

## Fertility control of rodent pests

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**Abstract.** Ricefield rats (*Rattus argentiventer*) in south-east Asian rice fields and house mice (*Mus domesticus*) in Australian grain fields are major pest species. They cause damage before and after harvest and carry zoonotic diseases. For both species, management techniques have been pursued using the approach of immunocontraceptive vaccination. We review results from a series of enclosure and field studies conducted with these species to assess the effects of fertility control in small rodents. In the experiments, fertility control was simulated by tubal ligation, ovariectomy or progesterone treatment. A once-off sterilisation of 50–75% of enclosed founder females considerably reduced reproductive output of ricefield rat populations until the end of the reproductive period. In house mice, similar success was achieved when a sterility level of 67% of female founders and offspring was maintained. Repeated antifertility treatments are required because of the much longer breeding period of house mice versus ricefield rats. Comparing the results of enclosure trials with the outcome of simulation models suggests that partial compensation of treatment effects can occur through enhanced reproduction of the remaining fertile females and improved survival of juveniles. However, such compensatory effects as well as behavioural consequences of sterility in field populations are not likely to prevent the management effect at the population level. The challenge for effective fertility control of small rodents in the field is the wide-scale delivery of an antifertility treatment to founders at the beginning of the breeding season and to fertile immigrants that are recruited into the population, which otherwise contribute to the reproductive output at the population level. Future research efforts should focus on species-specific techniques and on agents that can be effectively delivered via bait.

### Introduction

Most small rodent species have high reproductive rates and overabundant populations of some of these species can cause considerable damage to crops and stored produce. Significant losses in agriculture to rodents occur in Africa (Leirs *et al.* 1996), America (Elias and Fall 1988), Asia (Singleton 2003), Australia (Singleton *et al.* 2005a) and Europe (Myllymäki 1977). Apart from crop damage, pest rodents can also inflict damage to appliances and infrastructure (Caughley *et al.* 1994). Some species transmit zoonoses (e.g. Hantavirus infection, Leptospirosis, Tularaemia) or carry vectors of disease such as ticks infected with *Borrelia burgdorferi* (Lyme disease) or fleas infected with *Yersinia pestis* (Plague) that put people, livestock and companion animals at risk (Begon 2003). Invasive rodent species can also cause problems when they damage native plants or when native animal species are less competitive than the intruders (Ohashi and Oldenburg 1992). However, most rodent species are non-pests; on the global scale less than 10% of rodent species inflict serious damage to crops (Singleton *et al.* 2007). Therefore, management strategies need to be carefully directed towards the target species and balanced for potentially adverse effects on non-target rodents and other non-target species.

Rodents can also be beneficial in the ecosystem. They are a vital food source for a wide range of predators and scavengers and they are instrumental in soil turnover and fertilisation.

They influence plant species composition and diversity, and their burrow systems provide habitat for other species such as birds, insectivores, reptiles and invertebrates (review in Dickman 1999). As a result, management actions should also be balanced between the need to protect human interests from the impact of pest rodents and their role in the ecosystem.

Ecologically based rodent management requires an understanding of the biology and ecology of the pest species and the associated development of a range of strategies for their benign management (Singleton *et al.* 1999). It considers ecosystem effects as well as agronomic, social, health, and cultural aspects. Fertility control could contribute significantly to benign rodent-management strategies.

There has been considerable progress in the last decade towards better understanding of ecological processes and technical realisation of fertility control in population management for large mammalian species (reviews in Kirkpatrick *et al.* 1997; Miller *et al.* 1998; Fagerstone *et al.* 2002; Kirkpatrick and Turner 2008). Zero growth of the population can be achieved rapidly in wild horses and other species by the application of contraceptive vaccines (Kirkpatrick and Turner 2008). However, enhanced body condition and improved survival of sterilised females in some long-lived species, including horses, can delay substantial population declines by several years (Kirkpatrick and Turner 2008). A GnRH vaccine is in the

process of being registered for population management of white-tailed deer (*Odocoileus virginianus*) in the USA (Fagerstone *et al.* 2008). Products also have been registered for fertility control in birds. For example, Nicarbazin-based products were tested and then registered for fertility management in Canada geese (*Branta canadensis*) and pigeons (*Columba livia*) in the USA (Fagerstone *et al.* 2008).

There is no product registered for fertility management in rodents and little is known about the consequences of antifertility treatments for rodents at the population level. Clearly, fertility management in rapidly reproducing rodents (*r*-strategists) requires a different approach than fertility control in large mammals, which have slow reproductive rates (*K*-strategists). So far, trials have been conducted with house mice (*Mus domesticus*) (Chambers *et al.* 1999b), ricefield rats (*Rattus argentiventer*) (Jacob *et al.* 2004a) and black-tailed prairie dogs (*Cynomys ludovicianus*) (Garrett and Franklin 1983; Nash *et al.* 2007) to gather information about the effects of fertility control at the population level. In addition, models have been developed to predict possible outcomes of fertility control for the population dynamics of some pest rodents: the multi-mammate rat (*Mastomys natalensis*), Brandt's voles (*Lasiopodomys brandti*) and wild house mice (Chambers *et al.* 1997; Stenseth *et al.* 2001; Shi *et al.* 2002; Davis *et al.* 2003; Arthur *et al.* 2005). McLeod *et al.* (2007) reviewed the ecological potential of a disseminating virally vectored fertility-control agent for the management of house mice and concluded that it could represent an effective strategy if the virus persisted or could be introduced in the early stages of outbreaks.

In this paper we present an overview of current rodent pest-management techniques and approaches in fertility control that may be relevant to rodents, and review case studies for house mice and ricefield rats. These studies indicate the potential of fertility control for the management of a non-eruptive and an eruptive rodent pest species.

### Current rodent pest management

Current management practices in agroecosystems are based on culling animals, mostly through the use of poisons and traps (Singleton *et al.* 2007). Other methods used include hunting and flooding of burrows (Singleton *et al.* 1999). None of these methods is species specific. Although live-trapping gives the opportunity to release non-target captures if traps are checked frequently enough to ensure their survival, this is not always done.

Rodenticides are highly toxic. Their use is often regarded as inhumane due to the considerable suffering that occurs before the poisoned animal dies (Oogjes 1997). Further, due to their lack of species specificity, rodenticides can pose a considerable threat to non-target animals (Hegdal and Colvin 1988), owing to primary or secondary poisoning. Non-target rodent species are especially vulnerable. A recent study showed that anticoagulant bait applied to manage Norway rats (*R. norvegicus*) around agricultural buildings was eaten by 20–57% of the individuals of non-target rodent species (Brakes and Smith 2005). In the mid 1990s, >30% of dead barn owls collected across Britain contained residues of anticoagulant rodenticides (Newton *et al.* 1997). However, in only a few of these birds was the rodenticide

concentration high enough to cause death. Adverse effects can also occur in top predators (Riley *et al.* 2007). The scale of non-target impacts in other species, particularly the importance of sublethal poisoning with rodenticides, is largely unknown. Rat meat is widely consumed in Asia and Africa (e.g. Khiem *et al.* 2003), so humans can also be at risk of consuming rodenticide. The use of chemical rodenticides is of particular concern in developing countries where there is generally poor implementation of best management practice for their use under field conditions, and because of the illicit sale of banned products (Singleton *et al.* 2003b).

Management-scale experiments in Asia (Singleton *et al.* 2005b; Brown *et al.* 2006) and Australia (Brown *et al.* 2004) have shown that an ecologically based rodent management approach not only achieves effective crop protection, but also results in reductions of 50% in the large-scale use of rodenticides (Singleton *et al.* 2003b). However, the use of rodenticides will remain necessary at key times and in key habitats in both urban (Colvin and Jackson 1999) and rural (Singleton *et al.* 1999) ecosystems. Nevertheless, rodenticides – as well as many forms of trapping – still cause unwanted impacts on animal welfare. In addition to their lack of species specificity, genetic resistance to some anticoagulant rodenticides has developed in commensal rodents (Pelz *et al.* 2005). Also, at the landscape scale, culling creates vacant habitats available to immigrants. These habitats can be rapidly repopulated so that repeated culling is required (Sullivan *et al.* 2001; Brown and Tuan 2005). These drawbacks are the reason that farmers worldwide would benefit from additional, and more appropriate, management techniques for rodents.

### Fertility control in management of pest rodents

Decreasing the reproductive rate instead of increasing mortality is potentially a more humane approach than animal culling and it could lead to a reduction in the use of rodenticides, which would be beneficial for non-target species.

Some rodent pests cause chronic infestations to crops and the effects are particularly severe in the tropics. Other species cause problems only during outbreaks, usually in temperate regions (Korpimäki *et al.* 2004). For the latter, it may be sufficient to dampen population peaks below an economic threshold level during outbreak years (Davis *et al.* 2003; Singleton *et al.* 2005a).

In contrast to *K*-strategists, potentially improved survival of sterilised individuals may not be critical for the management outcome because life spans of wild rodents are relatively short (usually <6 months). *R*-strategist species, such as most rodents, have high reproductive rates and, therefore, a higher proportion of individuals needs to be sterilised than for *K*-strategists. Computer simulations indicate that it is necessary to sterilise 50–80% of females to achieve population effects in eruptive house mouse populations (Chambers *et al.* 1997; Davis *et al.* 2003) and >50% in non-eruptive ricefield rats (Jacob *et al.* 2004a). However, this could be as low as 33% if fertility control can be effectively applied to each cohort during a breeding season and if the presence of sterile females does not affect the reproductive output of the fertile females in a population (Davis *et al.* 2003).

Generally, there are two options for fertility control in *r*-strategists for achieving an effect at the population scale: (1) virally delivered immunocontraception and

(2) bait-delivered compounds. These compounds can be immunoconceptive vaccines or chemical actives. Virally delivered immunocontraception is species specific if the viral vector is species specific (Chambers *et al.* 1999a; Hinds *et al.* 2003; Hardy *et al.* 2006; Hinds 2006; Redwood *et al.* 2007). The efficacy of other bait-delivered immunoconceptive methods can be restricted to certain taxa (e.g. mammals or birds) but are still likely to be non-specific.

For fertility control through immunocontraception, the rodent's immune system is primed to develop immune responses to antigens that block structures or signalling pathways required for reproduction. Much attention has been on vaccines against reproductive proteins such as the *zona pellucida* proteins surrounding the oocyte (Millar *et al.* 1989; Jackson *et al.* 1998).

Other components of the reproductive system can be targeted by immunoconceptive vaccines, for example, gonadotropin-releasing hormone (GnRH) (Griffin 1992), which is required for the stimulation of the production of reproductive hormones in both sexes. A GnRH vaccine effectively blocks fertility in male and female Norway rats (Miller *et al.* 1997) and has recently proved to be effective as a single-dose vaccine in swine (Killian *et al.* 2006; Fagerstone *et al.* 2008).

For the delivery of immunoconceptive vaccines for rodent management a self-disseminating agent such as a virus may have the advantage of self-regulation depending on the density of the target species (Arthur *et al.* 2005). However, despite a large number of studies on virally delivered immunocontraception in house mice (e.g. Singleton *et al.* 2002; Hinds *et al.* 2003; Hinds 2006; Redwood *et al.* 2007), so far no product has been developed for field testing. Indeed, this work has recently been put on hold even though genetically modified murine cytomegalovirus and ectromelia virus was demonstrated to be highly efficient in preventing reproduction in directly inoculated female house mice (Redwood *et al.* 2007; Tyndale-Biscoe and Hinds 2007). Transmission of the genetically modified mouse virus did not occur at a sufficient level to transfer infertility from mouse to mouse (Redwood *et al.* 2007) and prior infection with other virus strains may offer some degree of protection from the virus. In addition, there are safety and regulatory concerns about maintaining the species specificity of the viral vector and potential unexpected changes in the infectiousness of genetically modified viruses. Once released, a vector cannot be recalled and may spread to a region where the original target species is not regarded as a pest, particularly through infected mice infesting export cargo. Although strategies have been proposed to mitigate export risk (see Williams 2007), this risk elevates the issue to the international regulatory level. These constraints in combination indicate that it is unlikely that a virally vectored immunoconceptive will be used for the control of wild house mice or other species in the near future (McLeod *et al.* 2007; Redwood *et al.* 2007).

Oral delivery of an immunoconceptive vaccine may be a more promising option because distribution of bait and collection of remaining bait can be handled similarly to rodenticide baits. About 80% of house mice eat bait distributed in grain fields (Jacob *et al.* 2003). This is a higher percentage than the level of sterility predicted by models to considerably reduce population size. Similar to virally vectored immunocontraception, there is no product available yet but

orally delivered GnRH vaccines are being developed (Miller *et al.* 2006) and should be tested soon. One advantage of GnRH vaccines is that there are different GnRH types in birds and mammals; non-target effects on birds may therefore be less likely (Sad *et al.* 1993).

Chemical sterilants are available and can be delivered orally (Zhang *et al.* 2004; Wan *et al.* 2006). In the past, steroid hormones were explored for their properties in rodent pest management (Marsh and Howard 1970). In field trials with prairie dogs, synthetic estrogens prevented all females from breeding (Garrett and Franklin 1983). However, steroid hormones in minute amounts affect reproduction and development of reproductive structures in many animal species and can have severe adverse effects on non-target animals (Kidd *et al.* 2007). Residues of chemical sterilants can, therefore, pose a threat to a wide variety of non-target species. One example of a non-hormone anti-fertility agent is 20,25-diazacholesterol (DiazaCon), which inhibits the production of cholesterol and reproductive steroid hormones. The only published information on the use of DiazaCon for the management of rodents indicates effects on reproduction of black-tailed prairie dogs (Nash *et al.* 2007). To be effective, DiazaCon must be consumed on a daily basis for several days, but if high doses are consumed, there are unwanted side effects (muscle tremors and liver failure). Therefore, its use as an antifertility agent for the management of pest rodents may be limited because of ethical considerations.

Another potential chemical sterilant is the industrial chemical 4-vinylcyclohexene diepoxide (VCD), which has been shown to rapidly and permanently deplete the follicle population in the ovaries in mice and rats (Mayer *et al.* 2002, 2004) and other mammals (Appt *et al.* 2006). VCD is ovary-specific and only targets the elimination of the primordial and primary follicle populations. There is no evidence of a regenerating follicle pool, and, thus, without any primordial follicle pool, the ovary ultimately runs out of follicles and the individual is sterile. However, the challenge remains to deliver this agent in an orally effective formulation, and in a species-specific manner.

## Case studies

The ricefield rat (*Rattus argentiventer*) in south-east Asia and the house mouse (*Mus domesticus*) in Australia are major rodent pest species. They cause damage before and after harvest and carry zoonotic diseases (Singleton 2003; Singleton *et al.* 2003a). For both species, studies have been undertaken to experimentally simulate the use of immunocontraception for management purposes.

Ricefield rats are the most important preharvest pests in lowland flood-irrigated rice systems of Java, Indonesia, causing 17% annual losses in rice crops (Geddes 1992). They also cause substantial damage in Vietnamese rice fields (Brown *et al.* 2006) and other regions of south-east Asia (Singleton 2003). Ricefield rats may be prime targets for the use of fertility control because they have short breeding seasons of ~8 weeks per cropping season. Breeding is strongly dependent on the stage of the rice crop (1 week before maximum tillering through to ripening) (Leung *et al.* 1999) and female ricefield rats are territorial (Tristian *et al.* 2000). If the fertility of the females could be compromised for the first one or two litters of founder females in

each rice crop, a significant reduction in the recruitment of rats and the damage to the rice crop may be achieved.

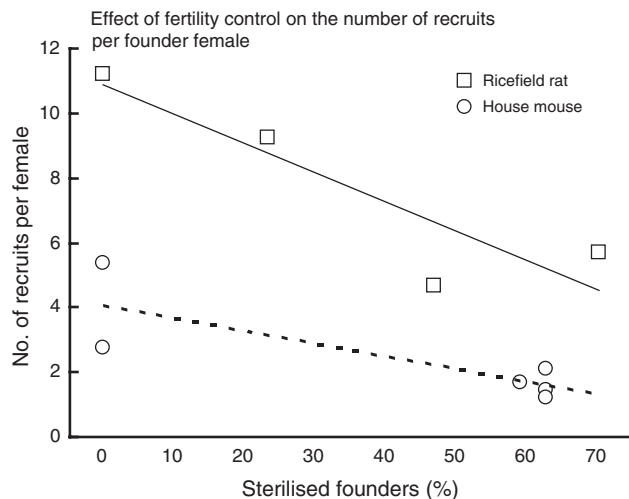
House mice are found worldwide and cause considerable preharvest damage to crops during outbreaks in the grain-growing regions of southern and eastern Australia (Singleton 1989). There, they have a reproductive period of several months with the potential to rapidly increase in abundance every 3–8 years, reaching population densities of several thousand individuals per hectare followed by a sudden collapse of populations to densities of less than 1 individual per hectare (Singleton *et al.* 2005a).

### Ricefield rats

An enclosure trial examined the effects of surgical sterilisation (tubal ligation) of 0, 25, 50 and 75% of females on the population dynamics and demography of ricefield rat populations (details in Jacob *et al.* 2004a). There was a strong correlation of the percentage of sterilised founder females and the number of individuals per founder female recruited to the enclosure population during the breeding season ( $R^2=0.80$ ). Sterilising at least 50% of female founders resulted in a decrease in the number of recruits per founder female by almost 50% (Fig. 1).

Partial compensation of the antifertility treatment occurred in the enclosures in which 75% of female founders ( $n=9/12$ ) were sterilised. There, reproductive output of the remaining fertile founders and survival of offspring was maximised. In addition, there was a tendency for F1-generation females to commence breeding at low bodyweight if the percentage of sterilised founder females was high. Survival rates of sterilised founder females and fertile founder females were similar. The same is the case in foxes (*Vulpes vulpes*) (Saunders *et al.* 2002) but not in European rabbits (*Oryctolagus cuniculus*), in which the survival of sterilised females is higher (Twiggs and Williams 1999; Williams *et al.* 2007).

The *per capita* feeding activity and resulting damage to rice plants grown in the enclosures was higher in populations without



**Fig. 1.** Effects of fertility control simulated through surgical sterilisation in small rodents. Numbers of recruits were derived from populations in seminatural enclosures after a period of ~12 weeks. Solid trendline, ricefield rats (data from Jacob *et al.* 2004a); dotted trendline, house mice (data from Chambers *et al.* 1999b; Singleton *et al.* 2002; L. A. Chambers, unpubl. data).

sterilised females than in populations with a large proportion of sterilised founder females (Jacob *et al.* 2004a). As damage occurred before the young of the first litter were weaned, much of the rice damage appeared to be correlated with feeding activity of females to meet the energetic demands of pregnancy and lactation. This highlights that not only abundance but also reproductive activity is related to crop damage.

In a field experiment, up to 76% of trappable females were sterilised by tubal ligation or progesterone injections to simulate fertility control in field populations (details in Jacob *et al.* 2006). Despite the promising results from the enclosure trial, there were no population effects of antifertility treatments on breeding performance, recruitment, feeding activity, crop damage or rice yield in the field. This was most likely due to the influx of fertile females during the breeding season.

Radio-tracking of fertile females and sterilised females (tubal ligation or progesterone injections) showed that their spatial behaviour changed (Jacob *et al.* 2004b). Progesterone-treated (hormonally incompetent) rats relocated their burrows ~3.5 times as often as fertile females or surgically sterilised females. This may indicate loss of social status and subsequent loss of territory. The consequences of that behaviour for the efficacy of fertility control are not entirely clear, but are assumed to be marginal because relocation of burrows did not cause the rats to leave the rice field system. These results are the first of their kind for rodents in cropping systems and indicate that further research is required. Of particular interest is the effect of scale on the efficacy of fertility control – over what area would control need to be conducted to minimise the impact of breeding females moving into areas where infertility has been imposed? The results also suggest that other management approaches would need to be applied in concert with fertility control.

### House mice

The results of two enclosure studies with house mice were reported previously (Chambers *et al.* 1999b; Singleton *et al.* 2002). In both studies, mice were sterilised by tubal ligation or ovariectomy to simulate fertility control. There was a considerable correlation between the percentage of sterilised founder females and the number of recruits per founder female ( $R^2=0.68$ ) (Fig. 1). The recruits per founder female decreased by up to 60% when 67% of females and their female offspring were sterilised. As a result, final population size decreased by 75% compared with untreated control populations.

Higher litter size leads to much higher numbers of recruits per founder female in ricefield rats than in house mice at 12 weeks into the breeding season. This might be different at outbreak conditions of house mice in the field when litter size reaches 8–9 pups (Singleton 1989). Interestingly, despite the high reproductive success of ricefield rats, a once-off antifertility treatment seems sufficient to considerably decrease reproductive output at the population level. In house mice, a similar reduction of reproductive output would require repeated treatment because the breeding season extends well beyond 8 weeks and, in contrast to ricefield rats, offspring generally breed during the breeding season of their birth.

In other *r*-selected species such as European rabbits, reproduction also is considerably reduced by sterilisation of a

portion of the population (Twigg and Williams 1999; Twigg *et al.* 2000). However, in rabbits, sterilisation improves survival, such that overall abundance, measured at the beginning of each breeding season, remains unchanged (Williams *et al.* 2007). In the mouse enclosure experiments, the effects of imposed sterility on survival could not be assessed because there was very high survival of animals in all enclosures during the study.

Modelling exercises suggest that a reduction of fertility in the founder generation can prevent outbreaks of house mice in the grain-growing region of south-eastern Australia (Davis *et al.* 2003; Arthur *et al.* 2005). As the breeding season of house mice in this region can last for up to 32 weeks (Singleton and Redhead 1990) it is necessary that not only the founders but also subsequent generations are sterilised. In such a scenario, constant infertility of 30% of females would be sufficient to prevent house mouse outbreaks (Davis *et al.* 2003).

## Conclusions

Fertility control has the potential to manage rodent pests that cause chronic problems, as well as those species that cause acute problems because of sporadic population eruptions. The effects of sterilisation on behaviour and compensation of fertility control at the population level did not prevent the desired management outcomes in the two rodent species studied. Rodent species with a relatively short breeding season of ~2 months, such as the ricefield rat, seem to require sterility levels of ~50–75% of the population for effective control. Sterilisation of founders with a once-off treatment may suffice if fertility control can be applied at a large scale. Species with extended breeding seasons such as house mice could be managed effectively with lower levels of sterility if founders and all subsequent cohorts were exposed to an antifertility treatment. In the case of ricefield rats, crop damage is related to rat abundance and the reproductive activity of females. Therefore, fertility control could be more effective in reducing crop damage than lethal methods.

Several sterilants are available but, so far, none that is available for field testing combines effective delivery of an environmentally friendly agent with species specificity. Recent developments indicate that bacterial ghost cells tailored to express species specific *zona pellucida* proteins that reduce reproductive output in females of a target species, but not in non-target species, can be delivered orally (Duckworth *et al.* 2008). Oral delivery of GnRH vaccines also may be available in the future (Miller *et al.* 2006). These results, and the requirements discussed earlier, suggest that future research needs to be directed towards approaches for species specific bait delivery of an immunocontraceptive agent to allow successful fertility control of rodent pest species at a landscape scale.

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