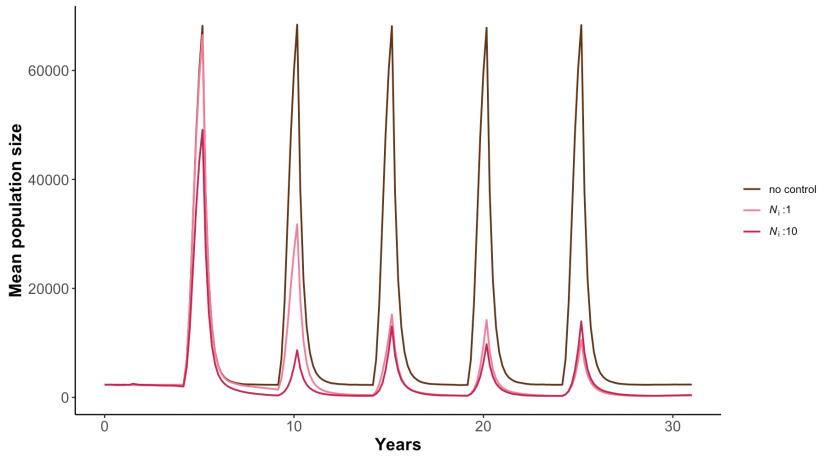

Figure 5. The mean population sizes observed in response to a single release (n_i = 1) with N_i = 1 individual and N_i = 10 individuals to n_p = 16 patches during a low-intensity plague that occurred repeatedly every 5 years. With N_i = 1, the maximum population sizes were reduced to 98%, 46%, 22%, 21%, 15% of the population sizes without control (in order of occurrence) and with N_i = 10, the maximum population sizes were reduced to 72%, 13%, 19%, 14%, 20% ($P_{duration}$ = 1, c_{im} = 0.05; based on 10 simulations for each scenario).

Discussion

The recent emergence of genetic biocontrol technologies demands careful investigation of their potential for suppression of overabundant and invasive populations. We showed previously that the recently developed t_{CRISPR} gene drive strategy in mice (Gierus et al. 2022) has considerable potential for eradicating invasive mouse populations on islands. Here, we investigate the deployment of t_{CRISPR} to mitigate mouse plagues in an open mainland population, modelled as a continuous influx of wild-type individuals into the simulated landscape at each breeding cycle. Excitingly, we find that t_{CRISPR} has considerable potential to mitigate the devastating impact of frequent and increasingly common mouse plagues in Australia.

The timing of the releases was critical to the effectiveness in suppressing mouse plagues. Significant reductions in population sizes were achieved when the frequencies of fertile individuals carrying t_{CRISPR} were high at the plagues' onset. Due to biased transmission, only in males, the spread of t_{CRISPR} and the eventual suppression/eradication is slower compared to other proposed drives like the 'homing' drives or the X-shredder, which are yet to be developed in mice (Gierus et al. 2022). Earlier releases allowed t_{CRISPR} to reach higher frequencies and had a greater impact on reducing population sizes during plagues. In some cases, ≥ 90% reductions were achieved. If releases were delayed and occurred closer to the onset of the plague, they were less efficient. In general, longer duration of releases had a greater impact than one-time releases. Expanding spatial coverage or increasing the number of individuals released per patch improved the impact of one-time releases. However, releasing a large number of transgenic mice at once is probably not the most preferred solution. Spreading the release effort temporally to multiple breeding cycles could significantly reduce the total number of individuals introduced in each breeding cycle. Ideally, releases should start early, stop at plagues' onset and be carried out as multiple releases to reduce the impact on farms.

Pulsed releases could be equally effective in reducing population sizes during outbreaks as continuous releases. Pulsed releases also have the added benefit of reducing the total release effort by introducing gaps between releases. In pulsed releases, the initiations of both the first and the second releases relative to the plagues' onset were critical in determining their effectiveness. An early first release, followed by a delayed second release, produced the highest impact.

Although one-time releases with few individuals (e.g. total of N_T = 16 individuals with N_i = 1 individual released to n_p = 16 release sites) had almost no impact on plagues that occurred within ~3 years, transgenic individuals continued to persist in the population and increased in frequency. These minimal release efforts had a great impact on recurring outbreaks ~15 – 30 years later and reduced population sizes ~80%, suggesting that even the smallest release efforts can have a large impact on plagues that occur later in the future.

In the model, we assumed that plagues were caused by sudden increases in the carrying capacity of patches, which increased the number of offspring through increased fertility and survival and resulted in population outbreaks. Our results were general and largely independent of the intensity and duration of the plagues; however, other factors, such as improved soil suitability, could contribute to the plagues by increasing survival rates of adults through greater availability of suitable burrowing sites (Newsome 1970). We suspect that increased survival of adults could affect both wild-type and transgenic mice equally; therefore, it would not

have a large qualitative impact on the results presented here. However, the effect of increased adult survival could be worth exploring in future modelling studies. We should also note that our model only includes immigration of wild-type individuals from adjoining areas; however, future modelling efforts could consider multiple farm scenarios where the effects of immigration and emigration of both wild type and drive-carrying individuals.

Although the spread of t_{CRISPR} is slower compared to other proposed drives, it also has several advantages (Gierus et al. 2022). Firstly, it harnesses a naturally occurring drive, t^{w2}; therefore, gene conversion through homing is not required. Secondly, the sterility of homozygous transgenic males contributes to suppression; therefore, suppression continues and ultimately leads to complete eradication even after resistant female fertility genotypes evolve (Gierus et al. 2022). In fact, t^{w2} can be locally fixed and cause population crashes due to homozygous male sterility (Dunn and Levene 1961; Lewontin 1962); however, only when both polyandry levels in the population and sperm competitive disadvantage of transgenic males against wild-type males are low (Manser et al. 2020; Gierus et al. 2022). The only disadvantage of t_{CRISPR} is against the naturally occurring t^{w2}: t_{CRISPR} fails to spread in a population that has t^{w2}, since fewer fertile females carry the engineered drive compared to the natural drive (Gierus et al. 2022). Reassuringly, t^{w2} have low frequencies in nature, potentially due to sperm competitive disadvantage (Manser et al. 2020). Consistent with this, a recent study failed to detect the *t*-haplotype in two Australian mainland cohorts (n = 40 each, Gierus et al. (2022)), although additional population sampling is required to obtain a more complete picture of *t*-haplotype frequency.

Mouse plagues in Australia cause significant economic and environmental costs and damage, and multiple factors influence their occurrence and severity (Kenney et al. 2003; Krebs et al. 2004). Given that current management strategies are primarily reactive to plagues' onset, comprehensive monitoring is critical to facilitate an early and effective response (Brown et al. 2022). The results presented here suggest a complementary strategy in which the release of t_{CRISPR} mice could serve as a pre-emptive tool against plagues, potentially reducing the need for extensive surveillance as well as the reactive use of rodenticides. Initiating the first release in an area that recently experienced an outbreak could provide the necessary time for the drive to spread. Depending on the frequencies of plagues in that particular region, reducing the overall effort with a no-release gap and restarting releases closer to the next expected plague would be an effective strategy. Our data indicate that genetic control with t_{CRISPR} could be an effective and sustained plague mitigation strategy (*sensu* Chambers et al. (1997)) that bypasses the requirement for onset prediction. While genetic biocontrol strategies like t_{CRISPR} offer significant potential for mitigating plague impacts, their deployment requires regulatory approval, which can only be granted after thorough safety protocols, risk assessments and social engagement have been considered.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statement

No ethical statement was reported.

Use of AI

No use of AI was reported.

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Author contributions

All authors designed the research. A.B. developed the computer code and produced the results. AB carried out the data analyses. A.B. wrote the initial draft of the manuscript with additional revisions by all authors. All authors provided comments and gave their final approval for publication.

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Data availability

C code is available at the Github platform (https://github.com/abirand/MousePlagues).

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Supplementary material 1

Supplementaryinformation

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Data type: pdf

Explanation note: **table S1.** The mean ($\bar{N}_{max}$) and the standard deviation (*SD*) of the maximum population sizes and the resulting density estimates per hectare ($\hat{d}$) observed during plagues with varying intensity ($P_{intensity}$) and duration ($P_{duration}$) when no control effort were deployed (based on 20 simulations for each combination). **table S2.** Total number of transgenic individuals released (N_T) under various release strategies sorted by N_T for easy comparison in fig. S5. **fig. S1.** The effect of immigration rates (c_{im}) on the maximum population sizes observed during high intensity plagues with various control release efforts that was initiated 3 years before the plagues' onset. **fig. S2.** The frequency of fertile t_{CRISPR} carrying individuals. **fig. S3.** The effect of total release effort (N_T) on the relative maximum population sizes. **fig. S4.** The effect of one-time release (n_i = 1) vs. multiple releases (n_i = 6, 12) on the relative maximum population sizes when the total number of individuals released were N_T = 1920 in all three release strategies. **fig. S5.** Comparison of releases where the total number of transgenic individuals released (N_T) were the same under various release strategies table S2. **fig. S6.** The relative influence of parameters on the maximum population sizes observed during high-intensity plagues using Boosted Regression Tree models fit to the sensitivity-analysis output. **fig. S7.** The mean and interquartile ranges for the frequency of fertile t_{CRISPR} carrying individuals at the time of plagues' onset in response to various *continuous* (1-5) and *pulsed* releases (6-10) for simulations presented in Fig. 4. **fig. S8.** The median and interquartile ranges for the frequency of fertile t_{CRISPR} carrying individuals at the time of plagues' onset for simulations presented in Fig. 5.

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