

The next generation of rodent eradications: Innovative technologies and tools to improve species specificity and increase their feasibility on islands

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Abstract

Rodents remain one of the most widespread and damaging invasive alien species on islands globally. The current toolbox for insular rodent eradications is reliant on the application of sufficient anticoagulant toxicant into every potential rodent territory across an island. Despite significant advances in the use of these toxicants over recent decades, numerous situations remain where eradication is challenging or not yet feasible. These include islands with significant human populations, unreceptive stakeholder communities, co-occurrence of livestock and domestic animals, or vulnerability of native species. Developments in diverse branches of science, particularly the medical, pharmaceutical, invertebrate pest control, social science, technology and defense fields offer potential insights into the next generation of tools to eradicate rodents from islands. Horizon scanning is a structured process whereby current problems are assessed against potential future solutions. We undertook such an exercise to identify the most promising technologies, techniques and approaches that might be applied to rodent eradications from islands. We highlight a *Rattus*-specific toxicant, RNA interference as species-specific toxicants, rodenticide research, crab deterrent in baits, prophylactic treatment for protection of non-target species, transgenic rodents, virus vectored immunocontraception, drones, self-resetting traps and toxicant applicators, detection probability models and improved stakeholder community engagement methods. We present a brief description of each method, and discuss its application to rodent eradication on islands, knowledge gaps, challenges, whether it is incremental or

transformative in nature and provide a potential timeline for availability. We outline how a combination of new tools may render previously intractable rodent eradication problems feasible.

Highlights

- Ten innovations, six transformative and four incremental were identified
- New methods that are highly species-specific are under development
- Increases are expected in rodent eradication feasibility, efficiency and humaneness
- Increases in the frequency and scale of rodent eradications are expected
- Reductions are expected in cost, non-target impacts and stakeholder resistance

Keywords

Rattus, *Mus musculus*, control methods, pest eradication, island restoration

1. Introduction

Invasive mammal eradications are powerful conservation tools to protect biodiversity and prevent extinctions on islands (Aguirre-Muñoz et al. 2008; Bellingham et al. 2010; Campbell et al. 2011). The opportunity to scale up existing eradication techniques is being realized, with larger and more challenging projects being undertaken (Phillips 2010; Sutherland et al. 2014). Yet despite these advances it is clear there are limits to what can be achieved and there is an urgent need to overcome these barriers. For example, approximately 50% of IUCN critically endangered and endangered insular tetrapods occur on islands with invasive rodents and human populations greater than 10,000 people, highlighting the challenge and need for innovative tools that abate the threat of invasive species (TIB Partners 2012).

Three *Rattus* species (*R. rattus*, *R. norvegicus*, *R. exulans*) and house mice (*Mus musculus*) are the most common rodents introduced to islands worldwide (Atkinson 1985). They cause population declines and extinctions of insular flora and fauna and interrupt ecosystem processes with negative cascading effects (Fukami et al. 2006; Jones et al. 2008; Kurle et al. 2008; Steadman 2006; Towns et al. 2006). Invasive rodents negatively impact stored foods, crops, and infrastructure and can carry zoonotic diseases that can impact the health of people and their livestock (Banks and Hughes 2012; Meerburg et al. 2009; Stenseth et al. 2003). To recover endangered species and restore ecosystem processes, invasive rodents on islands are increasingly targeted for eradication, with at least 474 successful rodent eradications to-date (DIISE 2014). Other larger, more complex and expensive campaigns, some of which are on inhabited islands, are underway or being planned (Sutherland et al. 2014).

Today, rodent eradications on any island larger than 5 ha rely exclusively on the use of anticoagulant toxicants (DIISE 2014). Toxicants are incorporated into cereal or wax baits applied to every rodent territory via bait stations, or broadcast by hand or from a modified agricultural spreader bucket suspended below a helicopter. Of the anticoagulants, brodifacoum is the most commonly used and has had the highest success rate (Howald et al. 2007; Parkes et al. 2011). Desirable characteristics of brodifacoum include: its high oral toxicity to rodents, likely lethal effects from a single feed, can be combined with bait that is highly palatable to rodents, delayed symptoms of toxicosis, low water solubility (Broome et al. 2013; Empson and Miskelly 1999), is relatively economic to manufacture and incorporate into a bait matrix, and it is currently registered for use in many countries. Disadvantages include brodifacoum's broad-spectrum toxicity to vertebrates, moderate duration of persistence, ability to biomagnify (i.e. process whereby the tissue concentrations of a contaminant increase as it passes up the food chain), mode of death and negative public perception (Broome et al. 2013; Eason et al. 2002; Fitzgerald 2009). In the planning phases of campaigns, impacts to non-target wildlife are predicted using risk assessments, and actions to avoid, minimize or mitigate risk (e.g. operational timing or captive holding) can then be taken to safeguard at-risk populations where required (e.g. Howald et al. 2009). Eradication projects have costs spread over time, leading to an implementation phase that involves a high percentage of total project costs, often over only a few weeks.

Rodent eradication on islands is currently limited by a lack of species-specific methods, animal welfare issues, high fixed costs, and socio-political opposition. Eradication projects may invoke controversy if they are perceived to be unlikely to succeed, costly, inhumane, or cause substantial collateral damage (Cowan and Warburton 2011; Simberloff 2002). In addition, implementing rodent eradications on inhabited islands with pets, livestock and non-target wildlife (all of which require management actions to eliminate or reduce risks from toxicants), have the potential to be highly controversial and will require innovative social approaches (Glen et al. 2013; Oppel et al. 2011) to secure sufficient consensus.

The current reliance on a single pesticide for any large project may be perceived as inflexibility to consider other approaches.

Horizon scanning is the systematic search for nascent trends, opportunities and risks that may affect the probability of achieving management goals and objectives, and is being applied in medical, defense and conservation fields (Sutherland et al. 2012; Sutherland et al. 2010). For the vertebrate pest eradication industry, this exercise can aid prioritization of research, strategic planning and policy development with an overall goal of identifying the next generation of tools to eradicate rodents from islands. We undertook a horizon scanning exercise across relevant medical, pharmaceutical, invertebrate pest control, social science, technology and defense fields and highlight here some of the most promising emerging or potential future technologies and tools for advancing rodent eradications on islands. Potential innovations include increasing the species specificity of rodent eradication methods, improving animal welfare, reducing cost of applying bait, detecting low-density rodent populations, protecting non-target species from existing rodent eradication methods, and increasing the socio-political acceptance of restoration projects. We classify innovations as incremental or transformative, identify next steps and challenges, and the projected timeframe of commercial availability.

2. Horizon scanning and identification of innovative approaches

Island Conservation staff (KC, JB, NH, GH, AW) searched for opportunities for innovation in eradicating invasive rodent populations on islands. We requested innovation ideas from other Island Conservation staff, interviewed eradication practitioners and researchers in a wide range of fields, conducted literature searches and used a variety of creative-thinking techniques (Michalko 2006). Potential innovations were listed, reviewed and those most promising were selected by a four-person panel (KC, JB, NH, GH). We classified innovation ideas as incremental or transformative. Incremental innovations provide supplemental improvements to existing tools to tackle rodent eradications with greater efficacy on islands where eradication is currently deemed possible, while transformative innovations provide tools that will allow the eradication industry to undertake rodent eradication projects on islands currently considered unfeasible. Ideas selected in the first process were investigated, articulated in more detail in a concept paper then subjected to another round of review and scoring against specific criteria including the ability to increase the feasibility of eradications, likelihood of success, potential payoff, and the relative investment required. The first and second processes were conducted twice between March 2010 and October 2012, and the resulting projects identified several incremental innovations (e.g. vitamin K1 implants), but few transformative innovations.

Between June-December 2011, in an attempt to identify additional transformative innovations, we identified the current barriers to eradications, listed the characteristics of methods that could overcome those barriers and reinitiated a search of the literature. We identified many of the ideas presented in this paper, identified specialists in those fields and held workshops (e.g. daughterless mice) or attended training sessions (e.g. conflict transformation) to develop the ideas further and evaluate their potential. These forums were rich in the exchange of ideas and discussion, often leading to the identification of additional innovation ideas. For example, ribonucleic acid interference (RNAi) had not been identified during our process, but was identified during discussions at a workshop. We had prior knowledge of other projects through exchanges with peers (e.g. norbormide, self-resetting traps and toxicant delivery devices).

3. Technologies and tools

Ten innovative technologies, techniques and approaches were identified that in the future might be applied to rodent eradications from islands (Table 1.). The following order of technologies, techniques and approaches presented does not reflect any ranking, but related issues are placed together.

Table 1. Innovative technologies, techniques and approaches that might be applied to rodent eradications on islands.

Innovation	Incremental or transformative	Potential timeframe for availability
Norbormide as a <i>Rattus</i> -specific toxicant	Transformative	<5 years
RNA interference as species-specific toxicants	Transformative	5-10 years
Crab deterrent in baits	Incremental	Unknown
Prophylactic treatment for protection of non-target species	Incremental	1-3 years
Transgenic rodents	Transformative	>2 years to field testing
Virus vectored immunocontraception	Transformative	Unknown
Drones	Incremental	<5 years
Species-specific self-resetting traps and toxicant applicators	Transformative	Traps available. Toxicant applicators 2-4 years
Detection probability models	Incremental	Available
Social processes	Transformative	Available

3.1 Rodenticides

The most prolific rodenticide development occurred between the 1940s and the 1980s. First generation anticoagulant rodenticides and zinc phosphide were developed in the 1940s, 50s and 60s. Then came cholecalciferol, bromethalin and second generation anticoagulant rodenticides in the 1970's and 80's, partly to overcome resistance to the less potent anticoagulants (Buckle and Smith 1994). Subsequently, despite the effectiveness of the second generation anticoagulants, it has been considered important to have two classes of rodenticides; anticoagulants and alternatives to anticoagulants. The need for non-anticoagulant toxicants that are effective but less persistent than second-generation anticoagulants, and therefore likely to be less hazardous to non-target bird species and other non-target species, has been highlighted over the last 15 years. Ironically, registration requirements in USA, Europe and around the world have reduced the number of options available for rodent management. We believe it is important to retain and refine the use of rodent control tools for conservation given that not using these tools could lead to the potential extinction of species and extirpation of populations. Ideally, alternatives to existing anticoagulants would combine limited persistence and humaneness; however this is a significant challenge (Eason et al. 2010a), however for the time being anticoagulants remain the most effective tool for insular rodent eradications.

A highly-specific rodenticide that is non-toxic to other species at rates that they could potentially encounter would dramatically increase the rate at which rodent eradication projects occur. Disadvantages of broad-spectrum anticoagulants such as risks to people, wildlife, pets and livestock would be overcome, increasing the feasibility for rodent eradications on islands and potentially reducing costs. Potential rodent eradications currently complicated by non-target species would become increasingly feasible. Lowered risks to non-target species would facilitate non-specialists implementing rodent eradications, allowing projects to be implemented more frequently, faster and cheaper than is currently possible. More than US\$600 million was spent on rodenticides in 2012 globally (Kline 2014)

and by 2019 this is expected to increase to US\$900 million (MarketsandMarkets 2014), providing considerable market-driven economic incentives for improved rodenticide products. A number of different approaches have been taken by researchers working on rodenticides including research, retrieval and retention of older alternatives as well as developing novel rodenticides. This has included improving the performance of older non-anticoagulant rodenticides, such as sodium fluoroacetate (1080) and zinc phosphide. Secondly, optimizing the performance of first generation anticoagulants. Thirdly, identifying alternatives to anticoagulant rodenticides with the same mode of action as para-aminopropiophenone (PAPP), which was registered in New Zealand for the control for stoats and feral cats in April 2011 (Eason et al. 2014). Similarly, sodium nitrite was registered in New Zealand for control of brushtail possum (*Trichosurus vulpecula*) and feral pigs (*Sus scrofa*). PAPP and sodium nitrite have both been referred to as red blood cell toxicants, however neither is sufficiently toxic to rodents. As such, recent research has focused on identification of methemoglobinemia inducing agents that are more potent in rodents (Conole et al. 2014; Rennison et al. 2013a). Older compounds that were evaluated as rodenticides but had their development terminated when anticoagulants became available are worth reconsidering as well as first generation anticoagulants with an ultra-low dose of cholecalciferol as a synergist.

3.1.1 Norbormide as a *Rattus*-specific toxicant

Norbormide is highly toxic to members of the genus *Rattus* compared to other mammals or birds (Roszkowski et al. 1965). Rats are 150-fold and 40-fold more sensitive to norbormide than mice and guinea pigs (*Cavia porcellus*) respectively, while most other mammals and birds tested are >100-fold less sensitive (Roszkowski et al. 1965). When consumed by rats, norbormide acts as a vasoconstrictor and calcium channel blocker, but is selectively toxic to rats by opening the permeability transition pores in rat mitochondria (Zulian et al. 2011). Norbormide was introduced as a rodenticide in the 1960s but was soon withdrawn due to low acceptance by rats. It is an acute toxicant with mortality achieved minutes after a rat consumes a lethal dose (Rennison et al. 2013b). A sublethal dose can deter rats from future consumption of the associated product (i.e. produce bait shyness) (Nadian and Lindblom 2002).

Prodrug forms of norbormide have been developed that aim to delay the action of the toxicant and increase palatability by masking the taste (Rennison et al. 2012; Rennison et al. 2013b). One prodrug formulation has been shown to delay symptoms up to three hours, compared to <5 minutes for norbormide alone (Rennison et al. 2013b). It is presently uncertain whether this is sufficient delay for the toxicant to be effective in the field nor whether other desirable characteristics are affected; anticoagulant toxicants are so effective on rodents in part because they typically take days before toxic effects occur (Fisher 2005). Choice trials with the most promising norbormide prodrug have shown high bait acceptability and 83% mortality (n=12) (Rennison et al. 2013b). For eradication projects, high bait acceptance leading to 100% mortality of the target population is a prerequisite. There a number of research teams around the world looking at different ways of improving the effectiveness of norbormide and producing it in forms which are more palatable (pers. comm. Duncan MacMorran, Connovation Ltd.).

Although norbormide has been tested on a relatively wide range of mammal and some bird species (Roszkowski et al. 1965), the toxicity to reptiles, amphibians, snails and other invertebrates remain to be assessed. Challenges ahead involve sufficiently delaying action of the toxicant in rats, effectively delaying the symptoms of poisoning until a lethal dose has been ingested, maintaining high toxicity, and incorporating the norbormide formulation into a bait matrix to produce a product that would be attractive to all rats in the wild to deliver a lethal dose while being relatively economic. A mix of chemistry refinement, animal trials in the laboratory and ultimately extensive field trials will be required. Due to the number of problems that modification of this toxicant would potentially overcome

(allows use near people, pets and vulnerable species) it must be regarded as a transformative innovation. At the current rate of development it is expected to be registered and available for field use within the next five years.

3.1.2 RNA interference as species-specific toxicants

Ribonucleic acid (RNA) interference (RNAi) is a naturally occurring intracellular mechanism, which causes sequence-specific posttranscriptional gene silencing. The reaction is triggered by the introduction of double-stranded RNA (dsRNA) into the cell cytoplasm and results in the specific, targeted destruction of messenger RNA. Genes can be targeted that are critical to life, effectively making this a species-specific toxicant (Huvenne and Smagghe 2010; Xue et al. 2012).

RNAi is the focus of a significant body of research for invertebrate pest control, and in animal models as a potential cure for cancer and other diseases. In mice and rats, RNAi selectively inhibits target gene expression with high specificity and efficacy, and is relatively easy to induce through injections (Caplen et al. 2001; Xue et al. 2012). Advances in RNAi technology including short (20-40 nt long) gene sequences (Xue et al. 2012), make the technology increasingly feasible for relatively small labs. For invertebrate agricultural pests, synthetic dsRNA that is species-specific has been developed that can be absorbed through the gut to cause lethal effects to the target species (Huvenne and Smagghe 2010; Xue et al. 2012). dsRNA sequence formulations have also been developed that are lethal to mice (Martin et al. 2011). The prescriptive nature of RNAi creates the opportunity for selecting a mode of death that meets or exceeds euthanasia criteria (e.g. Leary et al. 2013). Existing genome maps for mice and rats, and the use of these species as the primary animal models in genetic and medical research will facilitate identification of species-specific RNA that controls various life functions.

Until recently, delivery of dsRNA to target cells in live mice was accomplished only by injection or via a modified virus. Naked small interfering RNA (siRNA) is a type of dsRNA that is completely degraded upon contact with physiological fluids, indicating that a carrier is required to deliver orally ingested siRNA to their target. Recent work in live mice uses multifunctional nanoparticle-based encapsulation to facilitate siRNA transfer across the gut, into the blood stream and across cell membranes for effective delivery of orally provided doses containing siRNA into the target cells (He et al. 2013). Trials of orally delivered siRNA have been conducted where activation occurred at the proper time and location to overcome the extracellular and intracellular barriers (He et al. 2013).

Progress on development of this technology is likely to be rapid given the application to human disease and agricultural insect pests. However, its application in a field, as opposed to a clinical, setting might be controversial if it became rhetorically linked with genetic engineering and nanotechnology. Whether this controversy would be more than the current movement against today's chemical rodenticides is uncertain (Fitzgerald 2009). Many techniques and products in the RNAi and nanotechnology field are protected by patents, which will need to be addressed for developing RNAi rodenticides and bait products. The unique modes of action of dsRNA active ingredients, and the paucity of reliable data regarding the persistence and environmental fate of exogenously applied dsRNA present new challenges for ecological risk assessments of non-target taxa (USEPA 2013). Once available, effective RNAi rodenticides will be highly transformative, allowing hitherto unimagined applications and approaches. These rodenticides could be available within 5-10 years based on the potential market-driven demand for improved rodenticides, opportunities to leverage pharmaceutical developments, and expectations that registrations of RNAi based insecticides will provide regulatory precedents in the next few years.

This prediction is contingent upon carefully planned laboratory and field trials that demonstrate high efficacy and acceptable risk in support of product registration requirements.

3.2 Crab deterrent in baits

Land crabs, primarily Coenibitids and Gecarcinids, are the primary consumers on many tropical islands that lack native mammals (Burggren and McMahon 1988; Green et al. 2008). Their presence can limit the effectiveness of managing invasive rodents on tropical islands (Holmes et al. this issue) by consumption of rodenticide bait or interference with bait stations and mechanical control and detection devices (Griffiths et al. 2011; Russell et al. this issue; Wegmann 2008). Though land crabs are not susceptible to commonly employed anticoagulant rodenticides (Pain et al. 2000), such compounds can persist in crab tissue for at least 56 days (Primus et al. 2006) and present a secondary exposure pathway for other animals including humans (Wegmann 2008). Land crabs were a significant hindrance during recent unsuccessful attempts to eradicate invasive rats from tropical islands (Griffiths et al. this issue). One successful strategy for mitigating land crab consumption of rodenticide bait has been to saturate crabs by using higher baiting rates, allowing rats to access bait for the desired period of time (Pott et al. this issue). This strategy was successfully employed at Palmyra Atoll, but required greater than an order of magnitude more bait than is typically used in temperate rat eradications (Wegmann et al. 2012). High baiting rates, as used on Palmyra have the potential to increase negative impacts on non-target species (Pitt et al. this issue), and substantially increased the cost of operations and incurred an appropriately higher level of regulatory scrutiny (Wegmann et al. 2012).

A chemical deterrent that inhibits bait consumption by land crabs but does not inhibit rodent interactions would eliminate significant operational, logistical, ecological and financial risk from tropical rodent management programs. Yet little research has gone into developing a chemical deterrent for land crabs. Land crabs possess highly efficient olfactory systems (Burggren and McMahon 1988; Wellins et al. 1989) that aid in food detection (Wellins et al. 1989), acceptance (Thacker 1996), and avoidance (Thacker 1998). Because volatile odors are an important factor in land crab foraging behavior, it is probable that an existing, previously identified chemical deterrent could be utilized to reduce or eliminate land crab interference with bait products and devices used in rodent control projects. Chemical deterrents for crustacean predators have been identified in molluscs (Kamio et al. 2010) and algae (Cruz-Rivera and Paul 2007; Pereira et al. 2000). A number of volatile, food-grade compounds are used as lures or 'taste masks' in pesticide bait formulations and, at specified concentrations, do not appear to affect the palatability of the bait to target species. Examples of such 'essence' compounds that could be tested as potential crab deterrents are: cinnamon, anise, nutmeg, spearmint, clove, pennyroyal, orange, and lemon.

Crab deterrents would be an incremental advance. To our knowledge no group is currently engaged in research to advance this topic, hence we cannot estimate a time-frame for when solutions may be developed.

3.3 Prophylactic treatment for protection of non-target species

There are few intervention methods to minimize risks to non-target species during rodent eradication campaigns. Mitigation involving capture and translocation or captive holding has been used for a suite of species (e.g. Howald et al. 2009; Merton et al. 2002), but is costly and can be stressful for wild animals. Hazing may be less costly but is not appropriate in all cases (e.g. island endemic species). Current mitigation efforts are focused on avoiding all exposure to brodifacoum, either primary (direct ingestion) or secondary (predation of ill or scavenging of dead rodents). Elimination of non-target impacts can also be effected through increasing tolerance or providing an antidote such as vitamin K1 in the case of

anticoagulant rodenticides. Vitamin K1 is an effective antidote for anticoagulant rodenticides although treatment requires daily dosing for a prolonged period of time (James et al. 1998; Murray and Tseng 2008).

Delivery of almost any pharmacological agent to wild vertebrates in controlled quantities has been problematic. Injectable controlled drug delivery methods are being used increasingly in humans and animals to minimize the need for repeated injections while delivering long-term therapeutic effects (Medlicott et al. 2004). Sustained release systems such as biodegradable polymer-solvent subcutaneous implants and osmotic pumps have been used for drug delivery over extended periods of time, particularly for the delivery of contraceptives in zoos (Kreeger 1993). Biodegradable polymers can be dissolved into biocompatible solvents to form solutions that can be easily injected into the body. When bioactive agents are added to the polymer/solvent solutions and injected into the body, the biocompatible solvent diffuses into body fluid leaving an implant with the encapsulated drug (Catbagan et al. 2011; Foley et al. 2011). The drug is then released over time by diffusion from the polymer matrix and by biodegradation of the polymer. Such systems have produced sustained release of drugs for a few days to more than one year duration (Chasin and Langer 1990). Preliminary work has demonstrated successful incorporation of vitamin K1 into a biodegradable polymer system and evaluated its pharmacokinetics in two species of birds. Initial studies demonstrated an apparent half-life of 7-14 days for sustained release of vitamin K1 compared to an apparent half-life of 11 hours for oral vitamin K1 (J. Ponder, unpublished data).

Development of a vitamin K1 implant with controlled release technology has the potential benefit of providing targeted protection for key individuals or species, such as birds of prey. Although labor-intensive to trap and treat individuals, the effort would be much less intensive and stressful than captive holding or translocation. Most of the cost associated with this intervention would be the labor to trap and treat the animals. Disease or other risks associated with translocation would be avoided. Whether used as a primary mitigation tool or as an adjunct to other strategies, a controlled-release vitamin K1 system has the potential to provide a wider safety margin than other mitigation tools predicated upon zero exposure models.

Challenges of this technology include potential species variation in pharmacokinetics and drug delivery times. Drug absorption rates, dosages and tissue reactivity to implants can all vary greatly between species. This is further complicated by knowledge deficits about the physiology of island endemic species. In the initial avian trials, significant tissue reactivity occurred at injection sites, a side effect eliminated with subsequent formulations (J. Ponder, unpublished data). An additional consideration is the persistence of brodifacoum and other second-generation anticoagulation rodenticides in tissues, which requires that a long duration of therapeutic effectiveness be achieved. This may be complicated by limits on the amount of material that can be injected, species variability and effective implant pay-out duration. Development of these delivery mechanisms is underway and could be available in the near-term (1-3 years). They would be an incremental, but very efficacious advance.

3.4 Transgenic rodents

The 2014 conservation horizon scan identified genetic engineering as a technology for the control of invasive species (Sutherland et al. 2014). While invasive rats represent the most significant threat to island biodiversity, the house mouse represents an initially more promising system for pursuing genetic approaches as it is among the best studied species in terms of genetics, reproductive biology and sex determination, behavior, and tractability for genetic manipulation (Guénet and Bonhomme 2003). Successful approaches developed in mice could likely be extended to rats (Jacob and Kwitek 2002).

Genetic approaches can be designed to be species-specific and either self-limiting or self-replicating. Techniques such as gender distortion and Trojan females exist, and interest is increasing in their application for vertebrate pest control (Bax and Thresher 2009; Gemmell et al. 2013). Perhaps the most promising of the suite of potential genetic approaches is the 'daughterless' approach that has been successfully engineered for insect pest eradication and successfully tested in the laboratory, but not yet in the field. Genetically-modified males could carry transgenes that do not produce daughters (sex lethal) or induce XX individuals (normally female) to develop instead as sterile males (sex reversal resulting in daughterless mice), while XY individuals would develop as normal, fertile males capable of spreading the transgene. With a substantial reduction in the number of females, mouse populations should die out. Daughterless lab mice were documented over three decades ago (McLaren and Burgoyne 1983), but the potential application of this trait for population control was not realized until more recently. On its own, the daughterless mouse approach would require repeated releases of large numbers of male mice and might not be scalable. However, mouse eradications are considered more challenging than rat eradications (MacKay et al. 2007), and mouse populations on small islands could serve as a proof-of-concept. In order to scale-up, gene drive systems could be used to potentiate the effectiveness of the daughterless approach.

Gene drive systems work in several ways such as preferential inheritance of one allele or chromosome over the other from a parent that is called meiotic drive, and selfish genes that can be copied from one allele to the other. Gene drive systems can significantly increase the spread of specific genetic elements (Esvelt et al. 2014; Safronova and Chubykin 2013), like those designed for elimination of female offspring. For example, in mice a naturally occurring gene drive called the t-haplotype results in sperm from heterozygous carriers that effectively "disables" their non-t-haplotype meiotic partners and thus gains a relative advantage at fertilization over wild-type mice (Silver 1993). Engineered, artificial gene drive systems are also feasible in rodents. Recent advances in molecular biology offer the potential for much more simplified methods of building appropriate strains of transgenic mice using homing endonucleases or clustered regularly interspaced short palindromic repeats (CRISPRs) (Pennisi 2013). By coupling gene drive with a daughterless trait (Esvelt et al. 2014), the number of mice that would need to be released could be less than 5% of the male mouse population on the island immediately after the least favorable season for the species. Appropriate safeguards, such as simultaneously developing reversal and immunization drives, should occur in conjunction with the development of gene drive systems (Esvelt et al. 2014). Reversal drives could reverse genome alterations that have already spread through a population, and immunization drives could be used to block the spread of other gene drives (Esvelt et al. 2014).

The potential benefits of a genetic approach include: species specificity, utility in areas with human habitation, it allows a flexible financial model as investments could be over several years with variable investment per year, involvement of locals in the breeding and release of animals carrying engineered genomes, suppression of engineered genetic elements during breeding to allow rapid expansion, lack of toxicants, and the method is considered humane as no animals are killed. It could also potentially be used on areas of larger islands where conservation targets exist and, because daughterless mice are self-replicating, could potentially hold a low-cost buffer around areas of conservation or other value. Transgenic mice can be specifically designed for the situation and desired characteristics can be selected or engineered. The potential barriers are: socio-political controversies by both regulators and the public regarding whether genetically modified organisms should be released (Fitzgerald 2009), initial development costs, unpredictable success of released mice both ecologically and in successfully breeding, likely need for multiple releases of mice, and costs of breeding mice. Additionally, depending

on genetic and species differences in target populations, the same transgenic mouse system may not be usable in all situations. Trials of this approach that are untested in mammals could be conducted in locations with a model regulatory system for transgenic organisms that has a need for the end-product, such as Australia.

Technologies to engineer mice, and more recently rats, are well established and have been used for several decades for biomedical applications. Although genetic approaches for eradicating or reducing the impact of invasive rodents are still in their infancy, the timeline from conception to testing could be as short as a few years based upon the speed achieved in genetically engineering biomedical models. This technology represents a potentially transformative advance providing species specificity not readily achievable with any other technology.

3.5 Virus vectored immunocontraception

When selected appropriately, viruses can be highly species-specific (e.g. Smith et al. 2005). They have been used to control vertebrate pests, with the most well-known examples being myxomatosis and rabbit hemorrhagic disease to control rabbits (*Oryctolagus cuniculus*) in Australia and New Zealand (Saunders et al. 2010). Viruses have also been used, in conjunction with other techniques, in eradication projects on islands – most commonly with rabbits (e.g. Macquarie Island), but also on cats (*Felis silvestris catus*) using feline-specific viruses in South Africa, New Zealand and USA (Campbell et al. 2011). In these cases viruses were used to kill target species or to reduce their reproductive potential.

Immunocontraception is a process by which the immune system of an individual is made to attack its own reproductive cells and hence lead to sterility (Hardy et al. 2006). This is achieved by immunizing individuals with a gamete protein that triggers an immune response; the resulting antibodies bind to these proteins and block fertilization. Immunization occurs by injection, bait or living vectors. Virus-vectored immunocontraception (VVIC) utilizes a species-specific virus to disseminate the vaccine through a pest population by placing the gene encoding the reproductive protein into the genome of the virus (Arthur et al. 2009).

There are many advantages of immunocontraception for biological control. It is considered humane by the public and wildlife welfare organizations (Fitzgerald 2009), is likely environmentally benign, and it could potentially be cheaper than traditional control methods because it is to an extent self-disseminating. Therefore, VVIC could be used to treat large inaccessible areas at a minimal cost. This technology could conceivably be used at very large scales; archipelago, country and continent, or isolated single islands. Risk assessments are also required that will address the associated risks.

Disadvantages of VVIC include irreversibility, development of host resistance, need for engineering of a genetically modified vector, difficulty of controlling vectors once released, and the risks of irreversible genetic alterations of the population/species through selection (Henderson and Murphy 2008). Additionally, there is always the possibility of either unanticipated or acquired zoonotic transmission of infectious agents.

Attempts were made to develop VVIC in Australia for mice between 1992-2005 (Redwood et al. 2008). Driving this research was the concept that the genes for proteins that are critically involved in fertilization or implantation can be inserted into a virus that infects the target species, resulting in sterilization without affecting sexual activity or social status. In addition to the envisaged benefit-cost advantages of VVIC, interest in its development as a pest management tool focused on potential gains in humaneness and species specificity. The substantial research investment in VVIC produced encouraging

results (Redwood et al. 2008). However, these results have not yet been translated into a successful release of mice due to rapid attenuation in virus vectors and hence lack of dissemination in the house mouse (Redwood et al. 2008). Acceptance of VVIC by the public at large, as well as by national and international regulators, has been considered to be a difficult, if not prohibitive, barrier to successful release (Henderson and Murphy 2008). More recently researchers have been making advances on the technical barriers previously identified for house mouse VVIC (Arthur et al. 2009; Nikolovski et al. 2009).

An important precedent for VVIC is the oral rabies vaccine, which is based on a recombinant (genetically modified) vaccinia virus that is not self-disseminating and which has been used successfully for the last 25 years as a disease-eliminating vaccine in mesocarnivores in Europe and North America (Brochier et al. 1996). However technical development of mouse VVIC is no longer being financed by the Australian Invasive Animals Cooperative Research Centre (Saunders et al. 2010). This is clearly a transformative technology but will require significant investment and parallel socio-political programs to implement (Saunders et al. 2010).

3.6 Drones

The use of drones or unmanned aerial vehicles (UAVs) for military and civilian uses has grown rapidly in the last decade and continues to grow, reducing costs while increasing the diversity of products and applications (Fahlstrom and Gleason 2012). Relatively small UAVs fitted with high definition cameras are being used for wildlife census applications, although this is in its infancy it is an area receiving a great deal of attention from academics and wildlife managers (Anderson and Gaston 2013). UAVs can have programmed flight paths and navigate by GPS and/or be controlled by personnel at a remote base. They can be boat or land based, launched even if space is limited, and can fly day and night (Fahlstrom and Gleason 2012). UAVs have been used for crop spraying, seeding and other agricultural applications in Japan for >20 years and today UAVs spray 40 percent of that country's rice crop and a suite of other crops (Szondy 2013). The primary benefit of UAVs is to reduce the cost of operations traditionally done by ground crews or piloted aircraft. They come in a range of sizes, with smaller models being easily boxed and transported. However, securing permissions to operate UAVs can be challenging, and using them to deploy pesticides is currently not permitted in some countries such as the USA (Szondy 2013). Many UAV's of the size and type likely considered for use by eradication practitioners are limited to use in low wind conditions, particularly for take-off and landing.

Major applications for drones related to the eradication of rodents include animal detection via high definition infra-red cameras with pre-programmed night flights, the delivery of baits, securing timely high resolution imagery of the area of interest and facilitating the monitoring of population responses of conservation targets. Software programs have simplified the pre-programming of flight paths, take-off and landing, allowing operation by personnel with basic experience. Additional open-source software for managing, presenting and analyzing the massive amounts of high resolution imagery that can be collected by drones are now readily available to the public (e.g. <http://ecosynth.org/>).

UAVs are an incremental innovation and within the next five years we expect them to be adopted for aspects of planning and implementing rodent eradication projects. Within a decade we expect UAVs to be an integral part of many rodent eradications.

3.7 Self-resetting traps and toxicant applicators

Exclusion areas for certain primary methods (e.g. aerial baiting) are required on some rodent eradication projects to manage risks such as inhabited areas, corralled livestock or non-target wildlife. In these

exclusion areas alternative methods (e.g. bait stations or traps) are required to ensure all rodents are put at risk. Self-resetting traps and resetting target-specific applicators could be useful for exclusion areas to protect non-target species and reduce maintenance needs of traditional approaches. They may also be useful in targeting small islands where the regulatory, socio-political, risk to non-target species or other constraints mean that bait stations or broadcast techniques are inappropriate. There may also be application in managing rodents at potential reinvasion points.

A prototype self-resetting device that delivered a palatable liquid bait to small mammalian pests was designed in the 1990s & 2000s in New Zealand (King et al. 2007; McDonald et al. 1999), but was not commercialized. Building on this prototype, a self-resetting toxin delivery device (the Spitfire) has been developed by Connovation Ltd. (Auckland, New Zealand), Lincoln University and the New Zealand Department of Conservation (Blackie et al. 2011; Hix et al. 2009). Taking advantage of natural rat grooming behavior, the system sprays a measured dose of a toxicant in a highly palatable carrier paste onto the abdomen as the animal passes through a tunnel. The animal then grooms off the paste and ingests the toxicant. Each Spitfire is capable of delivering approximately 100 doses and is fitted with a counter and a delay mechanism. Different versions of the Spitfire are being developed to target different pest species; all use the same basic firing mechanism, but have different housings and may deliver different toxins. Originally designed for stoat (*Mustela erminea*) control, research is now focused on a self-resetting long-life toxicant delivery device for rats (Blackie et al. 2014; Murphy et al. 2014). To increase target specificity, a system of triggers has been incorporated in the application tunnel so that only target animals can activate the system. Trigger systems and device architecture have been designed to utilize natural behaviors of the target species. The provision of a single, measured, lethal dose of toxicant reduces the possibility of the target species receiving a sub-lethal dose. The device could remain active in the field for extended durations, minimizing maintenance needs (Blackie et al. 2014; Murphy et al. 2014). A digital tracking plate that can reliably identify species based on their footprint in a fraction of a second was developed independently and is now being integrated into the spitfire's design to increase species specificity (Triegaardt 2013; Welz 2014). Long-life attractants will be required to match the deployment potential of this product, and work is underway to identify them (Linklater et al. 2013; Murphy et al. 2014). The spitfire is expected to be available in 2-4 years.

Self-resetting traps (<http://goodnature.co.nz/>) for rats, stoats and brushtail possum have been available for a few years. Field trials in New Zealand and Hawaii produced refinements in the design and consumables, increasing reliability (Franklin 2013; Gillies et al. 2013). Improvements to trap design and increasing duration of attractiveness of lures are required before the full potential of these trap types is realized (Gillies et al. 2013). Self-resetting traps and toxicant delivery systems provide a potential opportunity to reduce non-target impacts, field effort and overall costs on projects that they can be integrated into. Self-resetting devices that are target-specific, have high efficacy and where deployed in a network are capable of eradicating rodent populations would be transformative.

3.8 Detection probability models

Detection probability models can account for the probability of recording false positive or false negative detections of animals, and for eradication project managers allow estimation of the likelihood of falsely declaring eradication success. These models have been used to confirm the eradication of feral pigs and cats targeted in multiple control-event style campaigns (Ramsey et al. 2009; Ramsey et al. 2011), and in the detection of invasive plants (Regan et al. 2006). The first detection probability model for rodents was recently developed for attempting to determine when an island targeted for rat eradication could be reliably declared rat-free (Samaniego Herrera et al. 2013). A general framework for developing

detection probability models has been developed (Ramsey and Will 2012), with consideration for target animal biology, pre-implementation and implementation data input and decision support.

Developing models that perform satisfactorily is reliant upon appropriate detection methods that allow adequate replication and statistical rigor. Detection methods that do not require a volitional action from rodents to interact with the lure or device (e.g. camera traps, trained detection dogs; Gsell et al. 2010) likely maintain a similar probability of detection before and after an eradication campaign and may provide such replication. Incorporating digital data collection and automated analyses, such as probability of detection will reduce costs in detecting survivors and confirming the eradication of rodents, while increasing the timeliness of results (Will et al. in press). These innovations represent incremental increases in the cost-efficiency and efficacy of eradications, are available now and can be readily adaptable to a variety of eradication approaches.

3.9 Social processes

Eradication requires improved social engagement and increased social receptivity to change as much as it requires success in technical expertise. Eradication of invasive species is often opposed by members of local communities. On the surface, opposition can stem from many causes, but some commonly reported concerns include animal welfare (Genovesi and Bertolino 2001), the safety of people and their domestic animals (Varnham et al. 2011), and the value placed on the species proposed for eradication by some people (Carrion et al. 2011). Yet, these tangible concerns are often only the tip of the iceberg; they can be symptoms of more deep-seated social conflicts that are not explicitly expressed such as a perceived lack of respect, meaningful participation and voice, or mistrust and resentment towards the institutions proposing eradication, or towards conservationists in general (Lederach 1997; Madden and McQuinn 2014). Opposition to eradication may become more entrenched due to unresolved conflicts about unrelated issues with the institutions seen to be leading the effort. Moreover, the sacrifices involved with ensuring a successful eradication fall heavily on the community and are often not acknowledged in light of professed benefits. These benefits may be less urgently sought after by the community in light of other more pressing needs, and ignoring these needs may be perceived as a sign of disrespect by eradication proponents. It is equally important to address these more subtle - but often more strongly felt - concerns.

To illustrate how tangible problems can be addressed we use the example of an invasive species that has value to some people. Feral animals are often hunted for food or recreation; invasive plants often have ornamental, culinary or medicinal value. However, people may still support eradication if they are convinced the benefits will outweigh the costs and the social conflict that underpins resistance is addressed. Social and economic benefits can include, among other things, increased eco-tourism, improved agricultural production and benefits to human health (Merton et al. 2002; Oppel et al. 2011; Samways et al. 2010). The eradication itself can also provide lucrative employment for local people (Oppel et al. 2011). Emphasizing these benefits can help garner community support (Glen et al. 2013). Successful solutions have also been found to satisfy community concerns over safety (e.g. Wilkinson and Priddel 2011) and animal welfare (e.g. Jolley et al. 2012). That said, if deep-rooted social conflict is not transformed, and the quality of the relationships and decision-making processes significantly improved, communities are still likely to resist any attempts at eradication, even if they logically see the social and economic benefits for their community.

Addressing community concerns will require a re-envisioning of the scope and scale of stakeholder engagement to create greater social receptivity to eradication (Madden and McQuinn 2014). This should go beyond simply addressing the superficial reasons for conflict (Lederach 1997). Conservation conflict

transformation (CCT) does not simply address the issues over which conflict has arisen, but aims to transform the relationship between the parties into a constructive partnership that is able to solve existing and future challenges (Madden and McQuinn 2014). This means identifying and overcoming the deeper causes of social conflict, which may include historical grievances, mistrust of decision makers, and a desire for some level of control and ownership (Lederach 1997; Madden and McQuinn 2014). CCT provides an approach that allows practitioners to understand, prevent and reconcile conflict. It employs an integrated suite of principles, techniques and processes that respond to the social and psychological needs of stakeholders. CCT goes beyond achieving short-term or superficial compliance, and instead aims to create long-term co-operation and shared decision-making between the parties in a dispute (Madden and McQuinn 2014). This approach has been successfully applied by peace mediators and proponents and is now being applied to conservation issues (Lederach 1997; Madden and McQuinn 2014).

Stakeholder communities will have varying degrees of initial receptivity to change and it is also expected that receptivity may be more easily created in some stakeholder communities than others. However, methods are lacking with which to assess initial stakeholder community receptivity, which would allow islands to be compared on social criteria in addition to existing biological ones (e.g. TIB Partners 2012). Doing so would allow eradication practitioners to optimize and direct limited conservation resources to the islands where there is a higher likelihood of support for eradication efforts. Hence, there is a need to develop a framework and set of indicators for determining and creating social receptivity for stakeholder community endorsement of eradication.

Although we emphasize that an engaged and supportive community can actively assist eradication efforts, social issues can undoubtedly complicate eradications (Glen et al. 2013). However, such complications otherwise considered intractable could potentially be overcome with integration of these new methods, and indeed must be attempted to protect insular species and ecosystems that only occur on inhabited islands.

These social processes have the potential to be highly transformative. Where applied, they could align partners, stakeholders and the community with a shared vision, minimizing opposition, and overcoming one of the main barriers to implementing eradication projects on islands. Challenges to implementation include that eradication practitioners lack these skills and the limited number and availability of conflict transformation practitioners. CCT requires a greater level of time, personal and financial investment than has been typical in planning restoration efforts on islands with multiple stakeholders to-date, but is expected to dramatically improve the likelihood of implementation occurring. Conflict transformation processes were recently initiated on Floreana Island in the Galapagos, and in the Juan Fernandez Islands, Chile with guidance from Human Wildlife Conflict Collaboration staff.

4. Discussion

This horizon scanning exercise identified ten innovations that have the potential to overcome many of today's barriers to rodent eradications on islands. Six innovations are transformative and four are incremental. Future horizon scanning exercises could benefit from having representation from defense technology developers, social change practitioners, fields that conduct practical manipulations of animals (e.g. geneticists involved in developing transgenic rodents, veterinarians) and researchers of novel invertebrate pest control systems for agriculture. The process could further benefit from incorporating an iterative component for developing ideas prior to their scoring (e.g. Sutherland et al. 2014).

Financial resources are a major limitation to implementing invasive species eradications (Campbell et al. 2011; Howald et al. 2007), however we did not investigate this aspect. Funding mechanisms such as debt for nature swaps, biodiversity offsets and tradable permit schemes may become important tools to leverage funding in addition to more traditional funding sources such as governments, bilateral and multilateral donors and philanthropists (Pascoe et al. 2011; Ring et al. 2010). A horizon scanning exercise, or systematic review of financial mechanisms potentially appropriate for supporting invasive species eradications would be valuable.

This review has illuminated a number of technological and procedural advances that have the potential to increase the feasibility, efficiency and humaneness of rodent eradication programs and to increase the scale and where those programs can be conducted. In addition to the advances described above, there is also an opportunity to leverage developments in the medical and pharmaceutical industry that use rodents as animal models (e.g. effective oral delivery of dsRNA in mice (He et al. 2013)). It appears that RNAi has significant potential to provide the next generation of rodenticides. Yet, to our knowledge no research group or rodenticide manufacturer is developing RNAi for use as a rodenticide. The only development of an RNAi vertebrate toxicant that we are aware of is for sea lamprey (*Petromyzon marinus*) (Heath et al. 2014). Simultaneously targeting multiple rodent and other bait consuming pest species (potentially including invasive ants) would be possible by incorporating dsRNA for each of the target species into a single bait matrix.

The degree to which these advances improve the ability to eradicate rodents from islands will also depend upon the degree to which they can be used in complimentary combinations. For example, an invasive rodent eradication on an inhabited tropical island with land crabs and critically endangered rodent, passerine, reptile and raptor species is currently intractable. Developments such as those described in this review may make eradication feasible. For example, in the future, innovative social processes may develop community buy-in and create a demand for eradication projects as a way to allow island communities to reach larger goals such as improving livelihoods. Baits incorporating a crab deterring compound and RNAi toxicants for targeting the invasive mouse and the rat species present could be dispersed aerially by drones day and night. In and around houses, shops and schools self-resetting RNAi toxicant applicators like the spitfire using digital tracking plates could be employed to ensure only the target species are dosed. Detection probability tools could be employed to determine when the eradication was to be declared successful so that limited resources were optimized. It is currently uncertain how these innovative methods could be applied to other identified challenges, such as mangroves, interacting rodent species and tropical islands in general (Harper et al. this issue; Russell et al. this issue; Russell and Holmes this issue). Identifying the probable causal mechanisms for eradication failure will enable practitioners to better modify and apply the suite of methods available to specific scenarios and to tailor development of future methods to meet those needs and increase the rate of successful eradications.

Conceivably, various combinations of methods may also enable reductions in the overall cost of an eradication when compared to using just a single method, especially when environmental variables can be incorporated. For example, at the end of a major drought, baits with RNAi mouse toxicant could be applied at a low rate to an insular mouse population in conjunction with the release of daughterless mice designed to be resistant to the RNAi toxicant, facilitating their dominance of the population.

Increasing the species specificity of eradication methods will reduce non-target impacts, yet may also reduce the ability to conduct simultaneous eradications of multiple pest species within a single campaign - a practice that minimizes the potential for negative consequences such as mesopredator

release (Griffiths 2011; Russell et al. 2009). However, when eradications are planned in an appropriate sequence, the removal of one species can increase the susceptibility of another pest to certain methods or cause them to die out (Ringler et al. this issue). The adoption of methods of increasing species specificity increases the importance of selecting the appropriate sequence of multiple pest eradications that need to weigh potential negative and positive impacts on conservation targets (Campbell et al. 2011). Further, species-specific methods will reduce risks to domestic livestock and pets, and reduce the sacrifices that need to be made by communities therefor facilitating receptivity of rodent eradications on inhabited islands.

Inhabited islands are at the extreme of the stakeholder complexity spectrum, and even with advanced social methods, such as CCT, will require significant investment to secure a demand for invasive vertebrate eradications from stakeholder communities. Although we have focused the need for CCT on inhabited islands these methods are also applicable to uninhabited islands, which often have a suite of stakeholders. Social engagement and shared planning with the broader community also needs to occur in parallel with technological developments to increase the acceptance of new eradication tools once developed (Saunders et al. 2010).

Based on current rodenticide regulatory trends aiming to minimize non-target impacts and the associated introduction of stricter regulatory conditions, the use of second generation anticoagulants as a tool has a limited future (Eason et al. 2010b). Regulatory agencies are likely to be supportive of continued use of second generation anticoagulants as long as efforts to develop alternatives are underway and until those alternatives become available. Species-specific toxicants such as norbormide and RNAi rodenticides form part of that strategy to phase out broad-spectrum toxicants. However, RNAi rodenticides present challenges to regulatory agencies and practitioners to effectively evaluate ecological and non-target risks, and new risk assessment methods will be required (USEPA 2013). In the absence of effective formulations of species-specific rodenticides self-resetting toxin delivery systems which limit non-target interactions or include species recognition capability will be a significant advance. Precedence setting trials and registrations should be conducted in countries with model regulatory systems or at other sites based on specific criteria to ensure appropriate evaluations occur (Brown et al. 2014; Eason et al. 2010b), and these will likely facilitate more effective evaluation by other countries in the future. Registrations and permitting are not the only potential barriers to developing and applying innovations. Technical, financial, public perception and other challenges exist for each innovation and will need to be appropriately navigated. We do not underestimate the challenges involved in bringing innovations into practice, and acknowledge that some innovations may not overcome all hurdles.

Some of the methods identified may, once developed, not be appropriate for eradications (e.g. efficacy may not be 100%), but they may be valuable methods for controlling rodents for conservation, agriculture and other purposes. For example, the self-replicating properties of daughterless mice may enable them to be used to maintain low-cost buffers around areas of conservation resources, crops or habitations (e.g. Goldwater et al. 2012).

Preventing extinctions and improving human livelihoods by eradicating invasive rodents from islands will require innovative approaches, technologies and tools. The potential and existing innovations identified in this horizon scan, either individually or in combination, have the potential to increase the feasibility of rodent eradications on islands. We hope the identification of these potential and actual innovations will catalyze applied research and developments in this field, assist policy makers and provide practitioners useful insight.

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6. Author contributions

KC, JB, NH, GH - Island Conservation innovation program management; KC, CE – rodenticides; KC, GH, AW, CE – *Rattus*-specific toxicant; FG, KC, JG, DT - RNA interference as species-specific toxicants and transgenic rodents; AW - crab deterrent in baits; JP - prophylactic treatment for protection of non-target species; KC - virus vectored immunocontraception and self-resetting traps; KC, CE - self-resetting toxicant applicators; KC, GB – drones; KC, NH - detection probability models; FM, AG - improved stakeholder community engagement methods; and KC, GB, NH - general manuscript development and improvement.

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