CSIRO PUBLISHING
Wildlife Research, 2014, **41**, 1–21
http://dx.doi.org/10.1071/WR13141

Review

Fertility control to mitigate human–wildlife conflicts: a review

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Abstract. As human populations grow, conflicts with wildlife increase. Concurrently, concerns about the welfare, safety and environmental impacts of conventional lethal methods of wildlife management restrict the options available for conflict mitigation. In parallel, there is increasing interest in using fertility control to manage wildlife. The present review aimed at analysing trends in research on fertility control for wildlife, illustrating developments in fertility-control technologies and delivery methods of fertility-control agents, summarising the conclusions of empirical and theoretical studies of fertility control applied at the population level and offering criteria to guide decisions regarding the suitability of fertility control to mitigate human–wildlife conflicts. The review highlighted a growing interest in fertility control for wildlife, underpinned by increasing numbers of scientific studies. Most current practical applications of fertility control for wild mammals use injectable single-dose immunocontraceptive vaccines mainly aimed at sterilising females, although many of these vaccines are not yet commercially available. One oral avian contraceptive, nicarbazin, is commercially available in some countries. Potential new methods of remote contraceptive delivery include bacterial ghosts, virus-like particles and genetically modified transmissible and non-transmissible organisms, although none of these have yet progressed to field testing. In parallel, new species-specific delivery systems have been developed. The results of population-level studies of fertility control indicated that this approach may increase survival and affect social and spatial behaviour of treated animals, although the effects are species- and context-specific. The present studies suggested that a substantial initial effort is generally required to reduce population growth if fertility control is the sole wildlife management method. However, several empirical and field studies have demonstrated that fertility control, particularly of isolated populations, can be successfully used to limit population growth and reduce human–wildlife conflicts. In parallel, there is growing recognition of the possible synergy between fertility control and disease vaccination to optimise the maintenance of herd immunity in the management of wildlife diseases. The review provides a decision tree that can be used to determine whether fertility control should be employed to resolve specific human–wildlife conflicts. These criteria encompass public consultation, considerations about animal welfare and feasibility, evaluation of population responses, costs and sustainability.

Additional keywords: contraception, fertility inhibitor, immunocontraception, population control, wildlife management.

Received 5 August 2013, accepted 27 February 2014, published online 19 May 2014

Introduction

Current trends of human population growth and landscape development show that human–wildlife conflicts are increasing (Rutberg and Naugle 2008; White and Ward 2010; Gionfriddo *et al*. 2011*a*). Many of these conflicts have been traditionally managed by lethal methods. However, opposition to culling has become widespread because of concerns about welfare, human safety in urban settings and environmental impact (e.g. Beringer *et al*. 2002; Cowan and Quy 2003; Sharp and Saunders 2008; McLeod and Saunders 2014). This growing antipathy toward lethal methods places increasing constraints on wildlife management options, particularly for high-profile, iconic species (Barr *et al*. 2002; Poiani *et al*. 2002; Druce *et al*. 2011). Consequently, there has been growing interest in non-lethal methods such as translocation and fertility control (Duka and Masters 2005; Barfield *et al*. 2006; Fagerstone *et al*. 2010).

Translocation of problem wildlife may cause stress and increase mortality, it is relatively expensive and has the potential to spread diseases and pathogens (e.g. Daszak *et al*. 2000; Massei *et al*. 2010*a*). Conversely, fertility control is increasingly advocated as a safe, humane and effective means of managing overabundant wildlife (Fagerstone *et al*. 2010; Kirkpatrick *et al*. 2011; McLaughlin and Aitken 2011). The potential market for human contraceptives and a growing public interest in alternatives to surgical sterilisation for companion animals and livestock have fostered investment in the development of novel fertility-control agents (Herbert and Trigg 2005; Naz *et al*. 2005; Massei *et al*. 2010*b*).

Early fertility-control agents lacked species-specificity, induced only transitory sterility, thus requiring repeated application, or had a limited window between the dose required to achieve sterility and the toxic or lethal dose. Other obstacles included manufacturing costs, concerns that residues might enter the human food chain and welfare issues regarding side effects (Gray and Cameron 2010; Kirkpatrick *et al*. 2011).

Several reviews on animal fertility control have been published in recent years. With the exception of the overview by Fagerstone *et al*. (2010) on issues concerning the use of reproductive inhibitors for wildlife in North America, these reviews have focussed on specific groups such as zoo species and companion animals (Asa and Porton 2005; Munson 2006; Purswell and Kolster 2006; Levy 2011; Massei and Miller 2013), on particular compounds such as immunocontraceptives (Cooper and Larsen 2006; Kirkpatrick *et al*. 2011), on selected species such as brushtail possums (*Trichosurus vulpecula*) (Ji 2009; Cross *et al*. 2011) or on groups of species such as ungulates (Patton *et al*. 2007). Here, we provide a comprehensive, critical overview of fertility control to mitigate human–wildlife conflicts, with the following aims:

(1) to analyse trends in research on fertility control for wildlife;
(2) to review recent developments in fertility-control technologies;
(3) to summarise delivery methods of fertility-control agents for wildlife;
(4) to provide a synthesis of the conclusions of empirical and theoretical studies of fertility control applied at the population level; and
(5) to offer a framework of criteria to guide decisions regarding the suitability of fertility control to mitigate human–wildlife conflicts.

Throughout the review, 'fertility inhibitors' or 'fertility-control agents' are used as a generic term to include chemicals used to block conception, or to prevent ovulation and sperm production, or that interfere with oogenesis and spermatogenesis.

Trends in research on fertility control for wildlife

We explored recent trends in wildlife fertility-control research since 1982 by searching five databases BIOSIS, CAB Abstracts, Web of Science, Zoological Records and Medline for the following keywords in the title or the abstract: immunocontraception/immunocontraceptive', 'fertility control', 'fertility inhibition/inhibitor', 'reproductive inhibition/inhibitor', 'contraception/contraceptive' and 'sterilisation'. All publications concerning empirical and theoretical studies of fertility control on wildlife species were included. Papers on laboratory animals, zoo animals and livestock were included only if they made specific references to potential wildlife applications. These searches generated data on (1) number of papers published per year, (2) type of study, including (i) laboratory and captive studies, (ii) field studies on free-living wildlife, (iii) reviews and (iv) theoretical studies based on modelling, and (3) number of gender-specific applications of fertility inhibitors, i.e. females only, males only or both.

In total, 460 papers were published between 1982 and 2010; the number of studies grew from 1–4 per year in the 1980s to an average of 27.3 per year in the past decade, with occasional peaks in numbers being due to special issues dedicated to this subject (Fig. 1). Overall, field studies followed laboratory ones with a noticeable lag of 5–6 years. Modelling studies progressively increased, whereas the number of reviews reached an asymptote with an average of 6.6 per year in the past decade. In total, 51% of papers focussed on immunocontraception, 31% on other fertility inhibitors and 18% on combinations of fertility inhibitors or on generic contraceptives. Of the 305 reported empirical and theoretical studies, 78% ($n = 238$) were on females, 7.5% ($n = 23$) on males and 14.5% ($n = 44$) on both genders. The bias toward female contraception is due to (1) studies focussed on human fertility (Barfield *et al*. 2006), (2) the recognition that polygyny and polyandry are common among many mammal species (e.g. Garrott and Siniff 1992; Kennis *et al*. 2008; Huchard *et al*. 2012) and, thus, extremely high levels of male sterility would be required to have any effect

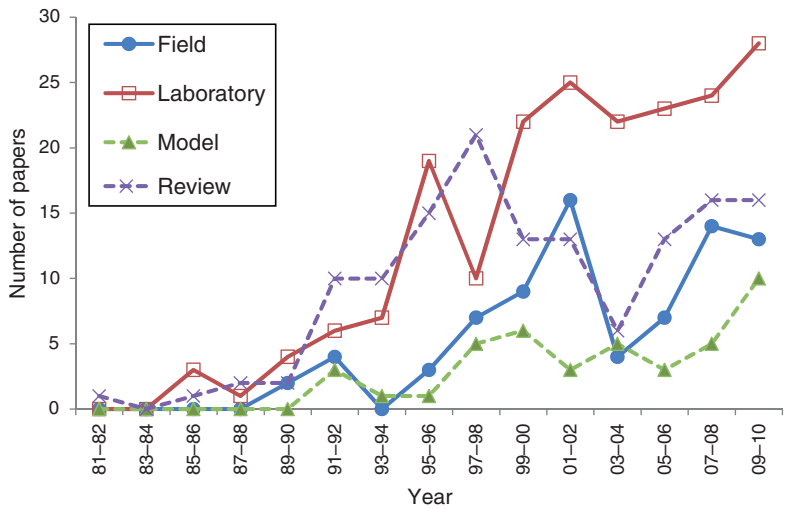

Fig. 1. Number of papers published every 2 years on fertility control for wildlife.

at the population level and (3) models demonstrating that effective control at the population level could be achieved only by rendering infertile a high proportion of females (e.g. Caughley *et al*. 1992; Hobbs *et al*. 2000; Merrill *et al*. 2006).

Fertility inhibitors for wildlife

A wildlife fertility-control agent suitable for field applications should have the following characteristics (Kirkpatrick and Turner 1991; Massei 2012; Massei and Miller 2013):

(1) nil or acceptable side-effects on animal physiology, welfare and behaviour,
(2) effective when administered in a single dose,
(3) render all or the majority of animals infertile for the duration of their potential reproductive life,
(4) inhibit female reproduction, but ideally prevent reproduction in both sexes,
(5) not compromise welfare by interfering with pre-existing pregnancy or lactation,
(6) relatively inexpensive to produce and deliver,
(7) no bioactive residues entering any food chain associated with treated animals,
(8) administrable through remote delivery,
(9) species-specific, and
(10) stable under a wide range of field conditions.

None of the fertility-control agents currently available meets all the above characteristics; however, several exhibit many of these features. The following review includes fertility inhibitors that (1) are commercially available or have been evaluated in several species, with particular focus on those used in wildlife, (2) can induce infertility for at least a year or for at least one reproductive season and (3) are primarily aimed at females, because this gender should remain the primary target for fertility control. Some examples are discussed of contraceptives that are very effective for other animals, but that cannot be regarded as suitable for wildlife.

Hormonal methods

Synthetic hormones, widely used in zoo animals and livestock, bind to endogenous hormone receptors and disrupt folliculogenesis, ovulation and egg implantation in females and impair spermatogenesis in males (Asa and Porton 2005). Those tested in wildlife include norgestomet, melengestrol acetate, levonorgestrel and quinestrol.

Norgestomet implants, used to suppress oestrus in beef cattle, inhibited reproduction in female white-tailed deer (*Odocoileus virginianus*) and black-tailed deer (*Odocoileus hemionus*) individuals for at least 1 year (Jacobsen *et al*. 1995; DeNicola *et al*. 1997).

Melengestrol acetate (MGA) with an estimated duration of efficacy of $\geq$2 years has been employed in zoos for wildlife contraception for ~20 years. MGA implants are effective on ungulates, carnivores and primates (Plotka and Seal 1989; Wood *et al*. 2001; Asa and Porton 2005; Hall-Woods *et al*. 2007). However, MGA causes uterine pathology in captive coati (*Nasua nasua*; Chittick *et al*. 2001), felids and canids (Munson 2006; Moresco *et al*. 2009) and a higher incidence of stillbirth and infant mortality in golden lion tamarins (*Leontopithecus rosalia*; Wood *et al*. 2001).

Levonorgestrel is the active component of a multi-year implant contraceptive originally approved by the US Food and Drug Administration (FDA) for human contraception. Because of side effects such as migraine and weight changes, the implant was withdrawn from the human-contraception market in some countries (Benfield and Darney 2011). A single administration of levonorgestrel implants inhibits reproduction in wildlife species for several years, without apparent adverse side effects (Nave *et al*. 2002*a*; Middleton *et al*. 2003; Coulson *et al*. 2008; Wheaton *et al*. 2011). In addition, levonorgestrel and quinestrol have been successfully used as contraceptives for rodents such as plateau pikas (*Ochotona curzioniae*) and Mongolian gerbils (*Meriones unguiculatus*) (e.g. Liu *et al*. 2012; Fu *et al*. 2013).

Regardless of proven efficacy, the use of hormonal methods on free-ranging wildlife is still debated because of potential welfare effects of long-term exposure, environmental impact and possible transfer of steroids via food chains (Nettles 1997; DeNicola *et al*. 2000; Asa and Porton 2005).

Gonadotropin-releasing hormone (GnRH) agonists are proteins that mimic GnRH and stimulate production and release of follicle-stimulating hormone (FSH) and luteinising hormome (LH). Administration initially causes the ‘flare up’ effect, i.e. stimulates oestrus in females and temporarily enhances testosterone and semen production in males (Patton *et al*. 2007). Because agonists do not quickly dissociate from the GnRH receptors, the ‘flare up’ is followed by prolonged ovarian quiescence and infertility (Gobello 2007).

Sustained-release subcutaneous implants of GnRH agonists, such as deslorelin (Suprelorin, Virbac, Milperra, NSW, Australia), have been used to inhibit reproduction for 1–2 years in cattle and in marsupials, including tammar wallabies (*Macropus eugenii*), grey kangaroos (*Macropus giganteus*) and brushtail possums (D’Occhio *et al*. 2002; Herbert *et al*. 2005; Eymann *et al*. 2007). In urban brushtail possums, deslorelin implants inhibited reproduction in 80% of the females treated (Lohr *et al*. 2009). Deslorelin has also been shown to be effective in cats, other felids and wild dogs (Herbert and Trigg 2005; Munson 2006; Bertschinger *et al*. 2008). Another GnRH agonist, leuprolide, found effective in suppressing reproduction for one breeding season in wapiti (*Cervus elaphus*; Baker *et al*. 2002; Conner *et al*. 2007) and female mule deer (*Odocoileus hemionus*; Baker *et al*. 2004), has not been used more recently. The effectiveness of GnRH agonists depends on agonist type, release system, dose rate and duration of treatment (Gobello 2007; Patton *et al*. 2007). The side effects of GnRH agonists are similar to those associated with gonad removal, but are reversible and there are no known effects on lactation (Asa and Porton 2005). Because GnRH agonists can cause abortion, they should be used outside the breeding season (Asa and Porton 2005).

Immunocontraceptive vaccines

Most recent studies of fertility control for wildlife have focussed on immunocontraceptive vaccines. Immunocontraception is achieved by exposing an animal to an antigen that stimulates the animal’s immune system to produce antibodies to proteins or

hormones essential for reproduction (Miller and Killian 2002). As a result, immunocontraceptives can prevent ovulation, sperm production or fertilisation. Adjuvants, which are inorganic or organic chemicals, macromolecules or entire cells of specific killed bacteria, are typically used to amplify the immune response to an antigen. The factors that affect effectiveness, longevity and side effects of immunocontraceptive vaccines include species, gender, age, individual variation in immunocompetence, as well as the active immunogen, formulation, delivery system and dose and type of adjuvant (Miller *et al*. 2008*a*, 2009; Holland *et al*. 2009; Kirkpatrick *et al*. 2011; Ransom *et al*. 2011). The most studied immunocontraceptives in wildlife are zona pellucida (ZP) and GnRH vaccines (Table 1).

The ZP is a layer of glycoproteins that surrounds an ovulated egg and allows species-specific sperm recognition and binding. There are four major ZP glycoproteins, named ZP1, ZP2, ZP3 and ZP4, each with different functions in the oocyte-sperm binding process and with varying degrees of homology among mammalian species (e.g. Kitchener *et al*. 2009; Gupta and Bhandari 2011). These differences are partly responsible for the variable results obtained when using a particular ZP vaccine on different species and have been exploited to make ZP-based vaccines more specific (Kitchener *et al*. 2009; Gupta *et al*. 2011; Levy 2011). Porcine ZP (PZP) immunocontraceptive vaccines, derived from ZP isolated from pig ovaries, have been effective in many ungulate species, monkeys, seals, bears and marsupials, but not in rodents, cats, dogs and wild pigs (Eade *et al*. 2009; Kitchener *et al*. 2009; Kirkpatrick *et al*. 2009, 2011; McLaughlin and Aitken 2011; Table 1). However, recently formulated recombinant PZP3 and PZP4 vaccines, delivered in three injectable doses, caused infertility in up to 89% mice, depending on the formulation type (Gupta *et al*. 2013).

Early formulations of ZP vaccines were delivered as a primer shot, followed by a booster, which placed major constraints on field applications with wildlife. Initial vaccine formulations also used Freund's complete adjuvant (FCA), which raised safety concerns regarding the occurrence of false-positive tuberculosis skin tests in deer treated with vaccines containing FCA, severe injection-site reactions and potential carcinogenicity for consumers of treated animals (Kirkpatrick *et al*. 2011). The development of a novel, safe and effective adjuvant (AdjuVac, National Wildlife Research Center, Fort Collins, CO, USA) combined with PZP-based vaccine succeeded in rendering animals of several species infertile for several years after a single dose (Table 1). Injectable formulations of PZP vaccines, such as the proprietary liposome-containing product SpayVac (ImmunoVaccine Technologies, Inc., Halifax, NS, Canada), with controlled-release properties, have been developed that generate responses for multiple years following a single administration (Brown *et al*. 1997; Turner *et al*. 2008; Rutberg *et al*. 2013). Modified FCA has also been used as a safe, effective substitute for FCA (Lyda *et al*. 2005). Recent studies have also shown that intra-nasal delivery of four doses of mouse ZP3 result in a significant reduction of reproductive output in mice (Ma *et al*. 2012; Kadir *et al*. 2013). In parallel, several newer alternative reagents, such as purified and/or receptor-specific adjuvants (e.g. monophosphoryl lipid A, ISCOMsm CpG oligonucleotides) are being investigated for either mucosal or parenteral route of vaccine administration (Sharma and Hinds 2012).

Possible negative effects of ZP vaccines include species-specific ovarian pathology and multiple infertile oestrous cycles (in polyoestrous species), leading to extended breeding season, increased movements, potential late births and disruption of social hierarchy (Miller *et al*. 2000; Curtis *et al*. 2007; Kirkpatrick *et al*. 2009, 2011; Nuñez *et al*. 2009, 2010). Other studies on white-tailed deer and feral horses have reported that treatment with ZP vaccines does not affect time budget, social behaviour and body condition (Miller *et al*. 2001; Hernandez *et al*. 2006; Ransom *et al*. 2010). The incidence of ovarian pathologies was significantly reduced when purified PZP proteins were used in vaccine constructs (Gupta *et al*. 2013).

PZP was found safe to administer to pregnant or lactating females (Turner *et al*. 1996; Kirkpatrick and Turner 2002; Perdok *et al*. 2007; Delsink and Kirkpatrick 2012). Differences in the results of studies using ZP-based vaccines may reflect different formulations of native, purified or recombinant ZP vaccines, or different adjuvants and methods of extraction of PZP from pig ovaries (Munson *et al*. 2005; Miller *et al*. 2009; Kirkpatrick *et al*. 2011). Injection-site reactions such as abscesses are rare (~1% in various species) in animals treated with ZP vaccines, whereas granulomas (thickened tissue filled with fluid) are more common at the injection site (Kirkpatrick *et al*. 2009; Gray *et al*. 2010). In 2012, a PZP-based vaccine ZonaStat-H was registered by The Humane Society of the United States and approved by the Environment Protection Agency (EPA) as a contraceptive for population control of feral horses and feral donkeys. ZonaStat-H is not commercially available, but can be obtained from The Science and Conservation Center ZooMontana.

GnRH-based vaccines cause infertility by generating antibodies toward GnRH, thus disrupting the downstream release of hormones that stimulate ovulation and sperm production. Multi-dose GnRH-based immunocontraceptive vaccines, currently used in livestock and companion animals, are unsuitable for wildlife (reviewed in Naz *et al*. 2005; McLaughlin and Aitken 2011), primarily because of the impracticality of recapturing individuals to administer multiple doses. One single-dose GnRH vaccine that has seen rapid developments in wildlife applications is GonaCon (National Wildlife Research Center, Fort Collins, CO, USA), registered in the US as a contraceptive for white-tailed deer, feral horses and feral donkeys. GonaCon consists of a synthetic GnRH coupled to a mollusk protein (Miller *et al*. 2008*a*). Formulated as an injectable, single-dose immunocontraceptive, GonaCon induced infertility for several years in deer, wild boar, pigs, cats, horses and bison (*Bison bison*) (e.g. Miller *et al*. 2000; Killian *et al*. 2008; Massei *et al*. 2008, 2012; Gray *et al*. 2010) (Table 1). As GonaCon prevents ovulation, treated females and males do not exhibit oestrous behaviour; however, male deer showed abnormal antler development (Fagerstone *et al*. 2008). In the years after treatment, GnRH antibody titres decrease and fertility may be restored (Miller *et al*. 2008*a*; Massei *et al*. 2012). In some studies, reproductive behaviour has been observed 1–2 years before fertility returned (Killian *et al*. 2008).

In some species, vaccination with GonaCon causes a granuloma or a sterile abscess at the injection site. Two years after vaccination with GonaCon, 5 of 15 treated female cats had a palpable non-painful injection-site granuloma (Levy *et al*. 2011). In white-tailed deer, injection-site lesions (granulomatous

Table 1. Captive and field trials conducted with different formulations of single-dose immunocontraceptive porcine zona pellucida (PZP)- and gonadotropin-releasing hormone (GnRH)-based vaccines on females of wildlife, feral and companion animal species

The effectiveness of these vaccines to cause infertility is expressed as proportion of infertile females in the control (C) and treatment (T) groups. The different percentages listed for each study are the responses recorded for successive years after first treatment

Species	*N*	Type of study	Antigen	Adjuvant	% infertile females	Reference
White-tailed deer *Odocoileus virginianus*	5 per group	Captive	GonaCon, various formulations	AdjuVac	GonaCon–KLH = 100% 60% 50% 50% 25% GonaCon–B = 100% 100% 80% 80% 80%	Miller *et al*. 2008*a*
White-tailed deer	T = 24 C = 13	Field	GonaCon–KLH	AdjuVac	T = 67% 43% C = 8% 17%	Gionfriddo *et al*. 2011*a*
White-tailed deer	T = 26 C = 13	Field	GonaCon–KLH	AdjuVac	T = 88% 47% C = 15% 0%	Gionfriddo *et al*. 2009
Feral horse *Equus caballus*	T = 15 C = 8	Captive	GonaCon–KLH	AdjuVac	T = 93% 64% 57% 43% C = 25% 25% 12% 0%	Killian *et al*. 2008
Feral horse	T = 18 C = 31	Field	GonaCon-B	AdjuVac	T = 61% 58% 69% C = 40% 31% 14%	Gray *et al*. 2010
Elk *Cervus elaphus*	T = 10 C = 8	Captive	GonaCon-B	AdjuVac	T = 90% 75% 50% 25% C = 0% 0% 0% 14%	Powers *et al*. 2011
Elk	T = 10 T = 12 C = 15	Captive	GonaCon–KLH	AdjuVac	GonaCon–KLH (1000 µg) = 92% 90% 100% GonaCon–KLH (2000 µg) = 90% 100% 100% C = 27% 25% 0%	Killian *et al*. 2009
Bison *Bison bison*	T = 6 C = 5	Captive	GonaCon–KLH	AdjuVac	T = 100% C = 0%	Miller *et al*. 2004
Wild boar *Sus scrofa*	T = 12 C = 12	Captive	GonaCon–KLH	AdjuVac	T = 92% infertile for at least 4–6 years C = 0%	Massei *et al*. 2008, 2012
Feral pig *Sus scrofa*	T = 18 C = 3	Captive	GonaCon–KLH	AdjuVac	T = 89% C = 0%	Killian *et al*. 2006
Cat *Felis catus*	T = 15 C = 5	Captive	GonaCon–KLH	AdjuVac	T = 93% 73% 53% 40% 27% C = 0%	Levy *et al*. 2011
Fallow deer *Dama dama*	T = 19 C = 152	Field	SpayVac	FCA	T = 100% 100% 100% C = 4% 3% 4%	Fraker *et al*. 2002
White-tailed deer	T = 5 per group C = 84	Captive	PZP and SpayVac, various formulations	AdjuVac or Alum	SpayVac–AdjuVac: 100% 100% 100 80% 80% IVT–PZP–AdjuVac: 100% 80% 80% 80% 80% SpayVac–Alum: 20% NWRC–PZP–AdjuVac (200 µg): 80% 0% NWRC–PZP–AdjuVac (500 µg): 100% 20% 20% 20% 0% C = 0%	Miller *et al*. 2009
White-tailed deer	T = 34 C = 11	Field	SpayVac	AdjuVac	T = 100% 100% C = 22%	Locke *et al*. 2007
White-tailed deer	T = 9 T = 11 C = 245	Field	SpayVac various formulations	AdjuVac	T SpayVac aqueous: 100% 75% T SpayVac non-aqueous: 64% 75% C = 22%	Rutberg *et al*. 2013
White-tailed deer	T = 36 C = 11	Field	PZP	AdjuVac	T = 100% C = 22%	Hernandez *et al*. 2006
Feral horse	T = 12 C = 8	Captive	SpayVac	AdjuVac	T = 100% 83% 83% 83% C = 25% 25% 12% 0%	Killian *et al*. 2008
Feral horse	T = 17 C = 21	Field	PZP	FCA and QS-21	T = 95% 85% 68% 54% C = 46% 43% 49% 48%	Turner *et al*. 2007
Feral horse	T = 14 C = 31	Field	PZP	AdjuVac	T = 63% 50% 56% C = 40% 31% 14%	Gray *et al*. 2010

nodules and sterile abscesses) occurred in the deep hind-limb musculature of >85% of GonaCon-treated animals, although no evidence of limping or impaired mobility was observed in these animals (Gionfriddo *et al*. 2011*b*). GonaCon had no adverse effects on health of wild boar, white-tailed deer and prairie dogs (*Cynomys ludovicianus*; Massei *et al*. 2008, 2012; Yoder and Miller 2010; Gionfriddo *et al*. 2011*b*). In white-tailed deer, reactions at injection sites and in lymph nodes were typical responses to injection of adjuvanted vaccines formulated as water-in-oil emulsions (Miller *et al*. 2008*a*). GonaCon administered to 3–4-month-old white-tailed deer fawns did not induce contraception or prevent sexual development (Miller *et al*. 2008*b*) and, when given to pregnant bison, it did not affect pregnancy (Miller *et al*. 2004).

The gradual reversibility of the infertility effect, at least in a proportion of animals treated with ZP- and GnRH-based vaccines, is regarded as desirable in some species (Druce *et al*. 2011; Kirkpatrick *et al*. 2011). Because both vaccines are broken down when ingested, they do not enter the food chain and hence do not pose unacceptable risks to predators or human consumers even if the muscle injected with the immunocontraceptive is ingested. Both ZP and GnRH are inherently poorly immunogenic and thus must be formulated to elicit an immune response, for instance, by conjugation to larger carrier foreign proteins. More recently, recombinant technology has been used to produce antigens fused to carrier peptides. Recombinant injectable GnRH vaccines have caused a strong immune response in feral pigs (Kemp and Miller 2008; Campbell *et al*. 2010). Fusion protein technology has also been used to produce a plasmid-DNA vaccine encoding GnRH; injection with this vaccine caused a significant reduction in fertility in both male and female mice (*Mus musculus*; (Khan *et al*. 2008). To overcome the lack of availability of the purified native ZP glycoproteins obtained from ovaries of slaughtered pigs, porcine ZP3 and ZP4 were expressed in *Escherichia coli*; immunisation with these recombinant proteins significantly decreased fertility in laboratory mice and dogs (Gupta *et al*. 2011, 2013).

Both ZP and mammalian GnRH are highly conserved in structure and function across mammalian species (e.g. Cariño *et al*. 2002; Temple *et al*. 2003). Consequently, the development of species-specific immunocontraceptives based on ZP or GnRH will be challenging, although there is evidence of differential ZP3 specificity between marsupial and eutherian mammals (Duckworth *et al*. 2008). However, species-specific binding of sperm to ZP has potential for developing species-specific immunocontraceptives based on sperm-surface antigens (e.g. Moore *et al*. 1997; Grignard *et al*. 2007; Naz 2011). Recognition of sperm antigens that participate in sperm–ZP binding can be achieved using phage display techniques (Eidne *et al*. 2000; Naz 2005). This approach has since enabled identification of putatively pig-specific phage antigens that stimulate production of sperm-binding antibodies with potential for immunocontraception (Samoylova *et al*. 2012).

Other contraceptives

Several putative fertility inhibitors are still in the early phase of development. These include GnRH-toxin conjugates and cholesterol mimics. GnRH-toxin conjugates are formed by linking synthetic analogues of GnRH to cytotoxins. This enables selective targeting and mortality of cells secreting reproductive hormones, potentially leading to permanent sterility in both males and females. Because of their proteinaceous nature, these conjugates are broken down by digestion and thus do not enter the food chain. Examples include an injectable GnRH-toxin conjugate that suppressed the secretion of LH for up to 6 months in female mule deer (Baker *et al*. 1999) and an injectable GnRH-cytotoxin (pokeweed antiviral protein, PAP) conjugate that disrupted reproduction in adult male dogs, female rats (*Rattus norvegicus*) and sheep (*Ovis aries*) for at least 6 months (Nett *et al*. 2003; Ball *et al*. 2006). The cholesterol mimic DiazaCon can affect reproduction in birds and mammals because it inhibits production of cholesterol, which is a parent compound of male and female reproductive steroids (Fagerstone *et al*. 2010). Following ingestion of DiazaCon for 1–2 weeks, reproduction was suppressed for a few months in black-tailed prairie dogs, rose-ringed parakeets (*Psittacula krameri*) and monk parakeets (*Myiopsitta monachus*) (Nash *et al*. 2007; Yoder *et al*. 2007, 2011; Avery *et al*. 2008; Lambert *et al*. 2010). DiazaCon also reduced cholesterol in grey squirrels (*Sciurus carolinensis*), although the effects on reproduction were difficult to interpret because of poor breeding success in the control group (Mayle *et al*. 2013). DiazaCon has a relatively narrow contraceptive window before undesirable side effects on physiology and behaviour occur (Sachs and Wolfman 1965; Yoder *et al*. 2004, 2007). The efficacy of this compound depends on its bioaccumulation; however, its consequently relatively long elimination half-life poses potential exposure risk to predators and scavengers of treated animals. Therefore, DiazaCon seems more suited for applications to captive wildlife, seasonal breeders and localised populations experiencing little or no predation and where non-target species can be prevented from feeding on DiazaCon-treated baits (Avery *et al*. 2008; Fagerstone *et al*. 2010).

Nicarbazin (NCZ) is a bird-specific oral contraceptive widely used as a veterinary medicine to manage coccidiosis in broiler chickens. NCZ disrupts the membrane between the egg albumen and yolk, thus compromising embryo development (Jones *et al*. 1990). NCZ is registered in the USA for use with Canada geese (*Branta canadensis*; Bynum *et al*. 2007) and feral pigeons (*Columbia livia*; Fagerstone *et al*. 2008) and, in Italy, to control urban populations of feral pigeons (Ferri *et al*. 2009). Because NCZ is rapidly cleared from the body once consumption ceases, the effect on fertility is reversible and, thus, NCZ poses minimal risk to predators and scavengers of treated birds. The disadvantage is that NCZ must be fed continuously before and during egg-laying to be effective (Fagerstone *et al*. 2010). This may underlie the equivocal results reported for population-level effects in the field (Giunchi *et al*. 2007; Ferri *et al*. 2009).

Other methods currently being investigated target the mammalian ovary and aim at inducing early menopause and permanent sterility (Tran and Hinds 2013). The epoxide 4-vinylcyclohexene diepoxide (VCD) has ovarian-specific toxicity and follicle-depleting properties (Hoyer *et al*. 2001; Mayer *et al*. 2002). The administration of VCD by injection or ingestion repeatedly over a period of up to 30 days depletes the ovary of follicles leading to ovarian senescence (Mayer *et al*.

2004; Hu *et al*. 2006). Similarly, repeated oral administration of triptolide, a diterpenoid triepoxide, affects the ovarian function by causing follicular atresia (Xu and Zhao 2010; Liu *et al*. 2011). Triptolide can also compromise sperm function in males (Singla *et al*. 2013). However, reduced fertility induced by free-feeding of epoxides has yet to be demonstrated in either males or females.

Delivery methods

Ideally, a fertility-control agent should be species-specific. In practice, this is rarely the case at present and most contraceptives can affect a variety of wildlife species. Therefore, specificity must be achieved by the delivery method.

Fertility-control agents are delivered through the parenteral and oro-nasal route or via live organisms. Parenteral delivery includes direct injection (usually intramuscular), subcutaneous implants and remote delivery systems such as bio-bullets and syringe-darts.

Subcutaneous implants that release fertility control agents into an animal over a sustained period of time have been successfully employed to induce infertility for 1–5 years in a variety of wildlife species (e.g. Plotka and Seal 1989; Nave *et al*. 2002*a*, 2002*b*; Coulson *et al*. 2008; Lohr *et al*. 2009). Bio-bullets are biodegradable projectiles used to administer remotely various veterinary substances (DeNicola *et al*. 2000). Syringe-darts, routinely employed to anaesthetise wild animals, have also been used to administer contraceptives (Aune *et al*. 2002). Distance-adjustable CO_2-powered dart rifles have been employed to fire 2–3-mL syringe-darts at ranges of $\leq$40 m into the hindquarter of large mammals (Rudolph *et al*. 2000; Delsink *et al*. 2007; Kirkpatrick *et al*. 2009; Rutberg *et al*. 2013). Such delivery systems have several advantages (Kreeger 1997), including the following: (1) they target individual animals, so specificity is assured; (2) they can administer an individually tailored dose based on a bodyweight; (3) they can deliver solid (e.g. silastic implants), semi-solid or liquid formulations; and (4) they can be used for remote delivery, to avoid the welfare and economic costs of trapping. Potential disadvantages include identification of previously vaccinated individuals, dose regulation and incomplete intra-muscular injection (DeNicola *et al*. 1997, 2000; Aune *et al*. 2002). Remote parenteral delivery of contraceptives is regarded as suitable for small or isolated groups of animals, for instance, in urban parks (DeNicola *et al*. 2000), on islands (Kirkpatrick *et al*. 2009) or in fenced wildlife reserves (Delsink *et al*. 2007; Delsink and Kirkpatrick 2012).

In oral delivery of antigens, a fundamental issue is the relatively high threshold of the immune system in recognising the antigen as ‘foreign’ before an immune response is mounted (Cross *et al*. 2011). Consequently, responses to orally delivered antigens will typically be short-lived and such vaccines are likely to require repeated applications. Miller *et al*. (1999) demonstrated the feasibility of oral vaccination of deer using a live recombinant Bacillus Calmette–Guerin (BCG) vaccine as the immunological vector of a model antigen. Vehicles for potential oro-nasal delivery of immunocontraceptives include bacterial ghost (BGs) and virus-like-particles (VLPs). BGs are bacterial-cell envelopes that have been deprived of their DNA but maintain their antigenic properties and have been engineered to be carriers of antigens (Cui *et al*. 2010). VLPs are compounds artificially constructed to resemble viruses that are non-infectious because they do not contain any viral genetic material (Cross *et al*. 2011). Initial results of BGs as an oro-nasal delivery system for ZP-based vaccines in brushtail possums showed a significant reduction in egg-fertilisation rates (Walcher *et al*. 2008) and offspring production (Duckworth in Cross *et al*. 2011). GnRH–VLP also elicited antibodies to GnRH (Cross *et al*. 2011). VLPs used to present zona (ZP3) and spermatozoa-specific peptides to laboratory mice, generated specific antibody responses and a significant reduction in litters born (Choudhury *et al*. 2009).

Because immunocontraceptive vaccines could typically affect multiple species, species specificity must be achieved through targeted delivery methods. Examples include floating rafts to deliver baits to aquatic species (Reynolds *et al*. 2004), baits placed inside burrow systems (Delahay *et al*. 2000) and species-specific delivery devices such as the BOS (Boar-Operated System), the latter developed to deliver baits to wild boar and feral pigs (Massei *et al*. 2010*c*; Campbell *et al*. 2011).

Immunocontraceptive vaccines can also be delivered through genetically modified self-sustaining infectious vectors. These include recombinant myxoma virus for rabbits, murine cytomegalovirus in mice and feline retroviruses for feral cats (Robinson *et al*. 1997; Courchamp and Cornell 2000; Seamark 2001; Singleton *et al*. 2002; Cowan *et al*. 2008). The main advantages of self-sustaining infectious vectors of immunocontraception include the feasibility of large-scale applications, both in terms of number of animals and areas covered, the availability of a humane and species-specific control method with potential for a good cost–benefit outcome and the possibility of providing long-term wildlife conflict resolution (e.g. McLeod *et al*. 2007; Tyndale-Biscoe and Hinds 2007). Criticism of this approach raised concerns regarding its irreversibility, the difficulty of controlling the vectors once released, possible mutations of the vectors that could affect non-target species and possible development of population resistance to these vectors (e.g. Barlow 2000; Tyndale-Biscoe and Hinds 2007; Williams 2007). For these reasons, none of these systems has been approved for field studies. In specific cases, the benefits of vectored immunocontraception may overcome the potential costs. For instance, Courchamp and Cornell (2000) suggested that actively disseminating immunocontraception systems should be employed for eradicating feral cats on islands, because of humaneness, environmental safety, low cost and wide coverage of inaccessible areas of these contraceptives.

In New Zealand, attention has recently turned to species-specific genetically modified non-transmissible and transmissible organisms (reviewed in Cross *et al*. 2011). Among the non-transmissible organisms, good candidates are the recombinant adenoviruses and the vaccinia virus belonging to the pox-virus family, the latter being widely used in veterinary and human vaccines. Among the transmissible organisms, research has focussed on possum-specific nematode parasites (Cowan *et al*. 2006, 2008).

Fertility-control impact on wildlife populations

Fertility control is employed to reduce population size or growth or to decrease the impact of wildlife on human

Table 2. Examples of empirical and theoretical applications of fertility control (FC) at population level in captive and free-living wildlife species
FC, fertility control

Aim	Species	Trial	Method	Results and conclusions	Reference
Evaluate effect of hormonal competence and imposed FC on population dynamics	House mouse (*Mus domesticus*)	Enclosure	Tubal ligation vs ovariectomy	No differences in effect of both methods on population size. 67% infertility, imposed at the beginning of an 18-week study, reduced population size and growth rate. Litter size of fertile females increased in the sterilised groups	Chambers *et al*. 1999
Evaluate impact of FC on population size	Ricefield rat *Rattus argentiventer*	Enclosure and model	Tubal ligation, ovariectomy,	FC-induced compensatory reproduction and improved survival of juveniles did not prevent a reduction in population size if 50–75% founder females were sterilised at the beginning of the reproductive season	Jacob *et al*. 2004
As above	European rabbit *Oryctolagus cuniculus*	Enclosure and field	Tubal ligation	FC dampened seasonal population changes but did not reduce adult abundance. Improved survival compensated for the effects of sterilising up to 80% of females	Twigg *et al*. 2000; Williams *et al*. 2007
As above	White-tailed deer *Odocoileus virginianus*	Field and model	PZP vaccine	FC feasible, over a 4-year study, to maintain small (<200) suburban deer populations at 30–70% of carrying capacity if ~60% females were treated with vaccine	Rudolph *et al*. 2000
As above	White-tailed deer	Field	PZP vaccine	FC induced a 7.9% population decline per year over a 6-year study, in a suburban deer population	Rutberg *et al*. 2004
As above	White-tailed deer	Field and model	PZP vaccine	FC caused a 27–58% % decline in population size in the 5–10 years following treatment of females	Rutberg and Naugle 2008
As above	Wild horse (*Equus caballus*)	Field	PZP vaccine	The effort required to achieve zero population growth decreased, as 95%, 83% and 84% of all adult mares were treated in each of the first 3 years, compared with 59% and 52% during the last 2 years. FC increased longevity and improved body condition	Turner and Kirkpatrick 2002

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Table 2. (*continued*)

Aim	Species	Trial	Method	Results and conclusions	Reference
As above	Wild horse	Field	PZP vaccine	FC prevented population growth within 2 years; by Year 11, the population had declined by 22.8%. FC also increased longevity of mares	Kirkpatrick and Turner 2008
As above	Wild horse	Model	PZP vaccine	FC can be used for small (<200), isolated populations to reduce population size to the target number in 5–8 years	Ballou *et al*. 2008
As above	Elephant *Loxodonta africana*	Field	PZP vaccine	FC of all sexually mature females in a small population (73 animals) prevented population growth for the 4-year study	Delsink *et al*. 2007
As above	Elephant	Model	Immuno-contraception	'Rotational' FC can be used to increase the span of calving intervals, slow population growth rate and alter age structure	Druce *et al*. 2011
As above	Possum *Trichosurus vulpecula*	Field	Tubal ligation	Immigration and increased survival rate of sterilised females compensated for effects of FC and maintained population stable. In a 4-year study, sterility rates of 50% and 80% females resulted in 60% and 74% reduction to *per capita* rate of recruitment	Ramsey 2005
Evaluate impact of culling and FC on population size	Brandt's vole *Microtus brandti*	Model	Generic contraception	In a 3-year study, FC applied in autumn to 85% of the females was more effective than culling in reducing population size	Shi *et al*. 2002
As above	Wildlife	Model	Generic contraception	FC was more effective than culling in reducing population size for medium and large-size animals	Zhang 2000
As above	White-tailed deer	Model	Generic contraceptive	FC was more efficient than culling in reducing population size provided >50% females were maintained infertile	Hobbs *et al*. 2000
As above	Elk *Cervus elaphus*	Model	Yearlong vs lifelong contraceptive	FC using lifetime contraceptives was more efficient than any other population control option	Bradford and Hobbs 2008
Evaluate impact of removal and FC on population size	Feral horse	Model	Generic contraception	Compared with removal, FC resulted in smaller, less fluctuating population size	Gross 2000

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Table 2. (*continued*)

Aim	Species	Trial	Method	Results and conclusions	Reference
Evaluate effects of FC on behaviour and survival	Fox *Vulpes vulpes*	Field	Tubal ligation	In a 3-year study, FC did not affect territorial behaviour, dispersal and survival	Saunders *et al*. 2002
Evaluate factors affecting time to reduce a population through FC	White-tailed deer	Model	Permanent sterilisation	FC could reduce a population by 30–60% in 4–10 years if 25–50% of fertile females were captured and sterilised every year	Merrill *et al*. 2003
Evaluate effects of immigration, stochasticity and variation in capture process on FC to manage population size	White-tailed deer	Model	Permanent sterilisation	FC was unlikely to reduce the size of an open population. In a closed population, permanent sterilisation could reduce population size if 30–45% deer were captured each year	Merrill *et al*. 2006
Assess potential of FC to eradicate cats on islands	Feral cat *Felis catus*	Model	Immuno contraception	Virus-vectored and bait-delivered contraceptives were predicted to eradicate a cat population	Courchamp and Cornell 2000
Evaluate impact of culling, vaccination and FC added to vaccination on rabies control	Fox *Vulpes vulpes*	Model	Generic contraceptive	Integrating FC with rabies vaccination was predicted to be more successful than rabies vaccination only for rabies control	Smith and Wilkinson 2003
As above, on rabies and bovine tuberculosis	Fox European badger *Meles meles*	Model	Generic contraceptive	FC added to rabies vaccination had a similar impact of culling on population reduction and disease eradication	Smith and Cheeseman 2002
Test FC to eradicate bovine tuberculosis	European badger	Model	Generic contraceptive	FC, integrated with culling was predicted to be more effective than culling alone to eradicate the disease	White *et al*. 1997;
Estimate effect of FC on leptospirosis and bovine tuberculosis transmission	Possum *Trichosurus vulpecula*	Field and model	Tubal ligation vs inhibitors that prevent oestrus	In a 3-year study, tubal ligation, that does not prevent oestrus, caused an increase of disease transmission. FC that prevents oestrus was predicted to decrease the horizontal transmission rate of diseases due to reduced contact rate between animals	Caley and Ramsey 2001
Estimate effect of FC, disease vaccination and culling on bovine tuberculosis transmission	Possum	Model	Generic contraceptive	An initial cull followed by FC and oral vaccination applied every 3 years was considered as the most cost-effective strategy	Ramsey and Efford 2010
Test effects of FC on possum behaviour and transmission of leptospirosis	Possum	Field	Tubal ligation vs gonadectomy	In a 5-year study, both FC types did not affect the spatial behaviour and dominance status of	Ramsey 2007

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Table 2. (*continued*)

Aim	Species	Trial	Method	Results and conclusions	Reference
				females. Gonadectomy reduced the seasonal breeding range size of males. In both sexes, gonadectomy decreased the horizontal transmission rate of disease due to a reduced contact rate between animals	
Test FC to improve efficiency of rabies eradication in urban dog populations	Dog *Canis familiaris*	Model	Immuno-contraception	FC added to rabies vaccination was predicted to reduce the proportion of dogs to be treated with rabies vaccines and the duration of vaccination campaigns	Carroll *et al*. 2010
Evaluate effect of FC on population size and rabies control	Dog	Field and model	Surgical sterilisazion	Sustained sterilisation of 62–86% dogs in 2 years led to a 34% reduction in population size. The model predicted that FC could reduce population size and in the long term lead to rabies elimination	Totton *et al*. 2010
Evaluate effect of FC on population size	Cat *Felis catus*	Model	Surgical sterilisazion vs contraception	>51–60% of females must be rendered infertile every year to halt population growth	Budke and Slater 2009

interests (Table 2). Understanding how fertility control affects population dynamics and social behaviour is crucial for evaluating the effectiveness of this method and estimating the effort required for successful practical applications. Here, we summarise the evidence from theoretical and empirical studies on factors that may influence population and behavioural responses to fertility control. We also offer an overview of advantages and disadvantages of fertility control compared with other methods used to mitigate human–wildlife conflicts. Ideally, fertility control would affect only natality. In practice, fertility control may also indirectly affect physiology and survival, as well as spatial and social behaviour of treated animals. These effects depend on species-specific behavioural and life-history traits, on the type of fertility-control agents used and on the proportion of a population treated with contraceptives.

Debates about the relative efficiency of fertility control and culling have largely centred on definitions. If efficiency is defined in terms of the time taken to achieve the desired effect, then culling will always be more efficient because fertility control alone cannot generate a larger, more rapid population decline than is the natural mortality rate (Bradford and Hobbs 2008; McLeod and Saunders 2014). Conversely, fertility control might be more efficient than culling if the remaining infertile animals maintain sufficient density-dependent feedback constraints on recruitment and survival (Zhang 2000). Typically, lethal control achieves an initial rapid reduction in population size; several models have suggested that fertility control can be used, following lethal control, to maintain density at the reduced level (e.g. White *et al*. 1997; Merrill *et al*. 2006).

When the size of a population is suddenly reduced, compensatory density-dependent processes may act to return the population to its previous level (Bomford 1990; Barlow 1994; Twigg *et al*. 2000; Sinclair 2003; Ramsey 2005). In short-lived species, fecundity can make a greater proportional contribution than survival to population growth, and the reverse occurs in long-lived species (Sibly and Hone 2002). Compensatory population changes that may occur in response to fertility control are likely to be less pronounced than those following population reduction by lethal methods, depending on whether populations are regulated by density-dependent mortality or recruitment (Johnson and Tait 1983; Bomford 1990; Bomford and O'Brien 1997). For instance, in populations of mice and rabbits, a compensatory response in female productivity did not offset the effects of sterilisation when 60–80% of the females were made infertile (Chambers *et al*. 1999; Twigg and Williams 1999; Twigg *et al*. 2000) (Table 2).

Initial models (e.g. Hone 1992; Barlow 1994) suggested that fertility control would be most effective for small-sized r-selected species, characterised by high fertility and low survival. These conclusions have been challenged by models showing that large,

long-lived species might be easier to manage with fertility control than are smaller, shorter-lived ones because a lower proportion of the population would need to be treated (Hone 1999), particularly if lifelong contraceptives were employed (Hobbs *et al*. 2000; Table 2).

However, in long-lived species, the benefits of using fertility control to decrease population size are accrued in the long term (Twigg *et al*. 2000; Cowan and Massei 2008; Kirkpatrick and Turner 2008). Others have suggested that contraception is likely to be better than culling for controlling species with medium to high instantaneous rates of population increase, but equivalent to culling for species with low instantaneous rates of population increase (Zhang 2000).

In some instances, fertility control might be required to reduce or halt population growth rather than to decrease population size. Druce *et al*. (2011) introduced the concept of individual-based 'rotational immunocontraception' and showed that using reversible immunocontraceptives on elephants on an individual rotational basis increased inter-calving intervals and lowered population growth to a predetermined rate.

In the context of wildlife diseases, fertility control has several specific advantages over culling. For instance, culling can increase disease transmission by disrupting social organisation and by increasing animal movements, thus leading to increased contact rates (e.g. Choisy and Rohani 2006; Carter *et al*. 2007; Wilkinson *et al*. 2009). Fertility control is likely to cause less social perturbation than is lethal control (Swinton *et al*. 1997; Tuyttens and Macdonald 1998). Where disease transmission has a substantial vertical component (from mother to offspring), such as brucellosis in bison, fertility control could be used to target such transmission (Miller *et al*. 2004). Fertility control removes the physiological costs of reproduction and lactation, which may thus enhance physical condition and improve immune function, thereby reducing susceptibility to disease. When fertility control is used as a tool for disease control, methods that prevent ovulation are likely to be more successful than those that only block fertilisation. For instance, the transmission coefficient of leptospirosis in possums was 28% higher in populations subjected to tubal ligation that leaves females cycling but unable to conceive, than in populations not subjected to fertility control (Caley and Ramsey 2001). In contrast, endocrine disruption caused by gonadectomy in possums decreased the leptospirosis transmission rate by 63–88% in sterilised female and male possums (Ramsey 2007).

Whether culling is more effective than disease vaccination for wildlife disease management will partly depend on assumptions about disease transmission, including whether the rate of transmission depends on the absolute density of susceptible individuals or the relative density of susceptible and immune individuals. Fertility control reduces the recruitment of new susceptible individuals. Thus, several models have suggested a synergistic effect of fertility control on disease vaccination that reduces the effort required to eliminate a disease from a population (Smith and Cheeseman 2002; Carroll *et al*. 2010). Complementary effects of disease vaccination and fertility control have also been suggested for the elimination of rabies from red fox (Smith and Wilkinson 2003) and free-roaming dogs (Carroll *et al*. 2010; Massei *et al*. 2010*b*; Massei 2012, 2013; Massei and Miller 2013) and for management of bovine tuberculosis in brushtail possums (Ramsey and Efford 2010).

In terms of behaviour, fertility control might affect hierarchically structured species where dominant females suppress breeding in subordinate females. If the social status of dominant females was compromised by sterilisation, intermediate levels of sterility could lead to increased productivity (Caughley *et al*. 1992). Conversely, if dominance was maintained, irrespective of reproductive output, contraception of dominant females should lead to decreased population-level productivity.

Although more research is clearly needed in this area, the disruption of female reproductive hormonal function does not affect social behaviour in several species (e.g. Chambers *et al*. 1999; Poiani *et al*. 2002; Kirkpatrick *et al*. 2011; Table 2). A few studies have suggested that changes in socio-sexual behaviour involving decreased libido, decreased sexual activity and aggressiveness could lead to disruption of social structure and spacing behaviour. For instance, in female ring-tailed lemurs (*Lemur catta*), Crawford *et al*. (2011) found that medroxyprogesterone acetate significantly altered the olfactory cues that signal fertility, individual chemical 'signature' and relatedness, and suggested that treatment with this contraceptive may disrupt social interactions, kin recognition and mate choice in primates. In brushtail possums, tubally ligated but hormonally competent females showed extended breeding seasons, which attracted higher densities of males into the study area (Ji *et al*. 2000). The average body condition of these males was significantly poorer than that of males in control areas. Similarly, an extension of the breeding season in deer treated with PZP vaccine resulted in an increase in energy expenditure by males (Killian and Miller 2000; Curtis *et al*. 2002). In contrast, decreased sexual activity of both males and females has been reported in deer treated with a GnRH vaccine (Miller *et al*. 2000, 2009).

Physiological responses to fertility control include increased improved health, body condition and, hence, survival, possibly linked to the reduced costs of reproduction. For example, sterilised feral Soay rams showed increased food consumption and survival compared with control rams, ultimately leading to increased animal numbers and impact on the plant community (Jewell 1986). PZP-based immunocontraceptives increased lifespan and body conditions of mares (Turner and Kirkpatrick 2002; Kirkpatrick and Turner 2007), tubal ligation increased survival in rabbits (Twigg *et al*. 2000; Williams *et al*. 2007) and GonaCon improved body condition of deer (Gionfriddo *et al*. 2011*b*). Conversely, Saunders *et al*. (2002) observed no differences in survival, dispersal or territory size of surgically sterilised foxes compared with fertile foxes, although sterilised vixens were more likely than fertile females to share their territories with each other.

Some authors hypothesised that the use of immunocontraceptive vaccines to manage wildlife could result in the evolution of resistance through selection for individuals that remain fertile because of low or no response to vaccination (e.g. Gross 2000; Magiafoglou *et al*. 2003; Holland *et al*. 2009). Although some studies concluded that the evolution of resistance was unlikely (Magiafoglou *et al*. 2003), research programs on mammalian immunocontraception should involve measurement

of the heritability of non-response (Cooper and Larsen 2006). For instance, in brushtail possums, two sets of alleles (haplotypes) were found to associate significantly with differences in response to immunocontraceptive vaccines (Holland *et al*. 2009). The characterisation of these haplotypes offers potential to identify factors affecting non-responders.

Criteria to assess the suitability of fertility control to mitigate human–wildlife conflicts

Conflicts involving overabundant species often demand immediate solutions. If fertility control is chosen to manage overabundant wildlife, Kirkpatrick and Franck (2005) proposed a three-step approach that consisted of (1) identifying a contraceptive suitable for the species to be managed, (2) assessing whether the contraceptive could be delivered under field conditions and (3) evaluating whether the desired population effect could be achieved in the field. We suggest expanding this approach by incorporating additional elements that include public consultation, evaluation of potential animal-welfare issues, population responses, costs and sustainability. Although these suggestions are presented as a decision tree (Fig. 2), the process is not necessarily linear; for instance, modelling would contribute to several stages in the process, such as informing the product specifications for the choice of contraceptives and assessment of the necessary efficacy. Likewise, costs can be estimated at an earlier stage and recalculated, if needed, later on in the process.

Local authorities and animal-welfare organisations advocate fertility control to manage human–wildlife conflicts, particularly in urban and suburban areas (Barr *et al*. 2002; Curtis *et al*. 2008). Conversely, many hunting groups, particularly in North America, oppose the use of fertility control because of concerns that this method will replace sport hunting (Kirkpatrick 2007; Curtis *et al*. 2008; Fagerstone *et al*. 2010). These polarised views suggest that at the planning stage, comprehensive stakeholder consultation and engagement is crucial to agree on common goals as well as methods to achieve these goals to manage wildlife.

Key questions when assessing the potential of fertility control to mitigate human–wildlife conflicts are ‘What is the overall proportion of the population that must be rendered infertile to achieve the target reduction in population size or to stop population growth or to achieve the desired reduction in damage?’, ‘What is the effort required to achieve the target population size within a certain timeframe?’ and ‘How frequently does the treatment need to be applied?’ (Chambers *et al*. 1999; Hobbs *et al*. 2000; Bradford and Hobbs 2008). The question of the impact of fertility control on damage reduction can be complicated as population size and damage are not always linearly related and a reduction in population size is not necessarily followed by a proportional decrease in damage (Hone 1995, 2002).

Captive studies or data collected on similar species could be used to inform decisions about the type of contraceptive to be employed. If the available data confirm the potential effectiveness of the approach, the study could progress toward modelling the effects of fertility control on population dynamics (e.g. Jacob *et al*. 2008). If modelling suggests that the objectives can be achieved within target time scale and available budget, the project can move to a field trial.

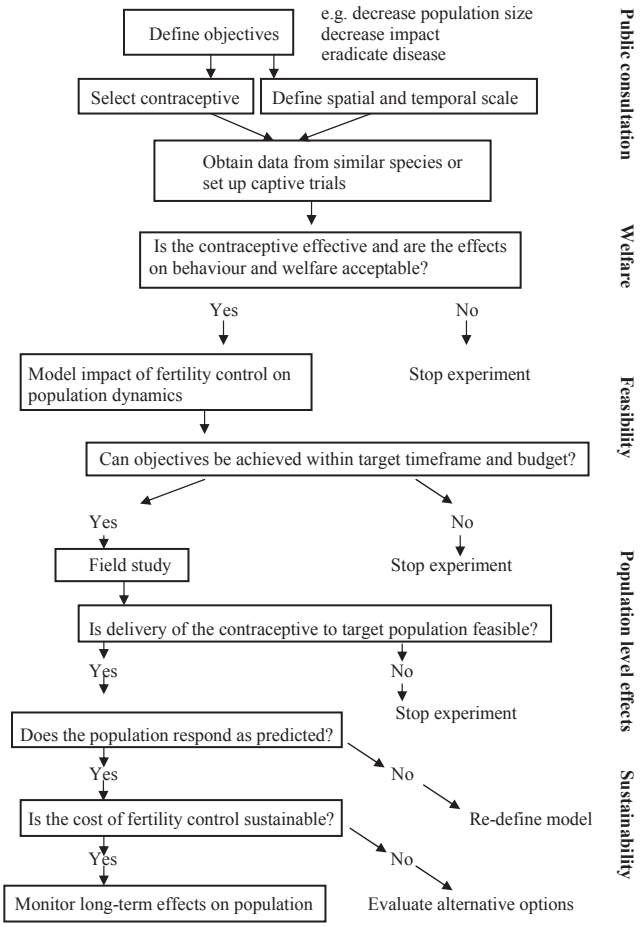

Fig. 2. Staged approach for assessing the suitability of fertility control to manage human–wildlife conflicts. This decision tree assumes that fertility control has been chosen over other options of population control.

The economic costs of reducing population densities through fertility control alone, with current delivery methods, are generally expected to be high. For instance, Rutberg (2005) estimated that the cost to render infertile a medium–large-size individual mammal varied between US$25 and US$500. Delsink *et al*. (2007) calculated that in 2005 the average cost of managing elephants through aerial vaccination with immunocontraceptives cost US$98–110 per animal, inclusive of darts, vaccine, helicopter and veterinary assistance. The cost of capture, handling and administering contraceptives to white-tailed deer in various contexts was estimated to be in excess of US$1000 per deer, with 75% of this cost being due to veterinary time and drugs (Boulanger *et al*. 2012). These costs would drop significantly if the contraceptives were delivered by trained wildlife managers and if animal capture were organised with the assistance of volunteers donating their time and skills to a project. In addition, the effort required to treat a wildlife population will be influenced by animal density, approachability of individual animals, access to private and public land, and efficacy of the contraceptive treatment (Rudolph *et al*. 2000).

Hobbs *et al*. (2000) suggested that fertility control of deer will be cost-effective, compared with culling, only where recreational hunting is not feasible and population control is carried out by employing professionals to cull deer. Comparing the costs of fertility control-based management with those of alternative control options and identifying who should bear these costs might raise awareness of the economics of current management practices among stakeholders and add a different perspective to wildlife management decision-making. This awareness would be further enhanced if the full costs, including negative environmental and welfare consequences, associated with each option were included. Once a field trial has been implemented, the effectiveness, costs and feasibility of using fertility control to manage human–wildlife conflicts can be evaluated, together with actual population responses to imposed infertility. The data collected can then be used to refine the model and to determine whether fertility control can be a sustainable approach. In addition, potential, unforeseen effects of imposing infertility must be evaluated; these include monitoring survival rate, immigration and emigration rates as well as disease transmission rates.

Conclusions

Ethical considerations regarding humane treatment of animals are shaping public attitudes toward acceptable methods of mitigating human–wildlife conflicts. The present review confirmed that the interest in fertility inhibitors for wildlife has steadily grown in the past three decades, as indicated by the trends in publications in this area. Possible reasons for the increasing trend in research and development include (1) new approaches based on advances in the understanding of the molecular mechanisms regulating mammalian fertility, (2) availability of new technologies that make practical applications for wildlife more feasible, (3) stakeholder interest in developing alternatives to culling, (4) increasing human–wildlife conflicts, (5) advances in other fields, such as contraceptives developed for livestock and companion animals, with potential for wildlife applications, (6) advances in analytical techniques used in population modelling studies and (7) internet-associated information flow raising public awareness of wildlife fertility control.

The review highlighted that several safe, effective and long-lasting fertility inhibitors such as levonorgestrel, deslorelin, PZP and GnRH-based immunocontraceptives are now available to manage wildlife and that successful population control has been achieved in several field applications (Table 2). So far, most empirical and theoretical studies have focussed on ungulates, marsupials and rodents, with the main aim of reducing population size or growth, and on carnivores, with studies aimed at decreasing disease transmission. In many instances, even when reduction in population size or growth has been successful, the mitigation of the conflict that caused fertility control to be employed is inferred but not quantified. Further research is required to address whether the application of fertility control can mitigate context-specific human–wildlife conflicts.

The use of fertility control to mitigate human–wildlife conflicts might raise inappropriate expectations if its costs and benefits were not clearly examined on a case-by-case basis. A general conclusion from the results of the studies summarised in the present review is that a substantial initial effort is required if fertility control is the sole method chosen to manage overabundant populations. However, as the proportion of infertile females increases, this effort will decline and remain constant once the desired density has been achieved. In addition, the review showed that there is growing recognition of the possible synergy between fertility control and disease vaccination to optimise the maintenance of herd immunity in the management of wildlife diseases. Before fertility-control applications can be advocated as a tool to mitigate human–wildlife conflicts, there are still many aspects that must receive further attention. These aspects include the development of contraceptives for wide-scale wildlife applications, the development of species-specific, inexpensive delivery methods, field applications demonstrating population responses to imposed infertility in species with different life-history traits, and the evaluation of feasibility, costs and sustainability of population-management programs based on fertility control.

Because efficacy and humaneness are often the primary public concerns regarding any type of wildlife management, defining these terms, particularly in relation to other methods of population control, is crucial for any management plan to obtain and maintain public support in relation to specific, well defined objectives. Efficacy can be defined as (1) the proportion of the population rendered infertile, (2) the speed of reduction in population size or damage or (3) the eradication of a disease. Humaneness can be defined as (1) the level of stress experienced by treated animals, (2) the severity and type of side effects, (3) the proportion of animals likely to experience negative side effects following the use of a contraceptive, (4) the proportion of animals likely to suffer from capture, handling and anaesthesia associated with administering the contraceptives, or (5) as a combination of all these definitions. Comparisons of fertility control and other population-management methods often fail to account for all the costs and benefits, including welfare costs. Defining these terms and adhering to guidelines for assessing and comparing the relative humaneness of wildlife control methods is one of the main challenges for human–wildlife conflict mitigation (Sharp and Saunders 2008). In addition to the scientific challenges of exploring the effects of fertility control on individuals and wildlife populations, regulatory and legal requirement for the application of contraceptives on wildlife must be met. The fact that in different countries fertility inhibitors can be registered as pesticides, biocides or veterinary medicines, depending on the mode of action and on the target species, coupled with the significant costs of registration, present hurdles for development and use of novel products (Humphrys and Lapidge 2008).

We suggested criteria that could be used during public and stakeholders consultations to determine whether fertility control should be used to manage overabundant wildlife. This assumes that fertility control represents a rational approach to the problems posed by animal populations. However, the review highlighted how for each context and species, the use of fertility control, alone or integrated with other methods of population control, should be evaluated and compared with alternative options to mitigate conflicts between human interests and wildlife.

Acknowledgements

The authors thank Roger Quy and Alastair Ward for reading the manuscript and providing comments and suggestions.

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